The Egyptian Journal of Hospital Medicine (Jan. 2016) Vol. 62, Page 95 - 104

Hepatoprotective and antidiabetic effects of apple cider vinegar (A Prophetic Medicine Remedy) on the liver of male rats

Nassar Ayoub Abdellatif Omar [1, 2], Amal Nor Edeen Ahmad Allithy[3, 4], Salah Mohamed El Sayed[5, 6]

[1]Department of Anatomy, Faculty of Clinical Pharmacy, Taif University, Saudi Arabia,[2] Department of Anatomy, Sohag Faculty of Medicine, Sohag University, Egypt, [3]Department of Pathology, Al-Ghad international medical sciences, Al-ghad University, Al-Madinah Al-Munawwarah, Saudi Arabia,[4]Department of Pathology, Sohag Faculty of Medicine, Sohag University, Egypt,[5] Department of Clinical Biochemistry and Molecular Medicine, Taibah Faculty of Medicine, Taibah University, Al-Madinah Al-Munawwarah, Saudi Arabia,[6] Department of Medical Biochemistry, Sohag Faculty of Medicine, Sohag University, Egypt.Corresponding author: Nassar A. A. Omar, Email: n.nassar395@gmail.com

ABSTRACT

Background: Diabetes mellitus is associated with biochemical and pathological alterations in the liver. The aim of this study was to investigate the effects of apple cider vinegar (ACV) on serum biochemical markers and histopathological changes in the liver of diabetic rats for 30 days. Effects were evaluated using streptozotocin (STZ)-induced diabetic rats as an experimental model. **Materials and methods:** Diabetes mellitus was induced by a single dose of STZ (65 mg/kg) given intraperitoneally. Thirty wistar rats were divided into three groups: control group, STZ-treated group and STZ plus ACV treated group (2 ml/kg BW). Animals were sacrificed 30 days post treatment. **Results:** Biochemical results indicated that, ACV caused a significant decrease in glucose, TC, LDL-c and a significant increase in HDL-c. Histopathological examination of the liver sections of diabetic rats showed fatty changes in the cytoplasm of the hepatocytes in the form of accumulation of lipid droplets, lymphocytic infiltration. Electron microscopic studies revealed aggregations of polymorphic mitochondria with apparent loss of their cristae and condensed matrices. Besides, the rough endoplasmic reticulum was proliferating and fragmented into smaller stacks. The cytoplasm of the hepatocytes exhibited vacuolations and displayed a large number of lipid droplets of different sizes. On the other hand, the liver sections of diabetic rats treated with ACV showed minimal toxic effects due to streptozotocin. These ultrastructural results revealed that treatment of diabetic rats with ACV led to apparent recovery of the injured hepatocytes. In prophetic medicine, Prophet Muhammad peace is upon him strongly recommended eating vinegar in the Prophetic Hadeeth: "vinegar is the best edible".

Conclusion: This study showed that ACV, in early stages of diabetes induction- can decrease the destructive progress of diabetes and cause hepatoprotection against the metabolic damages resulting from streptozotocin- induced diabetes mellitus.

Keywords: Streptozotocin, Diabetes mellitus, apple cider vinegar, Liver, Rat.

INTRODUCTION

According to recent estimates, diabetes mellitus is a growing problem. Over 171 million people were living with diabetes worldwide in the year 2000, and the estimated number is to increase to 366 million by 2030. [1]

Diabetes mellitus has been defined as a chronic disease with persistently elevated blood glucose concentration. [2] It is a major and growing public health problem throughout the world.

In modern medicine no satisfactory effective therapy is still available to cure diabetes mellitus, which is a syndrome resulting from a variable interaction of hereditary and environmental factors and characterized by abnormal insulin secretion or insulin receptor or post-receptor

events affecting metabolism involving carbohydrates, proteins and fats in addition to damaging β-cells of pancreas, liver and kidney in some cases. [3]

Management of diabetic patients depends on the dietary and lifestyle factors where they play an important role not only in the etiology but also in the control of the disease and its complication. [4] . Liver disease is one of the dealing causes of death in persons with type 2 diabetes. The standardized mortality rate death from liver disease is greater

Received: 01/12/2016
Accepted: 15/12/2016

DOI : 10.12816/0021418

than that cardiovascular disease. The spectrum of liver disease in type 2 diabetes ranges from nonalcoholic fatty liver disease to cirrhosis and hepatocellular carcinoma.[5] Experimental type 1 diabetes induced with streptozotocin or alloxan in rats displays many features seen in human subjects with uncontrolled diabetes mellitus.[6] Streptozotocin induced diabetes mellitus in many animals species has been reported to resemble human hyperglycemic nonketonic diabetes mellitus.[7] Many studies have shown an association between specific diabetic complications and disturbances in various tissues, such as diabetic nephropathy and peripheral neuropathy, but only limited data is available on the possible association between diabetic complication and liver functions. [8]

