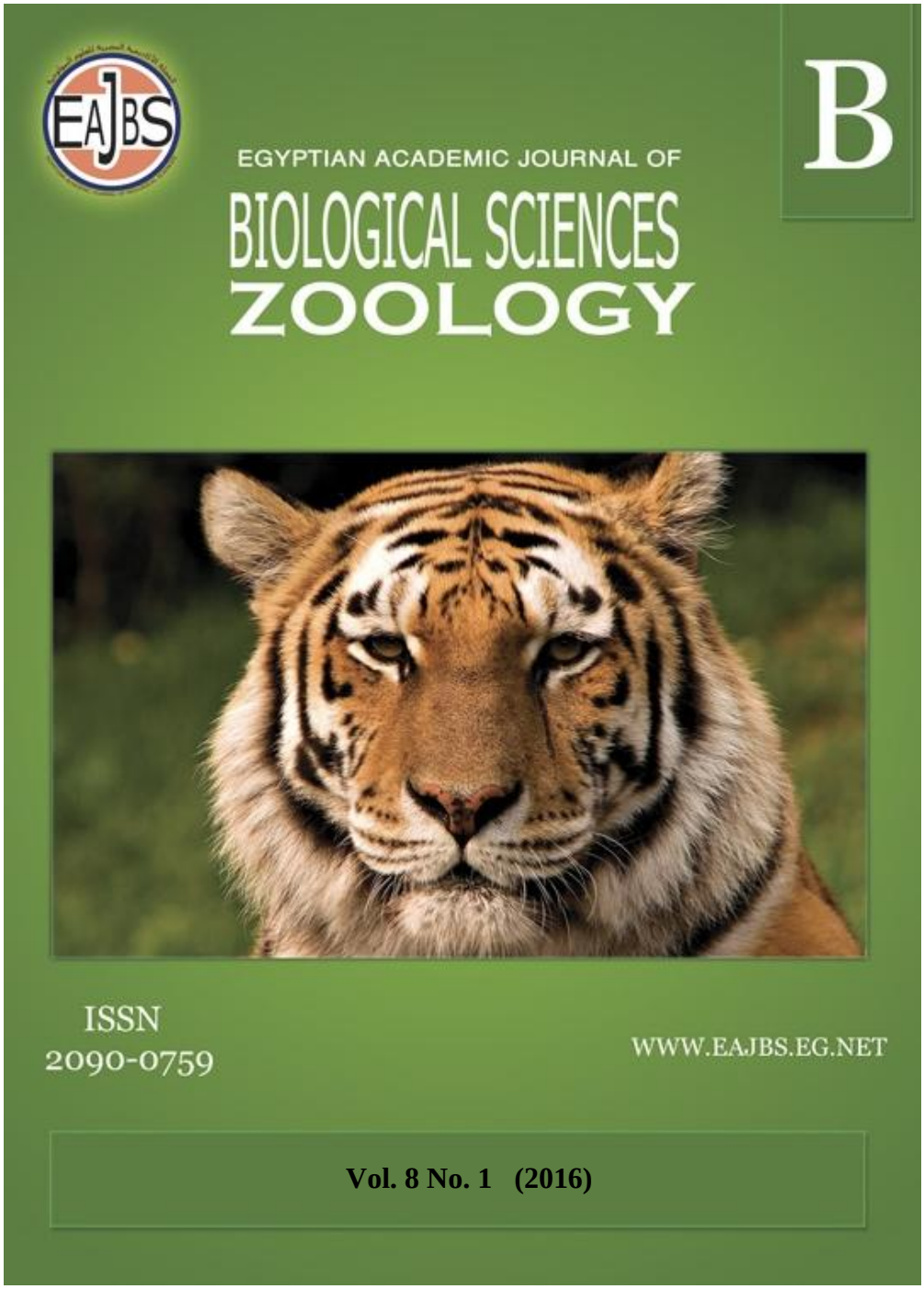

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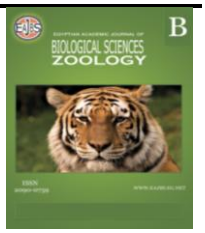

Protective Effects of *Androctonus Amoreuxi* Scorpion Extract and Sitagliptin Treatment on The Liver Injury of Diabetic Rats

