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Action of *Anastatica hierochuntica* plant extract on Islets of Langerhans in normal and diabetic rats

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ABSTRACT

The increase in number of diabetic patients motivated scientists to find new methods to control such disease. In the present study, the action of water extract of a common medicinal plant (*Anastatica hierochuntica*) used in the Arabian Peninsula was studied on normal and Streptozotocin (STZ)-induced diabetic rats. Experimental groups included control rats orally administered distilled water; plant treated group received oral daily dose of the plant extract (12.5 mg/rat) for two weeks; diabetic untreated group intraperitoneally injected with STZ (60 mg/kg); and diabetic-plant treated group included STZ-diabetic rats received the daily oral dose of the plant extract for two weeks. Blood samples were collected for determination of blood glucose level and samples from pancreatic tissues were processed to paraffin blocks for histological and immunohistochemical studies. The diabetogenic effect of STZ was proven by significant elevation of blood glucose in STZ-treated rats. STZ also showed islet cell disintegration and destruction with the presence of hyaline masses and empty spaces invaded with inflammatory cells. However, administration of the plant extract induced a hypoglycemic effect in both normoglycemic and diabetic rats. It also caused significant improvement in tissue injury induced by STZ. Immunohistochemical studies showed intensive reduction of insulin-positive cells in islets of Langerhans after the onset of diabetes, while the plant extract stimulates the appearance of those cells in STZ-diabetic rats. However, glucagon-secreting cells were increased in untreated and plant-treated diabetic rats comparable to control rats. The results indicate the ability of the plant extract to improve the diabetogenic action of STZ.

KEYWORDS: pancreatic islets, diabetes, Streptozotocin, histology, physiology, immunohistochemistry.

INTRODUCTION

Since the early 1970s, diabetes mellitus has become one of the most frequent complication-accompanying chronic diseases with high morbidity and mortality (Adeghate 1999b). It is a metabolic disorder characterized by hyperglycemia resulting from lack of insulin, lack of insulin effect, or both. Two types of diabetes are recognized; type I, known as insulin-dependent diabetes (IDDM), and type II, known as non-insulin-dependent diabetes (NIDDM) (Hansen 1998). In type I diabetes, the absolute deficiency of insulin attributed to ß-cell dysfunction leads to hyperglycemia, enhanced lipolysis, protein catabolism and Ketosis (Hansen 1998). Type II diabetes impairs the ability of insulin to stimulate both muscle glucose uptake and splanchnic glucose uptake, thus contributes to induce hyperglycemia (Basu *et al.* 2000). The severity and frequency of the late degenerative complications are high in patients with either type I or type II diabetes mellitus (Adeghate 1999a).

The available methods for treatment of diabetes mellitus include diet or diet and oral hypoglycemic drugs or diet and insulin (Boon *et al*. 1999). In traditional practices, medicinal plants are used to control diabetes mellitus in many countries. This caused an increase in the number of experimental and clinical investigations directed toward the validation of the hypoglycemic (El-Ridi 2001) and/or anti-diabetic (Alarcon-Aguilara *et al*. 1998) properties of different medicinal plants. It has been reported that the chard (*Beta vulgaris* L. var. Cicla) extract increased pancreatic beta cells in STZ-diabetic rats (Bolkent *et al*. 2000). Water extract of *Smallantus sonchifolius* (yacon) leaves fed to normal and STZ-diabetic rats also showed hypoglycemic effects (Aybar *et al*. 2001). Moreover, a long-term administration of

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olive leaves or cinnamon bark caused significant improvement in tissue injury induced by STZ treatment (Onderoglu *et al*. 1999).

Anastatica hierochuntica (Rose of Jericho) is among the common medicinal plants widely used in Hijaz, Najd, and Al Rub'Al Khali (Mossa *et al*. 1987). The plant is prescribed in folk medicine for difficult labor, uterine hemorrhage and to facilitates the expulsion of dead fetuses (Khalifa 1980). In a preliminary recent study, water extract of *Anastatica hierochuntica* showed non-significant hypoglycemic effect in normoglycemic rats (El-Ridi 2001). In the present study, the effect of *Anastatica hierochuntica* on the structural and functional pattern of the pancreas was tested in normal and STZ-diabetic rats.

