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Full Length Research Paper

Glucose and triglyceride lowering activity of *Pterocarpus santaniloides* leaf extracts against dexamethasone induced hyperlipidemia and insulin resistance in rats

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The triglyceride and glucose lowering potential of the leaf extracts of *Pterocarpus santalinoides* was investigated in dexamethasone induced hyperlipidemia and insulin resistance in rats. Acute toxicity test was performed according to standard methods. An oral glucose tolerance test was carried out in the presence of the extracts in normal rats. Then, graded doses of aqueous and methanol extracts of *P. santalinoides* (AEPS and MEPS) were administered orally to rats in four groups, respectively, after a 12 h fast followed by subcutaneous administration of dexamethasone (10 mg/kg body wt). Rats in a fifth group received saline (5 ml/kg p.o) followed by dexamethasone (10 mg/kg body wt s.c) and served as positive control while a sixth group served as normal control. The period of extract and dexamethasone administration was 10 days. Acute toxicity test showed that the extract had an oral LD_{50} > 5000 mg/kg in rats. Graded doses of aqueous and methanol extracts of *P. santalinoides* to glucose loaded normal rats resulted in significant lowering of blood glucose concentration which started at 90 min post-glucose load when compared with the 60 mine (peak) sample ($p < 0.001$) and also when compared with the negative control value at 90 min ($p < 0.001$). Administration of dexamethasone to fasted rats for 10 days resulted in hyperlipidemia and insulin resistance evidenced by the significant increase in mean glucose level (194.50 ± 9.87 mg/dl) and triglyceride level (268.75 ± 21.54 mg/dl) in the positive control when compared with the normal control with mean glucose and triglyceride concentrations of 64.00 ± 3.44 mg/dl and 100.00 ± 15.54 mg, respectively ($p < 0.01$; $p < 0.001$). Graded doses of the AEPS and MEPS significantly antagonized dexamethasone induced hyperlipidemia and insulin resistance in rats when compared with the positive control ($p < 0.001$) and the normal control, respectively ($p < 0.05$). The antagonistic potency of AEPS was dose dependent while that of the MEPS was not. The leaf extracts of *P. santalinoides* possess triglyceride and glucose lowering properties in dexamethasone induced hyperlipidemia and insulin resistance and could be of therapeutic value in the management of metabolic syndrome.

Key words: *Pterocarpus santalinoides*, leaf extracts, glucose tolerance, hyperlipidemia, insulin resistance, glucose, triglyceride, dexamethasone.

INTRODUCTION

Dexamethasone is a potent synthetic member of the glucocorticoid class of steroid hormones. It acts as an anti-inflammatory and immunosuppressant. Diabetes mellitus is a chronic metabolic disorder and a growing medical problem which the etiology and pathogenesis is not fully understood (Harris, 1995). In type 2 diabetes, insulin resistance leads to an inability of insulin to control the activity of gluconeogenic enzymes and results in significant elevation of hepatic glucose production (Barthel and Schmoll, 2003). This is accompanied by abnormalities in lipid and protein metabolism, and together these metabolic perturbations can lead to serious complications including

nephropathy, retinopathy, neuropathy and coronary artery disease (Cooper, 1998; Ferris et al., 1999; Backonja et al., 1998). Excessive glucocorticoid (GC) action is known to cause a spectrum of clinical features such as obesity, insulin resistance and glucose intolerance as exemplified in Cushing's syndrome (Andrew and Walker, 1999). GCs promote breakdown of protein and fat from storage, which causes an increased supply of free fatty acids and branched amino acids to the liver (Zimmerman et al., 1989).

Pterocarpus santaniloides (Fabaceae- Papilinoideae) is a plant commonly referred to as Red Sandal wood in English, Gunduru gyadar Kurmi in Hausa, Uturukpa in Igbo and Gbenghe in Yoruba. The leaves are claimed in folk medicine to be effective oral hypoglycaemic agents and its stem bark is used for the treatment of stomach ache. Phytochemical analyses of the leaves of the plant show the presence of saponins, flavonoids, phenols, triterpenoids, and tannins (Nworu et al, 2009). Most commonly employed oral hypoglycaemic agents are sulphonylureas and biguanides. These drugs, however, have disadvantages such as primary and secondary failure of efficacy as well as the potential for the induction of severe hypoglycaemia (Dow et al., 1991). There is need, therefore, for new candidate molecules that may effectively reduce insulin resistance or potentiate insulin action in genetically diabetic or obese individuals. New drugs that reverse insulin resistance without stimulating insulin release from β- cells also fulfil a major medical need in the treatment of non-insulin –dependent diabetes mellitus (NIDDM). The search for drugs with potential to reduce long term diabetic complications of NIDDM is, therefore, of current interest. Numerous medicinal plants have been used to treat diabetes mellitus and other forms of glucose intolerance or insulin resistance (Bajaj and Srinivasan, 1999; Mandal et al., 2000; Vikrant et al., 2000; Bhattacharya, 1995). The aim of this study is to evaluate the glucose and triglyceride lowering properties of the leaf extracts of *P. santalinoides* in dexamethasone-induced hyperlipidaemia and insulin resistance.

