Cinnamon bark extract improves glucose metabolism and lipid profile in the fructose-fed rat

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ABSTRACT

Introduction: The present study was designed to investigate whether cinnamon bark extract (CBEt) mitigates the adverse effects of fructose loading on glucose metabolism and lipid profile in rats.

Methods: Adult male albino rats of body weight 150-170 g were divided into five groups and fed with either control or high fructose diet (HFD). CBEt was administered to HFD-fed rats orally at two doses (a low and a high dose) while the control diet-fed rats were treated with a high dose of CBEt. The treatment protocol was carried out for 60 days after which the oral glucose tolerance test was carried out. Biochemical parameters related to glucose metabolism and lipid profile were assayed.

Results: The levels of glucose, insulin and protein-bound sugars were higher and activities of enzymes of glucose metabolism were altered in HFD-fed rats, as compared to control animals. The levels were brought back to near-normal when administered with CBEt at high dose. CBEt also prevented the hyperlipidaemia observed in fructose-fed rats and improved glucose tolerance. CBEt did not show any significant effect in fructose-fed rats when administered at low dose.

Conclusion: These findings indicate the improvement of glucose metabolism in-vivo by CBEt in fructose-fed rats.

Keywords: cinnamon bark, fructose diet, glucose metabolism, insulin resistance, lipids

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INTRODUCTION

Insulin resistance (IR) is defined as diminished tissue response to the hormone at one or more sites in the complex pathways of its action. The condition presents profound alterations in the metabolic pathways regulated by insulin. Defects in glucose uptake, hexokinase activity and glycogen synthesis have been reported in the insulin resistant states[1]. High dosage of fructose in the diet has been documented to induce IR accompanied by deleterious metabolic consequences including hyperinsulinaemia, hyperglycaemia, glucose intolerance, hypertriglyceridaemia and hypertension in rodents[2,3]. The fructose-fed rat is therefore used as an animal model of insulin resistance and is considered to parallel multiple metabolic syndrome (syndrome X) observed in humans[4]. Studies have demonstrated low levels of insulin-stimulated glucose oxidation in the liver[5], skeletal muscle[6] and adipose tissue[3] in fructose-fed rats.

Spices are plant-derived products, which are added to food preparations to impart taste and aroma. Their medicinal properties are well known and are documented to possess antioxidant, antidiabetic, antiallergic, antiatherosclerotic effects in animals[7,8]. In the past few years, there has been much consideration about the influence of spices on insulin action. Khan et al[9] reported that extracts of some spices have insulin-like or insulin potentiating action. Among the spices, we were interested in the bark of cinnamon used as a culinary herb in Indian homes and in oriental countries. Cinnamon is an evergreen tree, which has been traditionally harvested in Asian countries. It is one of the oldest herbal medicines that have been mentioned in Chinese texts as early as 4,000 years ago[10]. Cinnamon belongs to the family *Lauraceae*. The bark of cinnamon possesses significant antiallergic, antiulcerogenic, antipyretic and antioxidant properties[10-12].

The potential role of cinnamon on insulin action has been shown in several in-vitro studies. For example, an aqueous extract of cinnamon increased glucose metabolism roughly 20-fold in-vitro in the epididymal fat cells[13]. Further, a methyl hydroxy

chalcone polymer (MHCP) derived from cinnamon enhanced the glucose uptake, glycogen synthesis and phosphorylation of insulin receptor in 3T3-L1 adipocytes[14]. These studies suggest that cinnamon could act as an insulin mimetic.

In view of the above, it is of importance to generate scientific data to ascertain the effects of cinnamon in-vivo in the insulin-resistant state and to study dose-response of cinnamon on certain variables related to glucose metabolism. We used rats fed a high fructose diet (HFD) as a model of insulin resistance and determined the levels of glucose, insulin, glycated haemoglobin and protein-bound sugars in plasma and the activities of glucose metabolising enzymes and glycogen content in the liver, kidney and skeletal muscle of HFD-fed rats treated with low and high doses of cinnamon bark extract (CBEt). The response to oral glucose challenge and homeostatic model assessment (HOMA) values were determined to assess insulin action. Additionally, we determined the effect of CBEt on plasma lipid profile in HFD-fed rats.