MATERIALS AND METHODS

Experimental plant: Samples of whole dried *Anastatica hierochuntica* were brought from Kingdom of Saudi Arabia. The aerial parts of the plant were isolated and kept in airtight glass containers till the time of the experiments. Just prior to experimentation, the dried plant was ground to fine powder. Twenty grams of the powder were then mixed with 200 ml of distilled water and shaked overnight. Suspension was then filtered twice and the water extract was centrifuged then filtered again. Water extracts were prepared daily just before administration to the experimental animals in a dose of 4 ml/kg body weight (1ml/rat of 250g in b.wt.). Samples of each extract were freeze-dried and the average yield of the extracts was 12.5 ± 0.2 mg/ml.

Preparation of Streptozotocin: Fresh solution of STZ was prepared in phosphate citrate puffer (pH = 4.6 – suitable for dissolving STZ) just before injection. Diabetes mellitus was induced by a single dose of STZ (60 mg/kg body weight) given intraperitoneally (i.p.) to rats according to the method described by Adeghate *et al*. (2001).

Experimental animals: Thirty-six male albino rats of Wistar strain (250 ± 10 g each) were kindly supplied by Faculty of Medicine and Health Sciences, UAE University, and used in this research. Rats were maintained with free access to water and a standard pellet diet (containing protein (24%), fiber (5%), ash (8%), calcium (1%) and phosphorus (0.75%), made by Flour and Animal Feed Factory, Abu Dhabi). Experimental animals were divided into four groups (9 rats each):

1-Control group: Rats were orally administered (using a feeding needle to the esophagus) with a daily dose of 1 ml distilled water for 2 weeks;

2- Plant-treated group: One ml of the plant extract (12.5 mg) was orally administered daily to each rat in this group for 2 weeks;

3-Diabetic untreated group (positive control group): Rats were intraperitoneally injected with a single dose of STZ (60 mg/kg b. wt.), followed with a daily oral dose of 1ml distilled water administered to each rat for one week;

4-Diabetic plant-treated group: Rats were rendered diabetic via i.p. injection of STZ as in group 3. One week later, each animal received a daily oral dose (1 ml) of the plant extract for another 2 weeks.

Blood sampling: Rats from all groups were anesthetized with ethyl ether inhalation at the end of the experiments. Blood samples were collected from the retroorbital veins using heparinized capillary tubes. Serum was separated from blood samples, then frozen until used for determination of the glucose levels using the glucose oxidase method (Trinder 1969).

Statistical analysis: All serum glucose data are expressed as means ± standard errors of the means (S.E.). Statistical comparison between groups was performed with one-way analysis of variance (ANOVA) and Scheffes multiple comparison was used to assess any significant differences between the treated groups (Armitage & Berry 1987). A value of $P < 0.05$ indicates statistical significant difference.

Tissue sampling: At the end of each experiment, and after taking blood samples, anesthetized rats were abdominally sacrificed. Samples from the pancreas were removed from each rat and

washed in saline solution for removal of the blood then fixed in 10 mM phosphate buffered saline, pH 7.4 (PBS) containing 2% paraformaldehyde for 48 hr at 4ºC . The fixed samples were then washed in running water over night then processed to paraffin blocks, sectioned at 5 µm in thickness and used for histological and immunohistochemical studies.

Histological studies: Histological inspection was performed on paraffin-embedded pancreatic sections following hematoxylin and eosin (H&E) staining technique.

