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RESEARCH ARTICLE

COMPARATIVE STUDY OF THE PROTECTIVE ROLE ON CINNAMON AND METFORMIN IN STREPTOZOTOCIN-INDUCED DIABETIC OXIDATIVE STRESS

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ABSTRACT

Cinnamonnium cassia (*Cinnamon*) is a traditional folk herb with anti-oxidant and anti-diabetic properties. The present study was carried out to investigate anti-oxidant activity of aqueous bark extract of Cinnamon in streptozotocin-induced diabetic rats. In a 21 days treatment, rats were divided into four groups (n=8); Diabetes mellitus was induced by streptozotocin in a single dose of 50 mg/kg/bw. Metformin, an antidiabetic oral drug was used as reference in this study. A significant decrease in blood glucose level was observed but a significant body weight gain of diabetic rats. Besides, there was an increase in high density lipoprotein (HDL) level and a decrease ($P < 0.05$) in total cholesterol (TC), triglyceride (TG), and low density lipoprotein (LDL) levels were observed after 21 days of treatment with *Cinamon* extract. In addition, the activities of aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP), ($P < 0.05$) were diminished in the *Cinnamon* extract in liver of diabetic rats when compared with that of diabetic control. The study shows that the aqueous bark extract of Cinnamon possesses potent anti-diabetic activity

Keywords: Anti-diabetic, Cinnamon, Diabetic mellitus (DM), Oxidative Stress, Streptozotocin (STZ).

INTRODUCTION

Diabetic mellitus (DM) is a chronic metabolic disorder affecting approximately 4% of the population worldwide, and expected to increase to about 5.4% in 2025 (Kim et al., 2006). DM is caused by inherited and/or acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced (Sajeeth et al., 2011). This insulin deficiency results in increased concentration of blood glucose. Increase in blood glucose damages many of the body's systems, in particular, the blood vessels and nerves (Shetti et al., 2012). The hyperglycemia caused due to decreased insulin production is called Type-1 diabetes

(Insulin Dependent Diabetes mellitus – IDDM), and hyperglycemia due to insufficient insulin utilization is called Type-2 diabetes (Non-Insulin Dependent Diabetes mellitus – NIDDM) (Marshal and Bangret, 2004). Out of these two types, Type-2 diabetes is a major problem of today and it account for nearly 95% of total diabetic population of about 246 million (Mycek et al., 2000).

Renewed attention in recent decades to alternative medicines and natural therapies has stimulated a new way of research interest in traditional practices; and many plant extracts have been shown to possess significant anti-oxidant activity, which may be an important property of medicinal plants (Karuna et al., 2011)

According to the World Health Organization, more than 70% of the world's population must use traditional medicine to satisfy their principal health needs. A great number of medicinal plants used in the control of the diabetes mellitus have been reported (Bailey and Day, 1989). There are various medicinal plants in the world, which are the potential sources of the drugs. The discovery of the widely used hypoglycemic drug, metformin (N, N-dimethylguanylguanidine) came from the traditional approach through the use of Galega officinialis (Grover et al., 2002).

Cinnamon is one of the traditional folk herbs used in Korea, China, India and Russia for diabetes mellitus (Bailey and Day, 1989; Chung, 1994). Today cinnamon is widely used in Ayurvedic medicine (traditional India medicine) to treat diabetes in India (Abdul Rahim, 2009). Cinnamon is the bark of the cinnamomi cassia (Soheir et al., 2006), with its main constituents as cinnamon aldehyde (Wijesekera, 1987); cinnamamic acid (Hiromu et al., 1974); and methylhydroxychal cone polymer (Jarvull Taylor et al., 1984).

In addition, the aqueous extracts of cinnamon has been shown to potentiate the hypoglycemic effect of insulin (Saima et al., 2011); a good anti-oxidant activity (Ranjbar et al., 2006), as well as lowering triglyceride levels and serum cholesterol (Onderoglu et al., 1999; Broadhurst et al., 2000; and Khan et al., 2003). Therefore the present study was to study the anti-diabetic effects of aqueous extract of cinnamon in streptozotocin-induced diabetic rats.

