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Effects of *Cassia auriculata* Flower Buds Extract on Some Blood and Tissue Parameters in Streptozotocin-Nicotinamide Induced Diabetic Rats

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Abstract: The present study investigated the effects of *Cassia auriculata* flowers buds extract CFBEt (0.45 g/kg b wt), and metformin on plasma glucose, insulin, thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation, cholesterol, triglycerides, free fatty acids and phospholipids as well as on histopathological changes in liver and kidney of normal and streptozotocin (STZ) –induced diabetic rats. Oral administration of CFBEt (0.45 g/kg b wt) aqueous extract and metformin to diabetic rats for 45 days significantly resulted in reduction in blood glucose and increase in plasma insulin levels. In addition, CFBEt significantly decreased the levels of serum and tissue lipids as compared to untreated diabetic rats, with significant decrease in thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation in serum, liver and kidney, suggesting its role in protection against lipid peroxidation induced membrane damage. CFBEt has beneficial effect on plasma insulin and blood glucose level. Moreover, it prevented lipid metabolism defects which could represent a protective mechanism against the development of atherosclerosis.

Keywords: Lipids, *Cassia auriculata*, Metformin, Streptozotocin, Diabetes, Liver, Kidney

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Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by abnormalities in carbohydrate and lipid metabolism (Cowie and Eberhardt, 1996), which leads to hyperglycemia and hyperlipidemia (DeFronzo *et al.*, 1992). The relationship between diabetes and hyperlipidemia is a well-recognized phenomenon. Insulin deficiency/insulin resistance is considered to be a significant pathogenic factor in diabetes mellitus

and an obvious target for antidiabetic medications (Yamashita, 2002). Hyperlipidemia in diabetes mellitus is characterized by elevated levels of cholesterol (TC), triglycerides (TG), phospholipids (PL) and changes in lipoprotein composition (Haffner, 1991). These alterations may be relevant in explaining at least in part the increased predisposition of diabetes to atherosclerosis.

Hyperlipidemia in diabetes certainly contributes to the high prevalence of accelerated atherosclerosis and coronary artery disease (Gandhi, 2001). Coronary artery disease, as a result of premature atherosclerosis is a major cause of death both in type 1 and type 2 diabetes. It has been suggested that individuals possessing abnormalities in circulating lipids and glucose have strong tendency to develop diabetes (Zavaroni *et al.*, 1989).

Cassia auriculata L. (Ceasalpiniaceae) is a shrub that has attractive yellow flowers, commonly used for the treatment of skin disorders and body odour. It is a native plant present in different parts of India. Indigenous people use various parts of the plant for diabetes mellitus (Murugan, 2010; Murugan and Jawahar, 2020; Murugan and Sakthivel, 2020; Murugan *et al.*, 2020a). It is widely used in Ayurvedic medicine as a “Kalpa drug” which contains five parts of the shrub (roots, leaves, flowers, bark and unripe fruits) which are taken in equal quantity, dried and then powdered to give “Avarai Panchaga Choornam”, for the control of sugar levels and reduction of symptoms such as polyuria and thirst in diabetes (Murugan *et al.*, 2020b; Murugan and Sakthivel, 2021). A literature survey showed that a decoction of leaves, flowers, and seeds of the *Cassia auriculata* mediate an antidiabetic effect (Murugan, 2015a, 2022). Thus, the available reports show that very little work has been done with respect to *Cassia auriculata* flowers, other than its hypoglycemic effects. (Murugan, 2015b; Murugan, 2023 a, b, c). The present study investigated the effects of *Cassia auriculata* flowers buds extract CFBEt (0.45 g/kg b wt), and metformin on plasma glucose, insulin, thiobarbituric acid reactive substances (TBARS) and hydroperoxides formation, cholesterol, triglycerides, free fatty acids and phospholipids as well as on histopathological changes in liver and kidney of normal and streptozotocin (STZ) – induced diabetic rats.

Materials and Methods

Chemicals:

Stereptozotocin was obtained from Himedia Laboratory Limited, Mumbai, India. All other reagents used were of analytical grade.

Plant Material:

Cassia auriculata flower buds were collected freshly from Neyveli, Cuddalore District, Tamil Nadu, India. The plant was identified and authenticated at the Herbarium of Botany Directorate in Annamalai University.