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ABSTRACT

Liver injury is involved in both the pathogenesis and complications of diabetes. *Androctonus Amoreuxi* scorpion tea was previously reported to modulate physiological responses in streptozotocin-induced diabetic rats. This study attempts to evaluate liver protective effects of scorpion tea (*Androctonus Amoreuxi*) and sit agliptinin streptozotocin-induced diabetic rats. Forty rats were divided into four groups (n=10). Diabetes were induced in male albino rat by intraperitoneal injection of 65 mg/kg STZ. Three days later, the animals randomly divided to 3 groups: diabetic group, diabetic+ S.Tea(300 mg/kg)and diabetic+ ST (10 mg/kg) besides control group received intraperitoneal injection of saline. Liver histological and biochemical markers, were monitored at the end of experimental peroid. Results of our study revealed that treatment with scorpion tea or sitagliptin produced significant liver protection manifested by a significant decrease in serum levels of alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamy-ltransferase (GGT) and lactate dehydrogenase (LDH).Histologically, liver of diabetic rats showed severe liver injury. Histopathological changes were significantly attenuated in diabetic animals treated with scorpion tea or sitagliptin. Results of this study suggest that *A. amoreuxi* scorpion extract and sitagliptin have protective effects against hepatic injury.

INTRODUCTION

Diabetes is a serious metabolic disorder with micro and macrovascular complications that results in significant morbidity and mortality (Nathan *et al*., 2005). The prevalence of diabetes mellitus (DM) has reached epidemic proportions and has affected 6.4% of adults worldwide in 2010 (Shaw *et al*., 2010)

The liver plays a central and crucial role in the regulation of carbohydrate metabolism by maintaining glucose concentrations in a normal range by means of glycogenogenesis and glycogenolysis (Raddatz and Ramadori, 2007). This central role for the liver in glucose homeostasis offers a clue to the pathogenesis of glucose intolerance in liver diseases (Garcia-Compean *et al*., 2009). Excess glycogen accumulation in the liver is seen in 80% of diabetic patients.Glycogen synthesis in the liver is impaired in diabetes due to defective activation of glycogen synthase (Rui, 20114).

Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed disproportionately in diabetes by glucose oxidation, non-enzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation, and development of insulin resistance. These consequences of oxidative stress can promote the development of complications of diabetes mellitus (Maritim *et al*., 2003).

According to many reviews, diabetes cause an increase in production of reactive oxygen species (ROS) which initiating or promoting the development of chronic diabetic lesions on vessels, retina, kidneys, nerves and on the other organs whether antioxidant defenses of diabetic organism are unable to block the harmful action of such substances (Kumar *et al*., 2013).

Hence, this study aimed at evaluating hepatoprotective effect of *Androctonus Amoreuxi* scorpion Extract and sitagliptin as an antioxidants agents capable of neutralizing the harmful effects of ROS on the liver. Through study the histological lesion of the liver of STZ- induced diabetic rats compared to control could help in better understanding of the histopathological changes in diabetes mellitus and highlight the protective effects of the *Amoreuxi* scorpion Extract and sitagliptin.

MATERIALS AND METHODS

Chemicals:

Streptozotocinwas purchased from Sigma-Aldrich (MO, USA), Nicotinamide (NA) was purchased from modern lab. Sitagliptin (Januvia® tablet) was obtained from Merck Sharp &Dohme Ltd (Pavia, Italy). Glimepiride was kindly provided from Medical Union Pharmaceuticals (Abu-Sultan, Ismailia, Egypt). All other chemicals and solvents were of highest analytical grade. The feed ingredients such as lard and sucrose were procured from the commercial sources. Citric acid, sodium citrate and sodium carboxymethyl cellulose (Na-CMC) were also obtained from ADWIC CO. (Cairo, Egypt).

Animals:

A total of 40 male albino rats Rattusrattus, were purchased from animal house of National Research Center (NRC), Doky, Cairo. These were specific pathogen free. Animals were treated according to ethical guidelines of NRC. The animals were housed in polystyrene cages (five animals per cage) throughout the study, and room temperature was maintained at 25 ± 2°C and at a 12-h light/12-h dark cycle. Food and water were allowed ad libitum. Animals were kept 2 weeks before starting the experiment for acclimatization.