Streptozotocin (STZ) is a naturally occurring nitrosourea with molecular weight of 265 and empirical formula of C14 H27 N5 O12.[9] The diabetogenic action of STZ is the direct result of irreversible damage to the pancreatic beta cells resulting in degranulation and loss of capacity to secrete insulin.[10] It is widely used to induce insulin-dependent diabetes mellitus in experimental animals because of its toxic effects on islet beta cells.[11] STZ given intravenously or intraperitoneally to laboratory mice in multiple subdiabetogenic doses induces pronounced pancreatic insulitis with eventual destruction of insulin-secreting beta cells and diabetes mellitus. It is diabetogenic, hepatotoxic, nephrotoxic and also causes gastric ulceration. [12] In an experimental study in rats, STZ injected in a dose of 65 mg/kg body weight effectively produced hyperglycemia and gastric mucosal ulcerations. [12]

Apple cider vinegar is an acidic solution produced by fermenting apples. It contains vitamins, minerals and many trace elements. [13] It contains a potent supply of potassium. Potassium is essential for soft tissue repair and the replacement of worn - out tissues within the body. Cider vinegar improves the health and function of the vital organs of the body by preventing excessively alkaline urine. It is a strong detoxifying and purifying agent. It breaks down fatty, mucous and phlegm deposits within the body. It also oxidizes and thins the blood, which is important in preventing high blood pressure. Cider vinegar has been found to neutralize any toxic substances that enter the body. It neutralizes harmful bacteria that may be found in certain foods, promotes digestion, assimilation and elimination. [14] Toxic build-ups with the body can cause boils, blisters, acne, etc. Cider vinegar detoxifies and helps with the cleansing and clotting processes of the blood, by helping along the blood oxidation process. Cider vinegar can be taken alone or used in cooking. The best method of using apple cider vinegar is in its natural liquid form. Cider vinegar is thought to be beneficial in the treatment of high cholesterol, diabetes and many other diseases. [15]

MATERIALS AND METHODS

Animals: Thirty healthy male Wistar rats (about 180–200 g body weight) were purchased from the animal house facility in Assiut University, Egypt. A commercial balanced diet and tap water ad libitum were provided. The rats were randomly divided into three groups (10 rats each) as follows: Group 1, control rats received no treatment; Group 2, diabetic group; Group 3, diabetic rats were treated with vinegar (2ml/kg body weight diluted with distilled water at ratio 1:5) as a sole drinking source). At the end of the experimental period 30 days rats were sacrificed after overnight fasting.

Induction of Diabetes Mellitus: Diabetes was induced by intraperitoneal injection of streptozotocin (Sigma, St. Louis, Mo, USA) at a dose of 65 mg/kg body weight. Streptozotocin was dissolved in 0.1 M cold sodium citrate buffer, pH 4.5. After 18 h, animals with fasting blood glucose levels greater than 16.5 mmol/L were considered diabetic and then included in this study. [16] Fasting blood glucose was estimated by using one touch glucometer (Accu-Chek sensor of Roche Diagnostics, Germany).

Apple cider vinegar: ACV was supplied in the form of liquid 5% concentration obtained from Faculty of Agriculture, Sohag University, Egypt.

Biochemical markers: Lipid Profiles: Serum total cholesterol (TC), LDL-c, HDL-c and triacylglycerol (TG) were measured by enzymatic method using commercial kits. [17] Liver enzyme: ALT and AST were determined by the method of Reitman and Frankal. [18] The blood of each rat was collected in two tubes. The first tube was containing sodium fluoride to preserve glucose. The blood in the second tube was centrifuged at

3000 rpm for 20 minutes to obtain the serum, which is kept at -20 °C until analysis.

For light microscopic examination: Small pieces of the liver were immediately fixed for 24 hours in aqueous Bouin's solution and then preserved in 70% alcohol. The specimens were then dehydrated, cleared in terpineol and embedded in paraffin wax. Sections of 5µm thickness were stained with haematoxylin and eosin, [19] and then microscopically examined where photomicrographs were made as required.

For ultrastructural evaluation: Liver sections were cut into smaller pieces and fixed in 2.5% glutraldehyde for 4 hours and 2% paraformaldehyde in 0.1 M cacodylate buffer (pH 7.4). The samples were post-fixed in a buffered solution of 1% osmium tetroxide at 4ºC for one hour. This was followed by dehydration in ascending series of ethyl alcohol, clearing in two changes of propylene oxide, (5 min each), and embedding in Epon-epoxyresin. Semi-thin sections of 1 µm thickness were cut, picked up on glass slides, stained with toluidine blue and examined for general orientation under a bright field-light microscope. Specimens were then retrimmed to the detected region and ultra-thin sections, 60 nm thicknesses were cut and picked up on copper grades. Sections mounted on grids were double stained using uranyl acetate and lead citrate as was previously reported. [20]

Statistical analysis

Analysis of the data was done using Mean ± SD by SPSS version 17.0 .[21]

RESULTS

I- Bio chemical results: Blood glucose concentration increased from 142.32± 0.45 mg/dl in the control group to 192.13 ± 0.95 mg/dl in the diabetic group rats while in the vinegar treated group, blood glucose decreased to 152.43 ± 1.25 mg/ (Table I). In the vinegar treated group (Group III), serum lipid profile was estimated. TC, TT and LDL-c were significantly decreased ($P< 0.05$). HDL-c concentration showed significant increase compared to the diabetic group (Table II).

