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BIOCHEMICAL STUDY ON THE REGENERATIVE EFFECT OF BEE VENOM ON EXPERIMENTALLY INDUCED DIABETES

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ABSTRACT

In the present study, the potential therapeutic effect of bee venom administration diabetic rats was evaluated. Thirty male albino rats were divided into three equal groups of 10 rats each. Group I:(Control group): received no drugs. Group II:(Diabetic rats group): rats received a single dose of Streptozotocin (STZ) (50- mg/kg-b.wt i.p). Group III:(Diabetic rats + bee venom treated group): rats are treated with + bee venom 0.5 mg /kg body weight /day, i.p) for 21 days after diabetes induction. Blood samples and pancreatic tissue were collected at the 22th day from the onset of bee venom administration. The obtained results showed that, STZ-induced diabetic rats exhibited a significant increase in serum glucose, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) with marked decrease in HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px), superoxide dismutase (SOD). Treatment with bee venom was able to mitigate diabetic abnormalities through decreasing serum glucose, triacylglycerols, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) and increasing HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidease (GSH-px) and superoxide dismutase (SOD), These results suggest that bee venom are effective in increasing insulin sensitivity and secretion in diabetic rats and improving other biochemical blood parameters.

KEYWORDS: Bee venom; STZ; Diabetes; lipid profil; Antioxidant enzymes; AGEs and HBA1c.

INTRODUCTION

Diabetes mellitus (DM) is a serious disease in which the body cannot control the amount of sugar in circulation due to either a deficiency of insulin secretion or a decreased sensitivity of the tissues to insulin. There are two main types of diabetes as follows: Type 1 and Type 2 **(Vigneri et al., 2009).** Both types can cause serious health complications, including kidney failure, heart disease, blurred vision, ketoacidosis, peripheral neuropathy, itchiness, fatigue, and even coma (**Stolar, 2010).** An insulin deficiency leads to elevations of cholesterol, phospholipids, and free fatty acids **(Yadav et al., 2004).** Therefore, it is important that an ideal DM therapy should not only involve maintaining blood glucose levels but also involve the regulation of the lipid profile.

Diabetes Mellitus was a leading cause of most renal diseases and the cause of heart attacks leading to blindness and nontraumatic amputations **(Chan et al., 2016)**. Diabetes is the most serious disease with multiple complications and mortality and responsible for at least 10% of total health care disbursement in the world **(King et al., 1998).**

Diabetes mellitus was a serious metabolic disease that tendency to diseases and multiple-organ impairment **(De la Monte et al., 2014).** The lacks of β-cells in the pancreas were the main cause of pathophysiological markers in the progress of both two types of diabetes either 1 or 2 **(Harper et al., 2016).** Therefore, the great therapeutic goal is to achieve the remarkable production and generation of pancreatic islets that would consequently ameliorate diabetes and reduced its complications (**Ibrahim et al., 2016)**.

To treat DM, several antidiabetic drugs are used. However, these drugs are not without side effects and pose an economic burden to the patient. Therefore, scientists have turned to natural remedies, including bee venom (BV).

Bee venom (BV) therapy has been utilized for treatment of various diseases in traditional medicine. **(Abdela and Jilo, 2016)** It is formed of a complex mixture of many components including enzymes (phospholipase A2, hyaluronidase, and phosphatase), polypeptides (melittin, apamin, secapin) and low molecular compounds (histamine, dopamine, and norepinephrine) **(Son et al., 2007).**

The most active ingredient in BV is melittin that has powerful anti-inflammatory and anti-nociceptive effects, therefore BV was used to treat many inflammatory diseases such as

rheumatoid arthritis, osteoarthritis, tendinitis, dermatitis and psoriasis**.(Kang et al., et al., 2002)** Furthermore, apamin and phospholipase A2 present in BV have strong immunoregulatory effect, thus several reports suggested that treatment with BV may be helpful in neurodegenerative diseases such as multiple sclerosis, Alzheimer`s and Parkinson`s diseases **(Castro et al., 2005).**

