



ISSN NO. 2320-5407

Journal homepage: <http://www.journalijar.com>
Journal DOI: [10.21474/IJAR01](https://doi.org/10.21474/IJAR01)

INTERNATIONAL JOURNAL
OF ADVANCED RESEARCH

RESEARCH ARTICLE

Insulin augmentation and glucagon inhibition in cinnamon treated diabetic rats.

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Manuscript Info

Manuscript History:

Received: 14 February 2016
Final Accepted: 19 March 2016
Published Online: April 2016

Key words:

Cinnamon - Anti-diabetic effect -
Alloxan - β cells

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Abstract

To clarify if changing the diet helps to prevent development of diabetes, the current study aimed to provide the immunomodulatory effect of cinnamon (CN) in improving the histological picture in the pancreatic tissue in diabetic rats. This improving picture were visualized in the well-organized islets containing increased number of β cells, β cells appeared with normal chromatin distribution and normal cellular population. CN administration to alloxan diabetic rats reduced serum glucose, triglyceride, total cholesterol, LDL cholesterol levels and boosting the immune system by increasing HDL cholesterol levels and insulin expression. In conclusion, the regular intake of CN in the daily diet may show many immunological benefits.

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Introduction:-

Diabetes mellitus is a global problem and the number of people suffering from it all over the world has soared to 246 million; that encourage researcher to find the mechanism of the natural herbs in fighting this disease. Diabetes now kills more people than AIDS (Baldi&Goyal, 2011). Diabetes leads to major complication such as diabetic neuropathy, nephropathy, retinopathy and cardiovascular diseases. The increased incidence of infections caused by bacteria, virus, and fungi in patients with diabetes mellitus (Habib et al., 2008). Diabetes mellitus is caused due to the inhibition in insulin production by the pancreas, as a result of the failure of pancreatic β -cell function or by the ineffectiveness of the insulin produced (Plum, 2005). In conventional therapy, type I diabetes is treated with exogenous insulin and type 2 with oral hypoglycemic agents (Sulphonylureas, Biguanides, etc). These drugs also have certain adverse effects like causing hypoglycemia at higher doses, liver problems, lactic acidosis and diarrhea (Raz et al., 2008).

Worldwide studies have been done to make use of herbal medicine in different fields of medicine. Based on ancient Persians traditional books Use of herbal medicine has positive effect on treatment of different diseases especially on diabetes mellitus (Jiang, 1996). Investigation into chemical compounds of onion and ginger shows these plants contain antioxidant agent (Khaki et al., 2009). Cinnamon belongs to the Lauraceae family, and its main components are cinnamic aldehyde, cinnamic acid, tannin, and methyl-hydroxychalcone polymer; these play a key role in exhibiting insulin-potentiating capabilities and therefore may have beneficial effects on cellular glucose uptake (Bernardo et al., 2015). Adiponectin (30-kDa) is the most abundant peptide secreted by adipocytes, being a key component in the interrelationship between adiposity, insulin resistance and inflammation (Fisman&Tenenbaum, 2014). Leptin is a protein produced by fatty tissue which regulates the amount of fat stored in the body.

The present study carried out to identify the protective role of cinnamon on the histological picture of pancreas and its immunomodulatory effect on the distribution of insulin and glucagon in the pancreatic tissue as a result of alloxan administration.

Material and methods:-

Source of chemicals:-

Alloxan (AL) was purchased from Sigma Aldrich Company (St. Louis, MO, USA) and the tablets of cinnamon (CN) herbal extract was purchased from General Nutrition Corporation (GNC), USA.

Experimental Animals, Diabetes Induction:-

Male rats *Rattusrattus* were purchased from Animal House, Faculty of Medicine, Ain Shams University (Cairo, Egypt). The rats were housed in a room maintained at constant humidity ($60 \pm 5\%$), temperature ($23 \pm 1^\circ\text{C}$), and a 12-h light/dark cycle. The standard diet and tap water were available *ad libitum* throughout the study. All experimental procedures were approved by and carried out in accordance with the guidelines of Ain Shams University for the care and use of laboratory animals. After a one-week acclimatization period, twenty-four rats weighing between 150-170g were randomly divided into four groups of 6 animals each. Group A served as the normal control and received 0.5ml of normal saline daily. Group B received CN orally at a dose level of 300 mg/kg bw daily. Diabetes was induced in groups C and D using alloxan, a uric acid derivative. The animals were fasted overnight and a single i.p. dose of AL 150 g/kg bw (Baldi and Goyal, 2011) dissolved in distilled water was used to induce diabetes. After three days of diabetes induction, animals with blood glucose levels greater than 300 mg/dl were considered diabetic and selected for the study. Groups D received daily doses of 250 mg/kg of the CN after the induction of diabetes, via oro-gastric intubation according to Jia et al. (2009). The administration lasted for 15 days. All animal procedures are in accordance with the recommendations of the Canadian committee for care and use of animals (CCAC, 1993).

