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Efficacy of Cinnamon in Ameliorating Streptozotocin-induced Diabetic Liver Injury in Rats: Histological and Biochemical Studies

***Mona R. Alshathly*[*], *Amal A. E. Ibrahim*[*,**] *and Amira H. El-Etriby*[*]**

[*]*Department of Biological Sciences, Faculty of Science, Northern Border University, Saudi Arabia.*
[**]*Department of Zoology, Faculty of Girls' for Arts, Education and Science, Ain Shams University, Cairo, Egypt.*

(Corresponding author: Mona Alshathly)
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ABSTRACT: Natural herbs are considered beneficial and useful in alternative medicine with increasing research interest on their role in treating diseases. This study was designed to investigate the efficacy of cinnamon as a therapeutic agent for controlling hyperglycaemia and protecting liver tissue in diabetic rats. Experimental animals were divided into treated and untreated groups. Results showed body and liver weights decreased after six weeks of streptozotocin injection. The administration of cinnamon revealed a significant bodyweight increase compared to diabetic untreated group and restored liver enzyme levels as well as a decrease in glucose levels. Histological observation showed marked protection against hepatocytes nuclear and degenerative changes induced by diabetes, which concorded with the biochemical results.

Key words: Diabetes - Rat Hepatocytes - Liver Functions – Histology – Cinnamon – Metformin

INTRODUCTION

Diabetes mellitus is the most challenging clinical problem as it results in many complications involving vital organs such as heart, kidney, testis and liver (Casqueiro *et al.,* 2012). In 2030, diabetes will be the seventh leading cause of morbidity and mortality in the world (Shanmugam *et al.,* 2009; Shaw*et al.,* 2010; Whiting *et al.,* 2011). An increase of diabetic cases in Saudi Arabia will continue in the future unless definitive controlling program is established (WHO, 2007; Alqurashi *et al.,* 2011; Al Zahidy *et al.,* 2017).

Diabetes occurs when the pancreas is no longer able to synthesize insulin and is classified into two major categories, type 1 and type 2. Type 2 diabetes (T2DM) is the most prevalent form of diabetes, accounting for 90 to 95 percent of cases (Li *et al.,* 2012; Morakinyo *et al.,* 2018), it is characterized by insulin resistance, progressive loss of pancreatic B-cell mass due to accumulation of amyloid peptide within islets cells (Jaikaran and Clark, 2001). Type 2 diabetes was known to lead to both micro and macrovascular complications that targeting arterial and nervous systems; retinopathy that may end in blindness, diabetic nephropathy and foot ulceration are among such complication (Kovac *et al.,* 2013; Mann and Truswell, 2017). Diethabits were found to plays an important role on incidence, severity, and management ofT2DM (American Diabetes Association, 2007). In diabetes, cells become unable to utilize glucose and/or the liver and skeletal muscles cannot store glycogen with sub sequent development of diabetes (Luis-Rodríguez *et al.,* 2012). Oxidative stress and increased production of reactive oxygen species result from hyperglycaemia (increased extracellular and intracellular glucose concentrations) that lead to marked decrease in body antioxidants (Lucchesi *et al.,* 2013).

Streptozotocin (STZ) was well known to induce diabetes in animal models (Srinivasan and Ramarao, 2007; Lenzen, 2008). Via β cell depletion due to apoptosis induced by oxidative stress (Bell *et al.,*1994; Le May *et al.,* 2006). Medical treatment of diabetes using common synthetic drugs; could have serious side effects such as hypoglycaemia (Shafiee *et al.,* 2012). Herbal medication was found to be preparations safer than traditional medicines beside it could be administered for a long period of time (Vinothapooshan and Sundar, 2010). Synthetic chemical drugs prescribed for treating diabetes has many side effects; therefore, there is a great need to search for an alternative safe natural agent from medicinal plants, herbs and spices (Ismail, 2014; Ibrahim and Al-Shathly, 2015). Since ancient times herbs were used for the treatment of diabetes and its complications (Plutzky, 2011). Cinnamonis a common spice that was added as a flavour in food all over the world including Arabian countries. Cinnamon is a genus of the Lauraceae family (Shan *et al.,* 2007). Volatile oils (1-4%) and cinnamaldehyde (60-80%), eugenol (up to 10%), trans cinnamic acid (5-10%), phenolic compound (4-10%) such as condensed tannins, catechins and proanthocyanidins; monoterpenes and sesquiterpenes (pinene); calcium-monoterpenes oxalate, gum, mucilage, resin, starch, sugars 118 and traces of coumarin (Jayaprakasha *et al.,* 2006; Qin *et al.,* 2010). Both *C. zeylanicum* and *C. cassia* (1-4%) was found to be an effective mimetic of insulin (Jarvill-Taylor *et al.,* 2001).

