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COMPARATIVE STUDY BETWEEN BERBERINE AND EXENDINE 4 ON ADULT MALE DIABETIC ALBINO RATS

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ABSTRACT

Background: Exendin-4 is a similar peptide to glucagon - like peptide-1, and can interfere with various receptors of glucagon like peptide-1and is evaluated for the regulation of blood glucose in diabetes mellitus. Berberine (BBR) is demonstrated to have a hypoglycemic effect in vitro and in vivo.

Objective: Comparing between the effects of berberine and exendine 4 on adult male diabetic albino rats.

Materials and Methods: Thirty two adult male albino rats of local strain were housed in 8 suitable metal cages (20 × 32 × 20 cm for every 4 rats). They were divided into four equal groups: Group I served as a control group, group II was diabetic control, group III was diabetic group treated with berberine, and group IV was diabetic group received exendin-4. Body weight was measured daily till the end of the experimental period .Blood samples were collected for measuring fasting glucose, fasting insulin, homeostasis model assessment insulin resistance (HOMA –IR), C-peptide, glycosylated hemoglobin (Hb A1c), cholesterol(CHO), triglycerides (TG), low density lipoprotein cholesterol (LDL-c), and high density lipoproteins cholesterol (HDL-c). The pancreas of the sacrificed rats were excised and randomly processed for histological staining and biochemical assays for superoxide dismutase (SOD) and malondialdehyde (MDA)**.**

Results: Alloxan-induced diabetes mellitus was associated with significant higher levels of blood glucose, HOMA –IR, Hb A1c, total cholesterol, triglycerides, LDL-c and pancreatic MDA with significantly lower levels of body weight, insulin, C-peptide, HDL-c and pancreatic SOD as compared with normal control group. Berberine in diabetic rats produced significant lower levels of body weight, blood glucose, HOMA –IR, Hb A1c, total cholesterol, triglycerides, LDL and pancreatic MDA with significantly higher levels of insulin , C-peptide , HDL and pancreatic SOD as compared with control diabetic group. Exendin-4 showed significant lower levels of blood glucose, HOMA –IR, total cholesterol, TG, LDL-c and pancreatic MDA levels, and significant higher levels of insulin , HDL-c, C-peptide and pancreatic SOD as compared with the control diabetic rats. Results of the present study showed that the effects of exendin-4 produced insignificant changes of body weight as compared with control diabetic group.

Conclusion: Exendin-4 was more potent in reducing hyperglycemia than berberine, while berberine has a better body weight reduction. Furthermore, berberine treatment significantly increased pancreatic antioxidant enzymes activities as well as exendin-4. Berberine and exendin-4 treatment protected and preserved pancreatic β-cell architecture and integrity.

Key words: Alloxan, berberine, exendin-4, diabetes mellitus.

INTRODUCTION

Berberine (BBR) is an alkaloid present in plant extracts such as Berbis, Coptis, and Hydrastis species, and is isolated from the Chinese herb Rhizoma coptidis, which has been widely used in Chinese herbal medicine. Berberine has gained much

attention owing to its multiple biochemical and pharmacological effects including anticancer, antiviral, and antibacterial activities **(Imanshahidi et al., 2008)**. Berberine is demonstrated to have a hypoglycemic effect in vitro and in vivo. It also has anti-obesity and anti-dyslipidemia activities. The key findings of the antidiabetic actions of berberine include increasing secretion of insulin, improving insulin resistance, and ameliorating dyslipidemia **(Xiao et al., 2011).**

Exendin-4 is a glucagon like peptide-1 (GLP-1) agonist and is one of new lines of treatment of diabetes. Glucagon-like-peptide is the product of post-translational processing of proglucagon in the gut and the brain **(Chen et al., 2017).** It is insulinotropic and plays a role in the incretin effect, i.e. augments insulin response observed when glucose is absorbed through the gut **(Eunhui Seo et al., 2017).** Exendin-4 has structural similarity and binds to GLP-1 receptors (**Gupta, 2013)**. GLP-1 and its long acting agonist exendin-4 stimulate the proliferation and differentiation of stem cells in the pancreas into β cells **(Zaccardi et al., 2016).** This study was carried out to compare the effects of berberine and exendine 4 on adult male diabetic albino rats.

MATERIAL AND METHODS

Chemicals: Alloxan was obtained from Algomhoria Chemical Co. (Cairo, Egypt) and was dissolved in normal saline at a concentration of 100 mg/ml alloxan solution (to be administrated at a dose of 150 mg/ kg body weight). Berberine was purchased from Zayo-Sigma Aldrich Chemicals Ltd, St Louis, MO, USA. (To be administrated at a dose of 300 mg/kg body weight /day orally). It was dissolved in boiling water**(** 0.5 g of Berberine powder were dissolved in 5 cm sterile water, and 1 cm of solution contained 100 mg of Berberine **.** Exendin-4 was purchased from Zayo-Sigma Aldrich Chemicals Ltd, St Louis, MO, USA to be used at a dose of 1nmol/kg body weight /day, i.p. Each 1/2 cm of Exendin-4 solution contained 100 nmol of Exendin-4. All other chemicals were of analytical grade and were obtained from commercial kits purchased from Biodiagnostics Co., Dokky, and Giza, Egypt.