Diabetes is a metabolic disorder that is characterized by chronic high blood glucose levels that causes complications in the eyes, kidneys, heart, vessels and nerves. Another serious pathogenesis of diabetes is an abnormal lipid profile indicated by low levels of HDL and high concentration of triglyceride and LDL. Hence the potential remedy for diabetes not only needs the blood glucose levels lowering action, but also lipid regulating effect. Major component of bee venom is melittin and phospholipase A2, a polypeptide and an enzyme that increase insulin secretion from pancreatic β-cells via depolarization of beta cell membrane **(Morgan, and Montague, 1984).**

Another potential mechanism for bee venom blood glucose and cholesterol reducing action is lipolytic properties of BV. The components partially lyse cell membrane which increases glucose transport and lipid takeup into adipose tissue. Based on the above properties, BV could be considered as a therapeutic agent for diabetes. This study aims to investigate the effect of Mongolia's bee venom on blood glucose, cholesterol, low density lipoprotein and high density lipoprotein levels in diabetic subjects **(Khulan et al., 2015**).

MATERIALS AND METHODS

Experimental animals

Thirty white male albino rats of 10-14 weeks old and weighting 160-200 gm were used in the experimental investigation of this study. The rats were obtained from the Laboratory Animals Research Center, Faculty of Veterinary Medicine, Benha University. Rats Animals were housed in separate metal cages, exposed to good ventilation, humidity and to a 12 hr light/dark cycle. Fresh and clean drinking water was supplied ad-libtium. Constant supplies of standard pellet diet, fresh and clean drinking water were supplied ad-libitum. The animals were left for 15 days for acclimatization prior to the beginning of the experiment, and kept at constant environmental and nutritional conditions throughout the period of the experiment.

Chemicals used

Bee venom

BV was purchased from Faculty of Agricultural Environmental Sciences, benha University.

Dosage

Bee venom was freshly prepared by dissolving in distilled water just before treatment, and was administered every day Bee venom were injected intraperitoneal (IP) with 0.5 mg/kg (**Mousavi et al., 2012).**

Diabetes induction

Rats were fasted for 18 hrs. And allowed free access of water .The experimental induction of diabetes in male rats was induced by a single intraperetinoel (i.p) injection of 50 mg/kg body weight of Streptozotocin (STZ) freshly dissolved in citrate buffer, pH 4.5. A week later, STZ-treated rats were fasted for 12 h and blood samples were collected from the tail vein for glucose determination. Only those rats in diabetic group with blood glucose level higher than 250mg/dl were considered diabetic **(Ramanathan et al., 1999).**

Experimental design

Thirty male albino rats were divided into three equal groups of 10 rats each. Group I:(Control group): received no drugs. Group II: (Diabetic rats group): rats received a single dose of Streptozotocin (STZ) (50- mg/kg-b.wt i.p). Group III: (Diabetic rats + bee venom treated group): rats are treated with bee venom 0.5 mg /kg body weight /day, intraperitoneal (IP)) for 21 days after diabetes induction. Treating started 5 days after diabetes induction.

Sampling

Blood samples and tissue specimens (pancreas) were collected from all animals groups (control and experimental groups) at the end of experiment on 22th day.

1 - Blood sampling

Approximately 9 mL blood gathered into two tubes from each rat, EDTA was added to one sample to obtained whole blood, and serum were separated by centrifugation at 3000 r. p. m for 30 minutes the clean, clear-serum was separated by Pasteur pipette and received in dry sterile sample tubes, processed directly for glucose determination, then kept in a deep freeze at - 20°C until used for subsequent biochemical analysis. **(Sanford, 1954).** All sera were analyzed for glucose, Insulin, lipid profile, HBA1c.

Tissue samples

Pancreases were washed with ice-cold saline solution (0.9% NaCl), weighed and stored at -80ºC for the biochemical analyses.

(GSH-Px, Catalase, SOD, MDA and AGEs)

Tissue preparation

The tissues were homogenized with 0.1 M phosphate buffer saline at pH 7.4, to give a final concentration of 20% w/v for the biochemical assays.