MATERIALS AND METHODS

Animals

Male albino Wistar rats (100 -130 g) were procured from the Animal House of the College of Medicine University of Nigeria, Enugu Campus. These rats were housed in clean guazed cages at the Animal House of the College of Medicine, University of Nigeria, Enugu Campus under standard condition of temperature (28 ± 2°C) and with a 12:12 h light/dark periodicity. The period of acclimatization was (2) weeks. Animals were handled in this study according to international and institutional guidelines on experiments involving the use of animals.

Chemicals

Absolute methanol (May and Baker, Nigeria Plc) NaCl (May and Baker, Nigeria Plc). Dexamethasone sodium phosphate (Troge, Germany) triglyceride and glucose estimation kits (Quimica Clinica applicada laboratories, Spain). Other reagents were of the analytical reagent grade.

Plant collection and taxonomy

The leaves of *P. santaniloides* were collected from a residential quarters at the University of Nigeria, Enugu Campus between the month of January and February, 2009. The plant sample was authenticated by a taxonomist at the Department of Botany, University of Nigeria, Nsukka. A voucher specimen was deposited at the Department of Medical Laboratory Sciences, College of Medicine, University of Nigeria, Enugu Campus (MLSH/63 d). The leaves were dried under the shade and powdered using an electric blender or Mill grater (MS 223, Taiwan).

Plant extraction

Aqueous extraction

Powdered plant leaves (1000 g) were macerated in 500 ml of distilled water and agitated intermittently for 48 h. After 48 h the extract obtained was strained through muslin and then through a Whatman No.1 filter paper. The aqueous extract of *P. santalinoides* (AEPS) had an extractive value of 40 mg /ml.

Methanol extraction

Powdered plant leaves (1000 g) were macerated in 3.5 litres of 80% methanol for 48 h. After 48 h, the extract was filtered through a Whatman No.1 filter paper. The filtrate was evaporated to dryness on a rotary evaporator (model 349/2 Corning, England) and the residue stored in the refrigerator (4 ± 2°C) until required. The yield of the methanolic extract of *P santalinoides* (MEPS) was 10.2%. The methanolic extract (10 g) was dissolved in physiological saline and made up to 100 ml with the same solvent. Appropriate dilutions were made from this for the study.

Acute toxicity tests (LD_{50})

Oral acute toxicity test was carried out in rats as described by Lorke (1983).

Glucose tolerance tests

Rats were divided into six groups (A - E) of 5 rats each. Blood samples were collected from rats in all the groups following an overnight fast (Fasting or 0 h sample). Groups A - E received 200 mg/kg aqueous extract of *P. santalinoides* (AEPS), 400 mg/kg AEPS, 200 mg/kg methanol extract (MEPS) and 400 mg/kg MEPS,

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Abbreviations: NIDDM, non-insulin dependent diabetes mellitus; **GC,** glucocorticoid; **AEPS,** aqueous extract of *Pterocarpus* santalinoides; **MEPS,** methanolic extract of *Pterocarpus* santalinoides; **LD50,** half maximal lethal dose; **G,** glucocorticoid.

Table 1. The effect of the extracts of *P santalinoides* on glucose tolerance of normal glucose fed rats.