Immunohistochemical studies: Paraffin sections of control and treated rats were dewaxed then incubated for 1hr at room temperature in 0.3% hydrogen peroxide in PBS, followed by washing 3 times in PBS. Sections were then incubated for 16 hr, at 4 °C, in PBS containing 2% normal goat serum (NGS) and 0.5% triton X-100, then washed in PBS at room temperature. Sections were incubated overnight at 4°C with the primary monoclonal antibody (Mouse anti-EMA, anti-insulin, and anti-glucagon; ICN, Costa Mesa, CA, USA and Sigma Chem. Comp.). Incubation was followed by 3 times wash in PBS-2% NGS. The primary antibodies were then bounded by a biotinylated anti-mouse secondary antibody (rat adsorbed, 1:200, Vector Labs, Burlingame, CA, USA) in PBS for 1hr at room temperature. Sections were then incubated in avidin-biotin complex linked to peroxidase (ABC Kit, Vector Labs, Burlingame, CA, USA). The peroxidase was visualized with 0.03% diaminobenzidine hydrochloride and 0.005% hydrogen peroxide in 0.1 M Tris buffer. Sections were counter stained with hematoxylin.

RESULTS

Blood glucose levels: The diabetogenic effect of STZ was proved by a significant increase in the blood glucose level (488 mg/dl) in rats of the diabetic group. Nevertheless, administration of the plant extract induced hypoglycemic effects in both normoglycemic (131 mg/dl) and diabetic rats (318 mg/dl). This decrease was insignificant in case of normal rats. Moreover, the plant extract did not lower the blood glucose level of the diabetic rats to the control values (149 mg/dl) (Fig. 1).

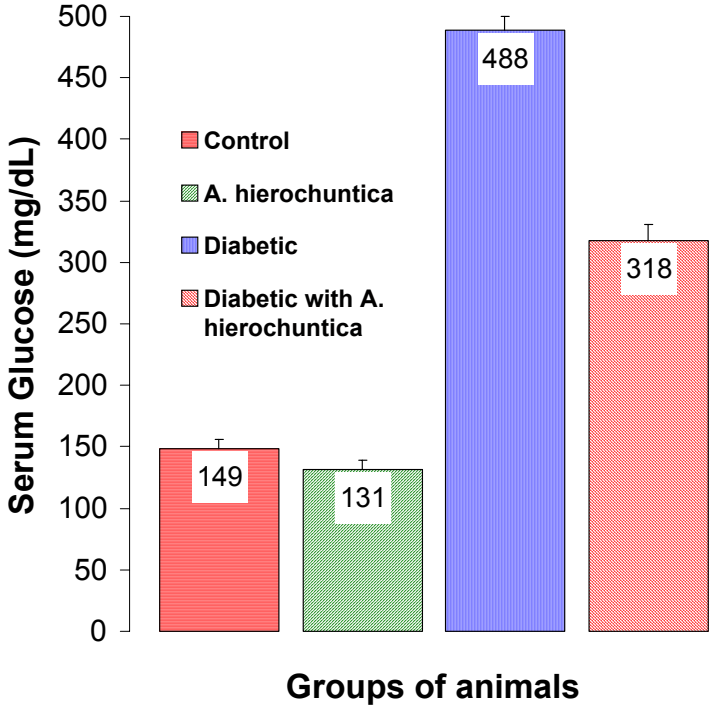

Figure 1 : Serum glucose levels in normal and diabetic rats given 1 ml daily of water or *A. heirocuntica* extract for two week. Data are shown as means ± S.E. Statistics: Different letters means statistical significant difference at $p < 0.05$. Bars with similar letters are insignificant.

Histological studies: Islets of Langerhans of normal rats were scattered throughout the exocrine tissues of the pancreas. They contain several cuboidal endocrine cells with a

vascularization of many blood capillaries (Fig. 2). Sections obtained from rats treated with the plant extract (Fig. 3) revealed the common histological appearance of islets of Langerhans.
The diabetogenic effects of STZ on the pancreas showed islet cell disintegration and destruction besides the appearance of necrotic endocrine cells. The endocrine cells lost their common characteristics and were separated by empty spaces and hyaline masses. Administration of STZ also led to the appearance of numerous inflammatory cells in-between the injured cells (Fig. 4). Nevertheless, treatment with the plant extract to diabetic rats caused significant improvement in tissue injury induced by STZ injection. No islet disintegration was observed, although a few densely stained nuclei were apparent. Intact newly formed cells were also recorded (Fig. 5).