Biochemical analysis:

Serum glucose was determined enzymatically according to the method described by **Trinder (1969).** Serum insulin was determined with the method described by (**Mattews *et al.*, 1985)**. Plasma triacylglycerols, cholesterol, HDL, LDL was determined enzymatically according to the method of **Young, (2001), Young, (2001), Warnick *et al.*, (1983)** and **Okada et al.,(1998)** respectively using diagnostic kit by Spin React Company, Egypt**.** Rat Advanced Glycation End Products (AGEs) **by (ELISA Kit Catalog Number. MBS700464).** Rat HbA1c (Glycosylated Hemoglobin/Hemoglobin A1c) **by ELISA Kit Catalog No: MBS2509196 (96T) 6th Edition, revised in June, 2015**. Serum lipid peroxidation (L-MDA) was calorimetrically determined according to the method adapted by **Esterbauer *et al.*, (1982).** Glutathione (GSH) was calorimetrically determined according to the method adapted by **Eyer et al., (1986)** using cayman chemical kit, USA. Erythrocyte superoxide dismutase activity was determined according to the method described by **Misra and Fridovich (1972).** Catalase activities were determined according to the method described by **(Sinha, 1972).**

Statistical analysis

All values were expressed as mean ± standard error (SE). All statistical analyses were performed using SPSS (version 19). Statistical differences among the experimental groups were assessed by ANOVA. Duncan's test was used as a follow-up test and significance was defined at $p<0.05$.

RESULTS

Effect of treatment with bee venom on some serum and pancreas tissue parameters in STZ-induced diabetic rats

The obtained results in table (1,2 and 3) revealed that, a significant increase in serum glucose, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced

glycation end products (AGEs) and glycated hemoglobin (HbA1c) with marked decrease in HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px), superoxide dismutase (SOD). Treatment with bee venom was able to mitigate diabetic abnormalities through decreasing serum glucose, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) and increasing HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px) and superoxide dismutase (SOD), These results suggest that bee venom are effective in increasing insulin sensitivity and secretion in diabetic rats and improving other biochemical blood parameters.

Table (1): Effect of bee venom on the serum level of glucose, insulin, Hb1AC and AGE in STZ-induced diabetic rats (Mean±SE).

Group	Glucose (mg/dL)	Insulin (mg/dL)	Hb1AC (ng/ml)	AGE (µg/ml)
Control (normal)	83.2±1.59^{c}	4.98±0.14^{a}	12.20±0.23^{c}	31.2±0.64^{c}
STZ	357.0±5.38^{a}	1.02±0.04^{c}	24.49±0.44^{a}	108.7±2.73^{a}
STZ + bee venom	96.8±1.69^{b}	3.87±0.11^{b}	15.43±0.62^{b}	51.0±2.25^{b}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.

Table (2): Effect of bee venom on lipid profile of serum in STZ-induced diabetic rats (Mean±SE).

Group	Triglycerids (mg/DL)	Total cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dl)
Control (normal)	140.80±2.27^{c}	105.40±0.75^{c}	53.40±1.44^{a}	23.84±1.49^{c}
STZ	226.20±2.15^{a}	194.20±2.46^{a}	42.20±0.86^{b}	106.76±2.86^{a}
STZ + bee venom	183.60±2.11^{b}	135.80±1.59^{b}	51.20±0.86^{a}	47.88±1.91^{b}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.

Table (3): Effect of bee venom on LDH, MDA, CAT, GSH, AGE and G6PD of serum in STZ-induced diabetic rats (Mean±SE).

Group	MDA (nM/g tissue)	CAT (IU/g tissue)	GSH (IU/g tissue)	SOD (IU/g tissue)
Control (normal)	34.12±0.38^{c}	7.10±0.29^{a}	25.07±0.36^{a}	12.30±0.56^{a}
STZ	73.53±0.78^{a}	1.25±0.13^{c}	8.08±0.32^{c}	3.13±0.28^{c}
STZ + bee venom	47.73±0.50^{b}	5.10±0.27^{b}	19.55±0.31^{b}	9.77±0.42^{b}

a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.

DISCUSSION

In this study, rats treated with STZ showed a significant increase in glucose concentration and decreased in insulin level compared to control group. These results are nearly similar to those reported by **Mousavi et al., 2012** who reported that, STZ-induced diabetic rats showed a significant increase in blood glucose level and decreased in insulin level in (diabetic) group compared with control group after 3 weeks ($P< 0.05$).

Also, **Baher et al., (2017)** reported that, In the diabetic group streptozotocin-injected dramatically increased blood glucose level rat had significantly higher blood glucose level and decreased in insulin level than non-diabetic rats Moreover, **Khulan et al., (2015)** reported that, continuous hyperglycemia in the diabetic state decreased insulin-stimulated glucose utilization by the skeletal muscle, whereas an acute rise in plasma glucose concentrations in the glucose-load state did not.