MATERIALS AND METHODS

Plant Material and Preparation of Extract

The bark of cinnamomi cassia was purchased from the vegetable market at Aideyan raod, G.R.A, Benin City, Nigeria. The plant was identified and authenticated by Sunny Nweke of the Herbarium unit, Department of Botany, University of Benin, Benin City, Nigeria. The quills of cinnamon were allowed to dry under shade and grinded into powder form in a milling machine used in grinding plant samples. 1.428kg of the powdered material was packed into soxhlet apparatus and extracted using 1.6liter of distilled water. The extract obtained was concentrated using evaporation dish to yield 1.02kg crude aqueous extract referred to as aqueous extract of cinnamon (AEC).

Experimental Animal

Adult wistar rats of both sexes with average weight of 275g were purchased, and maintained in standard animal cages from the animal house section of the Department of Anatomy, University of Benin, Benin City, Nigeria. The rats were left to acclimatize to laboratory conditions for two weeks and subsequently employed to testing for three weeks, during which they were fed with commercially formulated rat feed and water

was given ad libitum. The animals were exposed to natural room temperature and lighting conditions, and handled according to standard protocols for the use of laboratory animals (National Institute of Health Guide fro the Care and Use of Laboratory Animals (NIH, 1978).

Induction of Experimental Diabetes

Diabetes was induced by a single intraperitoneal (i.p) injection of a freshly prepared STZ solution dissolved in 0.1M citrate buffer, p.H 4.5, at a dose of 50mg/kg body weight to overnight-fasted rats. At three days post-administration, rats with stabilized diabetes as indicated by a fasting blood glucose level of more than 250mg/dl, were selected for the study. Treatment was started on the fourth (4^{th}) day after STZ administration and continued for 21 days.

Experimental Design

In the present experiment, 16 diabetic surviving rats, and 16 normal rats were used. The rats were divided into four (4) groups of 8 per group; standard grower's mash and water was provided ad libitum to the animals:

Group - I (Normal healthy rats receive 2ml of distilled water)
Group - II (Untreated diabetic control rats receive 2ml of distilled water)
Group - III (Diabetic treated rats with 30mg/kg body weight of Metformin)
Group - IV (Diabetic treated rats with 300mg/kg body weight of AEC)

Body weight was monitored at 7 days intervals. After 21 days of treatment, the animals were euthanized. Blood was collected and liver samples were dissected out and washed immediately with ice cold saline to remove as much blood as possible, and immediately stored at −20 °C until analysis. An extra sample of liver was excised and fixed in 10% formalin solution for histopathology analysis.

Biochemical Analysis

During the experiment blood samples were collected from 12 hour-fasted rats by amputation of the tail tip under mild anesthesia**.** Plasma glucose was estimated by glucometer and glucometer strip (ACU-check advantage, Roche diagnostic, Germany; purchased from Pyrex Laboratories, Benin City). Triglycerides (T), total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) were measured by using Span diagnostic reagent Kit. Very-low-density lipoprotein (VLDL) was calculated using formula High triglyceride (TG)/5 (Freidwalds et al., 1972). Low-density lipoprotein (LDL) concentration was estimated indirectly from the measured levels of TG, HDL, and TC using equation LDL = TC – (VLDL + HDL) (Freidwalds et al., 1972).

Statistical Analysis

Data were evaluated with SPSS/10 software hypothesis testing methods that included one way analysis of variance (ANOVA) followed by least significant difference (LSD) test. *P* values of less than 0.05 were considered to show statistical significance. All these results were expressed as mean ± SEM for eight animals in each group.

RESULTS

The effect of the different extracts of Cinnamon on the fasting blood sugar (FBS) level, serum total cholesterol (TC), serum triglyceride (TG), aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels and sugar content in liver were studied in the

control and STZ-induced diabetic rats using Metformin as reference anti-diabetic agents

Effects on Body Weight of Rats

The control group (group - I) gained weight over the three weeks of experimental period, with the mean body weight increasing by 23.8g after 3 weeks (Table 2). In contrast, the untreated diabetic group (group - II) lost an average of 42.4g after 3 weeks ($p<0.05$). Treatment with aqueous bark extract of cinnamon and Metformin resulted in significant weight gain of 13.0g and 19.0g respectively to level towards the control group.