Immunohistochemical expression of insulin: The control pancreatic tissues showed the presence of numerous insulin-immunoreactive cells in both central and peripheral parts of the islet of Langerhans (Fig. 6). Similar observation was noticed in pancreatic islets of rats administered the plant extract (Fig. 7). After the onset of diabetes, no immunohistochemical expression was recorded for insulin except for a few insulin-positive cells scattered within the islets of STZ-diabetic rats (Fig. 8). However, administration of the plant extract to diabetic rats stimulated the appearance of immunoreactive insulin-secreting cells in many parts of the pancreatic islets (Fig. 9).

Immunohistochemical expression of glucagon: In control pancreas, glucagon-immunoreactive cells were mainly localized at the peripheral regions of the islet of Langerhans (Fig. 10). Glucagon-positive cells were much fewer in number when compared to insulin-positive cells of control pancreas. The number of glucagon secreting cells did not change significantly in rats administered the plant extract. However, the stainability of these cells was more than that of the control cells (Fig. 11). After the onset of diabetes, the number and intensity of glucagon-positive cells were significantly increased at the periphery of the islets of Langerhans (Fig. 12). An increase in number of glucagon-positive cells persisted at the periphery of diabetic pancreas after administration of the plant extract (Fig. 13).

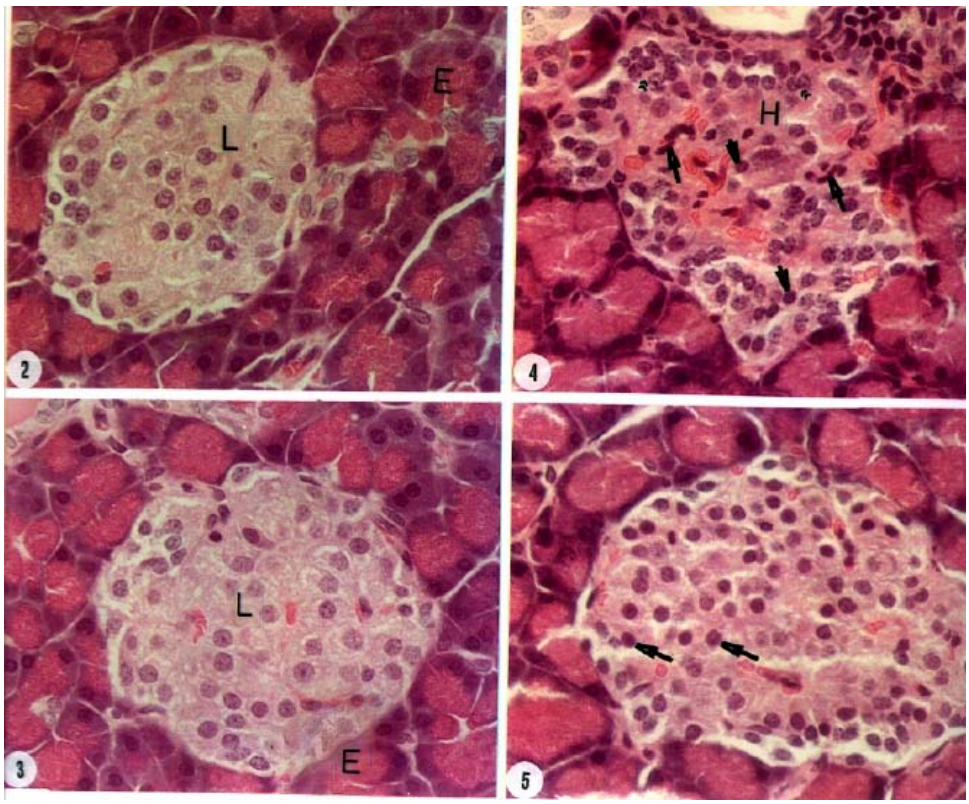

Fig. 2: Islets of Langerhans (L) surrounded by exocrine portion (E) of pancreatic tissues of a control rat. (H&E, X400)
Fig. 3: Normal characteristics of islets of Langerhans (L) and exocrine acini (E) in plant–treated rat. (H&E, X400).
Fig. 4: Disintegration and destruction of endocrine cells (Double arrowheads) in a STZ-diabetic rat. Note necrotic cells (arrowheads) and inflammatory cells (arrows) in a hyaline matrix (H). E: normal exocrine acini (H&E, X400)
Fig. 5: Improvement in the histological structure of the islets of Langerhans after administration of the plant extract to a diabetic rat. Note densely stained nuclei (H&E, X400)

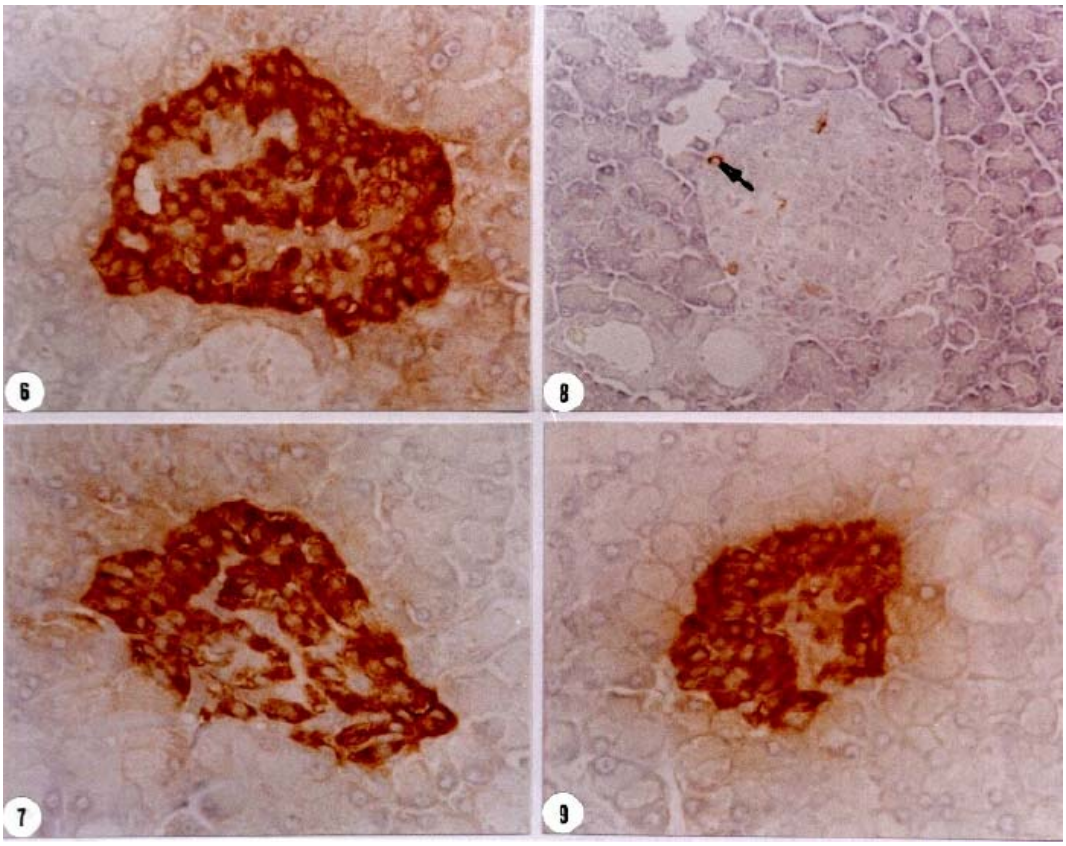

Fig. 6: Immunohistochemical expression of insulin secreting cells in pancreatic islets of a normal rat (X 400).
Fig. 7: Immunostained insulin secreting cells similar to those of the control materials (X 400).
Fig. 8: Negative staining for insulin secreting cells in a STZ-diabetic rat. Arrow indicates a positively stained insulin-secreting cell (X 400).
Fig. 9: Positive insulin-secreting cells in a diabetic rat after treatment with the plant extract (X 400).