The bee venom treatment lowered plasma glucose levels in diabetic rat compare to untreated diabetic group. Our results were consistent with findings of Mousavi et al. which also confirmed hypoglycemic activity of bee venom in diabetic mice (**Mousavi et al., 2012**). In another study, bee venom reduces glycaemia subjects depending on the inoculated dose (**Ivas, 2011)**. These effects could be attributed to melittin and phospholipase A2, a polypeptide and an enzyme that altogether make up to 62% of the bee venom. One mechanism for BV to lower blood glucose levels is through the suppression of beta cell inflammation **(Park et al., 2008)** and direct stimulation of insulin secretion **(Fujimoto, Metz 1987).** Fujimoto et al. studied agonist properties of phospholipase A2 and melittin and discovered that they induce monophasic release of insulin from beta cell **(Fujimoto and Metz 1987).** Melittin initiates membrane depolarization which leads to increased inflow of Ca2+ ion to beta cells, through calcium channel depending on the extracellular calcium (**Fletcher, Jiang 1993).** Also, **(Byung-Hyun and Jin-Woo 2001)** Blood glucose level decreased following bee venom treatment. This may be contributed to substances like mellitin and phospholipase A2 contained in the venom. They may play a role in diminishing inflammation of Islets of Langerhans and thus elevating blood insulin level. With regard to the fact that insulin regulates blood glucose level, bee venom could decrease glucose content via increasing insulin secretion **(Kim et al. 1999, Simonson et al. 2000).**

Han et al., 2002, demonstrated that the bee venom prevails the glucose from being taken through the apical membrane of the epithelium cells in the proximal renal tube causing thus a

shortage in tubular glucose reabsorption at renal level and consequently glucose elimination through urine and decrease in the blood glucose level **(Han H.J. et al., 2002).**

Our results revealed a significant (P≤0.05) increase in the pancreas level of advanced glycation end products (AGEs) and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) These results are nearly similar to those of (**Refat et al., 2016)** who reported that, STZ-induced diabetic rats showed a significant (P≤0.05) increase in the pancreas level of advanced glycation end products **(AGEs)** and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) after 3 weeks (P< 0.05).

Also, **Huang et al., 2014** reported that, In the diabetic group streptozotocin-injected dramatically increased in the pancreas level of advanced glycation end products **(AGEs)** and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) Moreover, Glycation is a non-enzymatic reaction between sugars and a free amino group of proteins resulting in advanced glycation end-products (AGEs) (**Li et al., 2010)**. Protein glycation and AGEs are accompanied by increased free radical activity that leads to the biomolecular damage in diabetes (**Sen et al., 2005)**. AGEs generate oxygen free radicals that may potentiate the development of atherosclerosis (**Bernheim et al., 2001)**.

Moreover, AGEs can produce oxygen free radicals through an indirect process, by inducing the release of cytokines through interaction of AGEs with their cellular receptors (**Grillo and Colombatto, 2008)**. Because of widespread occurrence of AGEs and the oxidative stress derived from them in a variety of diseases and diabetes complications, it has a great deal of interest to identify and develop AGE inhibitor that can suppress AGE formation (**Reddy and Beyaz, 2006)**. Numerous AGE inhibitors have been developed, such as amino guanidine the most well-known AGE inhibitor.

Honey bee venom (HBV) has significant anti-glycation impact and avoid glycation-induced change in the structure and function of hemoglobin, HBV can be established as a medication against glycation-associated complications in diabetes **(Behroozi et al., 2014).**

Also, data showed that BV increases the amount of free amino groups of glycated hemoglobin in a dose-dependent manner that means BV prevents binding of glucose and reactive di-carbonyls to proteins because the addition of these materials to proteins decreases the amount of free amino groups in proteins. **Behroozi et al., 2014.**

Our results can be considered the first report on antiglycation properties of BV The most reasonable hypothesis for destruction of heme by glucose is that oxidative stress induced during glycation is the initiating agent in the degradative mechanism (**Cussimanio et al., 2003)**.