Effect of aqueous bark extract of Cinnamon on blood glucose level

The blood glucose level in diabetic group was significantly higher ($p<0.05$) than those of the control group (Table 3). On the other hand, administration of aqueous bark Cinnamon extract for 21days was found to lower blood glucose significantly in treated diabetic groups ($p<0.05$) when compared with those of the untreated diabetic group (group - II)

The reference drug Metformin also lowers blood glucose level as compared to the diabetic control rats however; the anti-hyperglycemic activity of the cinnamon extract is more effective.

Serum Lipid Level

Serum total cholesterol (TC) and triglyceride (TG) levels were significantly elevated ($P < 0.001$) in STZ-induced diabetic group in respect to the untreated control group. Treatment of these extract at the above mentioned dose to diabetic animals resulted a partial recovery in the levels of these parameters towards the control level. Levels of TC and TG were significantly ($P < 0.05$) recovered towards the control level in composite (1:1) extract treated diabetic group than the individual extract treated diabetic groups.

Lipidemic parameters like serum LDL levels were elevated significantly in STZ-induced diabetic group in comparison with the untreated control group. Treatment of these extract in composite manner (1:1) to diabetic animals resulted a significant recovery in serum LDL level towards the control level. Insignificant variation was noted in the level. An insignificant difference was noted in the level of HDL in between metformin treated and diabetic group.

Serum HDL level were decreased in STZ-induced diabetic group in respect to the untreated control group. Treatment of the composite (1:1) extract at the above mentioned dose to diabetic rats reveals a significant ($P < 0.05$) recovery of this parameter towards the control level. The composite extract treatment resulted significant recovery in the levels of these parameters than the individual extract treated diabetic groups. An insignificant difference was noted in the level of HDL in between metformin treated and diabetic group.

Serum Enzymes Profile (AST, ALT and ALP)

The study evaluated the activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in all groups. A significant increase in AST, ALT, and ALP was observed in STZ-induced diabetic group of rats. Moreover, treatment of diabetic rats with aqueous bark Cinnamon extract resulted in significant decreases in the levels of serum

AST, ALT and ALP when compared with diabetic induced rats. A significant level of reduction in serum-marker enzymes (AST, ALT and ALP) were noticed due to the effect of aqueous bark Cinnamon extract

Table 1: ***Changes in body weight (wt.) in control, diabetic control and diabetic rats treated with Metformin and Aqueous Extract of Cinnamon***

GROUPS	I	II	III	IV
Initial body wt. (g)	256.40	222.60	235.00	249.40
Final body wt. (g)	280.20	265.00	254.00	262.40
Change in body wt. (g)	+23.8	+42.4	+19	+13
Values in mean (±SD)	267.47±6.70	247.33±14.49	245.47±5.84	256.16±3.43

Values are expressed mean ±S.E.M

** P<0.05 as compared to diabetic induced rats*

Table 2: ***Effects of aqueous bark extract of Cinnamon for 21 days on serum marker enzymes and serum sugar level on STZ-induced diabetic rats***

GROUPS	AST (U/l)	ALT (U/l)	ALP (KA unit)	Sugar (mg/dl)
I	11.0	6.75	22.36	90.15±4.49
II	11.75	7.5	50.96	394.40±110.55
III	16.25	7.75	20.40	327.84±79.93
IV	10.25	8.75	18.42	241.15±117.01

Values are expressed mean ±S.E.M

** P<0.05 as compared to diabetic induced rats*

Table 3: ***Effects of aqueous bark extract of Cinnamon on lipid profiles in control and experimental rats***

Groups	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
I	116.60±21.29	94.61±25.09	68.82±13.06	31.17±24.24
II	257.96±58.78	225.62±51.61	33.35±5.04	103.20±17.47
III	238.32±54.45	200.18±36.48	42.02±15.95	100.07 ±14.66
IV	89.38±8.93	104.87±20.09	74.61±7.90	28.21±7.37

Values are expressed mean ±S.E.M

** P<0.05 as compared to diabetic induced rats*

Histopathological Study

Fig. 1–4. illustrates histopathological investigation that also provided an essential evidence for the biochemical analysis. In control rats (Fig. 1), liver sections showed normal hepatic cells radiating from the central vein, with well preserved cytoplasm and nucleus, where as STZ-induced group of rats (Fig. 2) showed prominent halos around the nuclei which appeared distorted with fragmented nuclei and rampant vacuoles which were apparent signs of lipid infiltration. However, treatment with *Cinnamon* (Fig. 4) and Metformin (Fig. 3) improved the histological architecture when compared to STZ-induced diabetic rats.