II- Light microscopy observations: Group I (Fig.1): The liver of the control rats showed the common characteristic lobular organization of the mammalian liver. Each lobule is formed of cords of hepatocytes radiating from a central vein. The hepatic cords are separated from each other by blood sinusoids lined with endothelial cells and interspersed by the Küpffer cells. The hepatic lobules are separated by loose connective tissue containing (at certain angles) the portal triads including branches of the portal vein, hepatic artery and a narrow bile ductule.

Group II (Fig.2&3): The liver of streptozotocin-treated rats exhibited dilatation and congestion of the central veins. Dilated congested central vein possessed irregular lining formed of damaged and detached endothelial cells. Intact and haemolysed blood cells were occupying the severely dilated central vein. There was an inflammatory infiltrate in the portal tract. The inflammatory infiltrate varied in intensity from one tract to another. Küpffer cells were actively proliferating markedly increased in size and number and some of them were pushed into the lumina of sinusoids. Fatty changes were observed in hepatocytes. **Group III** (Fig. 4): The histological structure of the liver of most diabetic rats treated with ACV revealed little pathological change when compared with diabetic rats only and partly restored their normal configuration. The hepatocytes were well organized and the cytoplasmic vacuolations disappeared. Most nuclei exhibited normal shape, spherical outline and were centrally located, except for a few pyknotic ones.

III- Ultrastructural observations: Group I (Fig. 5): The ultrastructure of the liver of the control rat is shown in Figures 5. The cytoplasmic organelles as well as the nuclei of the hepatocytes exhibited the normal ultrastructural appearance. The cytoplasm contained numerous mitochondria dispersed all over the cytoplasm. The mitochondria are spherical or ovoid in shape with well-developed cristae. The rough endoplasmic reticulum consisted of closely packed parallel and flattened cisternae studded with ribosomes. Considerable electron-dense glycogen rosettes or granules are clearly detected. The nucleus is spherical with a distinct nuclear envelope, and the nucleoplasm showed aggregations of euchromatin and heterochromatin materials. **Group II** (Figs. 6 & 7): The electron micrographs of the liver cells of rats treated with streptozotocin revealed marked cytopathological alterations. The mitochondria

underwent swelling with obvious condensation of their matrices by materials that displayed high electron density and most of them lost their cristae. There was abundant rough endoplasmic reticulum that was usually localized near the mitochondria. The cisternae of the rough endoplasmic reticulum were fragmented into smaller stacks. **Group III** (Figs 8): Electron microscopic examination of the liver of these rats revealed marked improvement of the cytoplasmic organelles following ACV treatment. The hepatic cells contained numerous mitochondria exhibiting an almost normal appearance. The hepatic cells revealed well developed rough endoplasmic reticulum in the form of parallel and flattened cisternae studded with ribosomes. Few lipid droplets were seen.

DISCUSSION

In this study it has been revealed that apple cider vinegar has considerable reducing effect on blood glucose levels in diabetic mice suggesting a useful outcome in reducing the risk diabetes due to its antihyperglycemic effect in diabetic rats. Treatment with experimental DM (induced by streptozotocin) with ACV caused a significant decrease in blood glucose level compared to the diabetic group. This could be due to the presence of active ingredients in vinegar (acetic acid and organic acids) that enhanced the secretion of insulin from beta cell. It was suggested that vinegar slows the rate of gastric emptying, delays carbohydrate absorption and improves satiety, [22] while acetic acid enhances the uptake of glucose from the blood stream into the tissues thereby normalizing the blood glucose level. [23] It is not known how vinegar alters blood glucose concentration, but several mechanisms have been proposed. Acetic acid in vinegar may interfere with the digestion of starch molecules thereby reducing the amount of glucose absorbed into the blood stream after meals. [24] Other studies revealed that consumption of ACV slowed the rise of blood sugar after a high carbohydrate vinegar breakfast. [25] Although the full mechanism of this effect is unclear, whether apple cider vinegar has any effect on insulin action in peripheral tissues, such as skeletal muscles and adipocytes any other probable mechanisms are unclear that can be further studied. More work is needed to determine the exact nature of the active ingredients.