These results mean that glycation leads to conformational changes in hemoglobin. BV inhibits both reductions in absorption intensity and red shifting Absorption of the Soret band of glycated hemoglobin increased significantly in the presence of BV and aspirin. The Soret band intensity depends on the BV concentration, the higher the BV concentration, the greater the absorption of glycated hemoglobin.

Our data show that glycation induces structural changes in hemoglobin, such as reduced α-helix content and increased β-sheet and random coil content, which are in good agreement with previous reports However; BV significantly inhibits alterations in the percentage of different types of secondary structure induced by glycation.

Glycation leads to structural and functional alteration in proteins in diabetic people. Because of the significant role of proteins, their modifications should be prevented. Since previous studies have shown that glycated hemoglobin have not only structural changes but also a functional alteration such as reduced peroxidase activity and high oxygen affinity **(Sen et al., 2005).** Then, our results indicate that BV has a significant antiglycation effect and it can prevent glycation-induced alteration in the secondary structure and function of hemoglobin, thus BV could be developed as a natural drug against glycation-associated complications in diabetes **(Behroozi et al., 2014).**

Dietary antioxidants play an important role in mitigating the damaging effects of oxidative stress on cells. According to **Son *et al*. (2007)** Bee venom increases coronary and peripheral blood circulation, improves the microcirculation of blood in the tissues against blood coagulation fibrinolytic, also stimulates the building of erythrocytes and as a protective agent from radiation by improves regeneration of erythrocytes.

The obtained data showed significant increase in serum cholesterol, triglycerides, low-density lipoprotein (LDL) and significant decrease in high-density lipoprotein (HDL) in STZ-induced diabetic rats when compared with normal control animal groups.

These results are nearly similar to those of These results are nearly similar to those of **Ivas1 et al., 2014** who reported that, hypercholesterolaemia is common in diabetes. The pronounced increase in cholesterol levels in diabetic rats come in agreement with results reported previously by **Mousavi et al., 2012** who observed that, the untreated diabetic rats had the increased levels of triglycerides, cholesterol, HDL and LDL, as compared with the healthy control rat.

Also**, Khulan et al., 2015)** reported that, there was pronounced increase in triglycerides, cholesterol, HDL and LDL, in diabetic rats as compared with the healthy control rat. Dyslipidemia observed in experimental diabetes (high TG and low HDL levels) are attributed mainly to the decreased activity of lipoprotein lipase which is an insulin sensitive enzyme demonstrates significant alteration in diabetics **(Tsutsitmi *et al.*, 2001).** This enzyme can bind to glycosaminoglycans at the luminal side of capillary endothelium hydrolyzing TG and liberates free fatty acids joined with excessive uptake **(Semenkovich and Heineeke, 1997).**

Administration of bee venom in STZ-induced diabetic rats resulted in a significant amelioration in serum total cholesterol and triglycerides and significant increase in HDL compared to STZ group. These results go in hand with (**Ivas1 et al., 2014)** who reported that, The most researchers have shown as in our study the decreasing of the serum cholesterol level under the action of bee venom. In other few studies the hypocholesterolemic effect of the insect venom on cats and rats due to the hepatotoxicity promotion is mentioned **(Neuman et al., 1991)**. The lipoproteins (HDL, LDL, VLDL and chilomicrones) are known to be modified by two plasmatic enzymes: lecithin-cholesterol acyltransferase, with A2 phospholipasic activity and lipoproteinlipase. The action specificity of the two enzymes is the key for the lipid metabolism understanding. The A2 phospholipases in venoms were demonstrated to show enzymatic activity three times higher than that of the plasmatic lecithin-cholesterol acyltransferase (**Ivas1 et al., 2014)**.

Some authors proved that the A2 phospholipase in the bee venom shows a higher affinity to the plasmatic lipoproteins than to membranary phosphatidylcholines and exerts its cytotoxic effect mostly by generating free fatty acids and lisophospholipids. The free cholesterol in HDL is esterified by the phospholipase activity **(Guillaume, 2006).** However, the partial lysis of the membranary phosphatidylcholine in adypocites by A2 phosphofolipase in venom affords the binding of a greater number of insulin molecules promoting thus an increase in the glucose transport as well as an acceleration of taking the lipids in the adipose tissue **Ivas1**

et al., 2014. These effects generated by the A2 phospholipase in the bee venom can explain the hypocholesterolemic and hypotriglyceridemic effect unaniously accepted and made evident in the present study with both low and high venom doses.