Animals: Thirty two adult male albino rats of local strain weighing average 152-200 grams. They were chosen as an animal model for this study. They were brought from animal house, Faculty of Medicine, Assiute University, Assiute, Egypt. They were housed in 8 suitable metal cages (20 ×32× 20 cm for every 4 rats) at room temperature in the natural light / dark cycle in the animal laboratory of Pharmacology Department, faculty of Medicine, Al-Azhar University (Assiute). They were maintained on dry chow pellets and water ad libitum throughout the experimental period. All the experiments were performed during the same time of day, between 9 a.m. and 12 p.m. to avoid variations due to diurnal rhythms **(Shimizu et al., 2015).** They were kept for two weeks under these conditions to adapt the laboratory conditions before the start of the experiment. The experimental procedures were carried out at animal laboratory of Pharmacology Department, Faculty of Medicine, Al-Azhar University (Assiute).

Material and Methods: After 2 weeks of acclimatization, male albino rats were randomly divided into 4 equal groups as follows: **Group I** was served as a control

group received normal saline (i.p.) for 8 weeks, **Group II** was diabetic control group**, Group III** was diabetic group received berberine (300 mg/kg body weight /day orally) dissolved in boiling water for 8 weeks **(Xia et al., 2011)**, **Group IV** was diabetic group received exendin-4 (1nmol/kg body weight /day, i.p.) for 8 weeks **(Anping et al., 2017)**.

Experimental Induction of type 2 diabetes in rats**:** Alloxan monohydrate has been used to induce experimental diabetes due to its selective destruction of pancreatic islet cells (**Rohilla and Ali, 2012).** A fresh single intraperitoneal dose of 150 mg/ kg body weight of alloxan dissolved in 0.2 ml saline was used immediately after solubility **(Kumawat et al., 2010).** After the injection, rats were given glucose infusion (3 g/kg body weight) by gastric intubation to all diabetic rats to overcome fatal hypoglycemia caused by transient hyperinsulinemia due to destruction of beta cells. The injection was repeated in the 2nd day to obtain response **(Wang et al., 2010)**. After 48 hours, the rats were fasted overnight, and blood glucose levels of rats were determined. Rats with blood glucose levels greater than 250 mg/dl were considered diabetic and used in the experiment **(Zhang et al., 2006)**.

Body weight were measured daily till the end of experiment**.**

At the end of experiment, rats were fasted for 12 h and venous blood samples were collected by retro-orbital puncture. Blood was collected into a dry graduated glass centrifuge tube, and serum was separated by centrifugation at 5000 r.p.m for 10 minutes. The separated serum was stored in Eppindorffs tube at -20˚C until used for determination of fasting glucose, fasting insulin, Homeostasis Model Assessment insulin resistance (HOMA – IR) , C-peptide , glycosylated hemoglobin (Hb A1c), cholesterol(CHO), triglyceride (TG), low density lipoprotein clolesterol (LDL-c) and high density lipoproteins (HDL-c) levels by commercially available kits. HOMA-IR was calculated based on glucose concentration and serum level of fasting insulin. Insulin resistance index was calculated using insulin and glucose concentration of serum samples according to the formula**.** HOMA-IR: [insulin](in mu/l) x [glucose](in mg/dl) / 405 **(Eslam et al., 2011)**.

Immediately after blood samples were collected, under ether anesthesia, the abdomens of the rats were immediately opened after reaching the stage of surgical anesthesia, as evident by loss of withdrawal reflex. Then the pancreas of different groups were excised, weighed, perfused with normal saline to remove blood , blotted between filter papers and used for the preparation of tissue homogenate. About 0.5 g of pancreas was homogenized in 4.5 ml of phosphate - buffered saline (pH 7), the crude tissue homogenate was then centrifuged at 8000 rpm for 30 minutes. The clear supernatants from pancreatic homogenate was stored at 4 °C, and were used for assay of SOD **(Nishikimi et al., 1972)**, and MDA **(Ohkawa et al., 1978)** by colorimetric methods.

Histopathological examination of pancreatic tissues: Pancreatic tissues were fixed in Bouin's fixative solution, and were sequentially embedded in paraffin blocks according to the standard procedure, sectioned at 6 ?m thickness,

and stained with with Hematoxylin and Eosin (H&E) to assess the histopathological examination **(Mahesh et al., 2017)**.