Blood sampling and biochemical analyses:-

All the animals were anaesthetized using chloroform, 24 hours after the last administration of the extract. Blood samples were obtained by cardiac puncture; and collected in Eppendorff's tubes and allowed to clot for 10 min. Serum was separated by centrifuging the samples at 3000 rpm for 10 min and stored at -70°C until analyzed. Serum glucose, total cholesterol (TC), triglycerides (TG), HDL-cholesterol levels (HDL-Ch), free fatty acids (FFA) and malondialdehyde (MDA) were determined colorimetrically using commercial kits from Human, Germany. LDL-cholesterol levels (LDL-Ch) were calculated by the following equation: $\text{LDL-Ch (mg/dL)} = \text{TC} - \text{TG}/5 + \text{HDL}$ (Assman et al., 1984). Moreover, serum insulin, leptin levels were estimated by radioimmunoassay (RIA) specific kit for rats using solid phase component system purchased from ICN Pharmaceuticals Inc, USA. However, serum adiponectin levels were assayed using commercial ELISA (Sandwich Immunoassay Technique) specific kit for rats (Immuno-Biological Laboratories Co., Ltd. USA).

Histological Examinations:-

Specimens of pancreas were processed histologically, immersed in saline then fixed in 10% neutral buffered formalin and processed up to paraffin blocks, sectioned and stained with haematoxylin and eosin technique (Bancroft and Stevens, 1990).

Ultrastructure Investigations:-

Fresh small pieces of pancreatic tissue up to 1 mm^3 in size were fixed in 4% glutaraldehyde-formaldehyde for 5 h. then in (0.2 M) Na cacodylate for 2h. at 4°C (Sabatini et al., 1963) then washed in phosphate buffer pH 7.2 for 30 min. and post fixed in 1% osmic acid (2% OsO_4 + 0.3 M of Na cacodylate) for 2h. at 4°C , then washed in phosphate buffer (pH 7.2) for 30 min. at 4°C . Samples were dehydrated through ascending grades of ethanol and embedded in epoxy resin in an oven at 60°C for 14h. to produce a firm block. Ultrathin sections about 80 nm thickness with RMC ultramicrotome with diamond knife were obtained. Tissues were mounted on perforated copper grids for viewing in the electron microscope. Tissues were stained in 2 different solutions: The 1st one was done in the dark by using uranyl acetate for 30 min. followed by washing in absolute methanol for 15min. The 2nd one was carried out away from CO_2 by using lead citrate for 20 min. followed by washing in series of dist. water (Reynolds, 1963). Then the grids were examined by Transmission E.M. JOEL 1200 EX II at the Central Lab., Faculty of Science, Ain Shams University.

Statistical Analysis:-

To identify the significant differences among groups, the data were assessed by analysis of variance (ANOVA) followed by Duncan's multiple range test according to Duncan (1955) and Snedecor & Cochran (1982) using a computer program (Costate). Values of $P < 0.05$ were considered statistically significant.

Results:-

Biochemical Analyses:-

The blood glucose concentrations in the control group were 120.71 ± 0.63 mg/dL. The AL experimental groups had significantly increment blood glucose concentrations of 271.50 ± 1.54 mg/dL ($p < 0.05$). Significant differences in blood glucose concentrations between groups, which received CN ($p < 0.05$) when compared with AL group were reported (Table 1). Disturbances in hormonal profile were reported in AL treated animals as compared to control and CN treated rats. Significant decrease in insulin, and adiponectine reached 1.21 ± 0.03 and 4.09 ± 0.12 respectively. While, an increase in leptin levels reached 4.16 was reported. CN administration to diabetic rats reversed all these levels. CN showed a positive effect on the hormonal profile in diabetic rats.

Table (1): Blood glucose and hormonal profile (insulin, leptin and adiponectin) in control and experimental groups.

Groups	C M \pm SE	CN M \pm SE	AL M \pm SE	AL+CN M \pm SE
Glucose mg/dL	120.71 ± 0.63	$120.43 \pm 0.38^{\#}$	$271.50 \pm 1.54^*$	$169.83 \pm 1.04^{*/\#}$
Insulin ng/ml	1.83 ± 0.05	$1.86 \pm 0.03^{\#}$	$1.21 \pm 0.03^*$	$1.56 \pm 0.04^{*/\#}$
Leptin pg/ml	2.81 ± 0.16	$2.88 \pm 0.04^{\#}$	$4.16 \pm 0.05^*$	$3.50 \pm 0.04^{*/\#}$
Adiponectin ng/ml	5.49 ± 0.10	$5.59 \pm 0.04^{\#}$	$4.09 \pm 0.12^*$	$5.03 \pm 0.09^{*/\#}$

Values are mean \pm SE. The significant difference at ($P < 0.05$). * Significant to C, # Significant to AL group

The present results of lipid profile revealed that injection of AL caused a highly significant increase in total cholesterol (97.32 ± 0.85), triglycerides (117.98 ± 1.18), LDL-Ch (57.55 ± 1.33), and FFA (536.83) levels accompanied with significant decrease in HDL-Ch (14.57 ± 0.46) fraction as compared to normal control. This reversed by the administration of CN to diabetic rats. MDA levels increased in diabetic rats. MDA considered as a marker of lipid peroxidation, which can reveal the oxidative damage as a result of diabetes. Again, CN proved its protective effect through the attempts on decreasing the levels of MDA (0.68 ± 0.03) as compared to AL group.