In vitro study using fat cells showed that the previous active compounds can increase glucose metabolism by 20 folds (Ismail, 2014; Reimer-Kirkham *et al.,* 2009). Ranasinghe *et al.* (2012) reviewed the medicinal properties of cinnamon and its beneficial effects in reducing glucose in diabetic patients (Ibrahim *et al.,* 2015). Cinnamon extracts were also reported to have hepatoprotective (Moselhy and Ali, 2009), antioxidant, anti-inflammatory, antispasmodic and anti-ulcerative effects (Rafehi *et al.,* 2012; Ozbayer *et al.,* 2014), anti-obesity (Couturier *et al.,* 2010), hypolipidemic (Shatwan *et al.,* 2013), antidiabetic (Lee *et al.,* 2013; Li *et al.,* 2013) and activities in man and experimental animals was shown *in vitro* and *in vivo* (Singh *et al.,* 2009; Kwon *et al.,* 2009).

In previous studies, enhancing insulin signalling is the main mechanism by which dried aqueous cinnamon extracts potentiated insulin-regulated glucose utilization (Qin *et al.,* 2003).Abdelwhab *et al*. (2010) reported the marked antioxidant and scavenging activity of some *Cinnamomum* species and its effect in suppressing lipid peroxidation, and reducing malondialdehyde (MDA; Vanschoonbeek *et al.,* 2006;Qin *et al.,* 2010).However, some species (*Cinnamomum zeylanicum*) has very low content of coumarins and can be used for long time without any side effects (EFSA, 2008; Abraham *et al.,* 2010; Hong *et al.,* 2013).

The aim of the present investigation based on previous data the main objectives of the present study were: 1. Evaluating the therapeutic effect of cinnamon in controlling hyperglycaemia in diabetic rats induced by STZ. 2. Study the efficacy of such treatment in protecting rat liver possible changes associated with STZ induced diabetes.

MATERIAL AND METHODS

A. Materials

Organization: The experiments were conducted at King Fahd Medical Research Center, Jeddah, Saudi Arabia.

Source of drugs. Streptozotocin was obtained from Sigma Aldrich Chemical Company, St. Louis, MO, USA. Metformin was purchased from Shanghai Shiguibao Medicine Co., Ltd., China. Cinnamon and ginger were purchased from commercial sources in Jeddah, Saudi Arabia.

a) Streptozotocin preparation and diabetes induction

The working solution was freshly prepared prior to use(within 15minutes) because of the instability of STZ in aqueous medium, by dissolving in 0.01 M sodium citrate buffer, pH 4.5(solution containing 150 mMNaCl) at a dose level of 60 mg/kg bw (Salemi *et al.,* 2016).

Induction of diabetes: T2DM was induced in 12 hours in fasted rats by intraperitoneal injection (1ml/rat) of previously prepared STZ. After the administration of STZ, the animals were given 5% sucrose solution overnight to prevent hypoglycaemia and enhance STZ entrance to Beta cells. Blood was collected from periorbital venous plexus and blood glucose was neared after three days of STZ injection then after one week to confirm persistence of hyperglycaemia. Blood glucose levels greater than 250 mg/dl (above 13.89 mmol/l were considered and indicator for successful induction ofT2DM and rats having such levels were selected for the study.

b) Preparation of aqueous extract of cinnamon

Cinnamon (*Cinnamomum cassia*) powder (200gm) was soaked in one litre of water over night, kept in at 60^{o}C in water bath for two hours, then filtered and centrifuged at 3000rpm for ten mints. the clear supernatant was completed to one litre with water, dosage for rat (20mg/day/rat) was calculated accord to that previously reported (Longe *et al.,* 2015).

B. Experimental Animals and study design

Male rats *Rattus rattus* Sprague-Dawley were purchased form Animal House, Faculty of Medicine, King Abdulaziz University (Jeddah, Saudi Arabia) after approval from the ethical committee and in accordance with the OECD guidelines for the proper care and use of laboratory animals. Twenty-four male rats, three months old, weighing 200-250 g at age 8-10 weeks, were kept in clean and dry plastic cages, with 12-hours light-dark cycle at 25±2°C and left for one week for acclimatization before the start of the experiment. Water was provided in graduated polyethylene bottles placed in metal grids in the up per part of the cages. The standard diet and drinking water were available *ad libitum* throughout the study. The rats were sorted into nine groups of six rats each. All doses were given daily for six weeks via gastric gavage.

G1: NC (control group): which received a vehicle citrate buffer and normal saline (Pierre *et al.,* 2012).