Statistical analysis: Statistical analysis was done using the computer program (SPSS). The quantitative data were presented in the form of mean ± standard deviation (S.D). Statistical analysis of the difference between groups was performed by using One–way analysis of variance (ANOVA) followed by Tukey-Kramer test for differences between means. A value of $P<0.05$ were used as the limit for statistical significance.

RESULTS

Effects of injection of alloxan, berberine and exendin-4 administration on the measured parameters (Table 1): I.P. injection of alloxan into rats (group II) showed a significant higher levels of blood glucose from 98.6 ± 2.1mg/dl to 356 ± 3.5 mg/dl, HOMA –IR from1.14 + 0.07 to 1.23 + 0.08, Hb A1c from 4.58 ± .02 to 8.95±0.45, total cholesterol from 82.6 ±6.1 mg/dl to 256.0 ± 8.7 mg/dl, triglycerides from 86.7 ± 9.2 mg/dl to 161.27±11.7 mg/dl , LDL from 33.95 ± 9.7 mg/dl to 85.36 ± 4.2 and MDA from 88±1.3 to 138±0.17 mg/dl with a significantly lower levels of body weight from 225.5±7.6 to 191.1±7.4, fasting insulin from 4.7±0.6 to 1.4±0.2 , C-peptide from 30.75 ± 4.7 ng/dl to 8.8 ± 2.1 ng/dl , HDL from 37.7 ± 3.12 mg/dl to 30.12 ± 3.6 mg/dl and SOD from 26.9±1.8 to15.7±2.3 as compared to control group (group I).

Oral administration of berberine in diabetic rats (group III) produced significant lower levels of body weight from 191.1±7.4 to 180.2±4.9 blood glucose from 356 ± 3.5 mg/dl to 156 ±1.4 mg/dl, HOMA –IR from 1.23 + 0.08 to 1.07 +0.01, Hb A1c from 8.95±0.45 to 6.45± 0.08, total cholesterol from 256.0 ± 8.7 mg/dl to 162.0 ±1.9 mg/dl, triglycerides from 161.27±11.7 mg/dl to 123.7 ± 5.4 mg/dl , LDL from 85.36 ± 4.2 mg/dl to 55.7 ± 5.4 and MDA from 138±0.17 to 98 ± 0.13mg/dl with significantly higher levels of fasting insulin from 1.4±0.2 to 2.8 ±0.2 , C-peptide from 8.8 ± 2.1 ng/dl to 20.0 ±1.4 ng/dl , HDL from 30.12 ± 3.6 mg/dl to 34.4 ± 2.05mg/dl and SOD from 15.7±2.3 to 19.63+ 0.92 as compared to control diabetic group (group II).

I.P. injection of exendin-4 in diabetic rats (group IV) produced significant lower levels of blood glucose from 356 ± 3.5 mg/dl to 132±3.49 mg/dl, HOMA –IR from 1.23 + 0.08 to 1.14+0.05, Hb A1c from 8.95±0.45 to 6.24± 0.12, total cholesterol from 256.0 ± 8.7 mg/dl to 144±35.49 mg/dl, triglycerides from 161.27±11.7 mg/dl to 116.7±5.4 mg/dl , LDL from 85.36 ± 4.2 mg/dl to 49.2 4 ± 7.23 and MDA from 138±0.17 to 90±0.11mg/dl. Meanwhile, it increased the levels of fasting insulin from 1.4±0.2 to 3.5 ±0.9, C-peptide from 8.8 ± 2.1 ng/dl to 26±30.49 ng/dl , HDL from 30.12 ± 3.6 mg/dl to 35.4 ± 2.05 mg/dl and SOD from 15.7±2.3 to 21.73±0.66 as compared to control diabetic group (group II). Results of the present study showed that the effects of exendin-4 produced insignificant changes of body weight as compared to control diabetic group (group II).Moreover, results of the present study showed that the effects of exendin-4 produced insignificant changes of Hb A1C % and HDL in respect to berberine.

Exendin-4 produced significant higher levels of fasting insulin, HOMA –IR and C-peptide in respect to berberine. On the other hand, the effects of exendin-4 produced significant lower levels of blood glucose, total cholesterol, triglycerides and LDL in respect to berberine. By comparing the two diabetic groups treated with berberine and exendin-4, exendin-4 was more potent in reducing fasting glycemia than berberine. The results showed that glucose-lowering effect of berberine was less than that of exendin-4 but with a better body weight reduction. The insulin resistance index (HOMA-IR) increased in diabetics ((group II) as compared to the control group. Also, the HOMA-IR index decreased in diabetic rats treated with berberine and exendin-4 as compared to diabetic rats. Berberine was effective in reducing HOMA-IR more than exendin-4.