Table (2): Serum lipid profile and antioxidant status in control and experimental groups.

Values are mean \pm SE. The significant difference at ($P < 0.05$). * Significant to C, # Significant to AL group

Groups	C M \pm SE	CN M \pm SE	AL M \pm SE	AL+CN M \pm SE
TC mg/dL	54.53 ± 0.91	$53.38 \pm 0.95^{\#}$	$97.32 \pm 0.85^*$	$64.48 \pm 1.02^{*/\#}$
TG mg/dL	62.97 ± 1.18	$64.05 \pm 1.09^{\#}$	$117.98 \pm 1.18^*$	$76.83 \pm 1.63^{*/\#}$
LDL-Ch mg/dL	27.98 ± 0.66	27.21 ± 0.89	57.55 ± 1.33	34.39 ± 0.79
HDL-Ch mg/dL	14.42 ± 0.46	16.10 ± 0.57	14.57 ± 0.46	14.05 ± 0.75
FFA μ M/ml	362.52 ± 2.41	$352.23 \pm 3.76^{\#}$	$536.83 \pm 4.99^*$	$412.75 \pm 3.86^{*/\#}$
MDA nmol/ml	0.68 ± 0.03	$0.69 \pm 0.02^{\#}$	$1.21 \pm 0.04^*$	$0.86 \pm 0.03^{*/\#}$

Histological Examinations:-

Pancreas sections from control rats illustrated preserved architecture with normal islets of Langerhans, consisting of β cells in the center and α cells at the periphery, the endocrine cells within islets are arranged as irregular cords (Fig. 1). Sections of pancreas from CN treated rats showed no histopathological changes when compared with control animals (Fig.2).

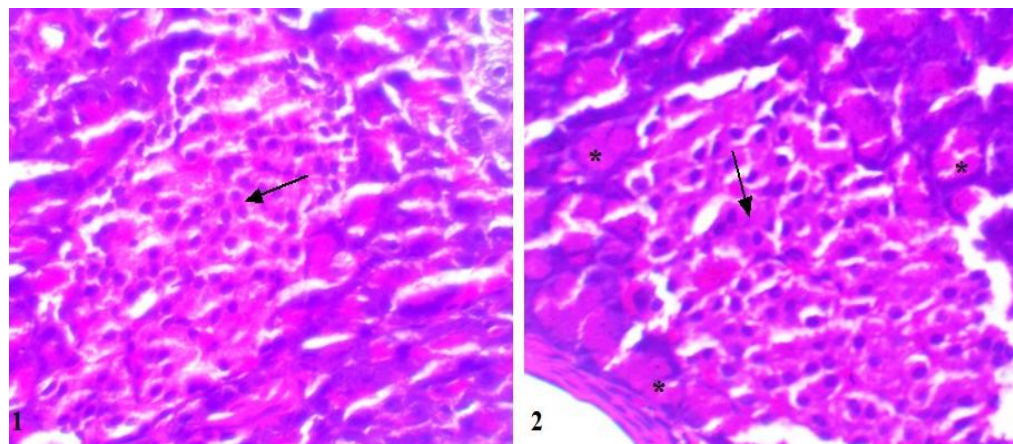


Fig 1: Photomicrograph of pancreas from control rat showing normal islet of Langerhans scattered within the acinar cells. α cells at the periphery and β cells at the center (arrows). (H-E, X400).

Fig. 2: Photomicrograph of pancreas from CN treated rat showing Normal distribution of β cells (arrows) in the islet surrounded by the acinar cells (*). (H-E, X400).

Rats treated with AL revealed abnormal histological alterations in the pancreatic tissue viz: shrunk islets with irregular outlines and decreased number of β cells, which appeared with pyknotic nuclei (Fig.3), α cells appeared with large size and β cells with cytoplasmic vacuolation (Fig. 4).

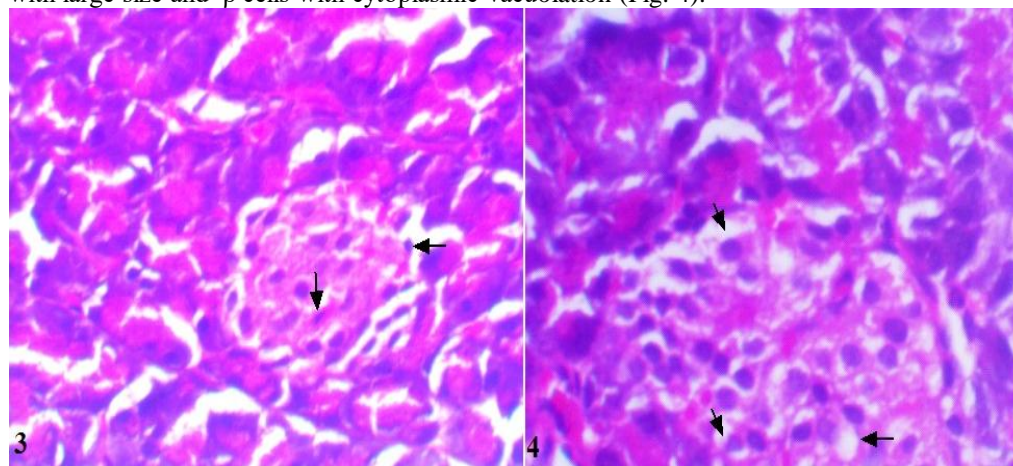


Fig. 3: Photomicrograph of pancreas from AL injected rats showing shrinkage islet with irregular outlines and decreased number of the endocrine cells (β cells), which appeared with pyknotic nuclei (arrow). (H-E, X400).

