

Modulation of Pancreatic β -Cells and Antioxidant Status by Cinnamon in Type 2 Diabetic Rats

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Abstract

The effect of *Cinnamomum cassia* was investigated in a non-obese type 2 diabetic rat model to explore possible cellular mechanism(s) of its *antidiabetic* activity. Non-obese type 2 diabetes was developed in rats by injecting 60 mg/kg streptozotocin (STZ) along with 120 mg/kg nicotinamide (NA) in adult Wistar rats. Type 2 diabetes was confirmed after 14 days of STZ-NA induction. Diabetic rats were treated with cinnamon extract at 250 mg/kg (Cn250) or 500 mg/kg dose (Cn500) and the positive control, glibenclamide (5 mg/kg) for 28 days. After treatment, blood glucose, serum insulin, HbA1c and antioxidant status were measured. Additionally, insulin and glucagon immunostaining was performed in pancreatic sections. Moderate hyperglycemia and β -cells dysfunction was found in this diabetic model rats. Interestingly, cinnamon extract treatment lowered the elevated blood glucose (Cn250: 269.8 ± 18.5 mg/dl vs. 322.5 ± 12.5 mg/dl, $p < 0.01$; Cn500: 195.2 ± 22.5 mg/dl vs. 322.5 ± 12.5 mg/dl, $p < 0.001$) and enhanced serum insulin levels (Cn250: 0.28 ± 0.032 ng/ml vs. 0.195 ± 0.03 ng/ml; Cn500: 0.45 ± 0.035 ng/ml vs. 0.195 ± 0.03 ng/ml, $p < 0.001$) in a dose-dependent manner. In diabetic rats, a drastic decrease of β -cell function was observed while cinnamon extract treatment elevated the β -cell function significantly ($p < 0.05$) in Cn500 treated group. Qualitative and quantitative improvement of pancreatic β -cell morphology was found in cinnamon-treated rats. Total antioxidant status was improved by cinnamon extract suggesting its antioxidant potential in Cn500 dose significantly (1.83 ± 0.05 mmol/L vs. 1.49 ± 0.09 mmol/L, $p < 0.05$). Glibenclamide showed similar action to that of 500 mg/kg cinnamon in all the assays. Collectively, the data suggest that cinnamon exerts antidiabetic activity by increasing insulin secretion, modulating β -cell function, and improving antioxidant status in non-obese type 2 diabetic model rats.

Keywords: *Cinnamomum cassia*; β -Cell function; Immunohistochemistry; Antioxidant

Abbreviations: ALT: Alanine Transaminase; AST: Aspartate Transaminase; Cn: *Cinnamomum cassia*; DAPI: 4',6-Diamidino-2-Phenylindole; ELISA: Enzyme Linked Immunosorbant Assay; GB: Glibenclamide; HbA1c: Glycated Haemoglobin; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; SEM: Standard Error of Mean; SPSS: Statistical Package for Social Science; STZ: Streptozotocin

Introduction

Traditional medicines are used for the treatment of various ailments all over the world [1]. In the past few years, there has been a growing interest in the herbal products/nutraceuticals for the management and care of diabetes both in developing and developed countries due to their natural origin and comparatively less side effects [2-4]. *Cinnamomum cassia*, commonly known as Chinese cinnamon or cassia bark has been used in several cultures for centuries as a spice and traditional herbal medicine [5]. According to the classification by Scicchitano et al. [6] cinnamon falls in traditional herbal nutraceutical category. The bark of cinnamon owes excellent pharmacological properties such as antioxidant [7], antimicrobial [8], anti-diarrheal [9] and antidiabetic [10]. In Ayurveda, cinnamon is used as a remedy for diabetes, indigestion, and colds [11-14]. In Indo-Pak region, people use cinnamon for flavoring and for the management of type 2 diabetes. In this regard, animal and human studies have been done; however, no clear-cut conclusion has been made. Khan et al. [15] reported that cinnamon is effective in the reduction of fasting blood glucose level and lipid profile in diabetic condition in human study [15]. Mang et al. [16] found a significant decrease in fasting glucose but no significant changes were observed either in lipid profile or in HbA1c after cinnamon intake. A clinical trial in type 2 diabetes patients has shown