The levels of lipid peroxidation, measured as malondialdehyde (MDA) were significantly elevated in diabetic pancreas compared to normal control group. On the contrary, MDA levels in berberine -treated diabetic rats were significantly decreased in pancreas compared to diabetic control rats. Also, the diabetic rats that received exendin-4 exhibited a significant decrease in MDA concentrations compared to diabetic control rats. Furthermore, this study showed that (SOD), were significantly decreased in diabetic pancreas compared to normal control group. On the other hand, SOD levels in berberine- treated diabetic rats were significantly elevated in pancreas compared to diabetic control rats (Table 1).Also, diabetic rats received exendin-4 exhibited a significant elevation in SOD concentrations compared to diabetic rats.

Table (1): Mean ± SD of body weight ,blood glucose level (FBS), fasting insulin, HOMA-IR, C-peptide, Hb A1c % ,CHO, TG, LDL-c, HDL-c and (SOD, MDA) in pancreatic homogenate in different studied groups.

Groups / Parameters	I	II	III	IV
Body weight (g	225.5±7.6	191.1±7.4* b	180.2±4.9* a	190.5±10.2* b
F BS (mg/dl)	98.6 ± 2.1	356 ± 3.5* b	156 ±1.4* a	132±3.49* a b
Fasting insulin (mU/L)	4.7±0.6	1.4±0.2* b	2.8 ±0.2* a	3.5 ±0.9* a b
HOMA –IR	1.14 + 0.07	1.23 + 0.08* b	1.07 +0.01* a	1.14+0.05 a b
C-peptide (ng/dl)	30.75 ± 4.7	8.8 ± 2.1* b	20.0 ±1.4* a	26±30.49* a b
Hb A1c % (g/dl)	4.58 ± .02	8.95±0.45* b	6.45± 0.08* a	6.24± 0.12* a
CHO (mg/dl)	82.6 ±6.1	256.0 ± 8.7* b	162.0 ±1.9* a	144±35.49* a b
TG (mg/dl)	86.7 ± 9.2	161.27±11.7* b	123.7 ± 5.4* a	116.7±5.4* a b
LDL-c (mg/dl)	33.95 ± 9.7	85.36 ± 4.2* b	55.7 ± 5.4* a	49.2 4 ±7.23*a b
HDL-c (mg/dl)	37.7 ± 3.12	30.12 ± 3.6* b	34.4 ± 2.05* a	35.4 ± 2.05* a
SOD (U/mg protein)	26.9±1.8	15.7±2.3* b	19.63+ 0.92* a	21.73+0.66* a b
MDA (nmol/mg protein)	88±1.3	138±0.17* b	98 +0.13* a	90±0.11* a b

*: Significantly different with control group(**I)**

a: significantly different with diabetic group **(I I)**.

b: Significantly different with diabetic received berberine (**III**)

Histopathological findings:

(A) Pancreases of normal control rats: Normal cells in the islets of Langerhans with no histopathological changes as (Fig. 1).

(B) Pancreases of Diabetic untreated rats: Atrophy and necrosis of islets of Langerhans with breakdown of micro-anatomical features as (Fig. 2, 3).

(C) Pancreases of diabetic rats treated with BBR: Mild necrotic changes in the islets of Langerhans with congested pancreatic blood vessels (Fig. 4)

(D) Pancreases of diabetic rats treated with exendin-4 : Slight lymphocytic infiltrate in some islets of Langerhans but most of them were preserving normal size and architecture as (Fig 5).

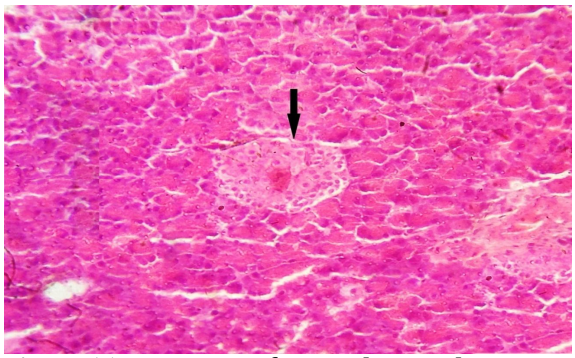

Figure (1): Pancreas of normal control rats: No histopathological changes in the cells of islets of Langerhans (arrow). (H & E stain x 400).

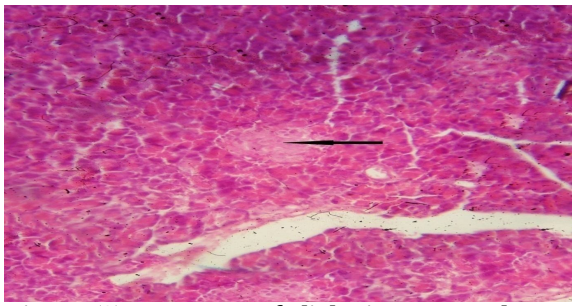

Figure (2): Pancreas of diabetic untreated rats: Atrophy and necrosis in the cells of islets of Langerhans (arrow). (H & E stain x 200).