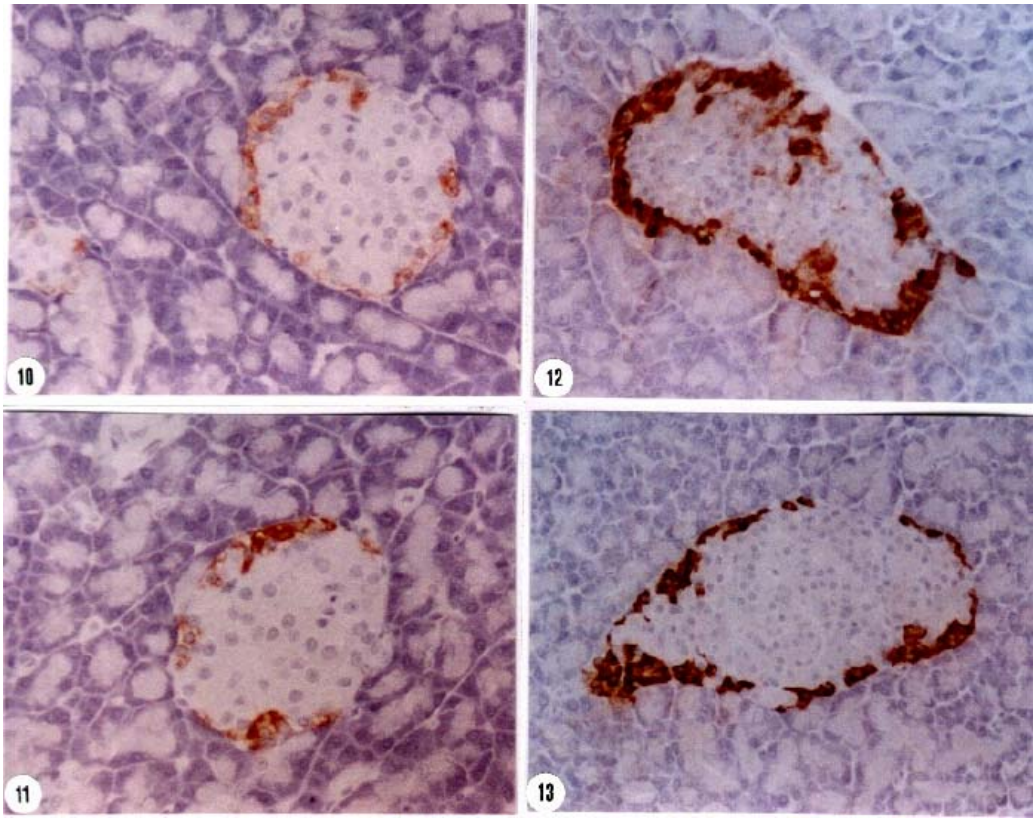

Fig. 10: Positively stained glucagon-secreting cells at the periphery of islets of Langerhans of a control rat (X 400).

Fig. 11: Immunohistchemical expression of glucagon in pancreas of a plant treated rat (X 400).

Fig. 12: Increased number of glucagon-secreting cells in pancreatic tissues of a STZ-diabetic rat (X 400).

Fig. 13: Numerous cells with glucagon immunostainability in a diabetic rat after administration of the plant extract (X 400).