Also in this study, serum TC, TT and LDL-c concentration significantly decreased in ACV treated group. These therapeutic benefits may be due to the possibility that acetic acid (active component in vinegar) reduced serum cholesterol via the inhibition of hepatic lipogenesis and the promotion of fecal bile acid excretion. [24] Acetic acid is converted to acetate in vitro, and acetate metabolism by tissues activates AMPK pathway, which plays a key role in lipid homeostasis. This may explain the lipid lowering effects of ingested acetic acid in animals. [27] While HDL-c concentration showed a significant increase compared to the diabetic group, serum TC decreased when 0.3% (w/w) acetic acid was administrated as a 19 days routine diet containing 1% cholesterol. [23] Similar findings were reported previously where vinegar caused a decrease in serum TC concentration in mice. [28] Apple cider vinegar improved the serum lipid profile in normal and diabetic rats by decreasing serum LDL, TG and increasing serum HDL. [29] In the present study, marked histological and ultrastructural alterations were observed in the liver of rats treated with streptozotocin. The histological changes included disorganized hepatic cords, fatty changes in the cytoplasm of the hepatocytes and mononuclear leucocytes, inflammatory cells infiltration, as well as diffuse proliferation of Küpffer cells. Similar observations have been reported previously in the liver of rats and rabbits treated with streptozotocin where there was erosion of the endothelial lining cells of the hepatic sinusoids with activation of the phagocytic Küpffer cells [30]. Similar observations were also obtained in the hepatic tissue of animals treated with alloxan [31], in the liver of hyperlipidemic rats [32], and in the pancreas of rats treated with streptozotocin [33]. These results are in agreement with previous reports.

In the present study the ultrastructural alterations were observed included, aggregation of opaque mitochondria, hepatocyte necrosis and hypertrophy of the rough endoplasmic reticulum. Many lysosomes, lipid droplets and active Küpffer cells were also noticed. Gradual

devastation of mitochondria was displayed; manifested obvious hypertrophy or swelling and condensation of their matrices. Similar mitochondrial injuries were obtained in the hepatocytes of hyperlipidemic rats. The mitochondria lost their internal ridges and matrices. Also the present results showed that the cisternae of RER were fragmented into smaller stacks in the liver of rats treated with streptozotocin, which are in accordance with previous reports [32] where distinct changes in the endoplasmic reticulum of the hepatocytes after treatment with diclofenac. ACV is commonly used as a traditional edible in Arabic societies. In prophetic medicine, Prophet Muhammad peace is upon him strongly recommended eating vinegar in the prophetic Hadeeth:" vinegar is the best edible". [34]

CONCLUSION

ACV has potential benefits in diabetic rats though ecreasing blood glucose, LDL-c and total cholesterol concentrations. Moreover, it caused increase of HDL-c. Using ACV may have a beneficial effect as a nutritional therapy in diabetic patients.

REFERENCES

1- Wild S, Roglic G, Green A, Sicree R, and King H (2004): Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care, 27(5):1047-1053.

2- Greenbaum C J and Harrison L C (2008): Diabetes: Translating research into practice. London: Informal Healthcare, P 1-2.

3- Ghosh S and Surawanshi S A (2001): Effect of Vinca rosea extracts in treatment of alloxan diabetes in male albina rats. Indian J. Exp. Biol., 8: 748 – 759.

4- Xuemei G, Hai- Lu, Jing G, Juliana C N and Peter C Y T (2012): White rice vinegar improves pancreatic beta- cell function and fatty liver in streptozotocin induced diabetic rats. Acta Diabetol., 49: 185 – 191.

5- Keith G, Tolman M D, Fonseca A V, Meng H and Dalpiaz A (2004): Narrative Review. Hepatobiliary disease in type 2 diabetes mellitus. Annals of Internal Medicine, 141:946 - 952.

6- Chattopadhyay S M, Ramanathan J D and Bhattacharya S (1997): Animal models in experimentals diabetes mellitus. Indian J. Exp. Bio., 35: 1141-1145.

7-Weir GC, Clore ET , Zmachinski CJ and Bonner Weir (1981): Islet secretion in a new experiment model for non-insulin dependent diabetes. Diabetes, 30: 590-595.

8- Arkkila P E, Koskinen P J, Kantola I M, Ronnemaa T, Seppanen E & Viikari J S (2001): Diabetic complications are associated with liver enzyme activities in people with type-1 diabetes. Diabetes Res. Clin. Pract., 52(2):113-8.

9- Dorr R T & Fritz W L(1980): Cancer chemotherapy. London, Kinapton, pp.632-7.

10- Magee P N & Swann P F (1969): Nitroso compounds. Br. Med. Bull., 25:240-4.

11- Merzouk H, Madani S, Chabane S D, Prost J, Bouchenak M & Belleville J (2000): Time course of changes in serum glucose, insulin, lipids and tissue lipase activities in macrosomic offspring of rats with Streptozotocin induced diabetes. Clin. Sci., 98(1):21-30.

12- Piyachaturawat P, Poprasit J & Glinsukon T (1990): Gastric mucosal secretions and lesions by different doses of Streptozotocin in rats. Toxicol. Let., 55:21-9.

