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Full Length Research Paper

Anti-hyperlipidaemic and antioxidant effect of aqueous and ethanolic extracts of *Cassia italica* leaves in streptozotocin-induced diabetes in rats

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The earth is richly endowed with a variety of plants. Most of the naturally occurring plants possess medicinal properties and are thus potential sources of remedies for virtually all human ailments. The present study was designed to evaluate the hypolipidaemic and antioxidant effects of aqueous and ethanolic extracts of *Cassia italica* leaves in streptozotocin (STZ)-induced diabetes mellitus in rats. Lipid peroxidation as assayed by thiobarbituric acid reactive substances (TBARS) was significantly reduced ($p \leq 0.05$) in STZ -induced diabetic rats on treatment with ethanolic and aqueous extracts of *C. italica* leaf. Oral administration of 200 mg/kg body weight of both extracts to diabetic rats for sixty-three days improved serum glucose, cholesterol, HDL-cholesterol, triglycerides levels, among other parameters. The observed anti-lipidaemic and antioxidative effect of the plant extracts against oxidative stress in diabetic rats may be attributed to the presence of flavonoids, ascorbic acid, carotenoids, tannins and phenols among the plant constituents. Flavonoids are known to be antioxidants, free radical scavengers and anti-lipoperoxidant. From the results of this study, it is evident that extracts (aqueous and ethanolic) of leaf of *C. italica* have anti-lipidaemic and antioxidative properties.

Key words: Streptozotocin, diabetes mellitus, *Cassia italica* extracts, antilipid, antioxidant.

INTRODUCTION

Diabetes mellitus is a metabolic disorder of the endocrine system, affecting approximately 5% of the world's population. Worldwide projections suggest that more 300 million people will have diabetes by the year 2025 and the global cost of treating diabetes and its complication could reach US $ trillion annually (Somani et al., 2006). It is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolisms, which not only lead to hyperglycaemia but also cause many complications, such as hyperlipidemia, hyperinsulinemia, hypertension, and atherosclerosis (Sepici-Dincel et al., 2007). Oxidative stress is reported to be increased in patients with diabetes mellitus (Scheen, 1997). Accumulating evidence suggests that oxidative cellular injury caused by free radicals contributes to the development and progression of diabetes and its complications (Prince et al., 2004).

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Reactive oxygen species (ROS) generated in the cells are scavenged by antioxidant enzymes. Moreover, diabetes also induces changes in the tissue content and activity of the antioxidant enzymes (Ugochukwu et al., 2003).

The use of medicinal plants for diabetes is not just a search for safer alternatives to pharmaceutical drugs. Rather, it makes for insight into the validity of traditional medicine, tonic and adaptogenic herbs. Such herbs can return valuable compounds to human diet, thereby making it more similar to our evolutionary diet with a minimum of effort (Nadro and Ochornogor, 2009). *Cassia italica,* a member of the family Caeslpinaceae, is a perennial shrubby plant known as Eshrinq and grows abundantly in the kingdom of Saudi Arabia. *C. italica* can also be grown in the West African region. It is found mostly in the northern parts of Nigeria and it is called 'Flesko' in Hausa. It also grows abundantly in Kenya, where it is known locally as 'Bali Bali. The plant grows up to three to eight feet in height, bearing primate leaves and racemes of yellow flowers in the upper leaf – axis.

The seeds are produced in autumn (www.savannahplant.com). In Adamawa State, North-East of Nigeria, the leaves of *C. italic*a popularly known as 'ganyen shayi' meaning tea leaf, is used in making tea especially for the people believed to have jaundice or diabetes. Some use it for protection against liver diseases. Also, the seed when roasted and powdered is used as local coffee (personal communication).