Preparation of standard drug (Januvia)

Januvia; Generic Name: Sitagliptin Phosphate. Sitagliptin is a traditional anti-diabetic drug that works by increasing levels of natural substances called incretins. Incretins help to control blood sugar by increasing insulin release, especially after a meal. They also decrease the amount of sugar made by liver. Januvia (1000 mg/tablet) was purchased from a local pharmacy. Three tablets of drug were grinded to fine powder and dissolved and drugs were administered orally as a suspension in 1% sodium carboxymethyl cellulose (Na-CMC) solution and continued for a period of 30 days. Rat dose of Januvia was calculated from the standard clinical human dose on the basis of surface area [rat dose = {(human dose/average body weight of rats)×7}] (Freireich *et al*., 1966).

Preparations and whole body *Androctonus Amoreuxi* extract

About 100 *A. amoreuxi* scorpions were collected from North Western Egypt, around the Western Mediterranean Costal Desert in Alexandria. To lower the toxic effect, the toxic sting in the tail of the scorpion was discarded before its whole bodies were used for further preparations. First, the scorpions were dried overnight at 60°C and then reduced to a powder. The scorpion powder was soaked in warm water for 2 h and filtered through four sheets of gauze. The solid material was extracted twice again under the same conditions. The filtrates were combined and centrifuged to remove water-insoluble materials. After centrifugation for 15 min at 3000 r/min, the supernatant was lyophilized to yield the crude. The obtained crude was weighted and dissolved in saline solution and then became ready to use (Xie *et al*., 2010).

Induction of diabetes in rat

Diabetes was induced in 16 h fasted male rats by a single intraperitoneal injection of a buffered solution (0.1 M citrate, pH 4.5) of streptozotocin (STZ) and Nicotinamide (NA). Overnight fasted animals were administered NA (90 mg/kg) dissolved in 0.9% NaCl and after 15 min, STZ (60 mg/kg) dissolved in 0.1 mmol/l citrate buffer (pH 4.5) was injected. To prevent hypoglycemia, animals were given a 10% glucose solution for the next 48 h. Blood glucose level was measured 9 days after diabetes induction using reagent strips (Accu-Chek®, Roche). Blood was collected from tail vein and rats with blood glucose values more than 200 mg/dL were considered diabetics

Experimental groups:

This work was carried out on 40 healthy male albino rats, with a body weight 130-150gm. Animals were randomly divided into four groups, 10 rats in each group. Group I, normal negative control group6 rats, intraperitoneally received isotonic saline (0.9% NaCl). Group II, STZ/NA-induced diabetic rats 21 rats. Group III, STZ/NA-induced diabetic rats and intraperitoneally received standard drug treatment (Januvia) at a daily dose 10 mg/kg for one month. Group IV, STZ/NA-induced diabetic rats and intraperitoneally received treatment with scorpion extract at a daily dose of 200 mg/kg for 4 weeks according to Weidong *et al*. (2010). All animal groups were sacrificed one month post treatment, blood samples and pancreases were collected.

Determination of liver enzymes activities

The activities of Alanine transaminase (ALT) and aspertate aminotransferase (AST) were determined in serum using commercial kit based on 2, 4-dinitrophenylhydrazine method (Reitman *et al*., 1957), Alkalinephosphatase (ALP) based on AACC method described by Point Scientific, INC kit (Tietiz *et al*., 1986). Determination of the total activity of Lactate dehydrogenase (LDH) was by the method of Moss *et al*. (1987).

Histopathological studies

For histopathological study, Small pieces of liver from each animal was removed after dissection and preserved in 10% formalin saline. These tissues were dehydrated in ethanol, embedded in paraffin wax, and stained with hematoxylin and eosin. Sections (5 μm) of livers stained with hematoxylin and eosin, were observed microscopically (Suvarna *et al*., 2013).

Statistical analysis

Statistics were calculated with SPSS for windows version 20.0, the means value obtained in the different groups were compared by one way ANOVA followed by Duncan's. All results were expressed as mean values ± SE and significance was defined as $p< 0.05$ (Field, 2000).