Preparation of plant extract:

500 g of *Cassia auriculata* flower buds were extracted with 1,500 ml of water by the method of continuous hot extraction at 60°C for 6 h and evaporated. The residual extract was dissolved in water and used in the study (Jain, 1968).

Induction of diabetes:

Non-Insulin dependent diabetes mellitus was induced (Masiello *et al.*, 1998) in overnight fasted rats by a single intraperitoneal (i.p.) injection of streptozotocin (65 mg/kg b wt), 15 min after the i.p. administration of 110 mg/kg b wt of nicotinamide. Streptozotocin was dissolved in citrate buffer (pH 4.5) and nicotinamide was dissolved in normal saline. Hyperglycemia was confirmed by the elevated glucose levels in plasma, determined after 72 h and then on day 7 after injection. The animals with blood glucose concentration more than 200 mg/dl were used for the study.

Experimental procedure:

In the experiment, a total of 24 rats (18 diabetic surviving rats, six normal rats) were used. The rats were divided in to 4 groups of six rats each and received following treatment:.

Group 1: Normal untreated rats.

Group 2: Diabetic control rats given 1 ml of aqueous solution daily using an intragastric tube for 45 days.

Group 3: Diabetic rats given CFBEt (0.45 g/kg b wt) in 1 ml of aqueous solution daily using an intragastric tube for 45 days.

Group 4: Diabetic rats given metformin (500 mg/kg b wt) in 1 ml of aqueous solution daily using an intragastric tube for 45 days.

At 45 days, the animals were deprived of food overnight and sacrificed by decapitation. Blood was collected in tubes containing potassium oxalate and sodium fluoride mixture for the estimation of blood glucose. Plasma was separated for the estimation of insulin and other biochemical parameters. Liver and kidney were immediately dissected out, washed in ice-cold saline to remove the blood. The tissues were weighed and 10% tissue homogenate was prepared with 0.025 M Tris - HCl buffer, pH 7.5. After centrifugation at 200 rpm for 10 min, the clear supernatant was used to measure thiobarbituric acid reactive substances and hydroperoxides. For the determinations of lipids the liver and kidney tissues were weighed and lipids were extracted from tissues by the method of Folch *et al.* (1957) using chloroform - methanol mixture (CHCl₃:MeOH)(2:1 v/v).

Analytical procedure:

Blood glucose was estimated colorimetrically using commercial diagnostic kits (Sigma Diagnostics (I) Pvt. Ltd., Baroda, India) (Lott and Turner, 1975). Plasma insulin was assayed by ELISA using a Boehringer-Mannheim kit with an ES300 Boehringer analyzer (Mannheim, Germany). Haemoglobin was estimated using the cyanmethaemoglobin method described by Drabkin and Austin (1932). Glycosylated haemoglobin was estimated according to the method of Nayak and Pattabiraman (1981) with modifications according to Bannon (1982). Thiobarbituric acid reactive substances were measured by the method of Fraga *et al.* (1988). Hydroperoxides were determined by the method of Jiang *et al.* (1992).

Extraction of lipids from serum and tissues was carried out according to the procedure of Folch *et al.* (1957) by using chloroform - methanol (2:1 v/v) mixture. From this, the total cholesterol, triglycerides (TG), free fatty acids (FFA) and

phospholipids (PL) were estimated by the method of Zlatkis *et al.* (1953), Foster and Dunn (1973), Falholt *et al.* (1973) and Zilversmit and Davis (1950), respectively.

Statistical analysis:

The data for various biochemical parameters were analyzed using Analysis of Variance (ANOVA), and the group means were compared by Duncan's multiple range test (DMRT). Values were considered statistically significant if $p < 0.05$ (Duncan 1957).

Results

Table 1 shows the level of blood glucose, total haemoglobin, glycosylated haemoglobin and plasma insulin of different experimental groups. There was a significant elevation in blood glucose level, whereas plasma insulin levels decreased significantly in streptozotocin diabetic rats, compared with normal rats. The effect of CFBet was more prominent when compared with metformin. The diabetic control rats showed a significant decrease in the level of total haemoglobin and significant increase in the level of glycosylated haemoglobin. Oral administration of CFBet to diabetic rats significantly restored total haemoglobin and glycosylated haemoglobin levels. In the case of normal rats, the level of haemoglobin and glycosylated haemoglobin remained unaltered.