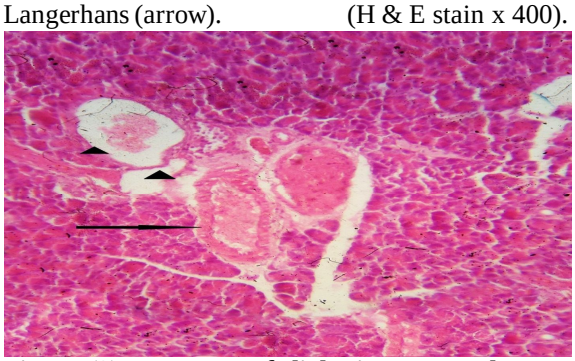

Figure (3): Pancreas of diabetic untreated rats : Congested blood vessels (arrow) and cystically dilated pancreatic ducts (arrowheads) 200.

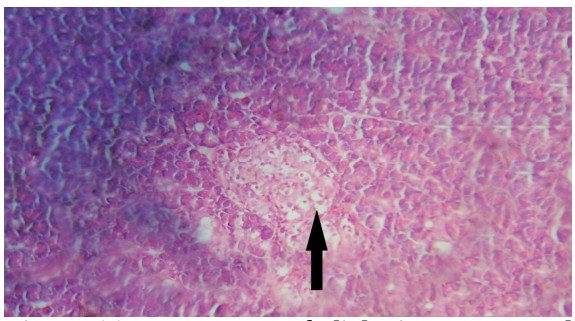

Figure (4): Pancreases of diabetic rats treated with berberine: Minimal degeneratve changes in the cells of islets of Langerhans represented by vaculization of few cells (arrow).

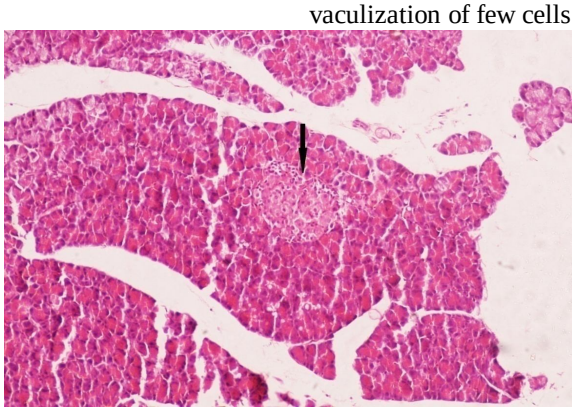

Figure (5): Pancreases of diabetic rats treated with exendine 4: Mild degenerative changes and subtle necrosis in the cells of the islets of Langerhans (arrow) with cystically dilated pancreatic duct (arrowhead).

DISCUSSION

The aim of the present study was to compare the effects of berberine and exendine 4 on adult male diabetic albino rats. Results of the present work showed significant differences in body weight among the four groups. Alloxan induced diabetes significantly decreased body weight as compared to the control group. Diabetes is accompanied with increased glycogenolysis, lipolysis, gluconeogenesis and these biochemical activities result in muscles wasting, loss of tissue protein and weight loss **(Marion and Franz, 2014)**.In the present study, oral administration of berberine in diabetic rats produced significant lower levels of body weight as compared to control diabetic rats. **Xie et al. (2011**) stated that berberine reduced body weight in obese mice. **Also, Yueshan et al. (2012**) demonstrated that berberine treatment produced a mild weight loss in obese human subjects.

The mechanism of body weight reduction of berberine could be due to inhibition of adipocyte differentiation and reduction of lipid accumulation in adipocytes which may be due to down regulation of several lipogenic genes **(Yoon et al., 2016).**

Also, results of the present study showed that the effects of berberine in diabetic rats produced marked lower levels of body weight as compared to control group.

Results of the present study showed that the effects of exendin-4 produced insignificant changes of body weight as compared to control diabetic group. On the other hand, **Yan et al. (2014)** reported that repeated administration of exendin-4 in diabetic mice has been shown to reduce food intake and body weight.

In the present study, oral administration of exendin-4 in diabetic rats produced significant lower levels of body weight as compared to control group.

Wilson et al. (2016) demonstrated that peripherally administered exendin-4 reduced body weight gain and improved metabolic profile in normal rodents consuming high fat (HF) diet.

Qiong et al. (2015) reported that exendin-4 treatment reduced high-fat-induced obesity by decreasing adiposity, increasing thermogenesis and also by shifting the energy balance from obesogenesis to thermogenesis in mice with diet-induced obesity.

All groups injected by alloxan showed significant higher levels in the blood glucose and HbA1c, and significant lower level of serum insulin level and C-peptide in comparison to normal control group. The toxic action of alloxan on pancreatic β cells is the summation of several processes such as generation of free radicals, inhibition of glucokinase, disturbances in intracellular Ca ++ homeostasis and deoxyribonucleic acid (DNA) damage **(Rohilla and Ali, 2012)**. The insulin resistance index (HOMA-IR) increased in (diabetic control group) as compared to the control group.