METHODS

Adult male albino rats of Wistar strain weighing 150-170 g were used for the study. Animals were purchased and maintained in the Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai Nagar, India. The animals were individually housed under controlled temperature and hygienic conditions in polypropylene cages under 12-hour light and dark cycles. They all received a standard pellet diet (Karnataka State Agro Corporation Ltd, Agro Feeds Division, Bangalore, India) and water ad libitum. The procedures used in the study are approved by the Institutional Animal Ethics Committee.

Cinnamon bark (*Cinnamomum zeylanicum*) was purchased from the local market at Chidambaram. All the chemicals were of analytical grade and were procured from local commercial companies. The bark was dried and finely powdered in a mechanical mixer. 10 g of finely-powdered cinnamon was weighed and mixed with 100 ml of water and kept in a water bath at 60°C for two hours and filtered[15]. This extract was diluted with water (1:10) and was administered orally to rats.

After acclimatisation, the animals were divided into following groups consisting of six rats per group and were maintained as follows: Group 1 (CON) received the control diet and tap water ad libitum. The control diet contained corn starch (60%) as the sole source of carbohydrate, 20% casein, 0.7% methionine, 5% groundnut oil, 10.5% wheat bran and 3.5% salt mixture and water ad libitum for 60 days. Vitamin mixture (0.2 ml) was added per kg feed. Group 2 animals (FRU) received a HFD and water ad libitum for 60 days. The HFD was similar in composition to the control diet except that starch was replaced by fructose. Group 3 (FRU + CBEt-1) received the HFD and tap water ad libitum for 60 days. CBEt (0.2 ml/day/rat) was administered orally from the 16th day of fructose feeding. Group 4 (FRU + CBEt-2) received HFD and tap water ad libitum for 60 days. CBEt (2 ml/day/rat) was administered orally from the 16th day of fructose feeding. Group 5 (CON + CBEt-2) received the control diet and tap water ad libitum for 60 days. CBEt (2 ml/day/rat) was administered orally from the 16th day of fructose feeding.

The body weights of the animals were recorded every day and food intake was measured daily. An oral glucose tolerance test[16] was carried out on Day 59. For this, the animals were fasted overnight (12 h) and were orally administered glucose (2 g/kg body weight) after collecting the fasting blood samples. Additional blood samples were drawn after one hour and two hours, by sino-ocular puncture in heparinised test tubes and centrifuged at 3,000 × g for 15 minutes to separate plasma. Glucose levels were determined and the area under the curve (AUC) for glucose was calculated.

At end of 60 days, the animals were sacrificed by cervical decapitation. Blood was collected from the jugular vein with heparin as anticoagulant and centrifuged at 3,000 × g for 15 minutes to separate plasma. Assays were carried in plasma for glucose[17], insulin, hexose[18], hexosamine[19], sialic acid[20], fucose[21], glycated haemoglobin[22], cholesterol[23], triglycerides[24], free fatty acids[25] and phospholipids[26]. Insulin was assayed using a immunoassay kit obtained from Medgenix-INS-EASIA, Europe. HOMA, as a measure of insulin resistance, was calculated using the formula [insulin (μU/ml) × glucose (mmol/L)/22.5][27].

The body was cut open, then the liver, kidney and muscle were removed and washed in ice-cold saline. Homogenates were prepared in 0.1M Tris-Hcl buffer, pH 7.4 and used for the assay of hexokinase[28], glucose 6-phosphatase[29], fructose-1,6-bisphosphatase[30], glucose-6-phosphate dehydrogenase[31] and glycogen[32].

All the values were expressed as means ± SD of six rats from each group and statistically evaluated by two-way analysis of variance, considering diet and CBEt-2 treatment as two factors. A value of $p<0.05$ was considered significant. The AUV for glucose, $AUC_{glucose}$, was calculated using GraphPad Prism version 4.03 (GraphPad Software Inc, San Diego, CA, USA).