that a daily intake of 2 g cinnamon for 12 weeks can reduce the levels of HbA1c, systolic blood pressure and diastolic blood pressure [17]. Ranasinghe et al. [18] reported beneficial effects including attenuation of diabetes associated weight loss, reduction of fasting blood glucose and HbA1c, and upregulation of circulating insulin levels. To the contrary, no effect of cinnamon was found against fasting blood glucose, HbA1c, and lipid profile [19]. In a recent report by Leach and Kumar [20] no significant effect on fasting or postprandial glucose, HbA1c and serum insulin was found. Recent reports, preclinical studies, and clinical trials demonstrate that cinnamon has potential to lower blood glucose in hyperglycemic conditions [21-24]. In a recent clinical study, Jain et al. [22] reported that cinnamon intervention has significant effects on metabolic profile in Asian Indians. In a preclinical study in db/db mice, cinnamon extract showed anti-diabetic effects by lowering blood glucose [23]. In another clinical study, Sahib [24] reported anti-diabetic and antioxidative effects of cinnamon in type 2 diabetic Iraqi patients. Allen et al. [25] showed effective role of cinnamon on fasting blood glucose, total cholesterol, triglycerides

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and LDL in a systemic review and meta-analysis. Cinnamon exhibits plasma glucose lowering effects reported by Pham et al. [26] and Davis et al. [27] in their meta-analysis. To the contrary, Blevins et al. [28] stated that cinnamon has no effect on plasma glucose and lipid levels in type 2 diabetic subjects in US population. The effects of cinnamon vary in different population as reported by Blevins et al. [28]. Therefore, controversies still exist and moreover, either it is effective on β -cell dysfunction or insulin resistance in type 2 diabetes is not clear. The mechanism of anti-diabetic effect of *Cinnamomum cassia* extract has been explored to some extent and β -cells regeneration was postulated one of the possible mechanisms [29]. However, these studies lack the direct evidence of pancreatic β -cells modulation. The present study was designed to explore pancreatic β -cells modulation by cinnamon extract in nicotinamide-streptozotocin-induced non-obese type 2 diabetic rats by biochemical, hormonal and immunohistochemical method for triple staining of insulin, glucagon and nuclei.

Methods and Materials

Streptozotocin (STZ) and glibenclamide were obtained from Sigma (St. Louis, MO, USA). Rat HbA1c, creatinine and insulin ELISA kits from Crystal chemicals (Downers Grove, USA). Triglycerides, total cholesterol, HDL-cholesterol and total antioxidant status assay kits from Randox (Crumlin, UK). Rat ultra-sensitive insulin ELISA kit was from Crystal Chem Inc. (IL, USA). Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) test strips were purchased from Roche Diagnostics (Mannheim, Germany). Primary antibody for insulin (guinea-pig polyclonal to insulin) was purchased from Abcam (Cambridge, UK), and glucagon (Clone K79bB10) from Sigma. The fluorescent secondary antibodies, Texas Red-donkey anti-guinea-pig IgG and Cy2-donkey anti-mouse IgG were from Jackson ImmunoResearch (Baltimore, PA, USA). 4',6-Diamidino-2-phenylindole (DAPI) was obtained from Wako Pure Chemical (Osaka, Japan).

Preparation of *Cinnamomum cassia* extracts

Bark of *Cinnamomum cassia* (2 kg) was purchased from a local market of Karachi, Pakistan. The bark was grounded into powder form and then soaked into hot water for 48 hours. Extract was evaporated to dryness under vacuum by using rotary evaporator. Finally, the crude extract was freeze dried to give the experimental extract (124 g). The extract was dissolved in distilled water before administration to rats.

Animals and induction of diabetes

Wistar rats (180-250 g) of both sexes from Animal House of International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, were used throughout the experiment after ethical clearance from the Animal Use Committee of the ICCBS (Animal study protocol number: 2016-0031.). The animals were housed in clean cages under a constant 12-hour light-dark cycle with free access to water and food. After 12-14 hours of fasting, 120 mg nicotinamide (NA) was administered intraperitoneally and 60 mg/kg solution of streptozotocin (STZ) in 1.0 ml citrate buffer (0.1 M, pH 4.5) was intravenously injected to these rats. Non-diabetic rats were injected with vehicle only. After 14 days of STZ-NA induction, fasting blood glucose levels were determined using a glucometer. Rats having fasting blood glucose above 15 mM were selected for the study.

Chronic extract treatment

The experimental rats were divided into five groups. Group I: non-diabetic control rats; Group II: untreated diabetic rats (Db); Group III:

250 mg/kg *C. cassia*-treated diabetic rats (Cn250); Group IV: 500 mg/kg *C. cassia*-treated diabetic rats (Cn250); Group V: glibenclamide-treated diabetic rats (GB); The *C. cassia* was fed orally once daily for 28 days. Non-diabetic control rats and untreated diabetic rats received equal volume of water, while glibenclamide (5 mg/kg) was given orally once daily to the GB-treated diabetic rats.