In a previous study, Nadro (2009) demonstrated the antidiabetic effect of *C. italica* leaf extract in alloxan diabetic rats. The present investigation was undertaken to study the effect of the potential antidiabetic extract of *C. italica* leaf, on lipid peroxidation and lipid profile in streptozotocin diabetic rats. The effects produced by this drug on different parameters were compared with chlorpropamide, a reference drug.

MATERIALS AND METHODS

The leaves of *C. italica* were obtained from the vicinity of Modibbo Adama University of Technology, Yola and Yolde Pate, a village in Yola South Local Government Area of Adamawa State. These were botanically identified by Basiri Bristone of the Department of Botany, Modibbo Adama University of Technology, Yola. A voucher specimen was deposited in the herbarium of the Department of Botany, Modibbo Adama University of Technology, Yola. The leaves were air-dried at room temperature, ground and sieved using a laboratory mortar and pestle and a 1 mm Endecoff sieve respectively. The finely powdered sample was stored at room temperature until required.

Experimental animals

Male Wistar strain albino rats weighing between 145.53 ± 6.31 g were purchased from the Animal Unit of the Nigeria Institute for Trypanosomiasis Research (NITR), Vom, Plateau State, Nigeria. They were fed with standard rat diet and drinking water *ad libitum*.

Chemicals and reagents

All the reagents used were of analytical grade.

Preparation of extract

A portion of 100 g of the powdered leaf was extracted by adding 500 ml 70% ethanol and with water. The mixture was left overnight at room temperature on a shaker. Next, the extract was decanted and the fibrous residue rinsed exhaustively. The extract and the risings were pooled together and filtered through Whatman No. 1 filter paper and the filtrate freeze-dried using a freeze dryer (Adzu et al., 2003). Water was used to reconstitute the solid extract to a desired concentration for the study. Phytochemical analyses were done according to the methods of Sofowora (1993).

Experimental design

Diabetes mellitus was induced by a single intraperitoneal injection of freshly prepared streptozotocin (STZ) in citrate buffer pH 4.5 at a dose of 65 mg/kg body weight to overnight fasted rats. Seven days after, diabetes was tested in the rats and those confirmed to be diabetic were divided into 5 groups of six rats each as follows: Group 1: normal control; Group 2: diabetic control; Group 3: diabetic rats treated orally with 200 mg/kg body weight aqueous extract of *C. italica* leaves; Group 4: diabetic rats treated orally with 200 mg/kg body weight ethanolic extract of *C. italica* leaves; Group 5: reference standard (rats treated with 250 mg/kg body weight chlorpropamide).

After 63 days of treatment, animals were sacrificed and blood was collected by cardiac puncture under mild anaesthesia from overnight fasted rats. Serum was separated and analyzed for biochemical parameters. Liver and kidney tissues were also removed and washed immediately with cold saline to remove as much blood as possible. Liver homogenates (5%w/v) were prepared in cold phosphate buffer (pH 7.4). The supernatant was used for the estimation of thiobarbituric acid reactive substances (TBARS), antioxidant enzymes such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx).

Biochemical estimation

Diagnostic kits were employed in the analysis of most of the biochemical parameters that were determined. Glucose (Barham and Trinder, 1972), SOD (Misra and Fridovich 1972), GPx (Paglia and Valentine, 1967), cholesterol (Zak et al., 1953), low density lipoprotein (LDL) and high density lipoprotein (HDL)-cholesterol (Chawla, 1999), triglycerides (Tietz, 1990), catalase (Sinha, 1972) and TBARS (Ohawa et al., 1979) were estimated using previously described methods.

Statistical analysis

Numerical data obtained from the study were expressed as the mean value ± standard error of mean. Differences among means of control and tested groups were determined using Statistical Package for Social Scientist (SPSS 11.0). A probability level of less than 5% ($p \leq 0.05$) was considered significant.