Fig. 4: Photomicrograph of pancreas from diabetic rat showing some β cells appeared with cytoplasmic vacuolation and α cells appeared with large size (arrows). (H-E, X400).

Pancreas sections from AL+CN treated rats delineated an improved histological picture that were visualized in the well-organized islets containing increased number of β cells as shown in figure (5), β cells appeared with normal chromatin distribution and normal cellular population (Fig.6).

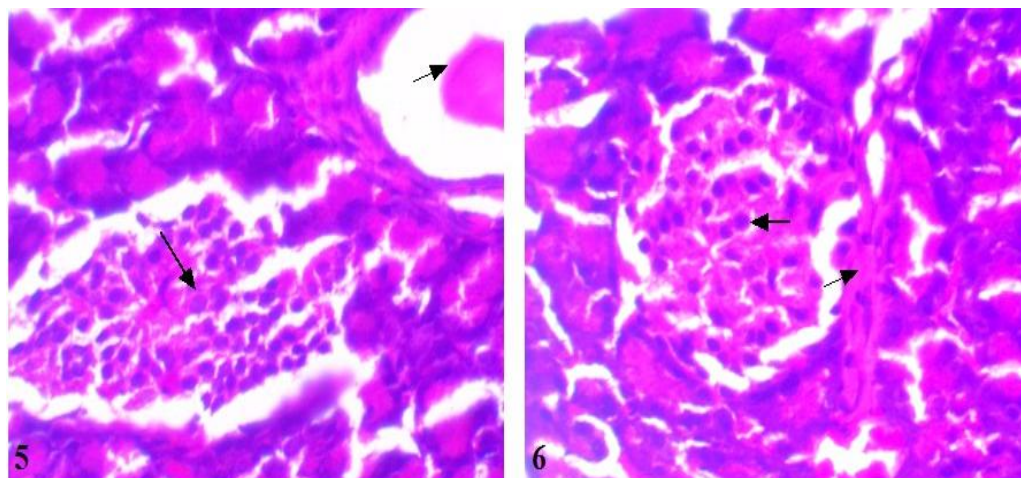


Fig. 5: Photomicrograph of pancreas from rat treated with AL+CN showing well organized islets containing increased number of β cells (thick arrow) and blood vessel filled with hyaline material (thin arrow) (H-E, X400).

Fig. 6: Photomicrograph AL+CN pancreas showing medium sized islet surrounded by connective tissue (thin arrow), with normal cellular population, and β cells (thick arrow) appeared with normal chromatin distribution. (H-E, X400).

Ultrastructural Investigations:-

The ultrastructural examination of normal control rat pancreas showed normal structure of β cell with mature granules which are in different stages of maturation (Fig. 7). Sections of pancreas from rat treated with CN revealed β cell with normal chromatin distribution and the mature granules show the characteristic halo; the core of the granules is polygonal in shape (Fig. 8). After the injection of AL, pancreas sections revealed many ultra-histopathological disturbances in β cells such as pyknotic nuclei and immature granules (Fig. 9&10), heterochromatin is abundant in some cells and the presence of inflammatory monocyte cells (Fig.11). The pancreatic tissues regained their normal appearance in the group of rats treated with AL+CN, as appeared by the restoration of normal cellular population and the well-defined β cells with normal shape and outline of the nucleus, rich in mitochondria and mature granules and normal chromatin distribution as appeared in figures (12 & 13).

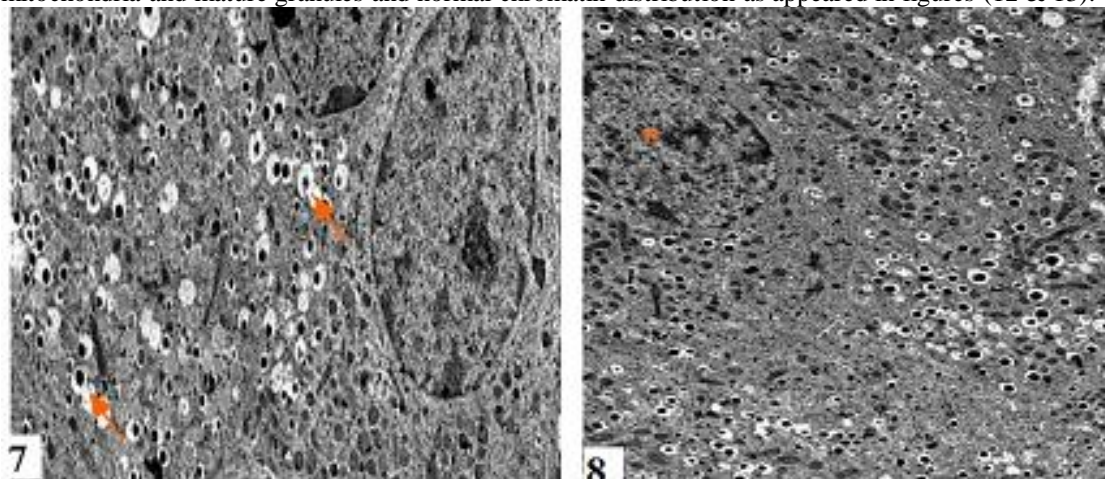


Fig. 7: An electron micrograph from control pancreas showing normal structure of β cell with mature granules (arrows), The secretory granules are in different stages of maturation (EM, X 6000).