G2: D (T2DM non -treated diabetic group).

G3: D&C (diabetic+cinnamon).

G4: D & Metf. (diabetic+metformin) received metformin in the recommended dose, 500mg/km/bw for six weeks diabetic animals (Meng *et al.,* 2017).

G5: NC (Normal cinnamon group) received cinnamon orally.

Consumption of water and food. The consumption of water and food pellets was evaluated in all the animals. Food (1000g/week); daily food intake supplied for each rat 20gmand graduated bottles containing 500ml of water were placed in the cages. Water volume and food intake were determined and recorded twice weekly.

% Feed efficiency ratio (FER) = weight gain (g)/ feed intake (g) was calculated according to Adeyemi *et al.* (2015).

Body weights. Rats will individually weight by means of a sensitive balance. Whole body weights were record to the nearest 1 mg to determine weekly changes. The weight of each rat was recorded before the start of the experiment and then weekly during the experimental period for six weeks.

% body weight = final body weight – 1st week body weight/ final body weight × 100

Liver weights and liver weight index. Fresh liver from autopsied rats will blotted dry and subsequently weighted. Absolute liver weights will be recorded to the nearest 0.1 mg by using an electric balance. In order to obtain a more precise measure of the change in organ weights, liver weights were recorded relative to body weight, i.e.:

Liver index = Liver weight/body weight × 100

Blood sampling and biochemical analyses. Blood samples (1.5ml) were collected from 12 hours fasted anesthetized rats via retro-orbital capillary plexus using capillary tubes. after six weeks from the beginning of the experiment. Serum samples were directly frozen at -80°C till biochemical analyses. Estimation of blood glucose was carried out using enzymatic glucose kits from Human Gesellschaft für and Diagnostic mbH, Germany.

Percentage changes in blood glucose = 6th week blood glucose – 0-week blood glucose / 6th week blood glucose × 100.

Liver enzymes, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were determined according to Reitman and Frankel (1957). Alkaline phosphatase (ALP) was investigated according to Bowers and McComb (1966). The values were expressed as units/litre (U/l).

C. Histological examinations

Following blood collection, rats were scarified by cervical dislocation, and cut with sterile scalpel, liver was removed, washed in saline the largest lobe of the liver was cut, fixed by immersion in 10% neutral buffered formaldehyde (phosphate buffer pH 7.4) for 24 hours, and processed routinely for paraffin blocking Blocks were cut in 4µm, stained with Harris haematoxylin and counterstained in 1% aqueous eosin according to Bancroft and Gamble (2002). Sections were then mounted in DPX (GURRM BDH, UK) and examined by light microscope (Olympus, USA) connected to digital camera. Photographs from all groups were compared for histological changes.

D. Statistical analysis

Data were presented as mean±standard deviation (SD) and were analysed using one-way analysis of variance (ANOVA) by the Statistical Processor System Support "SPSS" for Windows software, version 16.0 (SPSS, Chicago, IL), to compare all the treated groups. Once a significant t-test was obtained followed by post hoc-least significant difference analysis (LSD); LSD comparisons were performed to assess the significance of the difference among various treated groups, with the significance level set to $P<0.05$.

RESULTS

A. Body weight, food and water intake investigations

Body weight increased after 1st week in diabetic control recorded 244.76±14.51 gm as compared with normal control (161.36±8.47 gm), as tabulated in (Table 1). Body weight slightly decreased after 6 weeks of STZ injection recorded 294.32±36.84 gm as compared with control (298.17±22.41 gm). A significantly increase in body weight in diabetic cinnamon as compared with normal control after 1st week of administration. After 6 weeks of STZ and C these values are significantly decreased as compared with normal control and normal diabetic, with a % change reached 45.77 and 15.85 respectively.

Table 1: Comparison total body weight in 1st and 6th weeks, percentage changes in total body weight (%), food intake (gm), food efficiency (%), water intake (ml) in different studied groups in different weeks versus control and diabetic control.