RESULTS

Fig. 1 shows the effects of Januvia and *A. amoreuxi* extract, STZ/NA and their combination on serum ALT. STZ/NA treatment induced a significant increase in ALT activity, which increased from 49.24 U/L (the control value) to 65.43 U/L with a percentage of about +32.89%. Treatment with scorpion tea (Sc.tea) for 30 consecutive days after induction of diabetes significantly decreases the activity of ALT as compared with the DM group with percent of change 32.3%.

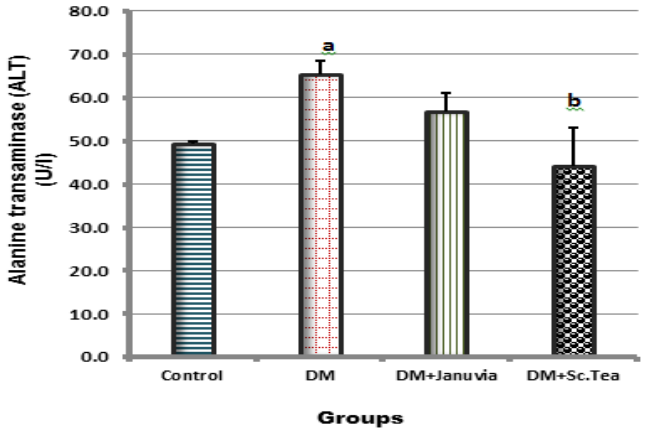

Fig.1: Effect of Januvia or *Androctonus amoreuxi* extract (Sc. Tea) on serum ALT in STZ/NA induced diabetic rats. Values are means ± SEM. n=10, One Way ANOVA followed by Duncan multiple comparison tests.[a] $p<0.05$ compared with normal control group, [b]$p<0.05$ compared with Diabetic group.

Fig. 2 shows the effects of Januvia and *A. amoreuxi* extract, STZ/NA and their combination on serum AST. Induction of diabetes with STZ/NA resulted in significant 9 fold increase in AST activity as compared to the control group. Treatment with Januvia for 30 consecutive days after induction of diabetes significantly decreases the activity of AST as compared with the DM group with percent of change 35%. Also *A. amoreuxi* extract exhibited a signicant decrease in AST activity with percent of change 43.1.

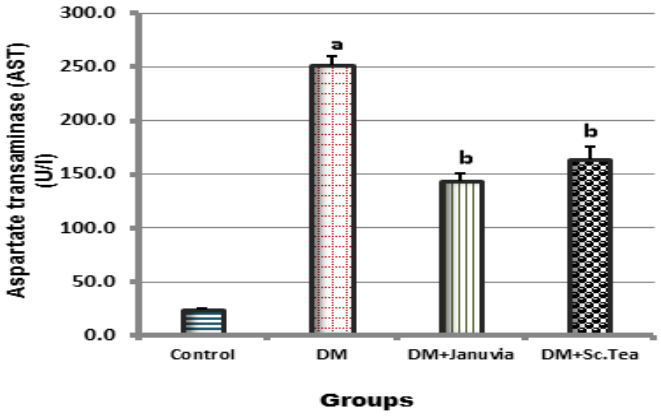

Fig. 2: Effect of Januvia or *Androctonus amoreuxi* extract (Sc.Tea) on serum AST in STZ/NA induced diabetic rats. Values are means ± SEM. n=10, One Way ANOVA followed by Duncan multiple comparison tests. [a] $p<0.05$ compared with normal control group, [b]$p<0.05$ compared with Diabetic group.

As shown in Fig. 3, Januvia treatment decreased significantly the serum ALP activity in diabetic animals as compared with diabetic rats by 2.9-fold. The treatment of diabetic rat with *A. amoreuxi* extract decreased the activity of ALP by 2.7-fold as compared to diabetic-group.