Table 2 represents the concentration of TBARS and hydroperoxides in tissues of normal and experimental rats. There was a significant elevation in tissue TBARS and hydroperoxides during diabetes, when compared to the corresponding normal group. Administration of CFBet, and metformin significantly decreased the lipid peroxidation in diabetic rats. The CFBet was more potent than metformin.

The levels of serum and tissue cholesterol, free fatty acids, TG and PL of normal and experimental rats are given in Table 3. Cholesterol, free fatty acids, TG and PL were significantly decreased in CFBet treated rats as compared to diabetic rats. Oral administration of CFBet at (0.45 g/kg)

Table 1: Effect of CFBET on the levels of blood glucose, plasma insulin, haemoglobin and glycosylated haemoglobin in normal and experimental rats

Groups	Fasting blood glucose (mg/dl)	Plasma insulin (μU/ml)	Total haemoglobin (g/dl)	Glycosylated haemoglobin (mg/g Hb)
Normal	98.51 ± 5.39 ^a	12.31 ± 0.51 ^a	12.71 ± 0.45 ^a	0.31 ± 0.02 ^a
Diabetic control	273.31 ± 7.42 ^b	3.71 ± 0.20 ^b	7.37 ± 0.40 ^b	0.71 ± 0.03 ^b
Diabetic + CFBET (0.45 g/kg)	110.32 ± 6.43 ^c	9.41 ± 0.32 ^c	11.31 ± 0.77 ^c	0.37 ± 0.02 ^c
Diabetic + Metformin (500 mg/kg)	137.39 ± 6.40 ^d	8.30 ± 0.30 ^d	10.49 ± 0.39 ^d	0.50 ± 0.03 ^d

Values are given as mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at p<0.05 (DMRT)

Table 2: Influence of CFBET on the content of TBARS and hydroperoxides in rats liver and kidney

Groups	Normal	Diabetic control	Diabetic + CFBET (0.45 g/kg)	Diabetic + Metformin (500 mg/kg)
<i>TBARS</i>				
Liver (mM/100 g tissue)	0.75 ± 0.03 ^a	1.83 ± 0.11 ^b	1.37 ± 0.04 ^c	1.20 ± 0.03 ^d
Kidney (mM/100 g tissue)	1.83 ± 0.10 ^a	3.91 ± 0.20 ^b	2.27 ± 0.10 ^c	2.13 ± 0.03 ^e
<i>Hydroperoxides</i>				
Liver (mM/100 g tissue)	82.13 ± 5.39 ^a	100.31 ± 5.51 ^b	90.74 ± 4.29 ^c	85.26 ± 0.03 ^d
Kidney (mM/100 g tissue)	56.10 ± 3.12 ^a	80.45 ± 4.51 ^b	65.13 ± 3.10 ^c	71.49 ± 4.30 ^d

Values are given as mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at p<0.05 (Duncan's Multiple Range test)

Table 3: Effect of CFBet on the levels of cholesterol, free fatty acids, triglycerides and phospholipids in serum, liver and kidney of normal and experimental rats