RESULTS AND DISCUSSION

Streptozotocin-induced diabetes is characterized by severe loss in body weight of untreated rats, which is due to increased muscle wasting in diabetes (Reyes et al., 2006). In this study, a decrease in body weight was registered in the case of STZ diabetes control group rats. Moreover, when aqueous and ethanolic extracts of *C. italica* leaf were administered to diabetic rats for a period of sixty three days, there were differences in weights of the rats (Table 1). The change in body weight showed that the rats given the extracts have a significant effect in controlling the loss of body weight, which arose during diabetes. The weight gains seem to be as a result of the ability of the extracts to reduce hyperglycaemia within the period of this study (Jaiswal et al., 2009).

In this study, the rise in blood glucose was accompanied with marked increase in cholesterol and triglycerides (TG) levels (Table 2). Diabetes mellitus is often linked with abnormal lipid metabolism (Onoagbe and Esekheigbe, 1999; Ju et al., 2008). The impairment of insulin secretion results in enhanced metabolism of lipids from the adipose tissue to the plasma. It has been

Table 1. Body weights of normal and STZ diabetic rats after with or without treatment of 200 mg/kg body weight of aqueous and ethanolic extracts of *C italica* leaf.

Treatment	Initial weight (g)	Final weight (g)	% WI
Normal	151.30 ±4.21	217.42 ± 0.94	43.70
Diabetic control	153.63 ± 3.83	139.32 ± 5.43	-9.31
Diabetic + aqueous extract	141.31 ± 6.45	156.92 ±1.34*	11.05
Diabetic + ethanol extract	148.23 ± 8.37	178.67 ±7.43*	20.54

WI, Weight increase; values are means of six determinations ± SEM. *, Significantly higher compared to values obtained for diabetic control ($p<0.05$).

Table 2. Effect of aqueous and ethanolic extracts of *C. italica* on triglycerides (mg/dl) levels of serum, kidney and liver of STZ- induced diabetic rats.

Treatment	Serum	Kidney	Liver
Normal	105.28 ± 10.64	66.10 ± 1.32	19.96 ± 0.23
Diabetic control	323.14 ± 8.63	134.00 ± 17.91	369.88 ± 31.98
Diabetic +AQE	166.83 ± 20.33**	119.87 ± 9.09*	190.17 ± 3.52**
Diabetic +EE	152.62 ± 17.08**	100.97 ± 13.58**	311.21 ± 44.22

Values are means ± SEM; n=6. **, Significantly lower compared to diabetic control ($p<0.01$); *, significantly lower compared diabetic control ($p < 0.05$). Triglycerides were tested in serum and tissues of rats treated with or without *C. italica* leaf extracts. Rats were administered extracts for 63 days, after which blood and tissues were collected for the analysis.

Table 3. Effect of aqueous and ethanolic extracts of *C italica* on total cholesterol, LDL and HDL- cholesterol levels (mg/dl) in serum of normal and STZ-induced diabetic rats.

Treatment	Total cholesterol	LDL-cholesterol	HDL-cholesterol
Normal	71.83 ± 3.18	15.35 ± 2.75	35.71 ± 1.51
Diabetic control	176.62 ± 6.89	94.31 ± 9.64	18.11 ± 1.36
Diabetic + aqueous extract	91.18 ± 11.40*	26.25 ± 4.12*	31.80 ± 0.43*
Diabetic + ethanol extract	128.97 ± 3.80*	63.15 ± 4.63*	24.34 ± 3.13*
Chlorpropamide 250mg/kg	103.01± 1.76*	57.07 ± 0.76*	32.81 ± 2.11*

Values are means of six determinations ± SEM; *, significantly different compared to values obtained for diabetic rats ($p<0.05$).

demonstrated that insulin deficiency in diabetes mellitus leads to a variety of derangements in metabolic and regulatory process, which in turn leads to accumulation of lipids such as cholesterol and TG. Accumulation of triglycerides is one of the risk factors in coronary heart disease (CHD). The significant increase in the level of triglycerides in liver and kidney of diabetic control rats may be due to the lack of insulin since under normal condition, insulin activates the enzyme lipoprotein lipase and hydrolysis triglycerides (Saravanan and Pari, 2005). The abnormal high concentration of serum lipids in the diabetes subject is due mainly to increase in mobilisation of free fatty acid (FFA) from the peripheral fat depots (Bopanna et al., 1997).