Fig. 8: Electron micrograph of pancreas from CN treated rat showing β cell with normal chromatin distribution (*) and mature granules, show the characteristic halo; the core of the granules is polygonal in shape (EM, X 6000).

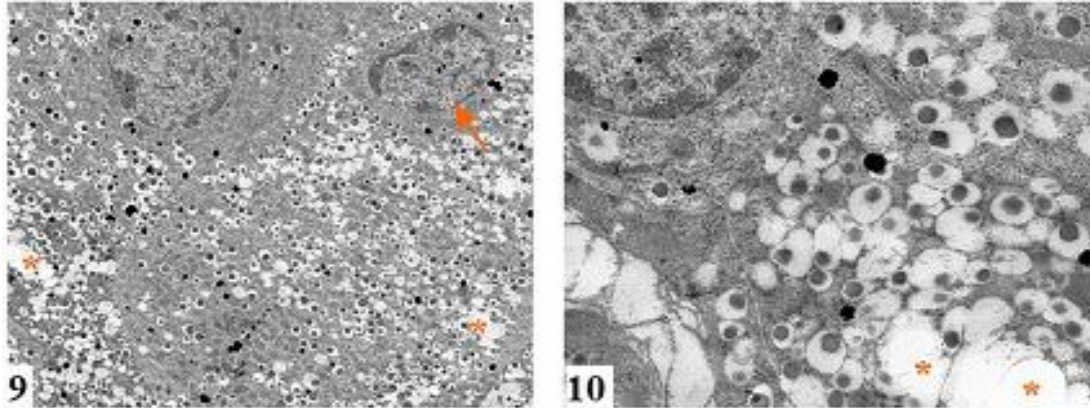


Fig. 9: Transmission electron micrograph of pancreas from AL injected rat showing β cells with pyknotic nuclei (arrow) and immature granules without center core (*) (EM, X6000).

Fig. 10: Magnification part of the previous micrograph showing immature granules (*) of β cells (EM, X20000).

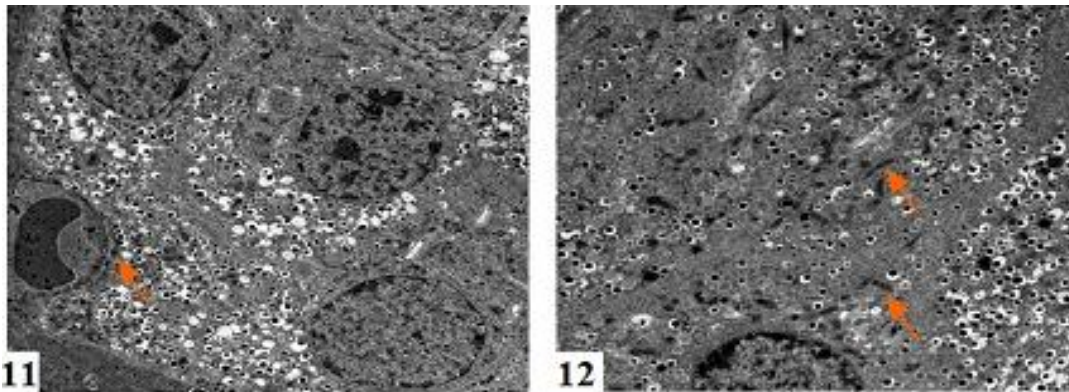


Fig. 11: Electron micrograph of pancreas from diabetic rat showing β cell with heterochromatin is abundant in the nucleus, immature granules in the cytoplasm, beside the presence of monocyte inflammatory cells (arrow), notice the presence of endoplasmic reticulum. (EM, X 5000).

Fig. 12: Transmission electron micrograph from rat pancreas treated with AL+CN showing β cells rich in mitochondria (arrows) and mature granules (EM, X5000).

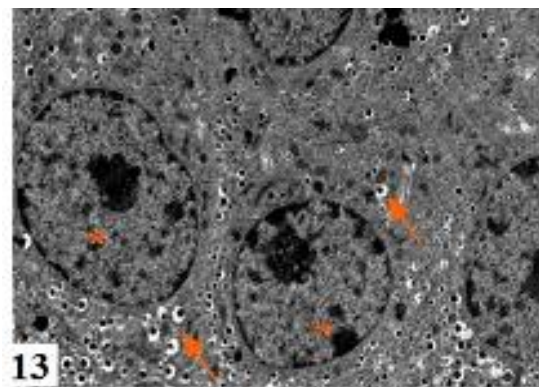


Fig. 13: An electron micrograph of pancreas from AL+CN treated rat showing restoration of normal cellular population, as appeared by the well-defined β cells with normal shape and outline of the nucleus and normal chromatin distribution (*) and the cells containing mature granules (arrows) (EM, X5000).