Groups	Normal	Diabetic control	Diabetic + CFBet (0.45 g/kg)	Diabetic + Metformin (500 mg/kg)
Cholesterol				
Serum (mg/100ml)	87.48 ± 5.15 ^a	169.13 ± 11.12 ^b	110.41 ± 7.15 ^c	131.10 ± 6.21 ^d
Liver (mg/100g wet tissue)	320.42 ± 13.41 ^a	500.12 ± 33.54 ^b	410.25 ± 23.40 ^c	450.22 ± 25.64 ^c
Kidney(mg/100g wet tissue)	365.36 ± 20.65 ^a	536.18 ± 31.15 ^b	420.11 ± 20.30 ^c	462.71 ± 24.15 ^c
Free fatty acids				
Serum (mg/100ml)	79.35 ± 4.51 ^a	149.47 ± 10.13 ^b	91.54 ± 5.15 ^c	118.20 ± 6.75 ^d
Liver (mg/100g wet tissue)	590.52 ± 30.54 ^a	853.10 ± 55.13 ^b	734.25 ± 40.30 ^c	785.12 ± 34.20 ^c
Kidney(mg/100g wet tissue)	423.74 ± 19.53 ^a	675.32 ± 36.63 ^b	542.60 ± 32.60 ^c	530.12 ± 25.20 ^d
Triglycerides				
Serum (mg/100ml)	57.35 ± 3.23 ^a	92.40 ± 6.25 ^b	64.41 ± 4.10 ^c	73.20 ± 4.51 ^d
Liver (mg/100g wet tissue)	330.43 ± 22.45 ^a	610.40 ± 35.15 ^b	421.50 ± 20.83 ^c	530.12 ± 24.65 ^d
Kidney(mg/100g wet tissue)	270.33 ± 14.11 ^a	420.39 ± 20.11 ^b	375.15 ± 22.25 ^c	430.35 ± 14.12 ^d
Phospholipids				
Serum (mg/100ml)	112.65 ± 6.32 ^a	165.11 ± 12.11 ^b	125.11 ± 8.25 ^c	160.65 ± 8.54 ^d
Liver (g/100g wet tissue)	1.45 ± 0.11 ^a	3.13 ± 0.15 ^b	1.92 ± 0.15 ^c	2.22 ± 0.12 ^d
Kidney (g/100g wet tissue)	1.57 ± 0.12 ^a	2.30 ± 0.14 ^b	1.71 ± 0.13 ^c	1.98 ± 0.13 ^d

Values are given as mean ± S.D for 6 rats in each group. Values not sharing a common superscript letter differ significantly at p<0.05 (DMRT)

significantly decreased the levels of serum and tissue lipids as compared to untreated diabetic rats. The CFBET administration was more effective than metformin.

Discussion

Type 2 diabetes is characterized by progressive deterioration of normal pancreatic β -cell function. Generally, hepatic and muscle tissues lose sensitivity to the action of insulin (Porte and Kahn, 2001). In the early stages of the disease, the β -cells of the pancreatic islets compensate for decreased insulin sensitivity by increasing insulin secretion. As the disease progresses, diabetes ensues when β -cell is no longer able to compensate for insulin resistance.

Glycated proteins are formed post-translationally from the slow, non-enzymic reaction between glucose and amino groups on proteins (Murugan, 2010). For haemoglobin, the rate of synthesis of glycated haemoglobin is principally a function of the concentration of glucose to which the erythrocytes are exposed. Glycated haemoglobin is the most important glycated fraction of the haemoglobin molecule. In diabetes, there is an increased glycation of a number of proteins including haemoglobin. Haemoglobin is highly susceptible to non-enzymic glycation.

In diabetic condition, the excess of glucose present in the blood react with haemoglobin to form glycated haemoglobin, which has altered affinity for oxygen and this may be a factor in tissue anoxia. Glycated haemoglobin was significantly increased in diabetic rats and this increase is directly proportional to fasting blood glucose. The significant decrease in haemoglobin observed in the present study was well correlated with results from other studies, which reported that there was a decrease in the level of haemoglobin in experimental diabetic animals (Murugan and Pari, 2006 a, b). *Cassia auriculata* supplementation prevents the increase of haemoglobin glycosylation and decreases the oxidative stress in erythrocytes exposed to high

levels of glucose (Jain *et al.*, 2006). The increase in the level of haemoglobin in rats given CFBET controls the glycation of haemoglobin by its normoglycemic activity and thus decreases the level of glycated haemoglobin in STZ diabetic rats. It may reduce the tissue damage and chronic complications associated with the eyes, kidneys, nerves and cardiovascular system.

In the present study an increase in serum, hepatic and renal thiobarbituric acid reactive substances and hydroperoxides concentration in streptozotocin induced diabetic rats was noticed when compared with the normal rats. In diabetes, hypoinsulinaemia increases the activities of the enzymes, fatty acyl coenzyme and coenzyme A oxidase, which initiates β -oxidation of fatty acids resulting in lipid peroxidation (Murugan and Pari, 2006a). Increased lipid peroxidation impairs membrane functions by decreasing membrane fluidity, and changing the activity of membrane-bound enzymes. Its products (lipid radicals and lipid peroxide) are harmful to the cells in the body and are associated with atherosclerosis and brain damage.