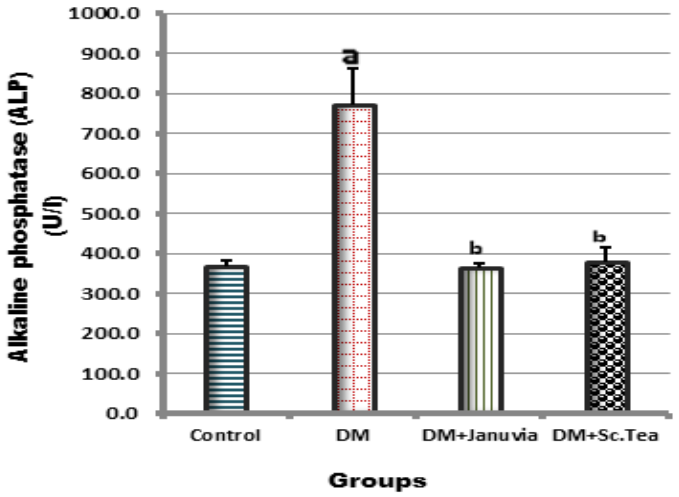

Fig. 3: Effect of Januvia or *Androctonus amoreuxi* extract (Sc.Tea) on serum ALP in STZ/NA induced diabetic rats. Values are means ± SEM. n=10, One Way ANOVA followed by Duncan multiple comparison tests.[a] $p<0.05$ compared with normal control group, [b]$p<0.05$ compared with Diabetic group.

The results in figure 4 represent the effects of Januvia and A. amoreuxi extract on serum lactate dehydrogenase (LDH) activity of chemically induced diabetic rats.

The results showed a significant increase in the level of LDH in DM group compared to control group. Administration of Januvia and A. amoreuxi extract in combination with STZ/NA resulted in a marked ($P < 0.05$) decrease of LDH by (-7.5 %, -29.1%, respectively) as compared with Diabetic group.

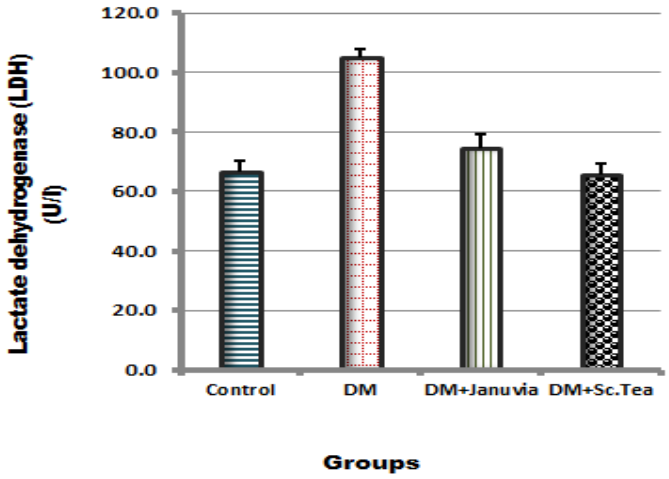

Fig. 4: Effect of Januvia or *Androctonus amoreuxi* extract (Sc.Tea) on serum LDH in STZ/NA induced diabetic rats. Values are means ± SEM. n=10, One Way ANOVA followed by Duncan multiple comparison tests.[a] $p<0.05$ compared with normal control group, [b]$p<0.05$ compared with Diabetic group.

In diabetic animals, after STZ-NA injection, the liver showed several alterations including cloudy swelling, infiltration of lymphocytes, sever congestion, necrotic foci,

hydropic changes (Figs. 5B, 6B). The degenerated cell has karyolysed nuclei, where others showed pyknosis in which nucleus shrinked. In addition, the hepatic portal vien were Congested (Fig. 6B). Treatment of rat with Januvia or *Androctonus amoreuxi* extract largely prevented DM induced histopathological alterations in the liver as indicated by a reduction in inflammatory cellular infiltration and hepatocytic damages (Fig. 5C and Fig. 5D respectively) when compared to diabetic group