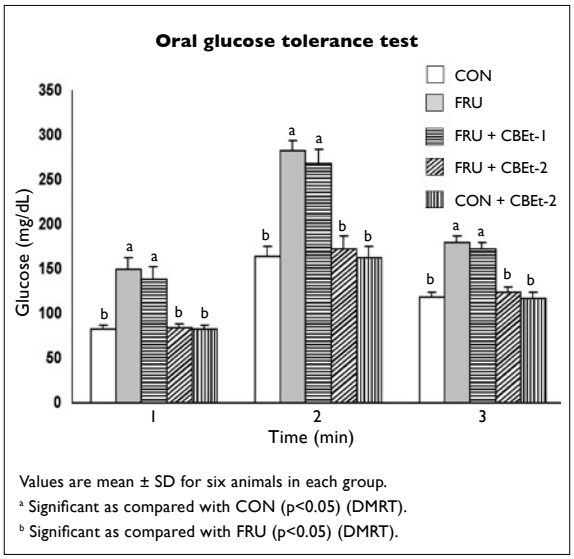

Fig. 1 Glucose tolerance test of control and experimental animals.

RESULTS

The results of the oral glucose tolerance test in experimental animals are depicted in Fig. 1. The mean value of fasting glucose was higher in HFD-fed rats as compared to control rats. The value was significantly decreased in fructose-fed rats treated with CBEt-2 compared to the untreated fructose-fed rats. In addition, significant elevations were observed in the glucose levels after the oral glucose load at all the time points in fructose-fed rats. The response was normal in CBEt-2 treated rats. $AUC_{glucose}$ (mg/ml/min) for control and experimental animals were CON=159.08 ± 11.23; FRU=268.51 ± 21.60; FRU + CBEt-1=254.85 ± 18.45; FRU + CBEt-2= 166.58 ± 11.30; and CON + CBEt-2=157.78 ± 10.97. $AUC_{glucose}$ was significantly higher in fructose-fed rats as compared to that of control rats. CBEt-2 supplementation to fructose-fed rats significantly reduced $AUC_{glucose}$ values.

The levels of plasma glucose, insulin, HOMA and glycated haemoglobin in circulation are shown in Table I. There was a significant elevation in glucose, insulin and glycated haemoglobin at the 60th day of fructose feeding. Co-treatment with CBEt-2 reduced the levels of glucose, insulin and glycated haemoglobin to near normal values. HOMA was elevated in fructose-fed rats and in CBEt-2 treated HFD-fed rats, the levels were close to normal. Table II shows the activity of hexokinase and the level of glycogen in the liver and skeletal muscle. The values were lower in fructose-fed rats as compared to normal rats. Treatment with CBEt-2 significantly increased the activity of hexokinase and glycogen content.

The activities of glucose-6-phosphatase, fructose-1,6-bisphosphatase and glucose-6-phosphate dehydrogenase in liver, kidney and skeletal muscle are presented in Table III. In fructose-fed rats significant increases were observed. Treatment with CBEt-2 prevented the increase. Table IV gives the levels of hexose, hexosamine, sialic acid and fucose in plasma. CBEt-2 administration to fructose-fed rats brought back the levels to normal levels.

HFD caused significant elevations of cholesterol, triglycerides, free fatty acids and phospholipids in plasma of control and experimental animals (Table V). On the other hand, CBEt-2 administered fructose-fed rats showed a normal lipid profile. In all the parameters studied, we observed no significant changes in cinnamon-treated control rats (CON + CBEt) as compared to control rats. Further, CBEt administration at low dose was not effective in controlling the changes associated with HFD.

Table I. Levels of glucose, insulin, glycated haemoglobin and HOMA values in plasma of control and experimental animals.