This study shows that administration of CFBET significantly decreased the serum, liver and kidney thiobarbituric acid reactive substances and hydroperoxides. This derives support from previous report which describes that *Cassia auriculata* increase hepatic GSH levels and induces certain forms of GSH transferase important in preventing lipid peroxidation and detoxification of toxic lipid aldehydes in diabetic cataract rats (Murugan *et al.*, 2020a).

Hyperlipidaemia is the major metabolic complication of both clinical and experimental diabetes (Bierman *et al.*, 1975). It has been demonstrated that insulin deficiency in diabetes leads to a variety of derangements in metabolic and regulatory process, which in turn leads to accumulation of lipids such as TC and TGs in diabetic patients (Jaiprakash *et al.*, 1993). Changes in the concentration of plasma lipids including TC are complications frequently observed in patients with diabetes and certainly contribute to the

development of vascular disease (Nikkila and Kekki, 1973).

Hypercholesterolemia and hypertriglyceridemia are independent major risk factors that alone or together can accelerate the development of coronary artery disease (CAD) (McKenney, 2001). The cause of hyperlipidemia has been related to increased lipid synthesis, decreased lipid clearance from the blood or a combination of these two processes.

The liver and kidney participates in the uptake, oxidation and metabolic conversion of FFAs, synthesis of TC and PLs and secretion of specific classes of plasma lipoproteins. In this study, CFBET decreases the blood glucose in diabetic rats. The possible mechanism by which CFBET mediates its antidiabetic action may be by potentiation of pancreatic secretion of insulin from existing β -cell or due to enhanced transport of blood glucose to peripheral tissue. It is evidenced by the significant increase in the level of insulin by CFBET in diabetic rats.

In this experiment, diabetes mellitus characterized by hyperglycaemia and hyperlipidemia, which indicate the increased risk for the complications of atherosclerosis. Lowering of serum lipid levels through dietary or drug therapy seems to be associated with a decrease in the risk of vascular disease and related complications (Brown *et al.*, 1993).

The results of this study indicate that lipid and lipoprotein abnormalities developed in diabetic condition were significantly counteracted by administration of CFBET. Excess of fatty acid in serum promotes the conversion of some liver and kidney fatty acids into PLs and cholesterol. These two substances along with excess TGs formed at the same time in the liver and may be discharged into the blood in the form of lipoproteins (Bopanna *et al.*, 1997). This high lipid concentration may lead to the rapid development of atherosclerosis in diabetic patients (Pushparaj *et al.*, 2000). Besides serum cholesterol, the

elevated levels of TGs and PLs are also reduced by CFBET.

Diabetic rats treated with CFBET showed significant decrease in serum and tissue lipids. The abnormal high concentration of serum lipids in diabetes is mainly due to the increase in the mobilization of FFAs from the peripheral depots, since insulin inhibits the hormone sensitive lipase.

PL are vital components of biomembranes and TC is responsible for the increased synthesis of ischemic PL (Marsch *et al.*, 1976). In this context, higher levels of cholesterol, TG and PL have been observed in diabetic liver and kidney (Murugan and Pari, 2006). Oral administration of CFBET to diabetic rats reversed all the above changes.

In this study the increased concentration of FFAs were observed in liver and kidney of diabetic rats. Elevated levels of FFAs may promote synthesis of PLs and cholesteryl esters by the liver (Frayn, 1993). The observed rise in FFAs in the liver and kidney may be attributed to the increased transport of fatty acid as a result of excessive mobilization of fatty acids (Woodside, 1972). The diabetic complication associated with renal tissue may be partly due to abnormality in lipid metabolism. Administration of CFBET decreased the FFAs in tissues such as liver and kidney.

Conclusion

CFBET significantly reduces the level of serum and tissue lipids and lipid peroxidation marker, which are actively raised in streptozotocin diabetic rats. CFBET has beneficial effect on plasma insulin and blood glucose level. Moreover, the prevention of lipid metabolism defects could represent a protective mechanism against the development of atherosclerosis. The CFBET administration was more effective than metformin.

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