Collection of blood samples and estimation of biochemical parameters

For the purpose of biochemical estimation, blood samples were collected from the tail vein on day 1 after overnight fasting. Finally after 28 days of extract treatment, overnight fasted rats were sacrificed and blood was collected for biochemical parameters. HbA1c was measured from EDTA blood by rat HbA1c assay kit. Remaining blood samples were allowed to clot and serum was separated by centrifugation. Serum samples were stored at -40°C for biochemical assay.

Estimation of serum insulin was performed by ELISA. Serum triglyceride was measured by enzymatic colorimetric method and total cholesterol and HDL-cholesterol were measured by cholesterol oxidase/peroxidase method. Total antioxidant status was measured using ABTS[®] substrate assay kit. Serum creatinine was measured by a rat creatinine assay kit according to the manufacturer's protocol. Serum ALT/GPT and AST/GOT were measured by standard techniques using the Reflotron[®] Plus Dry Chemistry Analyzer.

Assessment of β -cell function

β -Cell function (HOMA-B%) was measured from fasting glucose (mM) and fasting serum insulin (pM) concentration by homeostasis model assessment (HOMA) using HOMA-CIGMA software, where HOMA-B% indicates β -cell function [30].

Immunohistochemistry

Insulin and glucagon immunostaining was performed as described earlier [31,32].

Toxicity evaluation

The *C. cassia* extract was evaluated for toxicity in rats. Single oral administration of cinnamon extract at different doses (500, 1000, and 2000 mg/kg body weight) was given to experimental groups. Mortality and general behavior of the animals were observed continuously for the initial 4-h and intermittently for the next 6-h and then again at 24-, 48- and 72-h following extract administration. Serum creatinine, alanine aminotransferase (ALT/GPT) and aspartate aminotransferase (AST/GOT) were also evaluated to check the toxicity to kidney and liver, respectively.

Statistical Analysis

All statistical analyses were performed by using the SPSS (Statistical Package for Social Science) package for Windows version 16.0 (SPSS, Inc., Chicago, IL, USA). All values are expressed as mean \pm SEM. The significance of the differences among the mean values was calculated by one-way Analysis of Variance (one-way ANOVA) with Dunnett's and Bonferroni post-hoc tests. *P*-values less than 0.05 (*p*<0.05) were considered as statistically significant.

Results

Effects of cinnamon extract on body weight of the experimental rats

The gradual reduction of body weight was observed during the

experimental period in the untreated diabetic rats (Figure 1). The cinnamon extract 250 and 500 mg/kg dose increased the body weights of diabetic rats; however, significant body weight gain was observed only in 500 mg/kg dose after 14 days of treatment when compared with untreated diabetic rats (193.1 ± 6.7 g vs. 166.7 ± 10.3 g). GB treatment also improved the body weight. In sharp contrast, the non-diabetic control rats gained their body weights gradually during the experimental period.

Effect of cinnamon extract on fasting blood glucose in the diabetic rats

After 14 days of STZ-induction, the fasting blood glucose level was increased significantly compared to the non-diabetic control group (Figure 2). Interestingly, when the diabetic rats were treated with cinnamon extract, the fasting blood glucose levels were significantly ($p < 0.01$) reduced (269.8 ± 18.5 mg/dl vs. 322.5 ± 12.5 mg/dl) in Cn250-treated group. Cn500-treated group (195.2 ± 22.5 mg/dl vs. 322.5 ± 12.5 mg/dl) and standard drug glibenclamide (172.7 ± 11.1 mg/dl vs. 322.5 ± 12.5 mg/dl) exhibited more significant ($p < 0.001$) effect on lowering blood glucose when compared with untreated diabetic rats.

Effect of cinnamon extract on serum insulin in the diabetic rats

The fasting serum insulin level was decreased dramatically in the diabetic rats compared to control rats (Figure 3). Moderate increase of serum insulin was found in Cn250-treated diabetic rats and significant increase (0.45 ± 0.03 ng/ml vs. 0.19 ± 0.03 ng/ml) of serum insulin was found in Cn500-treated diabetic rats. The standard drug glibenclamide also increased the serum insulin level significantly.