DISCUSSION

The increase in number of diabetic patients have motivated scientists to find new methods to cure diabetes (Adeghate 1999b). In the present study, the effect of the water extract of *Anastatica hierochuntica* was tested on normoglycemic as well as STZ-diabetic rat models. The diabetogenic effect of STZ was reported by several investigators (Choi *et al*. 1991; Adeghate 1999b; Wang *et al*. 2000). It was indicated in the present study by the significant increase in blood glucose level in STZ-injected rats. This increase in circulating glucose level is believed to contribute to ß-cell dysfunction (Hansen 1998), indicated by the observed histopathological alterations and decreased immuoexpression of insulin-secreting cells in diabetic pancreas. STZ is known to induce severe histopathological changes in the pancreas (Mitra *et al*. 1996), which gives rise to hypoinsulinaemia and hyperglycemia features similar to those of type 1 clinical diabetes (Howarth *et al*. 2000). The effect of STZ relates to its structure as a DNA alkylating agent, which leads to necrosis of pancreatic beta cells and thus to a state of insulin – dependent diabetes mellitus (Elsner *et al*. 2000). The action of STZ could also be due to alterations in membrane fatty acid content, which may affect Na+, K+-ATPase activity, membrane fluidity, and fatty acid content (Sennoune *et al*. 1999).

Moreover, the observed islet infiltration by inflammatory cells could indicate destruction of insulin-producing cells (Sarukhan *et al*. 1999). In this concern, Figueroa *et al*. (2000) pointed out to the critical role of macrophages in the onset and progression of islet cell destruction in Type 1 diabetes.

The decreased immuoexpression of insulin-producing cells in diabetic pancreas also explained the gross clinical sign of hyperglycemia induced by STZ (Adeghate *et al*., 1999). This decrease was accompanied by an increase in glucagon-secreting cells, which may arise from the loss of the inhibitory effect of insulin on glucagon or may be due to a response to the increased blood sugar level in diabetes (Adeghate *et al*. 2000). The decrease of insulin-secreting cells and the increase in glucagon-secreting cells could point out to the specificity of STZ to destruction of insulin-secreting beta cells. The specificity of this beta cell toxin was reported by Adeghate (1999a) and Wright *et al*. (1999).

On the other hand, the results indicated that administration of *Anastatica hierochuntica* plant extract improved, but not completely normalized, the diabetogenic action induced by STZ. It showed a hypoglycemic effect on blood glucose level in plant-treated diabetic rats when compared with untreated diabetics. Choi *et al*. (1991) mentioned that the hypoglycemic effect of methanolic extract of *Prunus davidiana* Fr. stems is due to the presence of the main flavanone glycoside and prunin components. Moreover, Abdel-Hassan *et al*. (2000) attributed the hypoglycemic action of the aqueous extract of *Citrullus colocynthis* fruit to the presence of glycosidic components. Similarly, it is believed that the presence of flavone glycosidic components in the plant extract of *Anastatica hierochuntia* (Khalifa 1980), is responsible for reducing the blood glucose level in STZ-diabetic rats. Such hypoglycemic effect could be through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas. This agrees with the observed reduction of islet histopathology and immunoexpression of insulin secreting cells following plant administration to diabetic rats. It also agrees with the results of Das *et al*. (1996) who mentioned that the potential hypoglycemic nature of the leaf extract of *Aegle marmelose* improved functional state of pancreatic beta cells and help in regeneration of damaged pancreas. Puri and Baral (1998) also added that the hypoglycemic effect of *Biophutum sensitivum* leaf extract on diabetic rabbits is possibly due to pancreatic beta cell stimulating action. Moreover, administration of olive leaf or cinnamon bark was found to improve tissue injury induced by STZ treatment (Onderoglu *et al*. 1999).

Despite this effect of the plant extract in lowering the blood glucose level in STZ-treated rats, the persisted increase in glucagon secreting cells in their pancreas could be responsible for the incomplete recovery of the hyperglycemia induced by STZ. Adeghate (1999b) showed that

the increase in the tissue level of glucagon might play a role in the development of hyperglycemia. It is believed that long term administration of the plant extract could provide a chance for regeneration of more insulin producing-Beta cells with consequent decrease of glucagon immunoexpression and normalization of the blood glucose level.