Groups	1st week body weight (gm)	6th week body weight (gm)	Body weight changes (%)	Food intake (gm)	Food efficiency (%)	Water intake (ml)
G1 (Normal Control -ve)	161.36±8.47	298.17±22.41	45.77±2.71	1201.87±119.77	0.071±0.013	986.17±473.60
G2 (Diabetic Control)	244.76±14.51	294.32±36.84	15.85±10.48	1559.88±245.82	0.014±0.012	1640.00±357.14
Significance	[1]P=0.0001	[1]P=0.829	[1]P=0.0001	[1]P=0.0001	[1]P=0.0001	[1]P=0.026
G3 (Diabetic Cinnamon)	210.70±10.14	271.03±42.42	21.07±9.41	1146.34±89.71	0.024±0.013	1105.83±498.71
Significance	[1]P=0.0001 [2]P=0.0001	[1]P=0.134 [2]P=0.197	[1]P=0.0001 [2]P 0.266	[1]P=0.535 [2]P =0.0001	[1]P=0.0001 [2]P =0.228	[1]P=0.676 [2]P =0.067
G4 (Diabetic+Metformin)	242.58±14.07	320.57±16.74	24.21±4.98	1347.44±169.18	0.025±0.008	772.33±446.09
Significance	[1]P=0.0001 [2]P=0.748	[1]P=0.215 [2]P=0.147	[1]P=0.0001 [2]P= 0.078	[1]P=0.108 [2]P =0.021	[1]P=0.0001 [2]P =0.223	[1]P=0.456 [2]P =0.004
G5 (Normal Cinnamon)	167.83±13.14	282.98±28.55	40.30±6.83	1033.85±113.20	0.067±0.015	867.17±478.41
Significance	[1]P=0.343	[1]P=0.398	[1]P=0.244	[1]P=0.065	[1]P=0.583	[1]P=0.678

Data were expressed as mean±standard deviation. [1]P: significance versus normal control; [2]P: significance versus

Food and water intake recorded increased values reached 1559.88 gm and 1640.00 ml respectively in diabetic control group (Table 1), as compared with normal control 0.071±0.013 and 986.17±473.60 respectively. Food and water intake decreased significantly in diabetic cinnamon group as compared with normal diabetic, and recorded food efficiency ratio 0.024±0.013 %. Food efficiency ratio recorded inhibited values reached 0.014±0.012 in diabetic control as compared with normal control.

Liver weight investigations. Liver weight of rats showed decreased levels in diabetic control, diabetic cinnamon, diabetic + metformin, normal cinnamon as compared with control levels (Table 2), with a liver weight index recorded 3.49, 3.04, 2.92, and 3.08 respectively.

Blood glucose levels. Levels of blood glucose showed significantly increased values after the 6th week of STZ injection reached 454.83±94.43 mg/dl as compared with normal control (110.33±13.91 mg/dl) as tabulated in (Table 3). Treatment with cinnamon and metformin, recorded decreased levels in blood glucose as compared with diabetic normal control group which proved their hypoglycaemic effect.

Table 2: Comparison of liver weight (gm) and liver weight index (%) in different studied groups in different weeks versus normal and diabetic control.

Groups	Liver weight	Liver weight index
G1 (Normal Control - ve)	11.34±1.43	3.91±0.50
G2 (Diabetic Control)	10.22±1.29 ^{1}P=0.136	3.49±0.38 ^{1}P=0.054
G3 (Diabetic Cinnamon)	8.26±1.65 ^{1}P=0.0001; ^{2}P =0.008	3.04±0.40 ^{1}P=0.0001; ^{2}P=0.035
G4 (Diabetic+Metformin)	9.40±1.27 ^{1}P=0.012; ^{2}P= 0.253	2.92±0.24 ^{1}P=0.0001; ^{2}P=0.008
G5 (Normal Cinnamon)	8.74±1.43 ^{1}P=0.001	3.08±0.31 ^{1}P=0.0001

Data were expressed as mean±standard deviation. ^{1}P: significance versus normal control; ^{2}P: significance versus diabetic control.

Table 3: Comparison blood glucose levels (mg/dl) in the initial and six weeks, and percentage changes of blood glucose in different studied groups versus normal and diabetic control.

Groups	0-week blood glucose (mg/dl)	6th week blood glucose (mg/dl)	Blood glucose changes (%)
G1 (Normal Control - ve)	77.00±9.38	110.33±13.91	28.91±14.23
G2 (Diabetic Control) Significance	84.67±9.20 ^{1}P=0.202	454.83±94.43 ^{1}P=0.0001	80.76±3.99 ^{1}P=0.0001
G4 (Diabetic Cinnamon) Significance	69.50±11.02 ^{1}P=0.212; ^{2}P=0.014	183.00±99.01 ^{1}P=0.223; ^{2}P=0.0001	53.51±21.04 ^{1}P=0.012; ^{2}P=0.006
G6 (Diabetic+Metformin) Significance	87.50±8.91 ^{1}P=0.083; ^{2}P=0.634	282.83±188.15 ^{1}P=0.005; ^{2}P=0.005	56.72±24.08 ^{1}P=0.005; ^{2}P=0.014
G8 (Normal Cinnamon) Significance	73.50±8.41 ^{1}P=0.557	118.67±9.54 ^{1}P=0.888	37.90±7.12 ^{1}P=0.345

Data were expressed as mean±standard deviation. ^{1}P: significance versus normal control;^{2}P: significance versus diabetic control.