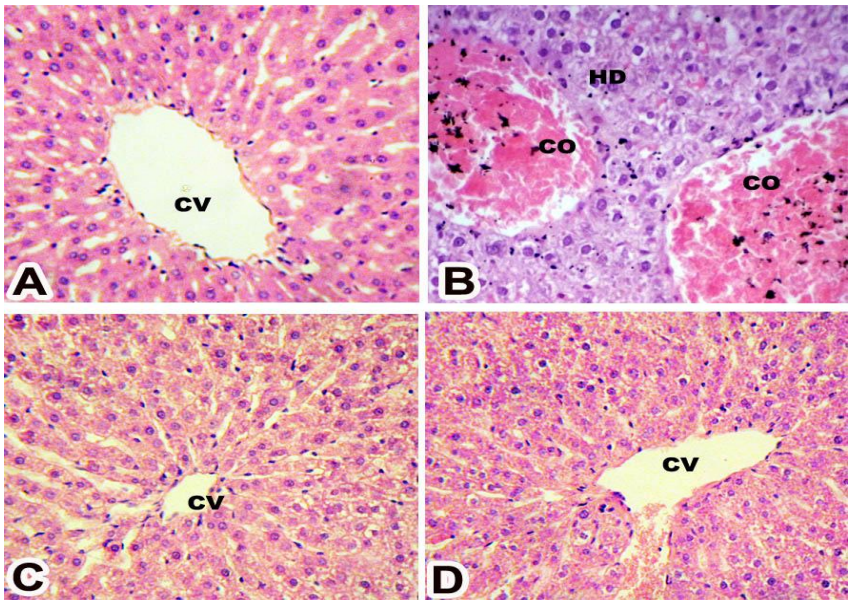

Fig. 5 A: Section from central area of liver in control group showing normal hepatic tissue, normal central vien ; B. Section from liver of a diabetic rat showing hydropic degeneration (HD) and sever congestion (CO); C. Section from liver of group (STZ/NA + Januvia 10 mg/kg) presenting very similar morphology to the control group; D. Section from liver of a group (STZ/NA+ scorpion extract 200 mg/kg) shows the nearly hepatic architecture with apparently normal appearance of hepatic strands. H&E staining (400X)

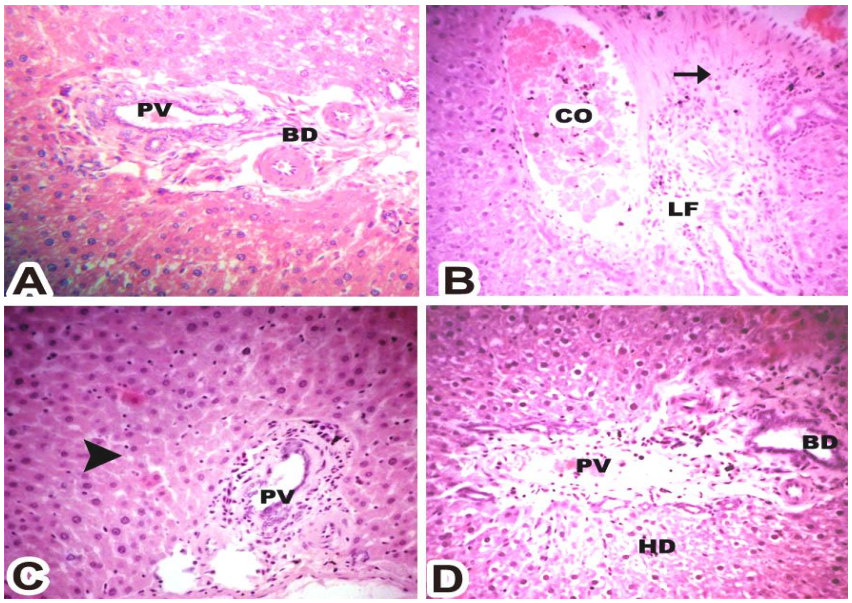

Fig. 6 A: Section from portal area of liver in control group showing normal hepatic tissue , normal central vien ; B. Section from liver of a diabetic rat showing hydropic degeneration (HD) and sever congestion (CO); C. Section from liver of group (STZ/NA + Januvia 10 mg/kg) presenting very similar morphology to the control group; D. Section from liver of a group (STZ/NA+ scorpion extract 200 mg/kg) shows the nearly hepatic architecture with apparently normal appearance of hepatic strands. H&E staining (200X).

DISCUSSION

The aim of the present study was to evaluate the hepatoprotective effects of of Januvia and *Androctonus amoreuxi* extract (Sc.Tea) in streptozotocin-induced type 1 diabetic rats. Streptozotocin-induced type 1 diabetes in rats provides a relevant model to study the hepatic dysfunction under diabetic conditions, as they exhibit a number of metabolic deficits that resemble those seen in human diabetics (Cotrozzi *et al*., 1997). Also, Saligram *et al*. (2012) stated that non-alcoholic fatty liver disease (NAFLD) is associated with Type 2 diabetes (T2DM) and the metabolic syndrome, and can progress to chronic liver disease.