13- Hlebowicz J, Darwiche G, Bjorgell O, Almer LO (2007): Effect of apple cider vinegar on delayed gastric emptying in patients with type 1 diabetes mellitus: a pilot study. BMC Gastroenterol., 7:46.

14- Vijayakumar C, Wolf-Hall CE (2002): Evaluation of household sanitizers for reducing levels of Escherichia coli on iceberg lettuce. J Food Prot., 65:1646-1650.

15- Wolman PG (1987): Management of patients using unproven regimens for arthritis. J Am Diet Assoc., 87:1211-1214.

16- Eddouks M, Maghrani M, and Michel J (2005): Hypoglycaemic effect of Triticum repens P. Beauv. in normal and diabetic rats, Journal of Ethnopharmacology, 102(2): 228–232.

17- Wieland H and Seidel D (1983): A Simple specific method for precipitation of low density lipoprotein. Journal of Lipid Research, 24 (7): 904-909.

18- Reitman S and Frankal S (1957): A calorimetric method for determination of serum AST. American Journal of Clinical Pathology, 18: 26.

19- Bancroft J D & Gamble M (2002): Theory and practice of histological techniques.5 Ed. Edinburgh. Churchill Livingstone Pub., pp 172-5, pp 593-620.

20- Dykstra M J, Mann P C, Elwell M R and Ching S V (2002): Suggested operating procedures (SOPs) for the preparation of electron microscopy samples for toxicology / pathology studies in a GLP environment. Toxicol. Pathol., 30:735-743.

21- Snedecor GW and Cochran WG (1967): Statistical methods. 6th Edition, the Iowa State University Press, Ames.

22- Ogawa N, Satsu H, Watanobe H, Fukay M, Tsukamoto Y, Miyamoto Y and Shimizu M (2000): Acetic acid suppresses the increase in disaccharides activity that occurs during culture of caco-2- cells. Journal of Nutrition, 130: 507- 513.

23- O'Keefe J H, Gheewaha N M, Joan M S and O'Keefe D (2008): Dietary strategies for improving post- prandial glucose, lipids, inflammation, and cardiovascular health. Journal of the American College of Cardiology, 51 (3): 249 – 255.

24- Fushimi T, Suruga K, Oshima Y, Fukiharu M, Tsukamoto Y and Goda T (2006): Dietary acetic reduced serum cholesterol and triacylglycerols in rats fed a cholesterol rich diet. British Journal of Nutrition, 95 (5): 916- 924.

25- Johnston C S, Kim C M and Buller A J (2004): Vinegar improves insulin sensitivity to a high carbohydrate meal in subjects with insulin resistance or type-2 diabetes mellitus. Diabetes Care, 27: 281-282.

26- McRac M P (2008): Vitamin C supplementation lowers serum low density lipoprotein cholesterol and triglycerides: a meta- analysis of 13 randomized controlled trials. Journal Chiropractic Medicine, 7 (2): 48- 58.

27- Yamashita H, Fujisaw K, Ito E, Idei S, Kawaguchi N, Kimoto M, Hiemori M And Tsuji H (2007): Improvement of obesity and glucose tolerance by acetate in Type-2 diabetic otsuka Long- Evans Tokushiwa Fatty (OLETF) rats. Bioscience Biotechnology and Biochemistry, 17: 123, 6- 1243.

28- Moon Y J, Choi D S, Oh S H, Song Y S and Cha Y S (2010): Effects of persimmon- vinegar on lipid and carnitine profiles in Mice. Food Science and Biotechnology, 19 (2): 343 – 348.

29- Saeed M K, Deng Y & Dai R (2008): Attenuation of Biochemical Parameters in Streptozotocin-induced Diabetic Rat by Oral Administration of Extracts and Fractions of Cephalotaxus sinensis. J. Clin. Biochem. Nutr., 42:21-8.

30- Merzouk H, Madani S, Chabane S D, Prost J, Bouchenak M & Belleville J (2000): Time course of changes in serum glucose, insulin, lipids and tissue lipase activities in macrosomic offspring of rats with Streptozotocin induced diabetes. Clin. Sci., 98(1):21-30.

31- Bopanna KN, Kannan J, Sushma G, Balaraman R and Rathod SP (1997): Antidiabetic and antihyperlipaemic effects of neem seed kernel powder on alloxan diabetic rabbits. Indian Journal of Pharmacology, 29(3): 162-167.

32- Sakr S M I (2010): Histological and ultrastructural studies on the effect of diclofenac sodium on the liver of hyperlipidemic male albino rats. Egypt. J. Zool., 54:77-96.

33- Prasad S K, Alka Kulshreshtha and Taj N Qureshi (2009): Antidiabetic activity of some herbal plants in Streptozotocin induced diabetic albino rat. Pakistan Journal of Nutrition, 8 (5): 551-557.