Liver function test. Alanine aminotransferase and AST recorded increased values in diabetic rats as compared with normal control which an evidence of liver damage reached 88.50 U/l and 140.33U/l respectively. These values reversed after the treatment of diabetic rats with cinnamon as tabulated in (Table 4). Alkaline phosphatase showed slight decrease levels in diabetic compared to control group. Cinnamon administration showed increased levels for ALT and AST as compared to diabetic group.

Table 4: Comparison of liver function tests in different studied groups versus normal control and diabetic control.

Groups	Alanine aminotransferase (ALT) (U/l)	Aspartate aminotransferase (AST) (U/l)	Alkaline phosphatase (ALP) (U/l)
G1 (Normal Control - ve)	57.60±13.87	111.80±24.36	154.20±35.24
G2 (Diabetic Control) Significance	88.50±26.10 ^{1}P= 0.001	140.33±24.43 ^{1}P= 0.023	151.67±30.34 ^{1}P= 0.900
G3 (Diabetic Cinnamon) Significance	56.67±14.94 ^{1}P= 0.918; ^{2}P= 0.001	94.33±7.60 ^{1}P= 0.157; ^{2}P= 0.0001	115.67±14.47 ^{1}P= 0.060; ^{2}P= 0.065
G4 (Diabetic+Metformin) Significance	62.67±14.79 ^{1}P= 0.575; ^{2}P= 0.004	119.33±25.17 ^{1}P= 0.538; ^{2}P= 0.076	125.83±35.88 ^{1}P= 0.163; ^{2}P= 0.182
G5 (Normal Cinnamon) Significance	48.60±5.82 ^{1}P= 0.321	97.00±12.59 ^{1}P= 0.229	149.13±10.75 ^{1}P= 0.801

Data were expressed as mean±standard deviation. ^{1}P: significance versus normal control;^{2}P: significance versus diabetic control.

B. Histological investigations

Sections of liver from central vein and portal area regions ofcontrol rat revealed normal hepatocytes arranged in cell plated and separated by thin wall blood sinusoids, Cells have acidophilic cytoplasm and rounded vesicular nuclei. Few cells are nucleated. Portal area showed branches of portalvein, bile duct and hepatic artery. hepatocytes nearby are also normal. (Fig. 1a&C).

The hepatic tissue sections from rat treated with cinnamon alone showed active hepatocytes as indicated by the rounded vesicular nuclei with dispersed chromatin granules. Blood sinusoids are of normal appearances and they are lined by endothelial cells while Kupffer cell nuclei are occasionally seen. Bile duct and hepatic artery, hepatocytes are also normal with active nuclei (Fig. 1b&d).