In this work we have studied the effect of post-treatment with Januvia or *Androctonus amoreuxi* extract on liver functions in STZ/NA -induced diabetic rats through 30 days of treatment. To examine these effects the levels of serum ALT, AST, ALP and LDH were determined, besides histological examination of liver tissue.

Our study shows a significant elevated ALT and AST in a STZ/NA -induced diabetic rats. Elevated ALT and AST was used as a representative marker of Non-alcoholic fatty liver disease (NAFLD), this result in agreement with Pagano *et al*. (2002) who stated that elevated ALT was commonly in people with diagnosis of diabetes mellitus, suggesting that development of NAFLD. Associations between elevations in ALT AST with diabetic animals have been reported (Rosen *et al*., 2007). Insulin deficiency, increased pro-inflammatory cytokine production, oxidative stress and mitochondrial dysfunction leading to hepatocyte damage/destruction, have all been posed as important pathophysiological mechanisms (Day, 2002).

The present study revealed that post-treatment with Januvia to the diabetic rats reduced the serum ALT and AST. These results are in agreement with the study of Arase *et al*. (2011) who found that A case-control study, using sitagliptin 50 mg/day for 48 weeks, showed no significant changes of average AST and ALT levels during follow up. Sitagliptin showed effectiveness and safety for the treatment of T2DM (Type 2 Diabetes Mellitus) complicated with HCV- positive chronic liver disease. Also, The results show that the concentrations of serum ALT and AST, significantly decreased in-diabetic rats after treatment with *Androctonus amoreuxi* extract, this may be due to enhanced insulin secretion which improve liver function as descriped by Fernanda *et al*. (2015). In an attempt to explain this phenomena (howida) stated that Administration of the scorpion-extract to the diabetic rats for 30-days caused enhancing the histological changes of islets of Langerhans and enhanced the expression of glucagon and insulin in pancreatic tissue. This may be due to the presence of some chemical compounds such as phospholipase A2 and its action can be related to possessing insulin-like action and had ability to induce DNA repair systems due to antioxidant activities which reduce or prevent generation of free radicals.

The elevated ALP levels in diabetic animals in the present study may be an indicator of early liver obstruction also persistent elevation of this enzyme with a simultaneous elevation in aminotransferase (ALT/AST) levels is a strong indicator of this complications (Regnell and Lernmark, 2011). Individuals with diabetes have a higher incidence of liver function test abnormalities than those who are not diabetic (Harris, 2005). The data of this study also indicated that daily treatment with Januvia or *Androctonus amoreuxi* extract considerably improves ALP of diabetic rats. Liver function tests (LFTs) are generally used in clinical practice to screen the liver diseases, monitor the development of known diseases, and monitor the effects of drugs that may cause hepatotoxicity. Hepatocyte injury or hepatotoxicity results in the release of the liver enzymes into the blood circulation, thus increases liver enzymes

level (Kamel *et al*., 2011). Diabetes induced by STZ in rats causes liver tissue injury, which is associated with the elevation of serum hepatic enzymes, such as ALT and AST (Maiti *et al*., 2004). The above mentioned enzymes turned partially back to their normal levels after treatment with Januvia or *Androctonus amoreuxi* extract perhaps due to prevention of intracellular enzyme infiltration created by cell membrane stability or cellular regeneration.

In our study it was observed that there were significant increments in LDH levels in diabetic control group than the normal control group. Treatment with Januvia or *Androctonus amoreuxi* extract significantly decreased LDH as a parameter of liver dysfunction indices activity in comparison with diabetes mellitus.

In STZ/NA model, our histological findings indicated notable alterations in the liver structure such as severe congestion in the portal area with necrotic foci, hydropic changes and aggregation further more infiltration of lymphocytes between hepatocytes. These findings in agreement with Salih *et al*. (2009).

Administration of the scorpion-extract and Januvia to the diabetic rats for 30-days caused enhancing the histological changes of liver. This may be due to the presence of some chemical compounds such as phospholipase A2 and its action can be related to possessing insulin-like action and had ability to induce DNA repair systems due to antioxidant activities which reduce or prevent generation of free radicals.