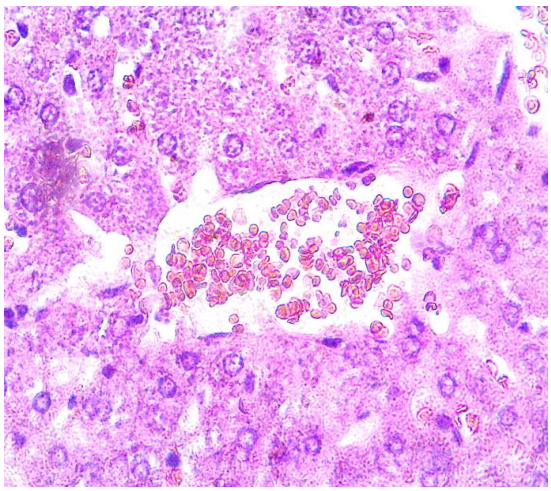

Fig. 1.

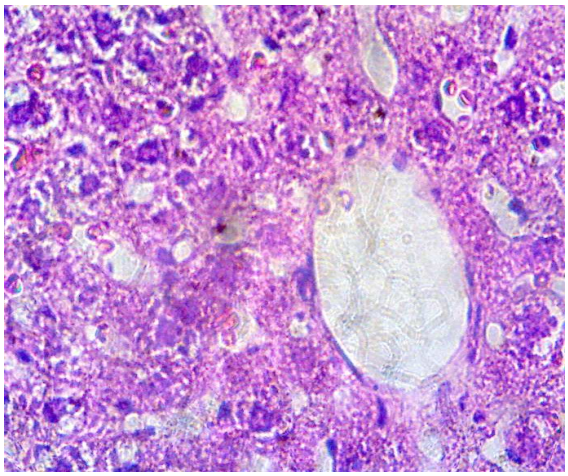

Fig. 2.

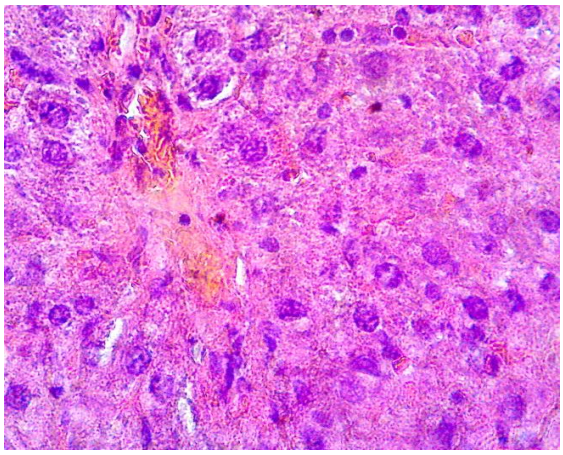

Fig. 3.

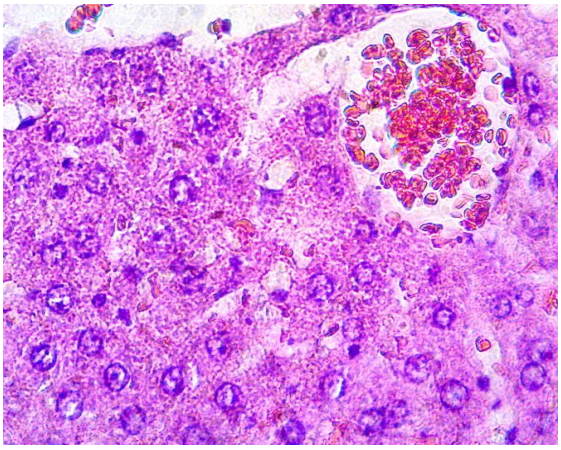

Fig. 4.