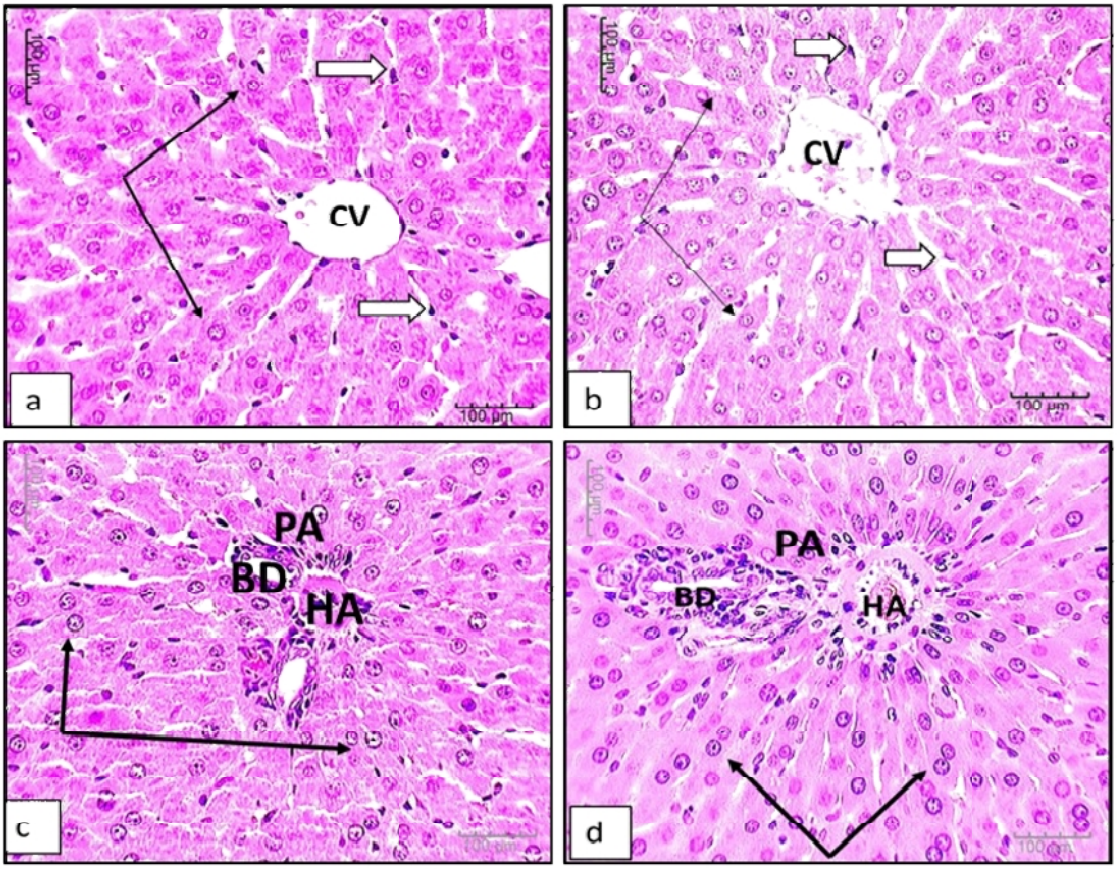

Fig. 1. Sections in rat liver at central vein (CV) and portal area (PA) region stained by H&E to show: G1: control (a&c). Showing hepatocyte arranged as cell plates (thin black arrows) separated by thin wall blood sinusoids lined with endothelial cells with few occasionally prominent Von Kupffer cell nuclei (white arrows). The cells have acidophilic cytoplasm and rounded vesicular nuclei with prominent nucleoli. Portal area contains branches of bile duct (BD), portal vein(PV) or hepatic artery (HA).G2: Cinnamon:(b&d). Showing normal hepatocytes with active vesicular nuclei (thin black arrows). Hepatocytes cell plates are separated by thin sinusoids lined with endothelial cells and von Kupffer cell nuclei are occasionally seen (white arrows).(Mag. X400 bar=100µ).

In diabetic group, hepatic tissue showed smaller hepatocytes with ill-defined outlines compared to control. Most nuclei exhibited pyknosis (small dark nuclei), some hepatocytes are binucleated or contain enlarged size (karyomegaly). Inflammatory cells could be seen aggregated at the site of necrotic hepatocytes, blood sinusoids are dilated with increased prominence of Kupffer cells (Fig. 2 a&d).

Liver sections from diabetic rats treated cinnamon (DC) revealed preservation of normal hepatocytes structure with well-defined outlines and large vesicular nuclei with dispersed chromatin (Fig. 2b&e). Binucleated cells are frequently seen, few cells still showed smaller dark pyknotic nuclei as compared with diabetic group. Blood sinusoids appeared normal with prominent Kupffer cells. Nevertheless, some portal veins showing dilatation and stuffed with R.B.Cs. (Fig. 2c&f).