Effect of cinnamon extract on β -cell function on diabetic rats

The pancreatic β -cell function was decreased dramatically in the diabetic rats compared to control rats (Figure 4). However, mild increase of β -cell function was found in Cn250-treated diabetic rats and significant ($p < 0.05$) increase in β -cell function was found in Cn500-

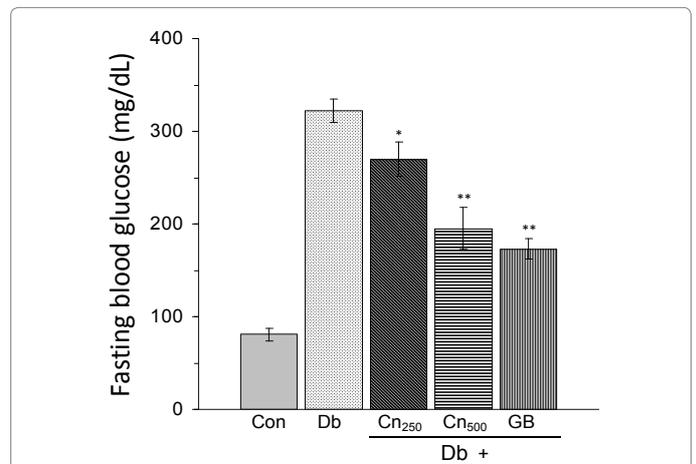


Figure 2: Effect of cinnamon extract on fasting blood glucose in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, ** $P < 0.01$, vs. Db group.

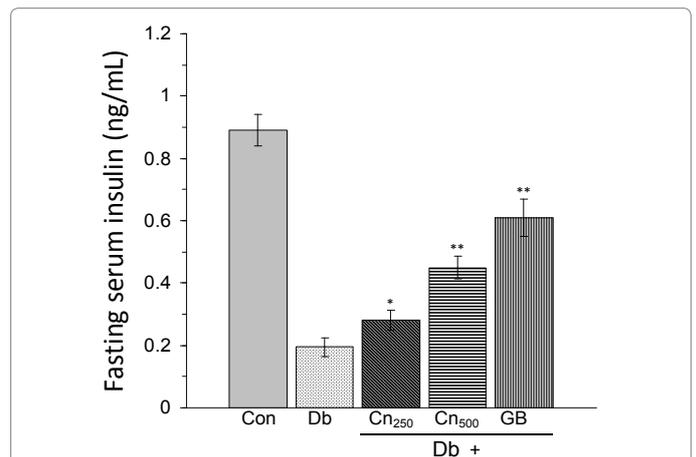


Figure 3: Effect of cinnamon extract on serum insulin in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, ** $P < 0.01$, vs. Db group.

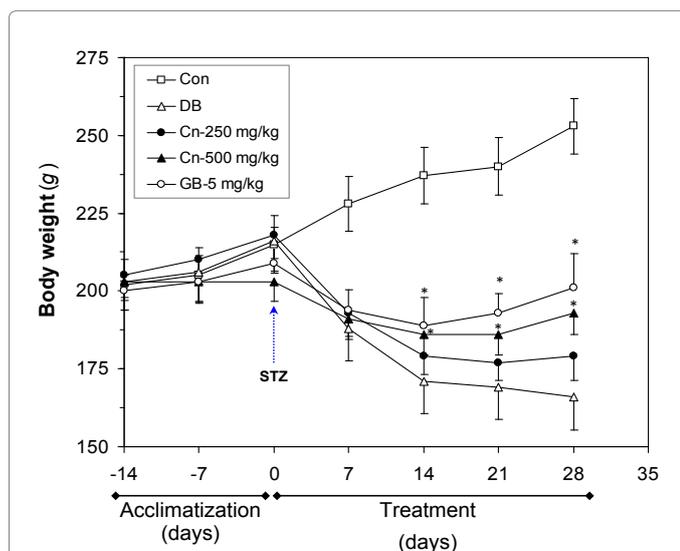


Figure 1: Effect of cinnamon extract on body weight of the experimental rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn-250 and Cn-500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, vs. DB group.

treated diabetic rats. The standard drug glibenclamide also increased the serum insulin level significantly ($p < 0.001$).

Effect of cinnamon extract on HbA1c in the diabetic rats

The HbA1c was significantly increased in the diabetic rats compared to control group (Figure 5). HbA1c levels were significantly ($p < 0.05$) decreased in Cn250-treated group ($8.3 \pm 0.31\%$ vs. $9.25 \pm 0.47\%$), while more significantly decreased was found in the Cn500-treated group ($7.5 \pm 0.29\%$ vs. $9.25 \pm 0.47\%$, $p < 0.01$).