This study indicated that 200 mg/kg body weight dose of aqueous and ethanol extracts of *C. italic* leaf significantly reduced total cholesterol and triglycerides concentrations (Table 3), which could be due to stimulating effect on insulin secretion from pancreatic β -cells (Figure 1). The possible mechanism by which aqueous extract from *C. italica* can exert lipid lowering activities is not clearly understood. It may be explained by decreasing the cholesterol biosynthesis, particularly by decreasing the activity of 3 hydroxyl-3-methylglutaryl-coenzyme A (HMG – CoA) reductase (Adoga and Bukar, 1994, Sharma et al., 2003) or by reducing the NADPH required for cholesterol synthesis and/or by stimulating glucose utilization. In a previous study, it has been proposed that aqueous extract from C*aesalpinia bonducella* seeds and glibenclamide acted in a similar way by increasing insulin production in STZ-induced diabetic rats and lowering TG level by activation of the

Table 4. Effect of aqueous and ethanolic extracts of *C. italica* 200mg/kg body weight on TBARS and vitamin C levels in the serum of STZ-induced diabetic rats.

Treatment	TBARS (nmol/L)	Vitamin C (mg/dl)
Normal	73.12 ± 3.16	1.85 ± 0.16
Diabetic control	185.03 ± 7.32	0.48 ± 0.02
Diabetic + aqueous extract	147.64 ± 1.37*	0.87 ± 0.01 *
Diabetic + ethanol extract	138.37 ± 5.10*	0.98 ± 0.12 *
Chlorpropamide 250mg/kg	120.32 ± 0.84*	1.32 ± 0.17 *

Measurement of non-enzymatic antioxidants in normal and STZ-induced diabetic rats treated with *C. italica* leaf extracts for was done sixty-three days. At the end of the treatment period, thiobarbituric acid reactive substances (TBARS) and vitamin C were determined in serum. Values are means of six determinations ± SEM; *significantly different compared to values of diabetic group ($p<0.05$).

Table 5. Effect of aqueous and ethanolic extracts of *C italica* leaf 200mg/kg body weight on TBARS levels in the kidney and liver of STZ-induced diabetic rats.

Treatment	Kidney (nmol/g tissue)	Liver (nmol/g tissue)
Normal	48.34 ± 0.48	53.05 ± 1.08
Diabetic control	89.73 ± 8.08	107.30 ± 0.94
Diabetic + aqueous extract	67.34 ± 1.01*	80.72 ± 5.78*
Diabetic + ethanol extract	56.60 ± 3.10*	66.75 ± 2.29*
Chlorpropamide 250mg/kg	58.43 ± 4.21*	59.41 ± 1.96*

Measurement of lipid peroxidation levels in tissues. Six per group of normal and STZ-induced diabetic rats were treated without or with aqueous and ethanolic extracts of *C. italica* leaf for sixty-three days. At the end of the treatment period, TBARS were determined in liver and kidney tissues. Values are means of six determinations ± SEM; *significantly lower compared to values of diabetic group ($p<0.05$).