34- Muslim Alqushiry& Sahih Muslim (2004): Sayings of the Prophet. Berut, Hadeeth no. 2051, Asria library.

Table I: Mean ± standard deviation and ranges of blood glucose levels in the three groups (mg/dl).

Group	Levels of glucose mg/dl
Group I (Control)	142.32± 0.45
Group II (Diabetic)	192.13± 0.95*
Group III(treated with ACV)	152.43± 1.25 *

*P ≤ 0.05

Table II: Mean ± standard deviation and ranges of lipid levels in the three groups (mg/dl).

Group	Total Cholesterol (TC) mg/dl	Total Triacylglycerol (TT) mg/dl	HDL Cholesterol (HDL-c) mg/dl	LDL Cholesterol mg/dl
Group I (Control)	205.26 ± 0.85	39.38± 6.44	43.42±4.51	144.52±6.22 d
Group II (Diabetic)	262.43 ±1.37	61.12 ±2.61	36.11±1.32	215.11±1.04
Group III (treated with ACV)	219.4 ± 2.3d	54.53± 2.11	44.52±12.6	164.12±1.4

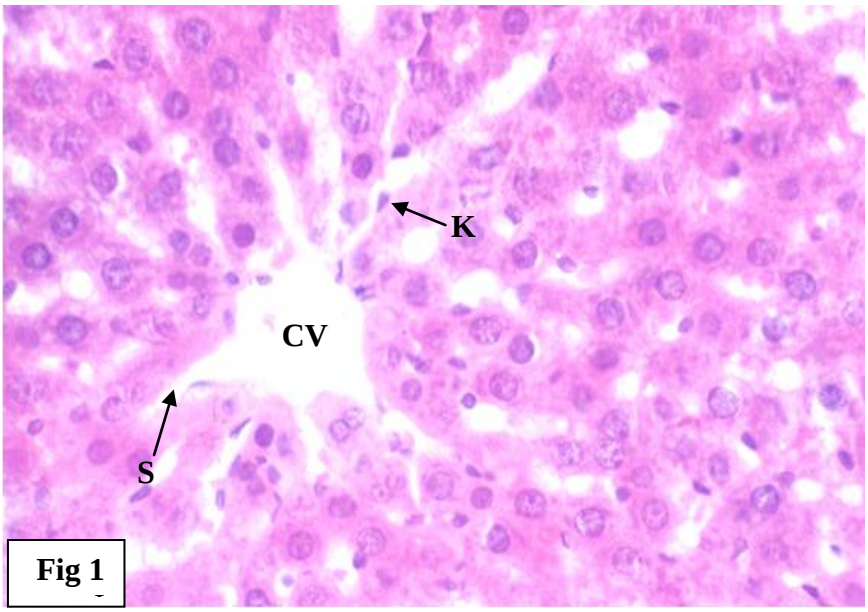
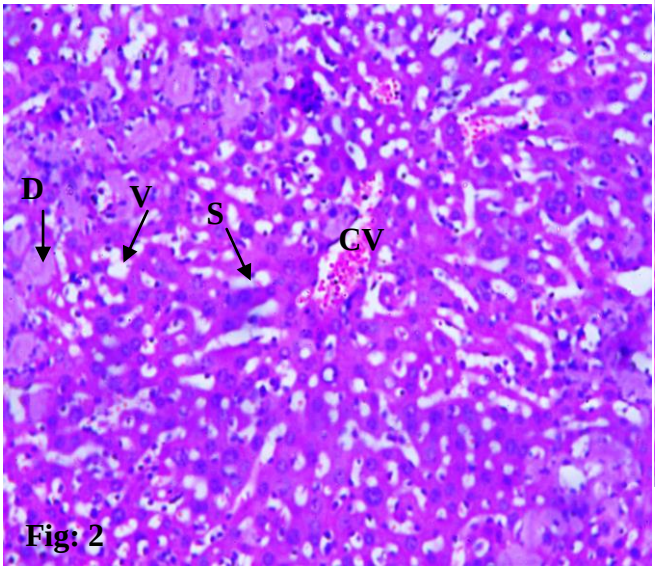
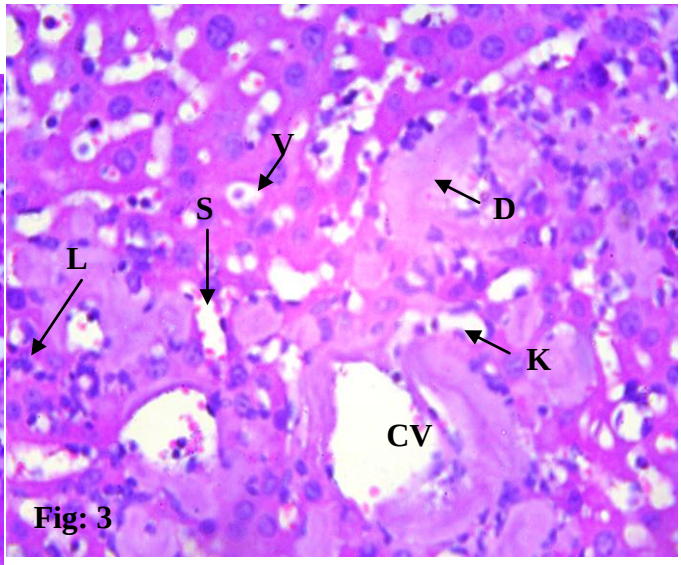