Induction of diabetes led also to disturbed lipid profile in the form of higher levels of cholesterol, triglycerides and LDL-c, and lower levels of HDL .c as compared to the control group. These effects of diabetes may be attributed to the

initiation of reverse cholesterol transport from cells to the liver for excretion **(Annema and Tietge, 2012).** In addition, the plasma LDL-cholesterol levels increase in diabetes mellitus possibly because insulin stimulates LDL receptors **(Gossain et al., 2010). Irshaid (2012)** stated that insulin promotes the esterification of fatty acids in adipose tissue. When triglycerides in adipose tissue are hydrolyzed, fatty acids are released and can be oxidized, re-esterified or they can enter the circulation. So, the net result of insulin lack on adipose tissue is enhancement of mobilization of fatty acids out of the tissue. Also, cholesterol synthesis is found to be greater in the gut of diabetic animals than in controls. This enhancement of sterol synthesis occurs soon after the onset of the disease, and causes elevation in plasma cholesterol concentrations **(Lee et al., 2014).** Cholesterol acyltransferase activity in intestinal mucosa is increased in diabetic rats. Therefore, an enhancement of cholesterol acyltransferase-dependent cholesterol esterification in the intestine might be one of the major factors that are responsible for hypercholesterolemia in diabetes **(Jiao et al., 2013).**

In the present study, diabetic group received berberine showed significant decrease in blood glucose level and HbA1c, and significant increase in insulin level and C-peptide level in comparison to diabetic control. **Ko et al. (2015)** suggested that treatment with BBR prevents the insulin expression and β cells number to decrease, and improve them near to the control level. The findings suggest that BBR may regenerate β cells and has a protective effect on β cells from glucose toxicity through insulin secretion from the remnant β cells and insulin sensitivity. Also, **Jing et al. (2017)** added that treatment with BBR takes the increased blood glucose in diabetic rats back to the control, and regulates insulin secretion partly through the CAMP signaling pathway.

Moreover, **Caliceti et al. (2016**) showed that BBR reduce fasting blood glucose through an insulin-independent signaling pathway such as adenosine monophosphate activated protein kinase (AMPK) activation, insulin receptor expression and inhibition of mitochondrial production of ATP. AMPK regulates several intracellular systems, including the cellular uptake of glucose, the beta-oxidation of fatty acids, and the biogenesis of glucose transporter type 4(GLUT4) (**Viollet et al., 2015**). However, **Chen et al. (2014**) suggested that BBR does not increase insulin release and synthesis. Also, **Zhou et al. (2014)** showed that BBR partially inhibits insulin release from β-cells and directly counteracts glucolipotoxicity. Moreover, **Al-Masri et al. (2009**) reported that berberine inhibited dipeptidyl peptidase-IV which degrades glucagon like peptide-1 (GLP-1). GLP-1 plays a critical role in insulin secretion and signaling (**Gallwitz et al., 2014**).

Insulin resistance index (HOMA-IR) decreased in diabetic received berberine as compared to the diabetic group.The treatment of the diabetic rats with berberine significantly lowered blood cholesterol, triglyceride and LDL levels, while HDL levels were significantly higher than that of diabetic group. This result was similar to that reported in vivo (**Wang et al., 2016)**. **Doggrell et al.**

(2015) stated that berberine reduces serum cholesterol and LDL-C, and increases LDL receptor mRNA as well as protein with hyperlipidemia. **Abid et al. (2015)** found that hypolipidemic effect of berberine was partly due to stabilization of LDL receptor mRNA mediated by the extracellular signal–regulated kinases (ERKs) signaling pathway .In addition to up-regulation of the LDL receptor, berberine was reported to inhibit lipid synthesis in human hepatocytes through activation of AMPK **(Brusq et al., 2015)**.

In diabetic group received exendin-4 blood glucose level and HbA1c were significantly lower than that in diabetic control group, while fasting insulin and C-peptide levels were significantly higher than that of diabetic group. Exendin-4 caused significant increase in insulin and C-peptide level when it was given in chronic dose to diabetic rate **(Lotfy et al., 2014)**. **Campbell (2013)** and **Kim et al. (2013)** concluded that exendin-4 can protect β cells by reducing its apoptosis, promoting its proliferation and neogenesis. This finding can be explained by **Liu et al., (2013)** who found that Exendin-4 can activate phosphoinsiti-deinsitide-3 kinase signaling pathway which has proliferative and anti-apoptotic effect on β cells.