The recorded data demonstrated a significant increase in MDA concentration in STZ-induced diabetic rats when compared with control group. These results are nearly similar to those reported by **Kailash, (2000)** who showed that, the diabetic rats had higher serum MDA than the normal rats. However increased lipid peroxidation has been observed in STZ-induced diabetes in rats and in patients with diabetes. This could be due to increased levels of reactive oxygen species (ROS)**.**

Also, **Doddigarla et al., (2016)** who showed that, the diabetic rats had higher serum MDA than the normal rats however increased lipid peroxidation has been observed in STZ-induced diabetes in rats and in patients with diabetes**.**

The increase in MDA could be due to increased production of ROS from macrophages through a mechanism stated by **Kailash, (2000)** that reactive oxygen species (ROS) has a role in the pathogenesis of diabetes mellitus and pancreatic islet β-cell destruction as a consequence of immune/inflammatory cell-mediated processes in rodents**.**

Regarding the antioxidant effects of BV samples, they have been related with the capacity to inhibit the lipid peroxidation process **(Rekka et al., 1990)** the present results recorded that a significant decrease of MDA in pancreas tissue, **(Abdel-Rahman *et al*., 2013). Stanley *et al*. (1984)** found that Bee venom inhibits production of superoxide anion by human neutrophils. **Rain (2009)** and **Hegazi (2012)** stated that BV therapy is a potent antioxidant led to a decrease in the levels of reactive oxygen species (ROS) and decreased MDA.

The recorded data demonstrated a significant decrease in tissue GSH-px, CAT and SOD concentration of STZ- induced diabetic rats when compared with control group. These results came in agreement with those reported by **Huang et al., 2014** also, **Doddigarla et al., 2016** who found an inverse correlation between blood glucose levels and tissue GSH, CAT and SOD

GSH-px, CAT and SOD are antioxidant known to protect lipids against oxidation by scavenging free radicals. In diabetes, GSH, CAT and SOD are significantly decreased, giving evidence of consumption of this molecule to fight oxidative stress **(Davi et al., 2005).**

There is a significant association between acute blood glucose, GSH, CAT and SOD in patients with type 2 diabetes. Fluctuations in blood glucose induce oxidative stress and metabolic disarrangements that may be risk factors for chronic complications. A decrease in the efficacy of the antioxidant response may be a warning signal of metabolic defense **(Chia *et al*., 2012).**

Wu *et al.*, (2004) reported that, GSH, CAT and SOD is an abundant antioxidant within the blood and decreases both in type 1 and 2 diabetic patients.

Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation **(Fatmah et al., 2012).** An enhanced oxidative stress has been observed in diabetic patients by increased free radical production, lipid peroxidation and diminished antioxidant status **(Palmieri and Sblendorio, 2007)**. During oxidative stress, endogenous mechanisms, enzymes and antioxidant molecules are deployed to destroy reactive oxygen species and reduce the harmful effect of oxidants. In normal conditions, these mechanisms are sufficient to counteract free radical production, but in diabetes, they are overwhelmed due to an increased oxidative stress **(Tewthanom et al., 2008).**

Regarding the antioxidant effects of BV samples, they have been related with the capacity to inhibit the lipid peroxidation process **(Rekka et al., 1990)** and to increase superoxide dismutase (SOD) activity **(Han et al., 2010).**

The present results recorded that a significant decrease of MDA in liver tissue, associated with a significant increase SOD, CAT and GSH activities in liver tissue **(Abdel-Rahman *et al*., 2013). Stanley *et al*. (1984)** found that Bee venom inhibits production of superoxide anion by human neutrophils. **Rain (2009)** and **Hegazi (2012)** stated that BV therapy is a potent antioxidant led to a decrease in the levels of reactive oxygen species (ROS), which may be associated with the observations of BV affecting glutathion, superoxide dismutase (SOD) and catalase. **Salman et al., (2015).**

CONCLUSION

In conclusion, the present study demonstrated that Bee venom administration provided an effective treatment against insulin resistance in STZ-induced diabetic rats, since Bee venom were able to ameliorate serum biochemical parameters and increase insulin secretion in STZ-induced diabetic rats.

This study has demonstrated the antidiabetic and anti-inflammatory effect of Bee venom on diabetic animal models of male rats.

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