Treatment group	FBS (0 h)	Gluc at 30 min	Gluc at 60 min	Gluc at 90 min	Gluc at 120 min	Gluc at 150 min
A(200 mg/kg AEPO	97.50 ± 3.86	163.85 ± 4.50	195.35 ± 3.94	150.47 ± 4.56**	110.83 ± 3.87**	80.60 ± 4.38**
B(400 mg/kg AEPO)	85.00 ± 4.32	155.60 ± 4.45	180.50 ± 3.81	135.45 ± 5.70**	96.33 ± 5.21**	69.50 ± 4.56**
C(200 mg/kg MEPO)	84.62 ± 2.45	177.67 ± 5.92	200.00 ± 5.25	156.50 ± 6.20**	114.83 ± 4.22**	90.37 ± 3.75**
D(400 mg/kg MEPO)	70.15 ± 6.38	160.83 ± 3.36	220.33 ± 5.06	137.24 ± 5.12**	99.60 ± 4.57**	68.83 ± 3.40**
E(Saline Negative control)	91.67 ± 3.53	166.83 ± 4.38	216.17 ± 3.90	248.00 ± 9.07*	220.45 ± 5.91	146.67 ± 4.81**

*$p < 0.05$; **$p < 0.001$ with respect to the 60 min (peak) glucose level; n = 5. Glucose concentrations are in mg/dl and expressed as mean ± SEM. FBS = fasting blood sugar; Gluc = glucose.

respectively. Group E received saline (5 ml/kg) and served as vehicle control. All administration was by oral route (p.o). The rats in all the groups were loaded with 60% glucose (3 gm/kg, p.o) (Babu et al., 2002), thirty (30) min after extract administration. Blood samples were collected from the tail at 30, 60, 120, and 150 min after glucose loading. Blood glucose levels were measured immediately with a glucometer (Contour® Bayer Health Care Systems LLC, Mishawaka IN, USA).

Dexamethasone induced insulin resistance and hyperlipidemia

Twenty-four (24) male albino wistar rats (100 - 130 g) were divided into six (6) groups (A - F) of 4 rats per group. Rats in group A - E received saline (vehicle, 5 ml/kg body weight), 200 mg/kg of AEPS, 400 mg/kg of AEPS, 200 mg/kg MEPS, and 400 mg/kg MEPS, respectively. Additionally, dexamethasone (10 mg/kg sub-cutaneously) was given to all the animals in groups A - E. Group A served as the positive control group while group F received only vehicle (Saline, 5 mg/kg) and served as normal or negative control group. All the animals received their respective treatments daily for a period of 10 days. Rats in group A - E were fasted overnight before dexamethasone treatment as described by Manhendran and Devi (2001). On the 11th day, blood was collected from the animals by retro-orbital puncture under ether anesthesia and serum was separated for the estimation of glucose and triglyceride.

Blood glucose determination

Fasting blood sugar was measured with the glucose oxidase/Peroxidase method as described by Trinder (1969).

Triglyceride determination

Triglyceride was estimated by enzymatic method as described by Fossati and Precipe, (1982).

Statistical analysis

The results were expressed as mean ± standard error of mean (SEM). Differences between means was determined by student's t-test followed by Scheffes post-hoc multiple comparisons. $P < 0.05$ was considered significant.

RESULTS

Acute toxicity test showed that the extract had an oral $LD_{50} > 5000$ mg/kg in rats. Oral administration of a glucose load in fasted rats resulted in an increase in blood glucose level which peaked at 1 h post glucose load (Table 1). Administration of graded doses of aqueous and methanol extracts of *P. santalinoides* (AEPS and MEPS) resulted in significant lowering of blood glucose concentration which started at 90 min post-glucose load when compared with the 60 min (peak) sample ($p < 0.001$) and also when compared with the negative control value at 90 min ($p < 0.001$). The glucose lowering effect of both extracts was consistent and normoglycemic values were obtained at 120 min when compared with the negative control.

In Table 2, the mean glucose and triglyceride levels of treated animals were compared with those of the untreated (normal) control. Results showed that administration of dexamethasone (10 mg/kg) resulted in insulin resistance and hyperlipidemia as evidenced by the significant in increase in mean glucose (194.50 ± 9.87 mg/dl) of the positive control (Dexamethasone + saline) when compared with the baseline (negative control) that had mean glucose and triglyceride concentrations of 64.00 ± 3.44 mg/dl as 100.00 ± 15.54 mg/dl, respectively ($p < 0.01$, $p < 0.001$). Group C which received 400 mg/kg of the aqueous leaf extract of *P. santalinoides* (AEPS) prior to dexamethatone administration had mean glucose (GLU) and triglyceride (TG) levels of 76.75 ± 6.28 mg/dl and 141.25 ± 21.44 mg/dl which were not significantly different from the baseline values ($p > 0.05$), indicating an antagonism

Table 2. Comparison of mean glucose and triglyceride concentration (mean ± SEM) of treatment groups with normal and positive controls.