Discussion:-

The pancreas is the primary organ involved in sensing the organism's dietary and energetic states via glucose concentration in the blood. In response to elevated blood glucose, insulin is secreted. The bulk of the pancreas by

volume consists of exocrine cells that secrete an alkaline solution of digestive enzymes. Only about 5% of the volume of the pancreas consists of endocrine cells. These cells secrete peptide hormones that play a role in controlling carbohydrate metabolism. Insulin deficiency causes elevation of blood glucose and underutilization leading to hyperglycemia (Standl et al., 2003). Hyperglycemia is the primary clinical manifestation of diabetes mellitus, a major degenerative disease affecting people worldwide (Schwartz, 2006); by altering circulating lipoproteins, vascular cellular metabolism, and vascular matrix molecules (especially glucose and lipids).

The majority of islet cells are formed of β cells which are responsible for insulin production. Depletion of β cells will therefore result in insulin deficiency which will lead to a disorder in carbohydrate, protein and fat metabolism with hyperglycaemia as a final result. In this study, alloxan (AL) which selectively destroy β cells of the islet was used to induce type 1 diabetes mellitus. Additionally, there was a strong relationship between increase of glucose levels and hyperlipidaemia, inhibition of leptin and adiponectine levels in diabetic rats. High-glucose concentrations may induce macrophage production of IL-12, which can stimulate $CD4^+$ cell production of IFN- γ which initiate and induce further inflammation and oxidative stress (McArdle., 2013).

The present investigation showed that CN administration caused decrease in blood glucose, triglycerides, and total and LDL-cholesterol concentrations. This is come in accordance with Khan et al., (2003) who reported that CN have been shown to increase in vitro glucose uptake and glycogen synthesis and to increase phosphorylation of the insulin receptor; in addition, CN is likely to aid in triggering the insulin cascade system (Jarvill-Taylor et al., 2001). Because insulin also plays a key role in lipid metabolism, the authors postulated that consumption of CN would lead to improved glucose and blood lipids in vivo. Extracts of CN activated glycogen synthase, increased glucose uptake, and inhibited glycogen synthase kinase-3 (Jarvill-Taylor et al., 2001). CN also activated insulin receptor kinase and inhibited dephosphorylation of the insulin receptor, leading to maximal phosphorylation of the insulin receptor (Jarvill-Taylor et al., 2001). All of these factors would lead to increased insulin sensitivity, which is associated with improved glucose, lipid levels and lead to enhance cellular glucose uptake. CN also function as potent antioxidants, which would lead to additional health benefits of this substance. Khan et al. (2003) tested the administration of CN (1-6g/day) to diabetic rats, and suggested that there is a wide range of its intake that may be beneficial and that intake of 1g daily is likely to be beneficial in controlling blood glucose and lipid levels. It has been shown that CN prevents the development of insulin resistance in rats fed a high-fructose diet by enhancing the insulin signaling, possibly via the nitric oxide pathway in skeletal muscle (Qin et al., 2004). While, Hlebowicz et al. (2007) delineated that ingestion of 6g CN reduces blood glucose concentrations. This finding could indicate that the reduction in the blood glucose response seen after the ingestion of CN could be partly explained by an accompanying reduction in gastric emptying, because the rate of gastric emptying acts as a major factor in blood glucose homeostasis in normal subjects by controlling the delivery of carbohydrate to the small intestine (Horowitz et al., 1993). The maintenance of lower serum glucose and lipid levels, even when the individuals were not consuming CN for 20 days, denotes sustained effects of CN, indicating that it would not need to be consumed every day (Qin et al., 2003). There was an altered antioxidant enzyme profile which resulted in a notable increase in the levels of oxidative stress markers like lipid peroxides, nitric oxide and carbonylated proteins (Kain et al., 2010).

Alloxan injection caused a decrease in adiponectine and an increase leptin levels, this come in accordance with (Saad et al., 2015), reflecting a state of adiponectin deficiency and leptin resistance. Leptin is a hormone that regulates appetite and metabolism. Also, it has been found to have many biological effects on various systems and may be the signal that integrates vascular, metabolic and neuroendocrine responses (Leung & Kwan, 2008). Moreover, insulin has a direct influence on the synthesis and secretion of leptin. It is thought that leptin participating in glycol-metabolism and fat-metabolism in liver mainly depends on the regulation of gene expression of phosphoenolpyruvic acid and efficiency of glyconeogenesis which stimulates liver intake of lactic acid and genesis of hepatic glycogen (Mohammadi et al., 2004). Insulin is one of the necessary factors that may act by transferring of glucose into the adipose cells, so glucose as intracellular signal stimulates leptin secretion from adipose tissue of diabetic rats. Adiponectine and leptin levels were reversed after CN administration. This comes in accordance with (Schmid et al., 2013). Adiponectin is well documented to reduce plasma concentration of fatty acids and triglycerides in mice models of obesity and hyperlipidemia. The effect is mediated by acceleration of fatty acid oxidation in muscle cells, which leads to decrease in cellular triglyceride content (Fruebis et al., 2001). CN may possess the ability to enhance leptin sensitivity and correct leptin resistance (Kim et al., 2006).