Effect of cinnamon extract on total cholesterol, triglycerides, and HDL-cholesterol in the diabetic rats

The total cholesterol, triglycerides, HDL-cholesterol levels in the experimental rats are shown in Figure 6. After 28 days of extract treatment, no significant changes were observed in total cholesterol levels; however, in Cn500-treated group, drastic change was observed

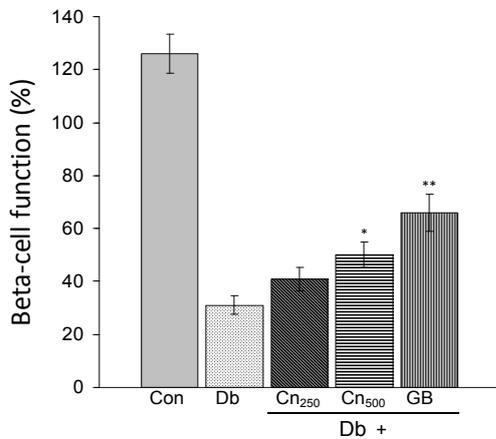


Figure 4: Effect of cinnamon extract on β -cell function in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, ** $P < 0.01$, vs. Db group.

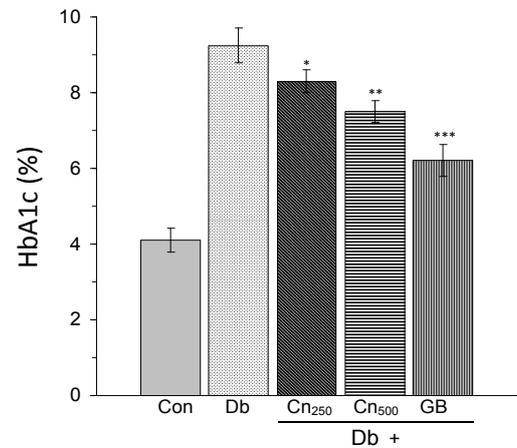


Figure 5: Effect of cinnamon extract on HbA1c in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. Db group.