Histopathological examination indicated notable alterations in the liver structure of STZ/NA group such as cloudy swelling, infiltration of lymphocytes, sever congestion, necrotic foci, hydropic changes. In the present study, administration of Januvia or *Androctonus amoreuxi* extract improved structural changes induced by diabetes. This preservation by Januvia or *Androctonus amoreuxi* extract may be due to both inhibition of metabolism and/or detoxification of cytotoxic radicals. In addition, its presumed contribution to DNA repair may be the other important attribute, which plays a role in its protective effects.

CONCLUSION

STZ/NA-induced diabetes in rats represents well-established animal model for both types of diabetes mellitus. Increased production of high levels of oxygen free radicals had been linked to glucose oxidation. Furthermore, characteristic diabetes raised liver enzyme activities which contributed the development of hepatic injury as a results of diabetic complications. The present study clearly revealed that Januvia or *Androctonus amoreuxi* extract potentiated hepatoprotective effect against diabetic complications. Therefore the present study suggested that Januvia or *Androctonus amoreuxi* extract might be effective in the treatment of diabetes with hepatic injury. However, further study is necessary to clarify the exact mechanism of hepatoprotection on diabetes with NAFLD.

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ARABIC SUMMERY

التأثير الوقائي لمستخلص جسم العقرب أندروكتونوس أموريوكسي وعقار سيتاجليبتين على إصابة الكبد في الجرذان المصابة بالسكري

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تشارك إصابة الكبد في كل من التسبب في حدوث ومضاعفات مرض السكري .وجد مؤخرا ان العلاج بمستخلص جسم العقرب أندروكتونوس أموريوكسي يؤدي الي تعديل الاستجابات الفسيولوجية في الجرذان المصابة بمرض السكري والذي يتم استحداثة بمركب الإستريبتوزوتوسين .تهدف هذه الدراسة لتقييم الآثار الوقائية للعلاج بمستخلص جسم العقرب أندروكتونوس أموريوكسي وعقار سيتاجليبتين لنسيج الكبد بعد استحداث مرض السكري في ذكور الجرذان البيضاء .تم تقسيم أربعين من الجرذان إلى أربع مجموعات (ن = ١٠) .تم استحداث مرض السكري في الجرذان البيضاء عن طريق الحقن داخل الصفاق بجرعة ٦٥ ملي جم/ كجم من الإستريبتوزوتوسين و بعد ثلاثة أيام، تم تقسيم الحيوانات عشوائيا إلى ٣ مجموعات: مجموعة السكري، ومجموعة مصابة بالسكري ومعالجة بمستخلص جسم العقرب (٣٠٠ ملي جم/ كجم) والمجموعة الثالثة تمثل الحيوانات المصابة بالسكري والمعالجة بعقار سيتاجليبتين (١٠ ملي جم/ كجم) إلى جانب المجموعة الضابطة التي تلقت محلول ملحي متعادل داخل الصفاق .تم تعيين القياسات البيوكميائية الخاصة بوظائف الكبد الي جانب فحص انسجة الكبد هستولوجيا، والتي تم تعينها في نهاية فترة التجربة .كشفت نتائج دراستنا أن العلاج بمستخلص جسم العقرب وعقار سيتاجليبتين له تأثير وقائي لنسيج الكبد يتجلى في انخفاض معنوي في مستويات مصل الدم لانزيمات الكبد. ألانين أمينو ترانسفيريز(ALT) ، الفوسفاتيز القلوية (ALP) و نشاط اللاكتات ديهيدروجينيز .(LDH) . مقارنة مع مجموعة الحيوانات المصابة بالسكري والغير معالجة. من الناحية النسيجية المرضية، أظهرت قطاعات الكبد من الجرذان المصابة السكري إصابة الكبد الحاد .أظهرت النتائج ان الكبد في الحيوانات المعالجة بمستخلص جسم العقرب وعقار سيتاجليبتين بعد الاصابة بالسكري الي تحسن نسيج الكبد والحد من اصابة الكبد بالمقارنة مع المجموعة المصابة بالسكري فقط .نتائج هذه الدراسة تشير إلى أن علاج الحيوانات المصابة بالسكري بمستخلص جسم العقرب أندروكتونوس أموريوكسي وعقار سيتاجليبتين لهما آثار وقائية ضد الاصابة الكبدية.