The histological and ultrastructure damage reported in pancreas tissue as a result of AL injection come in agreement with those of Kumar and Clark (2005) who showed that islets containing residual β cells and it supports the possibility of a specific, immunologically mediated destruction of β cells as the cause of type 1 diabetes mellitus

(Anderson, 1985); causing decrease in insulin expression and increase in glucagon expression (Amiri et al., 2015). There was heavy inflammatory infiltration in and around the islet (Eliakim-Ikechukwu&Obri, 2009). The histopathological study of the pancreas indicated increased volume density of islets and increased numbers of beta cells, in the diabetic rats that received CN, which may be a sign of enhancing the production of insulin as revealed by the immunohistochemical and biochemical investigations. Signs of regeneration of β cells appeared in diabetic rats treated with CN, potentiation of insulin secretion from surviving β cells of the islets of Langerhans; which come in concomitant with the decreased blood glucose levels. CN has the ability of inducing the quiescent cells to proliferate to replace the lost cells; by increases the number of β cells and decreases blood glucose. It has also may have stopped further destruction of the remaining β cells in the islet by mopping up the circulating reactive oxygen species generated by the AL to destroy the β cells and then allowing the induction of regenerative activities (Yadav et al., 2008). Cinnamon had the ability to reduce blood glucose via reduction of insulin resistance and increase of hepatic glycogenesis (Couturier et al., 2011). Cinnamon phenolics and cinnamaldehyde had antihyperglycemic and antihyperlipidemic effects on rodent models of diabetes by the modulation of insulin signaling (Li et al., 2012).

Conclusion:-

The findings of this study indicated that consumption of the CN exerts significant hypoglycemic effect in rats. Histopathological studies showed evidence of increase in β cell number and size in diabetic rats which receiving CN, thereby stimulating the secretion of insulin. These data support the use of CN as dietary supplement for controlling glucose levels in diabetics. In view of the restorative potential on pancreatic islet cells, and because CN does not contribute to caloric intake, those who have diabetes or those who have elevated glucose, or lipid profile levels may benefit from the regular intake of CN in their daily diet. Also, the present study suggested a further investigation with longer period of higher doses required to show clearer features of these results.

References:-

1. Amiri L, John A, Shafarin J, Adeghate E, Jayaprakash P, Yasin J, Howarth FC, Raza H (2015). Enhanced glucose tolerance and pancreatic beta cell function by low dose aspirin in hyperglycemic insulin-resistant type 2 diabetic Goto-Kakizaki (GK) rats. *Cell PhysiolBiochem* 36:1939-1950.
2. Anderson JR (1985). Muir's Textbook of Pathology. 12th ed. ELBS. pp. 20-63.
3. Assman G, Jabs H, Kohnert U, Note W, Schriewer H (1984). Enzymatic determination of LDC-Cholesterol. *ClinChemActa* 140: 77-83.
4. Baldi A, Goyal S (2011). Hypoglycemic effect of polyherbal formulation in alloxan induced diabetic rats. *Pharmacologyonline* 3: 764-773.
5. Bancroft JD, Stevens A (1990). Theory and Practice of Histological Technique. 3rd ed. Churchill Livingstone, NY, USA.
6. Bernardo MA, Silva ML, Santos E, Moncada MM, Brito J, Proença L, Singh J, de MesquitaMF (2015). Effect of cinnamon tea on postprandial glucose concentration. *J Diabetes Res* 2015, Article ID 913651, 6 pages.
7. CCAC, Candian Council on Animal Care (1993). Guide to the care and use of experimental animals, CCAC, Ottawa, Ontario, Canada 1:1-298
8. Couturier K, Qin B, Batandier C, Awada M, Hininger-Favier I, Canini F, Leverve X, Roussel AM, Anderson RA. (2011). Cinnamon increases liver glycogen in an animal model of insulin resistance. *Metabolism* 60(11):1590–1597.
9. Duncan DB (1955). Multiple range and multiple F-tests. *Biometr* 11:1-42.
10. FismanEZ, Tenenbaum A (2014). Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovascular Diabetology* 13:103
11. Eliakim-ikechukwu CF, Obri AI (2009). Histological changes in the pancreas following administration of ethanolic extract of *alchorneacordifolia* leaf in alloxan- induced diabetic Wistar rats. *Niger J PhysiolSci* 24 (2):153 -155.
12. Fruebis J, TsaoTS, Javorschi S, Ebbets-Reed D, Erickson MRS, Yen FT, Bihain BE, LodishHF (2001). Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *ProcNatlAcadSci USA* 98:2005-2010.
13. Habib AG, Gebi UI, Sani BG, Maisaka MU, Oyenyi T, Musa BO, Onyemelukwe GC (2008). Insulin dependent diabetes mellitus complicating follicular lymphoma in an adult Nigerian: immunobiological aspects. *Intern Diab Dig* 7:334.
14. Hlebowicz J, Darwiche G, Björgell O, Almér LO (2007). Effect of cinnamon on postprandial blood glucose, gastric emptying, and satiety in healthy subjects. *Am J ClinNutr* 85 (6): 1552-1556.