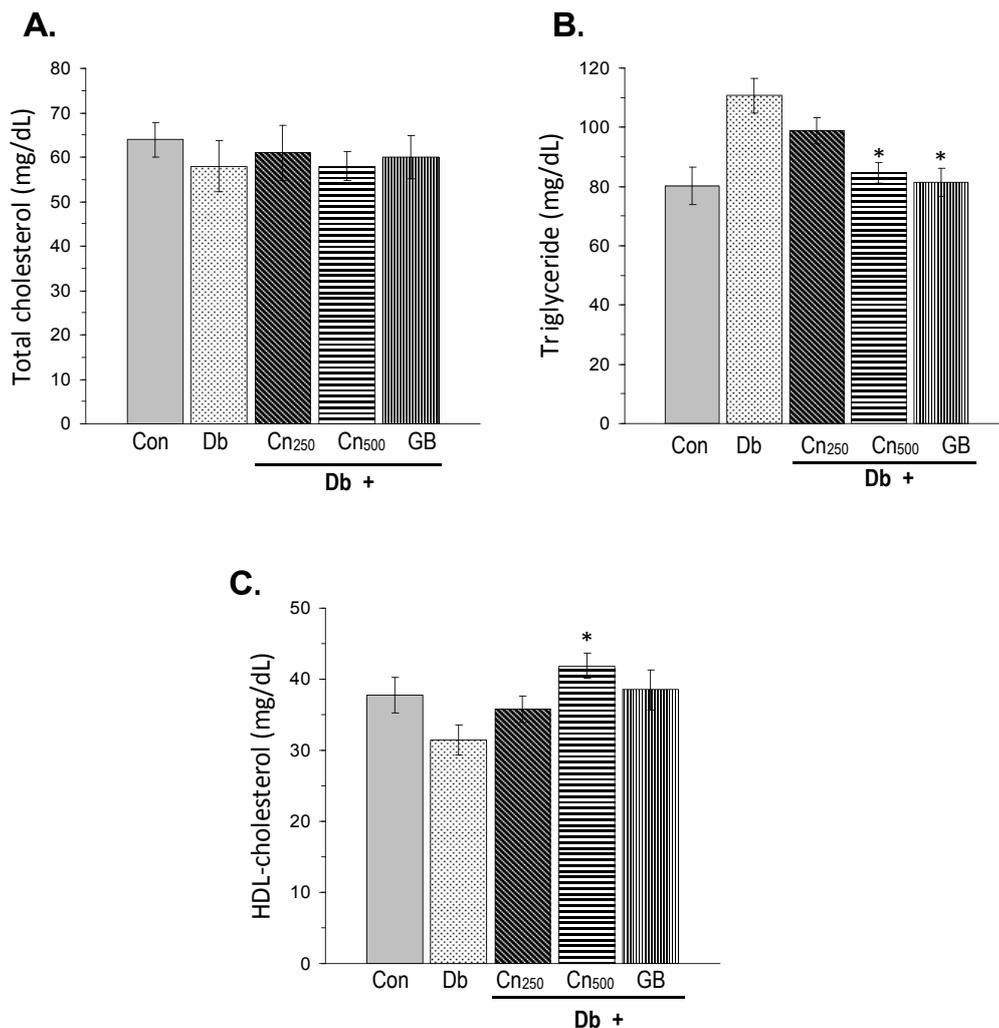


Figure 6: Effect of cinnamon extracts on total cholesterol (A), triglycerides (B) and HDL-cholesterol (C) in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250 and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, ** $P < 0.01$, vs. Db group.

as TG level was decreased (84.7 ± 3.5 mg/dl vs. 110.7 ± 5.8 mg/dl) significantly ($p < 0.01$) and HDL-cholesterol levels were increased significantly (41.9 ± 1.8 mg/dl vs. 31.5 ± 2.1 mg/dl, $p < 0.05$) compared to the untreated diabetic group.

Effect of cinnamon extract on total antioxidant status in the diabetic rats

In the diabetic rats, the total antioxidant status (TAS) level decreased significantly compared to the control rats (1.49 ± 0.09 mmol/l vs. 2.02 ± 0.11 mmol/l) (Figure 7). After 28 days of extract

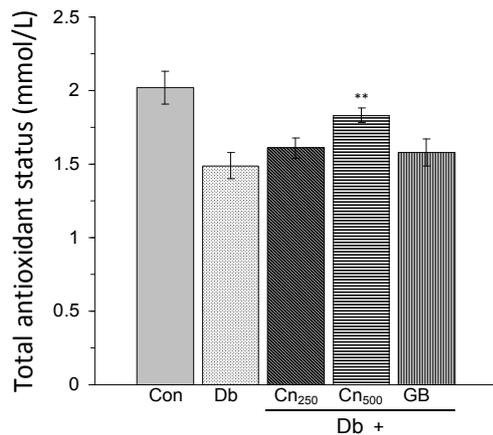


Figure 7: Effect of cinnamon extract on total antioxidant status in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide. * $P < 0.05$, vs. Db group.

treatment, TAS levels were increased significantly ($p < 0.05$) in Cn500-treated group compared to the untreated diabetic group (1.83 ± 0.05 mmol/l vs. 1.49 ± 0.09 mmol/l).

Toxicity of cinnamon extract on kidney and liver

There was almost no significant change in serum creatinine (Figure 8A), serum GOT (Figure 8B), and serum GPT (Figure 8C) levels were found among the experimental rats, suggest that there is no toxic effect of cinnamon extract treatment.

Immunohistochemical studies of insulin and glucagon in experimental rat pancreas

The immunohistochemical images of insulin-expressing β -cells and glucagon-expressing α -cells along with the nuclei from the selected experimental groups are shown in (Figure 9). β -cells were found in the core of the islets and α -cells were found in the periphery of the islets (Figure 9a). The results revealed that insulin-expressing β -cells were present in all these groups in different extent. In control rats, the distribution pattern of β -cells appeared normal showing abundant β -cells in the central position of islets (Figure 9a). In contrast, the β -cells were reduced drastically in the untreated diabetic group and expression of α -cells were increased drastically (Figure 9b). Both 250 mg/kg cinnamon (Figure 9c) and 500 mg/kg cinnamon (Figure 9d) extract improved the insulin-expressing β -cells as compared to the untreated diabetic rats. The standard drug glibenclamide also improved the β -cells (Figure 9e).

The staining of nuclei in non-diabetic control, untreated diabetic, Cn250-treated, Cn500-treated and GB-treated groups is represented for comparison.