Parameter	CON	FRU	FRU + CBEt-1	FRU + CBEt-2	CON + CBEt-2	ANOVA[2]		
						Diet	Treatment	Interaction
Glucose (mM)	4.46 ± 0.21	7.00 ± 0.55[a]	6.70 ± 0.47[a]	4.71 ± 0.35[b]	4.35 ± 0.16	0.05	0.05	0.05
Insulin (μmoles/L)	42.31 ± 3.84	79.68 ± 3.98[a]	75.52 ± 4.62[a]	45.62 ± 3.39[b]	43.38 ± 4.14	0.05	0.05	0.05
HOMA	8.36 ± 0.58	24.82 ± 2.67[a]	23.21 ± 1.04[a]	9.55 ± 0.78[b]	8.30 ± 0.59	0.05	0.05	0.05
Glycated haemoglobin (% total Hb)	1.21 ± 0.10	3.66 ± 0.29[a]	3.51 ± 0.26[a]	1.42 ± 0.12[b]	1.25 ± 0.13	0.05	0.05	0.05

Values are mean ± SD of six rats from each group.

CON: control rats; FRU: fructose-fed rats; FRU + CBEt-1: fructose-fed rats treated with CBEt (0.2 ml); FRU + CBEt-2: fructose-fed rats treated with CBEt (2 ml); CON + CBEt-2: control rats treated with CBEt (2 ml).

[a] Significant as compared with control rats (p<0.05) (DMRT).

[b] Significant as compared with fructose-fed rats (p<0.05) (DMRT).

Table II. Hexokinase activity and glycogen content in liver, kidney and skeletal muscle of control and experimental animals.

Parameter	CON	FRU	FRU + CBEt-1	FRU + CBEt-2	CON + CBEt-2	ANOVA[2]		
						Diet	Treatment	Interaction
Liver								
Hexokinase*	0.23 ± 0.02	0.18 ± 0.01[a]	0.19 ± 0.01[a]	0.21 ± 0.02[b]	0.24 ± 0.01	0.05	0.05	NS
Glycogen[#]	42.76 ± 3.45	30.85 ± 2.56[a]	33.53 ± 2.90[a]	40.23 ± 3.35[b]	43.03 ± 3.64	0.05	0.05	0.05
Kidney								
Hexokinase*	8.40 ± 0.32	5.10 ± 0.23[a]	5.16 ± 0.44[a]	8.13 ± 0.36[b]	8.43 ± 0.42	0.05	0.05	0.05
Skeletal muscle								
Hexokinase*	4.41 ± 0.32	2.36 ± 0.21[a]	2.39 ± 0.12[a]	4.29 ± 0.34[b]	4.51 ± 0.25	NS	0.05	NS
Glycogen[#]	8.85 ± 0.44	3.21 ± 0.24[a]	3.69 ± 0.34[a]	8.63 ± 0.40[b]	8.99 ± 0.58	0.05	0.05	0.05

Values are mean ± SD of six rats from each group. Treatment of animals and comparisons are as given in Table I.

* μmoles of glucose phosphorylated/h/mg protein.

[#] mg of glucose/g tissue.

NS - not significant.

Table III. Activities of G6Pase, F1, 6pase and G6PDH in tissues of control and experimental animals.

Parameter	CON	FRU	FRU + CBEt-1	FRU + CBEt-2	CON + CBEt-2	ANOVA[2]		
						Diet	Treatment	Interaction
Liver								
G6pase*	4.11 ± 0.23	6.24 ± 0.46[a]	6.07 ± 0.38[a]	4.27 ± 0.30[b]	3.94 ± 0.24	0.05	0.05	NS
F1,6pase[#]	3.96 ± 0.26	11.79 ± 0.80[a]	11.23 ± 0.69[a]	4.24 ± 0.20[b]	4.07 ± 0.34	0.05	0.05	0.05
G6PDH[#]	4.78 ± 0.36	3.58 ± 0.28[a]	3.72 ± 0.24[a]	4.53 ± 0.22[b]	4.87 ± 0.37	0.05	0.05	0.05
Kidney								
G6pase*	3.81 ± 0.28	4.40 ± 0.34[a]	4.31 ± 0.38[a]	3.92 ± 0.29[b]	3.74 ± 0.32	0.05	0.05	NS
F16pase*	4.22 ± 0.37	12.88 ± 0.81[a]	12.49 ± 0.70[a]	4.57 ± 0.87[b]	4.12 ± 0.28	0.05	0.05	0.05
G6PDH[#]	3.29 ± 0.27	2.61 ± 0.24[a]	2.76 ± 0.24[a]	3.16 ± 0.24[b]	3.22 ± 0.27	0.05	0.05	0.05
Skeletal muscle								
G6pase*	4.97 ± 0.37	5.79 ± 0.44[a]	5.67 ± 0.36[a]	5.08 ± 0.36[b]	4.79 ± 0.46	0.05	0.05	NS
Glycogen[#]	8.85 ± 0.44	3.21 ± 0.24[a]	3.69 ± 0.34[a]	8.63 ± 0.40[b]	8.99 ± 0.58	0.05	0.05	0.05
F16pase*	4.09 ± 0.37	11.08 ± 0.73[a]	10.71 ± 0.40[a]	4.55 ± 0.36[b]	4.36 ± 0.27	0.05	0.05	0.05
G6PDH[#]	4.71 ± 0.32	3.40 ± 0.33[a]	3.55 ± 0.27[a]	4.59 ± 0.21[b]	4.86 ± 0.25	0.05	0.05	0.05