enzyme lipoprotein lipase (Ju et al., 2008) because insulin activates lipoprotein lipase. It is a well known fact that in uncontrolled diabetics, there will be increase in LDL, total cholesterol and triglycerides with decrease in HDL-cholesterol, all of which contribute to the coronary artery disease seen in some diabetic patients (Arvind et al., 2002). In the present study, increases in serum cholesterol, LDL and triglyceride levels were observed in STZ- induced diabetic rats. It is interesting to note that *C. italica* ethanolic and aqueous extracts did not only lower the total cholesterol (TC), TG and LDL level, but also enhanced the cardio protective lipid HDL-cholesterol of the diabetic rats after 63 days of treatment. The increased in HDL-cholesterol is a desirable feature. In addition, the reductions in TC, TG and LDL-cholesterol could be beneficial in preventing diabetic complications as well as improving lipid metabolism in diabetics (Sivajothi et al., 2008). This would definitely reduce the incidence of coronary events being the major cause of morbidity and deaths in diabetes subjects (Singh et al., 2007). HDL-C transports cholesterol from peripheral tissues to the liver, thereby reducing the amount stores in tissue and decreasing the likelihood of getting athero-sclerotic plagues (Kochhar et al, 2007). Unlike the hypoglycaemic component which is more extractable in ethanol, the hypolipidemic component in *C. italica* is more extractable in water.

Several studies have demonstrated the involvement of free radicals in the genesis of diabetes mellitus and their role in the induction of lipid peroxidation during diabetes (Prakasam et al., 2005). It has been reported that in diabetes mellitus, oxygen free radicals are generated by stimulating H_2O_2 *in vitro* as well as *in vivo* and in pancreatic β-cells (Mahalinga and Krishnan, 2008). Oxidative stress can be associated with the peroxidation of cellular lipids, which is determined by measurement of TBARS (Nadro et al., 2006; Kumar et al., 2007). The concentration of lipid peroxidation products may reflect the degree of oxidative stress in diabetes. It has been reported previously (Baynes, 1991) that in the tissues and blood of rats with STZ-induced diabetes, malondialdehyde, the production of lipid peroxidation, is increased. Further, the increased level of TBARS results in increased levels of oxygen free radicals, which attack the polyunsaturated fatty acids in cell membranes. STZ also can give rise to oxygen free radicals because of the increased blood glucose level in diabetes (Halliwell and Gutteridge, 1999; Onoagbe and Esekheigbe, 1999).

We evaluated TBARS in our study to determine the activity of *C. italica* in protection from oxidative damage in diabetes. The levels of TBARS in the liver and serum of diabetic rats treated with 200 mg/kg body weight/day of *C. italica* leaves were significantly decreased when compared to the STZ-induced diabetic rats (Tables 4 and 5).

Table 6. Effect of aqueous and ethanolic extracts of *C. italica* leaf (200mg/kg body weight) on liver levels of enzymatic antioxidant parameters in normal and STZ-induced diabetic rats.

Treatment	GPx (U/mg tissue)	SOD (units/mg tissue)	CAT (units/mg tissue)
Normal	6.76 ± 0.94	10.34 ± 1.21	40.83± 7.53
Diabetic control	3.48 ± 0.08	5.03 ± 0.11	28.32 ± 1.12
Diabetic + aqueous extract	5.56 ± 1.07*	7.31 ± 2.43*	32 01 ± 1.23
Diabetic + Ethanol extract	5.12 ± 0.11*	8.61 ± 2.76*	37.63 ± 3.21*
Chlorpropamide 250 (mg/kg)	6.79 ± 0.86*	9.11 ± 0.02*	42.35 ± 0.12*

GPx, Glutathione peroxidase; SOD, superoxide dismutase and CAT, catalase. Values are means of six determinations ± SEM; *significantly higher compared to values of diabetic group ($p<0.05$).

Table 7. Quantitative analysis of some phytochemicals of *C. italica* leaf.