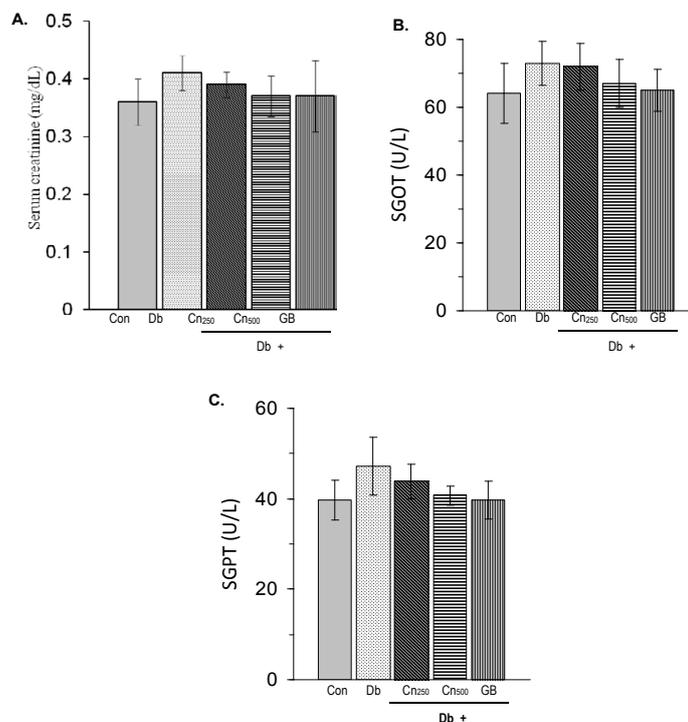


Figure 8: Effect of cinnamon extract on serum creatinine (A), GPT (B), and GOT (C) levels in the diabetic rats. Values are mean \pm S.E.M. for 6-8 rats per group. Con, non-diabetic control; DB, untreated diabetic rats; Cn250 and Cn500, diabetic rats treated with 250, and 500 mg/kg cinnamon extract, respectively; GB, Glibenclamide.

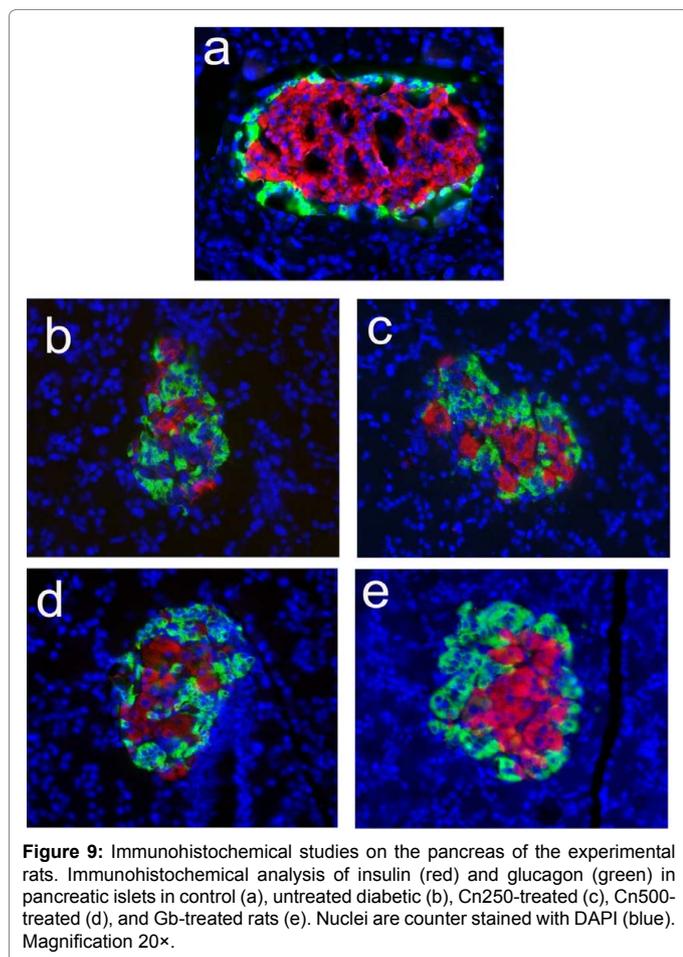


Figure 9: Immunohistochemical studies on the pancreas of the experimental rats. Immunohistochemical analysis of insulin (red) and glucagon (green) in pancreatic islets in control (a), untreated diabetic (b), Cn250-treated (c), Cn500-treated (d), and Gb-treated rats (e). Nuclei are counter stained with DAPI (blue). Magnification 20 \times .