DISCUSSION

The morphological findings of weight gain affected both the experimental (groups treated with aqueous Cinnamon extract, metformin and Stz-treated only) and the control group. The weights of the Wistar rats that were made diabetic by STZ administration and subjected to various treatment measures including metformin, and aqueous Cinnamon extract for 21 days were subjected to one way analysis of Variance (ANOVA). The Anova statistics indicated a highly significant difference ($p<0.01$), table 4.1. The Duncan Multiple Range (DMR) test revealed that the weights of the diabetic rats (STZ-induced) that were treated with aqueous extract of Cinnamon were significantly higher than the untreated group and those treated with metformin. The weights of the untreated diabetic group and the diabetic group treated with metformin

were not significant different from each other. The reduction in weights of diabetic Wistar rats treated with metformin could be attributed to poor glycemic control of type 1 diabetes mellitus. This collaborates the earlier work by Ryan et al., 2011 which states that metformin is specific for the control of type11 diabetes mellitus. Also the reduction in weights observed in the diabetic untreated group is due to hyperglycaemia, lipolysis and hyperlipidaemia which are characteristic of uncontrolled diabetes mellitus, Chait and Brunzell, 1996.

The observed blood sugar levels of both treated and untreated groups as well as the control group showed a highly significant difference ($p<0.01$) was observed as shown in table 4.1. A posteriori, Duncan Multiple Range test revealed that the blood sugar levels of the diabetic groups of experimental Wistar rats (those induced with STZ alone and those treated with metformin) were not significantly different from each other ($p>0.05$) but significantly higher than other groups. Also worthy of note is that there was no statistical significant difference ($p>0.05$) in blood sugar levels of the groups of experimental Wistar rats that were rendered diabetic with STZ and later treated with aqueous Cinnamon extract. This supports the earlier claim by Saima and Aishat et al., (2011) that aqueous extract of Cinnamon has been shown to potentiate the hypoglycaemic effect of insulin through up-regulation of glucose uptake in cultured adipocytes of rats. In 1990, Khan et al stated that aqueous extract of Cinnamon has a potentiating effects on insulin and can be used in the treatment of type11 diabetes mellitus. In the same vein, Karalee et al., 2001; Qin et al., 2004; and Lee et al., 2003 have demonstrated that Cinnamon has effect on insulin signal transduction. The significant reduction in blood sugar level following administration of aqueous extract of cinnamon is in consonant with the work of Rekha and Balaj et al., 2010 who investigated the anti-diabetic effect of the aqueous extract of Cinnamomum Zeylanicum and concluded that the administration of the extract in diabetic rats resulted in a significant reduction on blood glucose levels.

Most prominent in the untreated STZ-induced diabetic group of Wistar rats (Fig. 1B) is the distortion of hepatic architecture which radiates from the central veins there is presence of vacuoles which may have resulted from fat infiltration. There is halo and distortion of cell nuclei in this group. However, it was observed that the cytoachitecture was normal in the control group as well as groups that were induced diabetic and subsequently treated with aqueous extract of Cinnamon respectively. The normoglycaemic state that was restored following treatment of diabetes with these agents could be responsible for this normal histologic picture. In 2009, Moselhy and Ali have demonstrated the hepatoprotective and antioxidant effects of Cinnamon extract in CCl4-intoxicated rats.

CONCLUSION

Diabetes Mellitus is one of the major chronic diseases in all populations (Wild et al., 2004). The currently available agents for treatment of diabetes are expensive, not easily accessible and have several side effects (Ramesh and Pugalendi, 2005). Thus a large number of studies are involved to find natural

hypoglycaemic products as alternatives to the synthetic ones.

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STATEMENT OF COMPETING INTEREST

The authors have no competing interests.

LIST OF ABBREVIATIONS

AEC – Aqueous Extract of Cinnamon
H & E – Haematoxylin and Eosin
HDL - High Density Lipoprotein
LDL - Low Density Lipoprotein
STZ - Streptozotocin
TC - Total Cholesterol
TG - Triglyceride
AST - Aspartate transamination
ALT - Alanine transaminase
ALP - Alkaline phosphatase
DM - Diabetic mellitus
IDDM – Insulin dependent diabetes mellitus
NIDDM – Non-insulin dependent diabetes mellitus

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