Values are mean ± SD of six rats from each group. Treatment of animals and comparisons are as given in Table I.

* μg of Pi liberated/min/mg protein.

[#] mIU/mg protein $\leftrightarrow 10^{-4}$.

NS - not significant.

Table IV. Protein-bound carbohydrates in plasma of control and experimental animals.

Parameter	CON	FRU	FRU + CBEt-1	FRU + CBEt-2	CON + CBEt-2	ANOVA[2]		
						Diet	Treatment	Interaction
Hexose (mg/dL)	97.77 ± 8.3	114.46 ± 9.90[a]	111.01 ± 7.33[a]	98.27 ± 8.47[b]	94.54 ± 7.20	0.05	0.05	NS
Hexosamine (mg/dL)	74.15 ± 6.99	92.87 ± 5.24[a]	87.90 ± 6.95[a]	78.49 ± 6.44[b]	76.62 ± 6.04	0.05	0.05	0.05
Fucose (mg/dL)	30.52 ± 2.86	39.62 ± 2.74[a]	37.73 ± 2.36[a]	33.09 ± 2.21[b]	30.95 ± 2.33	0.05	0.05	0.05
Sialic acid (mg/dL)	54.44 ± 4.20	65.37 ± 3.13[a]	63.55 ± 5.24[a]	56.24 ± 3.40[b]	52.18 ± 3.37	0.05	0.05	0.05

Values are mean ± SD of six rats from each group. Treatment of animals and comparisons are as given in Table I.

NS - not significant.

Table V. Plasma lipid profile in plasma of control and experimental animals.

Parameter	CON	FRU	FRU + CBEt-1	FRU + CBEt-2	CON + CBEt-2	ANOVA[2]		
						Diet	Treatment	Interaction
Cholesterol (mg/dL)	70.57 ± 6.40	80.01 ± 7.39[a]	80.37 ± 5.90[a]	71.87 ± 5.55[b]	68.60 ± 6.57	NS	0.05	NS
Triglycerides (mg/dL)	86.34 ± 6.67	153.29 ± 11.75[a]	144.69 ± 11.15[a]	91.33 ± 6.37[b]	84.35 ± 6.83	0.05	0.05	0.05
Free fatty acids (mg/dL)	17.63 ± 1.48	24.03 ± 1.95[a]	22.90 ± 2.04[a]	18.01 ± 1.77[b]	16.93 ± 1.50	0.05	0.05	0.05
Phospholipids (mg/dL)	92.43 ± 8.18	103.22 ± 8.93[a]	102.44 ± 9.13[a]	93.82 ± 5.13[b]	89.84 ± 2.66	0.05	0.05	NS

Values are mean ± SD of six rats from each group. Treatment of animals and comparisons are as given in Table I.

NS - not significant.