Figure. (1): Photomicrograph of liver section of the control group showing normal hepatic cords radiating from a central vein (CV), blood sinusoids (S) and Küpffer cells (K). (X. 400).





Figures (2 & 3): Photomicrographs of liver sections of diabetic rats after treatment with streptozotocin. Liver sections showing marked fatty change (V) of most of the hepatocytes, deteriorated nuclei of the hepatocytes and necrotic hepatocytes (areas of degeneration D) with loss of the regular arrangement of hepatic configuration and dilatation of some hepatic sinusoids (S). Dilated congested central vein (CV) with apparent erosion of its endothelial lining, besides its dilatation together with Kupffer cells (K) proliferation in between the hepatocytes and lymphocytic infiltration (L).

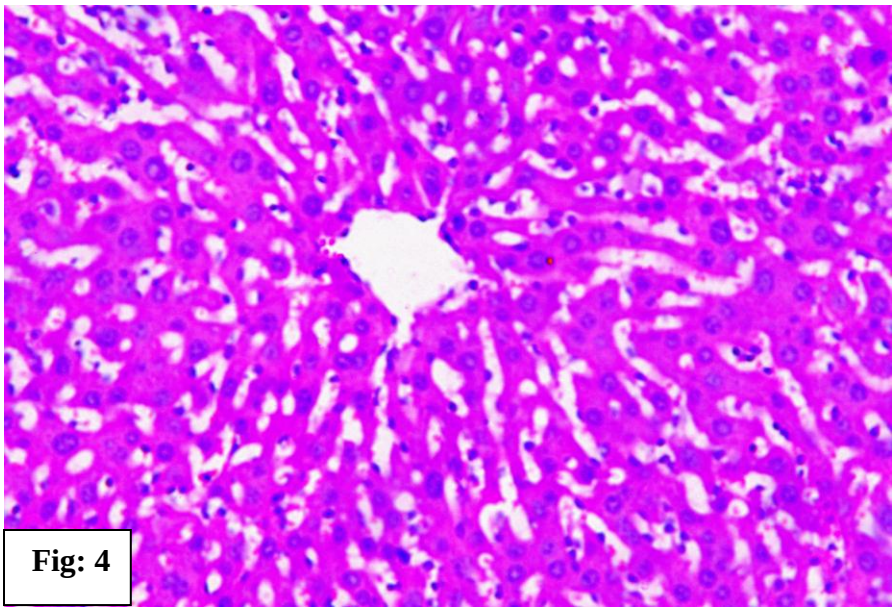
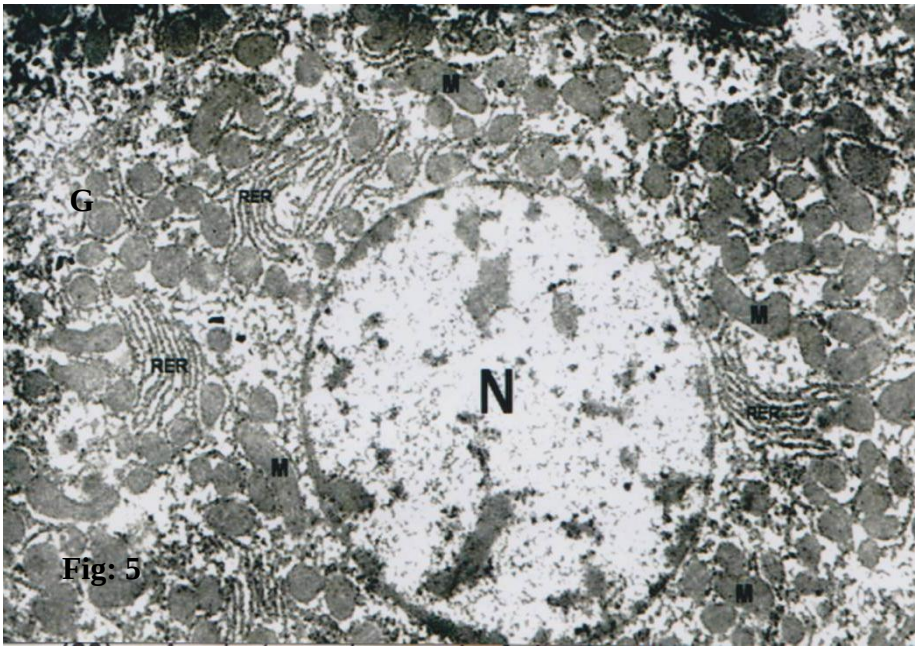
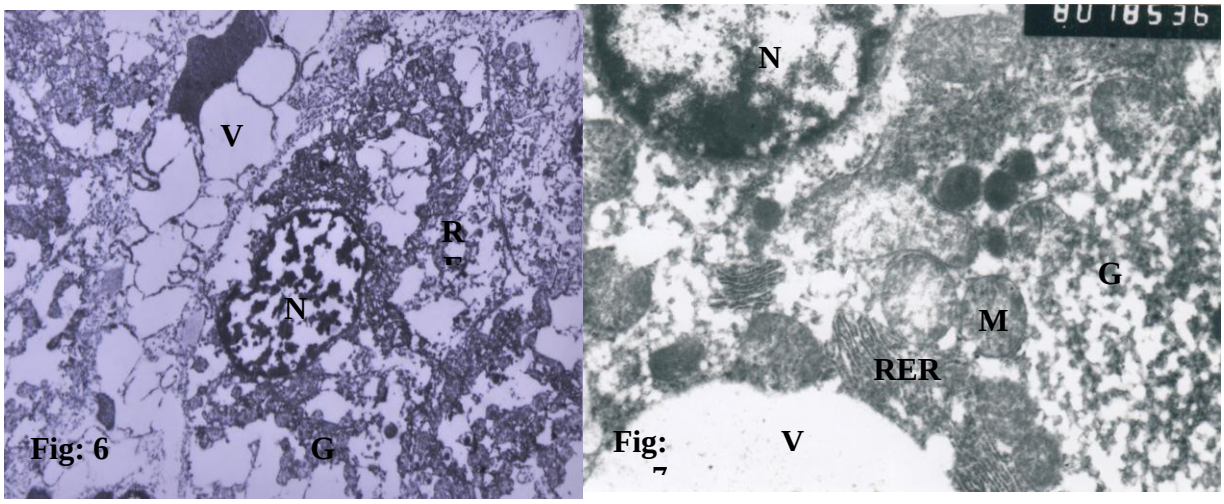