Phytochemicals	Results
Alkaloids (%)	4.33 ± 0.88
Flavonoids (%)	1.75 ± 0.78
Oxalate (%)	0.81 ± 0.10
Phenols mg/g	3.56 ± 0.05
Phytate (mg/g)	0.78 ± 0.02
Saponins (mg/g)	6.33 ± 0.37
Tannins µg/g	0.81 ± 0.10
β-carotene (mg/100 g)	9.50 ± 0.5

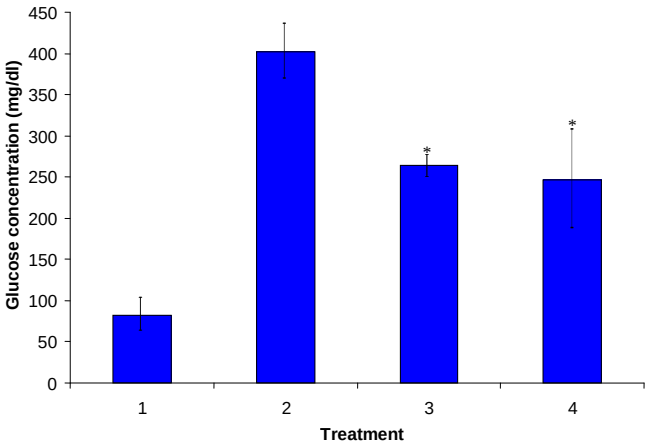

Figure 1. Effects of treatment of 200 mg/Kg body weight aqueous and ethanol extracts of *Cassia italica* leaves on serum glucose levels in normal and STZ- induced diabetic rats. Treatment: 1, Normal; 2, diabetic control; 3, diabetic plus aqueous extract; 4, diabetic plus ethanolic extract. Values are means of six observations. *Significantly lower compared to values obtained for diabetic rats ($p<0.01$).

The decreased level of TBARS indicates that *C. italica* had improved the defective state of diabetes by means of inhibition of lipid peroxidation. The decreased in TBARS levels may increase the activity of glutathione peroxidase (GPx) in rats treated with the extracts and hence cause inactivation of lipid peroxidation (LPO) reactions (Ugochukwu et al., 2003).

These results (Table 6) therefore indicate the possibility that the major function of the extracts may be in protecting vital tissues such as liver and kidney, thereby reducing the complications of diabetes. Significant reduction in lipid peroxidation can be attributed to the antioxidant activity of various phytochemicals (Table 7) present in the aqueous and ethanolic extracts of the *C.*

italica leaf.

Moreover, vitamin C can efficiently scavenge free radicals before it can initiate lipid peroxidation, and contribute to the stability of cellular and basal membrane (Karakilaik et al., 2005). Vitamin C or ascorbic acid is an excellent hydrophilic antioxidant in plasma and disappears faster than other antioxidants on exposure to ROS (Sies, 1997). It is a major extracellular non-enzymatic antioxidant which prevents binding of toxic free radicals to nucleic acid or proteins both *in vivo* and *vitro*. Decrease in plasma vitamin C and its urinary excretion leads to impairment in renal reabsorption and regene-ration of ascorbic acid from dehydroascorbic acid have been reported in STZ-induced diabetic rats (Punitha and Manoharan, 2006). The decreased level of ascorbic acid in diabetic rats may be due to either increased utilization as an antioxidant defense against increased ROS or to a decrease in glutathione level since glutathione is required for the recycling of ascorbic acid (Punitha et al., 2005). The lowered levels of ascorbic acid recorded in serum of STZ-induced diabetes was significantly increased in STZ–induced diabetic rats treated with therapeutic dose of 200 mg/kg of aqueous and ethanolic extracts of *C. italica* leaves.

Conclusively, our observations have clearly demonstrated that the *C. italica* extract exert significant hypoglycaemic and anti-hyperglycaemic activity due to its possible multiple effect involving both pancreatic and extra-pancreatic mechanism. The extracts possessed a capability to inhibit the lipid peroxidation and activate the antioxidant enzymes (SOD and CAT) in diabetes. The ability to reduce oxidative stress may help to prevent diabetic complications.

In addition, the extracts have lipid lowering effect as evidenced by their remarkable improvement on hyperlipidaemia due to diabetes. Its specific effect on HDL cholesterol has additional advantage in checking coronary risks.

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