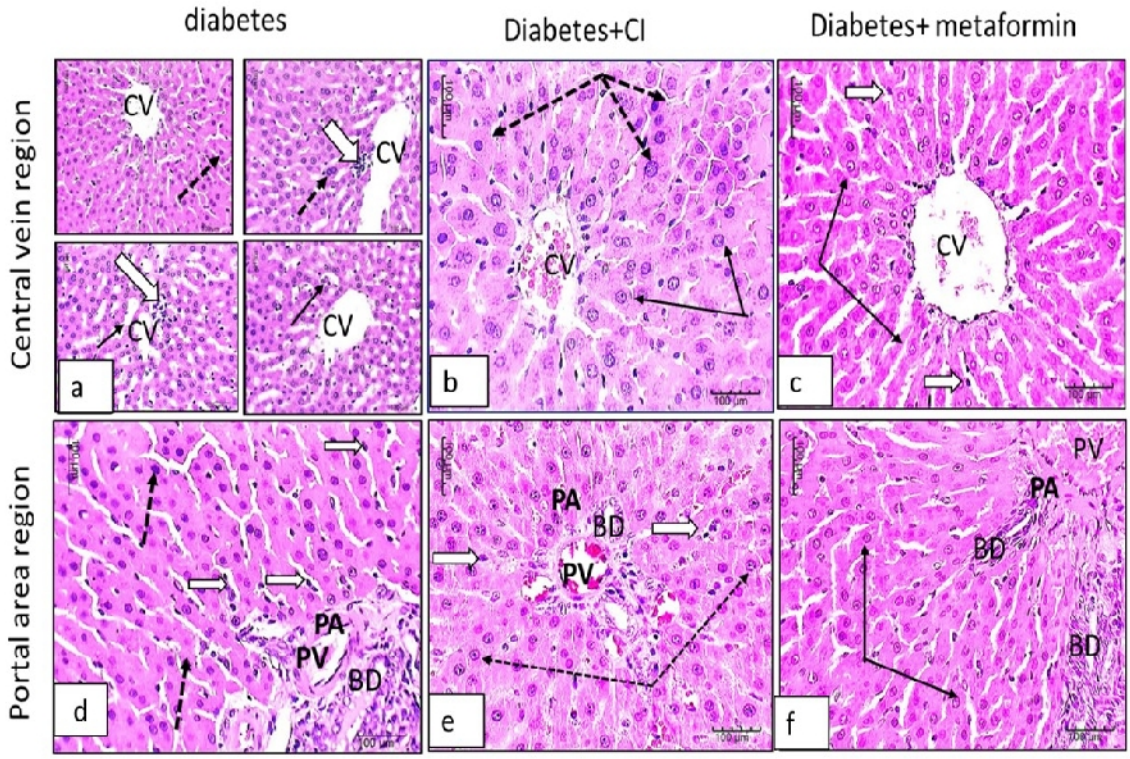

Fig. 2. Photomicrographs of sections from rat liver at central vein (CV) and portal area (PA) regions stained by H&E to show: G3: diabetic group (a&d). Sections from 4 animals showing that hepatocytes are smaller than control with ill-defined outlines compared to control. Nuclear changes (dotted arrows) are the most prominent features (smaller and pyknotic–binucleation–or increase chromatin density). Aggregation of inflammatory cells near the central veins marked the presence of necrotic hepatocytes (white arrows) are observed. Dilated sinusoids with prominent Von Kupffer cells could be seen (thin black arrows). G4: Diabetes+Cinnamon (b&e). Sections appeared to protect against diabetes induced changes; liver architecture is more or less similar to control with few residual degenerated hepatocytes having dark acidophilic cytoplasm and small pyknotic nuclei (dotted arrows). Most hepatocytes appeared normal with rounded vesicular nuclei having dispersed chromatin. Some are bi-nucleated (black arrows). Blood sinusoids are normal and lined by endothelial cells (black arrows). Large blood vessels are slightly congested. G4: Diabetes+metformin (c&f). Marked improvement of diabetic induced changes was observed; hepatocytes at both central vein and portal area region appeared normal with acidophilic cytoplasm and rounded vesicular active nuclei (black arrows). Sinusoids between the cells are not dilated and showed normal cell lining. (Mag. X400 bar= 100µ).

DISCUSSION

The present results reported decrease in body and liver weight in diabetic rats. This data was reversed by the administration of cinnamon. This comes in accordance with many previous studies. This decrease was attributed to tissue proteins wasting and increased muscle loss (Shirwaikar *et al.,* 2004). Administration of cinnamon result in significant recovery in body weight. This may be due to the fact that of cinnamon controlling hyperglycaemic status and improve insulin secretion which both decrease protein degradation (Al-Amin *et al.,* 2006; Rekha *et al.,* 2010). The dose of1-6 g/day was proved to be safe and without any side effect (Leach and Kumar, 2012).

The mechanism by which STZ in ducehyperglycaemia was discussed in details by its action as a protein alkylating agent (Wang and Gleichmann, 1998) or via induction of nitrous oxide (Szkudelski, 2001), because STZ enters the cell via GLUT2, the toxic action is not specific to β cells and can cause damage to other tissue including the liver and kidney (Imparl-Radosevich *et al.,* 1998; Lenzen, 2008).

Ramakrishna *et al.* (2015) reported that complications in diabetes are mainly due to increased free radical production, reduced antioxidant defence responses that give rise to increased oxidative stress (Halliwell and Gutteridge, 1990).

Cinnamon administration lead to decrease glucose levels in diabetic rats. Many studies reported that cinnamon have hypoglycaemic effect by reducing glucose levels in blood in diabetic rats. This may be related to that herbal aqueous extract has the ability to increase glucose uptake and glycogen synthesis and to increase phosphorylation of the insulin receptor (Khan *et al.,* 2003).

In an *in vitro* assay of the insulin-dependent utilization of glucose the aqueous extracts of cinnamon were reported to potentiate insulin activity >20 fold (Broadhurst *et al.,* 2000). Stimulation of glucose uptake, autophosphorylation of the insulin receptor occurred after administration of water-soluble cinnamon compounds (Imparl-Radosevich *et al.,* 1998; Qin *et al.,* 2003; Cao *et al.,* 2007).