In summary, the results of the present study suggest that the water extract of *Anastatica hierochuntica*, in the dose given and rout of administration used, has hypoglycemic effect in both normoglycemic and diabetic rats. This effect is believed to be through regeneration and / or repair of insulin-secreting beta cells. Moreover, although administration of the plant extract has no side effect on the pancreatic endocrine tissues, determination of the plant effect to other tissues of the experimental animal is a major topic requiring further studies.

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الملخص العربى

تأثير مستخلص نبات كف مريم على جزر لانجرهانز في الجرذان الطّبيعية والمصابة بالسكر

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في البحث الحالي تم دراسة تأثير المستخلص المائي لنبات كف مريم - وهو نبات طبي شائع الاستخدام في شبه الجزيرة العربية - على جرذان طبيعية وأخرى مصابة بالسكر عن طريق حقنها بعقار ستربتوزوتوسين.

وقد تضمّنت مجموعات التجارب المجموعة الضابطة (جرذان تجرعت الماء المقطر عن طريق الفم)، ومجموعة تجرعت مستخلص نبات كف مريم (تجرعت يومياً 12.5مليجرام/جرذ من مستخلص النبات ولمدة أسبوعين)، ومجموعة غير معالجة بالنبات ومصابة بالسكر عن طريق حقنها بريتونياً بجرعة واحدة من الستربتوزوتوسين (60 مليجرام/كيلوجرام من وزن الجرذ)، ومجموعة معالجة بالنبات بعد إصابتها بالسكر وقد تضمّنت جرذان مصابة بالسكر عن طريق حقنها بنفس الطريقة السابقة ثم تجرعت جرعة يومية من مستخلص نبات كف مريم لمدة أسبوعين. وقد تم تجميع عينات الدم لتحديد نسبة جلوكوز الدّم في جرذان كل مجموعة، كما تم تجميع عينات من الأنسجة البنكرياسية تم إعدادها وطمرها في الشمع لاستخدامها في بعض الدراسات الهستولوجية والهستوكيميائية المناعية.

وقد تم التأكد من تأثير عقار الستربتوزوتوسين من خلال الإرتفاع المعنوي في نسبة جلوكوز الدّم في الجرذان المعاملة بالستربتوزوتوسين.كما سبب العقار تفكك ودمار لخلايا جزر لانجرهانز مع ظهور مناطق زجاجية المظهر مكتظة بالخلايا الالتهابية وتتخللها مناطق فارغة. أما تعاطي الجرذان لمستخلص نبات كف مريم فقد خفض نسبة السكر في كل من الجرذان الطبيعية والمصابة بالسكر. كما أدى استخدام النبات إلى تحسن الصورة الهستولوجية لأنسجة البنكرياس المصابة في الجرذان المحقونة بالستربتوزوتوسين. أما الدراسات الهستوكيميائية المناعية فقد أظهرت تناقصاً واضحاً في الخلايا البنكرياسية المنتجة للإنسولين في جزر لانجرهانز للجرذان المصابة بمرض السكر، بينما أدى التجرع الفمي لمستخلص النبات إلى تحفيز ظهور تلك الخلايا في الجرذان المصابة بالسكر. على الجانب الآخر فقد تزايدت أعداد الخلايا المنتجة لهرمون الجلوكاجون في جزر لانجرهانز للجرذان المصابة بالسكر وغير المعالجة بمستخلص النبات، وكذلك في الجرذان المصابة بالسكر والمعاملة بمستخلص النبات مقارنة بجرذان المجموعة الضابطة. وتشير النتائج إلى قدرة مستخلص نبات كف مريم على تحسين تأثيرات الحقن بالستربتوزوتوسين والمسببة للإصابة بمرض السكر.