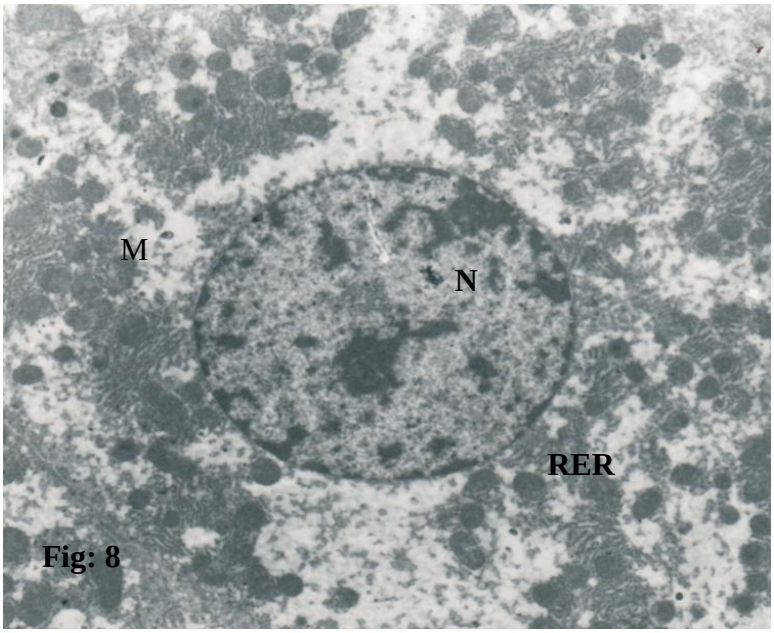
Figure (4): Photomicrograph of liver section of a diabetic rat treated daily with ACV showing that the hepatocytes partly restored their normal configuration (X. 200).



Figures 5: Electron micrograph of liver section of a control rat showing that: The cytoplasm of hepatocyte is occupied by rough endoplasmic reticulum (RER), mitochondria (M), glycogen deposits (G) and the nucleus (N). (X. 4000).



Figures (6&7): Electron micrographs of liver sections of diabetic rats showing hepatocyte with swollen mitochondria (M), most of them have lost their cristae, the nucleus (N) with irregular nuclear envelope, presence of large lipid droplets (V) and fragmented rough endoplasmic reticulum (RER). (X.3500)



Figures (8): Electron micrograph of liver section of diabetic rats treated daily with ACV showing a hepatocyte with mitochondria (M) in the form of rounded configuration, rough endoplasmic reticulum (RER) in the form of parallel cisternal localization near the nuclear envelope are scattered into the cytoplasm. The nucleus (N) with distinct regular nuclear envelope and nucleoplasm with euchromatin and heterochromatin. (X. 3600).