DISCUSSION

Increase in plasma glucose level associated with hyperinsulinaemia suggests impaired insulin action in fructose-fed rats. The degree of insulin resistance was higher in fructose-fed rats as indicated by high HOMA values. The rats also showed impaired glucose tolerance after the oral glucose challenge. Insulin resistance in fructose-fed rats has been attributed to a low level of insulin-stimulated glucose oxidation due to modifications in the post-receptor cascade of insulin action[33]. Increased glycated haemoglobin level is an index of hyperglycaemia. During hyperglycaemia, glucose reacts non-enzymatically with neighbouring proteins through the Maillard reaction. Haemoglobin is particularly susceptible to glycation among the other proteins[34].

Decreased activities of hexokinase and glucose-6-phosphate dehydrogenase indicates impaired glucose oxidation and decreased peripheral glucose utilisation, while the increased activities of glucose-6-phosphatase and fructose-1,6-bisphosphatase and decreased glycogen content in fructose-fed rats confirm the gluconeogenic state. Decreased glycogen content in tissues could be due to reduced synthesis or increased breakdown of glucose. Reduction in hepatic glycogen concentration in liver and muscle has been reported in fructose-fed rats[3,35].

We also looked at the levels of sugars and amino sugars bound to proteins. Glycosylation is an enzymatic process utilising amino sugars during the post-translational covalent modification of proteins. Increase in glucose can increase the flux through the hexosamine biosynthetic pathway in tissues. Increase in the level of amino sugars and protein-bound sugars represents the liberation of these substances from tissues. HFD also upregulates lipogenesis pathway[36] which leads to increased production of triglycerides, cholesterol, free fatty acid and phospholipids. Triglycerides accumulation in turn, contributes to hepatic insulin resistance and glucose intolerance[37].

We used a low and a high dose of CBEt corresponding to 8 mg of cinnamon bark/kg body weight and 80 mg of cinnamon bark/kg body weight, respectively. CBEt administration at the high dose (80 mg/kg body weight) was effective in mitigating the adverse effects of HFD. Glucose tolerance and insulin sensitivity were improved by CBEt treatment. CBEt brought back the activities of glucose metabolising enzymes, levels of glycogen and protein bound sugars to near normal values when administered along with fructose.

Khan et al[9] isolated a factor from cinnamon, which could effect a three-fold increase in glucose metabolism in rat epididymal fat cells and attributed it to the presence of MHCP. Cinnamon extract can stimulate autophosphorylation of the insulin receptor and can inhibit protein tyrosine phosphatase-1 (PTP-1), which inactivates insulin receptor in the adipocytes. It was suggested that cinnamon could affect protein phosphorylation-dephosphorylation reactions in the intact adipocytes[38]. Cinnamon was the most bioactive product among the 49 botanic products tested for the in-vitro effects on insulin-dependent metabolism of glucose in adipocytes[39].

Oral treatment of normal rats with cinnamon extract enhances the glucose utilisation in-vivo in a dose-dependent manner and potentiates the insulin-stimulated tyrosine phosphorylation of insulin receptor substrate (IRS)[40]. Qin et al[41] also found that cinnamon extract prevents the development of insulin resistance in HFD rats. They attributed this to the activation of the insulin signaling possibly via the nitric oxide pathway in the skeletal muscle.

Improved insulin action in CBEt-treated rats could be responsible for the regulation of lipid metabolism, and hence we observed normal plasma lipid profile in them. However, studies

show that cinnamon might also have a direct role in lipid metabolism. For example, cinnamon bark powder at different doses 1, 3 and 6 g/day prevents hypercholesterolaemia and hypertriglyceridaemia and lowers the levels of free fatty acids and triglycerides in plasma of type 2 diabetic subjects by its strong lipolytic activity[42]. Cinnamate, a phenolic compound found in cinnamon bark and other plant materials, lowers cholesterol levels in high fat-fed rats by inhibiting hepatic 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase activity[43].

Research findings clearly show that cinnamon triggers the insulin cascade system. Considering the increased intake of fructose as high fructose corn syrup and the high incidence of insulin resistance in the general population, inclusion of cinnamon in the daily diet could be recommended. Our findings provide evidence for the therapeutic potential of cinnamon in the treatment of insulin-resistant states.

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