Exendin-4 increases insulin secretion through calcium/calmodulin-dependent serine protein kinase **(Zhu et al., 2014),** and promotes hepatic insulin signaling by potentiating tyrosine phosphorylation of insulin receptor substrate-2 **(Park et al., 2010)**. Exendin-4 enhances glucose utilization by different tissues, and inhibits gluconeogenesis and glycogenolysis by hepatocytes. Insulin stimulates glycogenesis in liver and skeletal muscle **(Parlevliet et al., 2012).** Exendin-4 has extra pancreatic effect where it increases glucose uptake by muscle and adipocyte through its direct stimulating effect on glucose transporter-4 (GLUT-4) expression mRNA or protein (**Wu et al., 2012)**. The hypoglycemic effect of exendin-4 could be related to delay gastric emptying and inhibition of glucagon secretion **(Marathe et al., 2013)**. On the other hand, **Nachnani et al. (2010)** reported that chronic use of exendin-4 in rats leads to pancreatitis with associated beta cells dysfunction.

The insulin resistance index (HOMA-IR) decreased in diabetic rats received berberine) as compared to the diabetic group. It was effective in reducing insulin resistance more than exendin-4.

The treatment of the diabetic rats with exendin-4 significantly lowered blood cholesterol, triglyceride and LDL levels, while HDL levels were significantly higher than that of diabetic group. The lipid lowering effect of exendin-4 could be due to hormonal and non-hormonal mechanisms. Exendin-4 stimulates insulin secretion and inhibits glucagon secretion. Both effects lead to inhibition of lipolysis, reduction of free fatty acids as well as lipogenesis in adipose tissue. Exendin-4 also augments lipid lowering effects through reduced production of chylomicrons after fat rich meal. Also, it inhibits fat absorption from the gut, either by producing deceleration of gastric emptying or preventing the production of cholesterol and triglycerides. Exendin-4 inhibits gastric lipase and inhibits lymph flow **(Campbell and Drucker, 2013).**

Evaluation of oxidative parameters showed that induction of diabetes in rats resulted in a significant decrease in pancreatic SOD and significant increase in plasma Malondialdehyde (MDA) as compared to the control group. However, pancreatic activity of SOD increased and MDA decreased in diabetic rats received berberine as compared to the diabetic group. This was compatible with that of **Moghaddam (2014)** who revealed that Berberine ameliorates oxidative stress and astrogliosis in the hippocampus of streptozotocin (STZ) -induced diabetic rats. Also, **Patil et al. (2015)** demonstrated that treatment with berberine prevents the changes in oxidative stress and consequently memory impairment in ethanol treated rats. Increase of antioxidant (SOD) and decrease of oxidants (MDA) in diabetic rats received berberine may be due to either glucose regulatory and antioxidative effects of berberine **(Li et al., 2016).**

Treatment with exendin-4 in diabetic rats prevented the changes in oxidative stress and compensated these distractive effects as compared to the diabetic group. This was consistent with reports that revealed clear benefit of exendin-4 in the prevention of reactive oxygen species (ROS) production, mitochondrial dysfunction and increase in blood glucose level, which could increase the production of ROS and could participate in oxidative damages **(Kim et al ., 2017). Akram et al. (2016)** revealed that Exendin-4 has antioxidant effect and hypoglycemic effect against bisphenol A induced diabetes.

As regard histopathological findings, berberine and exendin-4 partly protected pancreatic β-cell integrity. They saved the tissue from the usual shrunken islets, degeneration, degranulation, hydropic and necrotic changes peculiar to alloxan-induced pancreatic injuries. These histological results were in agreement with the finding of **Layasadat (2013)** who stated that treatment of diabetic mice with GLP-1 or Exendin-4 from day 2 to day 6 after birth resultes in stimulation of β-cell neogenesis and proliferation with persistent expansion of β-cell mass detected at adult age. On the other hand, **Nachnani (2010)** stated that extended use of exendin-4 in rats leads to pancreatic acinar inflammation and pyknosis.

CONCLUSION

Berberine has beneficial effects on blood glucose control in the treatment of diabetic rats and exhibits efficacy comparable with that of exendin-4.Also , glucose-lowering effect of berberine was less than that of exendin-4 but with a better body weight reduction .Exendin-4 showed increased insulin and anti-oxidative stress levels than berberine. Exendine-4 was more effective on the metabolic disorders of lipid compared with that of the berberine -treated group.

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دراسة مقارنة بين بربارين واكسندين ٤ على ذكور الجرذان البيضاء البالغة المصابة بالداء السكرى

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خلفية البحث :إكزندين٤هو ببتيد شبيه لناهض بيبتيد - ١ مثيل الجلوكاجون ويمكن أن يتداخل مع مستقبلات مختلفة من ناهض بيبتيد - ١ مثيل الجلوكاجون. وقد تم تقييمها لتنظيم مستوى السكر في الدم في داء السكري ويتجلى التأثير المخفض للسكر في الدم للبربارين في المختبر وفي الجسم الحي.