Discussion

Traditional medicines have been used extensively for the management of many diseases all over the world and it was used 100% before discovery of modern drugs. Even today 50% of the modern drugs directly or indirectly came from plant materials [33]. However, there are some issues regarding the use of the natural products, most important “safety” and “toxicity”. Though it is believed that natural products are safe, but it is not true always. Many natural products have been reported for the management of diabetes; however very few plant materials are in clinical use. Cinnamon is reported for its anti-diabetic action and we also found (unpublished observation) that cinnamon is effective in pre-diabetic and obese diabetic rats. In this study, we also used cinnamon because it is available, affordable and commonly used in Pakistani society as spice as well as for the management of diabetes. In scientific literature, it is reported that cinnamon can lower blood glucose [16,34-36]. However, claims and counter-claims are still there [19,28,37]. Some research groups suggest that cinnamon improves blood glucose level [16,34-36]. To contrary, other suggests that cinnamon has no effects on the blood glucose level [19,28,37]. Clinical trials and several reports suggest effective role of cinnamon in type 2 diabetes [22,24,25]. However, other clinical study reported variable effect of cinnamon on different populations [28]. In addition to efficacy of cinnamon, its extract preparation is also a major concern. Ethanolic, methanolic, ethyl acetate, and hot water extracts are commonly used for antidiabetic activity. In our preliminary studies, we found that cinnamon extract of ethanol, methanol, and ethyl acetate

are less soluble in water therefore they are less active. Interestingly, hot water extract of cinnamon give consistent results and efficiently lowers blood glucose. Therefore, we used hot water extract of cinnamon in STZ-NA induced diabetic rats to evaluate its anti-diabetic effects and to explore its mechanism(s). Though cinnamon is reported for its anti-diabetic activity; however, its mechanism of action is still less known. Most importantly the role of cinnamon at cellular level is almost lacking. Here we used cinnamon to evaluate anti-diabetic activity focusing on β -cell function, β -cell morphology as well as its antioxidant property. Additionally, one big concern is the use of standardized extract from same plant. Same extract from same plant may show different results due to different confounding factors. The collection of extract and seasonal variations also matters a lot. Extract collection in winter and summer season may or may not produce same results. Based on these facts, we did standardization of the cinnamon extract in order to find the exact amount of components and their respective percentages. In cinnamon, cinnamaldehyde and cinnamic acid were found as two major compounds. Following standardization, we checked anti-diabetic activity of standardized extract and tried to explore the possible cellular and molecular mechanism(s). We found that cinnamon extract decreased blood glucose levels in a dose-dependent manner (Figure 2). Cinnamon extract also increased serum insulin in diabetic rats (Figure 3), suggest that blood glucose lowering effect is mainly due the insulin secretion. The serum insulin levels were significantly decreased in the diabetic rats. The decreased insulin levels may be due to the impaired β -cell function in the diabetic rats (Figure 4). Interestingly, cinnamon extract treatment significantly improved the serum insulin levels (Figure 3) as well as β -cell function (Figure 4) and β -cell morphology (Figure 9). The increased serum insulin may relate to the upregulation of insulin biosynthesis and/or enhanced insulin secretion from β -cells. Previously, we reported that cinnamic acid one of the main constituents of cinnamon, has insulin secretory activity in mice isolated islets [38]. Thus, the increased serum insulin is most likely due to the enhanced insulin secretion from the pancreatic β -cells. We found that β -cell function improved in diabetic rat treated with cinnamon extract (Figure 4), suggests that the blood glucose lowering effects may be due to modulation of β -cell function. Cinnamon extract has little effects on cholesterol (Figure 6A); however, it has decreased TG level (Figure 6B) and increased HDL cholesterol (Figure 6C) significantly. Cinnamon extract improves β -cell morphology and quality (Figure 9). Taken together, these results suggest that the possible anti-diabetic mechanism(s) may seems to be due to improvement of β -cell function, β -cell quality and morphology thus play an active role for the management of diabetes. Cinnamon also has an important antioxidant activity. In diabetic rats, serum total antioxidant status was improved in cinnamon-treated rats (Figure 7). Cinnamon is well known for its rich polyphenolic components and these polyphenolic components may responsible for its antioxidant activity. The improved antioxidant status by cinnamon in diabetic rats may add antioxidant defense for β -cells, and may protect β -cells from oxidative damage and induced β -cells apoptosis that ultimately help in β -cell modulation.

Conclusion

Cinnamon is effective in many ways, by modulating pancreatic β -cells and improving antioxidant status, and thus can be a good alternative nutraceutical for the management of type 2 diabetes. Cinnamon holds a long history of serving as a spice and today it is widely used as a dietary ingredient in various traditional foods and tea. Indeed, its exact in-depth mechanism of action has yet to be explored but, its cost effectiveness and safety profile make it a relatively low-

risk alternative to traditional glucose-lowering medication and a strong candidate for drug research.

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