15. Horowitz M, Edelbroek MA, WishartJM, StraathofJW. (1993). Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia* 36: 857–862.
16. Jarvill-Taylor KJ, Anderson RA, Graves DJ (2001). A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3–L1 adipocytes. *J Am Coll Nutr* 20: 327–336.
17. Jia Q, Liu X, Wu X, Wang R, Hu X, Li Y, Huang C (2009). Hypoglycemic activity of a polyphenolic oligomer-rich extract of *Cinnamomum parthenoxylon* bark in normal and streptozotocin-induced diabetic rats. *Phytomedicine* 16(8):744-750.
18. Jiang GY. (1996). *Practical Diabetes* 1st ed. Beijing: People's Health Publishing House.
19. Kain V, Kumar S, Puranik AS, Sitasawad SL (2010). Azelnidipine protects myocardium in hyperglycemia-induced cardiac damage. *Cardiovascular Diabetology* 9:82-91.
20. Khaki A, Fathi Azad F, Nouri M, Khaki AA, Jabbari–kh H, Hammad M (2009). Evaluation of androgenic activity of *Allium cepa* on spermatogenesis in rat. *J Folia Morphologica* 68(1): 45-51.
21. Khan A, Safdar M, Khan MMA, KhattakKN, Anderson RA (2003). Cinnamon improves glucose and lipids of people with type 2 diabetes. *Diabetes Care* 26:3215–3218.
22. Kim YW, Kim JY, Park YH, ParkSY, Won KC, ChoiKH, HuhJY, MoonKH (2006). Metformin restores leptin sensitivity in high-fat-fed obese rats with leptin resistance. *Diabetes* 55(3): 716–724.
23. Kumar P, Clark M (2005). *Clinical Medicine*. 6th ed. Elsevier Saunders. p1107, 1148.
24. Leung Y, Kwan C (2008). Dual vascular effects of leptin via endothelium: hypothesis and perspective. *Chin J Physiol* 51: 1–6.
25. Li J, Liu T, Wang L, Guo X, Xu T, Wu L, Qin L, Sun W (2012). Antihyperglycemic and antihyperlipidemic action of cinnamaldehyde in C57BLKS/J db/db mice. *J Trad Chinese Med* 32(3): 446–452.
26. McArdle MA, Finucane OM, ConnaughtonRM, McMorrow AM, Roche HM (2013). Mechanisms of obesity-induced inflammation and insulin resistance: insights into the emerging role of nutritional strategies. *Front Endocrinol (Lausanne)*. 2013; 4: 52.
27. Mohammadi NM, Ebrahimi H, Homauonei MF (2004). Effects of insulin on plasma levels of leptin in male diabetic rats. *MJTUMS* 63: 87-94.
28. Plum L (2005). Transgenic and knockout mice in diabetes research: novel insights into pathophysiology, limitations, and perspectives. *Physiology (Bethesda)* 20:152–161.
29. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato S (2003). Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. *Diabetes Res Clin Pract* 62: 3:139–48.
30. Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato S (2004). Cinnamon extract prevents the insulin resistance induced by a high-fructose diet. *Horm Metab Res* 36: 119–25.
31. Raz I, Chen Y, Wu M, Hussain S, Kaufman KD, AmatrudaJM, Langdon RB, Alba M (2008). Efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. *Curr Med Res Opin* 24(2):537-550.
32. Reynolds ES (1963). The use of Lead citrate at high pH as an electronopaque stain in electron microscopy. *J Cell Biol* (17): 208-212.
33. Saad MI, Kamel MA, Hanafi MY (2015). Modulation of adipocytokines production and serum NEFA level by metformin, glimepiride, and sitagliptin in HFD/STZ diabetic rats. *Biochem Res Int* 2015, Article ID 138134, 7 pages.
34. Sabatini DD, Bens K, Barnett RJ (1963). Cytochemistry and electron microscopy: the preservation of cellular ultrastructure and enzymatic activity by aldehyde fixation. *J Cell Biol* (17): 19-24.
35. SchmidPM, Resch M, Schach C, Birner C, Riegge GA, Luchner A, Endemann DH (2013). Antidiabetic treatment restores adiponectin serum levels and APPL1 expression, but does not improve adiponectin-induced vasodilation and endothelial dysfunction in Zucker diabetic fatty rats. *Cardiovascular Diabetology* 12:46
36. Schwartz SL (2006). Diabetes and dyslipidemias. *J Diabetes Obes Metabol* 8(4): 355-364.
37. SnedecorGW, Cochran WG (1982). *Statistical Methods*. 7th ed. Twa State University Press, Ames, Iowa, USA.
38. Standl E, Ballestshoffer B, Dahl B, Shagler H (2003). Predictors of 10 years macrovascular and overall mortality in patients with NIDDM: the Munich practitioner project. *Diabetologia* 39:540-545.
39. Yadav JP, Saini S, Kalia AN, Dangi AS (2008). Hypoglycemic activity of ethanolic extract of *Salvadora oleoides* in normal and alloxan-induced diabetes rats *Indian J Pharmacol* 40 (1): 23 – 27.