الهدف من البحث :مقارنة تأثير بربارين واكسندين ٤ على ذكور الجرذان البيضاء البالغة المصابة بالداء السكرى.

مواد وطرق البحث :أجريت هذه الدراسة علي اثنين وثلاثين جرذًا بالغا ذكرا أبيضا، وتم تقسيمها إلى أربع مجموعات متساوية : **المجموعة الأولى** بمثابة المجموعة الضابطة **والمجموعة الثانية** هي مجموعة ضابطة مصابة بداء السكرى خضعت للحقن بجرعة واحدة من الألوكزان في التجويف البريتوني تعادل ١٥٠ مجم / كجم لإحداث الإصابة بداء السكرى **والمجموعة الثالثة** مصابة بداء السكرى وأعطيت بربارين بجرعة ٣٠٠مجم / كجم بالفم يوميا لمدة ٨ أسابيع و**المجموعة الرابعة** مصابة بداء السكرى أعطيت إكزندين -٤ بجرعة (١ نانومول/ كجم)يوميا لمدة ٨ أسابيع. وقد تم قياس وزن الجسم يوميا كما تم سحب عينات دم وريدية في نهاية التجربة وذلك لقياس مستوى الجلوكوز بالدم والإنسولين والسي ببيتايد وتقييم التوازن لنموذج مقاومة الأنسولين، والهيموجلوبين الجليكوزيلاتي ، والكوليستيرول، والدهون الثلاثية ، والبروتين الدهني منخفض الكثافة، والبروتين الدهني عالي الكثاف ، ومستوى السي ببيتايد وقد تم صبغ نسيج البنكرياس لفحص نسيجه ولقياس تركيز سوبر أكسيد ديسميوتاز ومالون داى الديهيد بنسيج البنكرياس.

النتائج : أظهرت نتائج البحث أن الحقن بالألوكزان يحدث إرتفاعاً ذا دلالة إحصائية فى مستوى الجلوكوز وتقييم التوازن لنموذج مقاومة الأنسولين والهيموجلوبين الجليكوزيلاتي والكولستيرول والدهون الثلاثية و مالون داى الديهيد بنسيج البنكرياس ، وإنخفاضاً ذا دلالة إحصائية فى وزن الجسم والإنسولين والسي ببيتايد ومستوى البروتين الدهني عالي الكثافة وسوبر أكسيد ديسميوتاز بنسيج البنكرياس مقارنة بالمجموعة الضابطة الغير مصابة بالداء السكرى . من ناحية أخرى فقد أظهرت النتائج أن إعطاء بربارين للجرذان المصابة بالداء السكرى أدى إلى إنخفاض ذو دلالة إحصائية فى

وزن الجسم ومستوي الجلوكوز وتقييم التوازن لنموذج مقاومة الإنسولين والهيموجلوبين الجليكوزيلاتي والكولستيرول والدهون الثلاثية الثلاثية والبروتين الدهني منخفض الكثافة و مالون داى الديهيد بنسيج البنكرياس وإرتفاع مستوى الإنسولين والسي بيبتايد ومستوى البروتين الدهني عالي الكثافة وسوبر أكسيد ديسميوتاز بنسيج البنكرياس مقارنة بالمجموعة الضابطة المصابة بالداء السكرى .ولقد أظهرت النتائج أن إعطاء إكزندين - ٤ للجرذان المصابة بالداء السكرى أدى إلى إنخفاض ذو دلالة إحصائية في مستوي الجلوكوز وتقييم التوازن لنموذج مقاومة الإنسولين والهيموجلوبين الجليكوزيلاتي والكولستيرول والدهون الثلاثية الثلاثية والبروتين الدهني منخفض الكثافة و مالون داى الديهيد د بنسيج البنكرياس وإرتفاع مستوى الإنسولين والسي بيبتايد ومستوى البروتين الدهني عالي الكثافة وسوبر أكسيد ديسميوتاز بنسيج البنكرياس مقارنة بالمجموعة الضابطة المصابة بالداء السكرى.وأظهرت نتائج الدراسة أن إكزندين -٤ أدي الي تغييرات ضئيلة في وزن الجسم مقارنة بالمجموعة الضابطة المصابة بالداء السكرى.

الإستنتاج :الإكزندين -٤ أكثر فعالية في الحد من إرتفاع السكر بالدم من تأثير البربارين بينما البربارين كان له تأثير أفضل في خفض وزن الجسم علاوة على ذلك، فالعلاج بالبربارين أدي الي زيادة كبيرة في أنشطة الإنزيمات المضادة للأكسدة بنسيج البنكرياس وكذلك إكزندين -٤. وأظهرت النتائج أن العلاج بالبربارين وإكزندين -٤ أدي الي الحماية والحفاظ علي سلامة والشكل الهندسي لخلايا بيتا بالبنكرياس.