The active component cinnamaldehyde was suggested to be responsible for glucose metabolism modulation (Ulbricht *et al.,* 2011). This active component was thought to be responsible for promoting insulin release, enhancing insulin sensitivity, increasing insulin disposal (Sheng *et al.,* 2008). In animal studies, aqueous cinnamon extracts have been shown to improve lipid and glucose metabolism (Anand *et al.,* 2010).

Extracts of cinnamon also activated glycogen synthase and increased glucose uptake (Imparl-Radosevich *et al.,* 1998; Jarvill-Taylor *et al.,* 2001). Extracts of cinnamon increased insulin sensitivity. Khan *et al.* (2003) through activated insulin receptor kinase leading to maximal phosphorylation of the insulin receptor (Jarvill-Taylor *et al.,* 2001). Cinnamon extracts of also function as potent antioxidants, which antagonized oxidative stress and scavenge free radicles that accumulate in hyperglycaemicstatus. Dhuley (1999) also showed that cinnamon exerted antioxidant activity in hyperlipidaemia rats. Ranasinghe *et al.* (2012) demonstrate that cinnamon administration to healthy animals provide better ability to handle a glucosevia potentiating insulin-regulated glucose utilization and enhancing insulin signalling (Imparl-Radosevich *et al.,* 1998; Qin *et al.,* 2003).

Liver is the main organ responsible for drug metabolism and appears to be the sensitive target site for substances modulating biotransformation (Gu and Manautou, 2012). Serum ALT, which is a widely available serum marker of liver damage, is elevated in about 20% of children and adolescents with T2DM, and in most cases this is attributable to non-alcoholic fatty liver disease (Pinhas-Hamiel and Zeitler, 2007). Westerbacka *et al.* (2004), had demonstrated that ALT was closely associated with liver fat unlike AST and gamma glutamyl transferase (GGT) and hence, ALT is used as a surrogate marker for many epidemiological studies (Schindhelm *et al.,* 2006). Saligram *et al.* (2012) showed a high incidence of elevated ALT in a well-defined population of newly diagnosed people with T2DM.Alanine aminotransferase, AST and GGT levels exceeding the upper limit of normal were present in T2DM (Forlani *et al.,* 2008). Also, Ko *et al.* (2015) found that elevated levels of ALT and GGT (positive correlation) and the lowest levels of AST/ALT (negative correlation) are associated with a higher prevalence for T2DM and prediabetes.

In the present study, cinnamon extract caused restored levels of the activity of AST and ALT which pointed to its ability to reduce hepatic damage (Pierre *et al.,* 2012). In clinical field, elevated values of ALT and AST is indicative of liver damage (Giboney, 2005). Increased level of ALP has been also attributed to the damaged structural integrity of hepatic cells (Pierre *et al.,* 2012).

The histopathological examination of diabetic rats injected with STZ revealed many histological alterations that was most probably due to oxidative stress are cell injury, *i.e.* increase lipid peroxidation, decreased antioxidant enzyme system, and accumulation of free radicles (Jakus, 2000; Bilal *et al.,* 2016). Congestion, necrosis of the hepatic cells, degeneration, vacuolation in hepatic cells were previously described in association with diabetic status (AL-Shaikh, 2010; Mhammad *et al.,* 2015).

In diabetic groups treated with cinnamon hepatic lobules appear more or less like normal controlhepatic tissue which is similar to the results of Mhammad *et al.* (2015). Phytoconstituents that found in Cinnamon such as flavonoids, triterpenoids, saponins and alkaloids (Shihabudeen *et al.,* 2011) are possessing antioxidant activity that can play a role as hepato protective agents. Cinnamon is reported to be a natural insulin sensitizer (Dugoua *et al.,* 2007). Cinnamon is an insulin sensitizer was proved both *in vitro* and *in vivo* animal studies (Talpur *et al.,* 2005; Kim *et al.,* 2006). Polyphenols of cinnamon have been identified as up-regulators of mouse adipocyte insulin receptors (Kim *et al.,* 2006; Cao *et al.,* 2007). Peng *et al.* (2008) formation of advanced glycation end products in bovine serum albumin was inhibited by cinnamon polyphenols.

The histological studies authenticated with the biochemical investigations, proving that cinnamon have the ability to protect liver tissue in diabetic rats. Cinnamon acts as antioxidant against STZ induced hepatocytes damage.

CONCLUSION

Cinnamon is well known for its antioxidant effect beside its activity in controlling diabetes. Histological supported by biochemical investigation proved its hepatoprotective effect against STZ induced diabetic changes in rat liver. Further studies will be done to identify its exact mechanism regarding controlling blood glucose level and antagonizing oxidative stress impact on liver tissue.

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