Group	Dose (mg/kg)	Glucose (mg/dl)	Triglyceride (mg/dl)
A(Positive control)	5 ml/kg saline+ Dexamethazone	194.50 ± 9.87[a]	268.75 ± 21.54[b]
B (AEPS)	200 mg/kg AEPS+ Dexamethazone	108.75 ± 26.21[d]	167.50 ± 17.38[c,d]
C (AEPS)	400 mg/kg AE + Dexamethasone	76.75 ± 6.25[e]	141.25 ± 21.44[f]
D (MEPS)	200 mg/kg MEPS +Dexamethasone	72.25 ± 10.99[e]	116.25 ± 19.29[f]
E (MEPS)	400 mg/kg ME + Dexamethasone	138.00 ± 15.25[c,d]	238.75 ± 27.94[b]
F Normal control	5 ml/kg saline	64.00 ± 3.44	100.00 ± 15.54

a = $p < 0.001$ with respect to normal control (N.C); b = $p < 0.01$ with respect to N.C; c = $p < 0.05$ with respect to N.C; d = $p < 0.05$ with respect to positive control (P.C); e = $p < 0.001$ with respect to P.C; f = $p < 0.01$ with respect to P.C. n = 4.

to the glucose and triglyceride elevating property of dexamethasone. Group B rats received 200 mg/kg AEPS prior to dexamethasone injection and their mean glucose level was not significantly different from that of the baseline group ($p > 0.05$). However, the mean triglyceride concentrations of group B rats (167.50 ± 17.38 mg/dl) were signi-ficantly higher than that of the baseline group (100.00 ± 15.54 mg/dl) ($p < 0.05$). Administration of the methanol leaf extract of *P. santalinoides* (MEPS) at a dose of 200 mg/kg prior to dexamethasone injection resulted in a non-significant mean difference between the mean glucose and triglyceride levels of this group and the baseline group ($p > 0.05$). However, 400 mg/kg MEPS, had mean glucose (138.00 ± 15.25 mg/dl) and triglyceride (238.75 ± 27.94 mg/dl) concentrations that were significantly higher than those of the baseline group ($p < 0.01$, $p < 0.001$).

In Table 2, the mean glucose and triglyceride concentration of extract treated groups was compared with the positive control (Dexamethasone control) group. Results indicate that cumulative doses (200 and 400 mg/kg) of the AEPS and 200 mg/kg of MEPS significantly reduced mean glucose and triglyceride levels after dexamethasone injection when compared with the positive control ($p < 0.001$). The 400 mg/kg dose of AEPS lowered glucose significantly after dexamethasone injection ($p < 0.05$). However, there was non-significant mean difference in the triglyceride value. Results from this work indicated that the AEPS had a dose independent reduction in mean glucose and triglyceride levels. The lower dose (200 mg/kg) of MEPS had significant glucose and triglyceride lowering property in the setting of Dexamethasone induced insulin resistance and hyperlipidemia in rats.

DISCUSSION

Insulin resistance in humans has been shown in conditions like obesity, non-insulin dependent diabetes mellitus (NIDDM), and dyslipidemia. Thus, interventions to decrease insulin resistance may postpone the development of NIDDM and its complications. Treatment with natural herbs is likely to be fraught with lesser side effects compared to the presently used synthetic oral antidiabetic agents. Many medicinal plants have been reported to posses significant anti-diabetic effect in both type 1 and II diabetes mellitus as well as improved glucose tolerance (Bajaj and Srinivasan, 1999; Mandal et al., 2000; Vikrant et al., 2000; Bhattachanya, 1995). Dexamethasone is a potent synthetic member of the glucoscorticoid class of steroid hormones. Dexametha-sone administration leads to insulin resistance, hyperglycemia, and dyslipidemia in human and experi-mental animals (Amin et al, 1999; Bruder et al., 2004). Insulin resistance and hyperinsulinemia are often asso-ciated with a group of risk factors such as obesity, dyslipidemia, hypertension and impaired glucose tolerance. This cluster of metabolic abnormalities, first defined as syndrome X by Raven (1988) and supported by additional evidence (Raven, 1991: Defronzo and Ferrannini, 1991), is now often referred to as metabolic syndrome and has been recognized as potent risk factors for coronary heart disease.

In the present study, dexamethasone administration for 10 days in rats resulted in increased triglyceride and glucose levels similar to previous studies (Shalam et al., 2006; Dai et al., 1995). The low dose (200 mg/kg) of MEPS and the high dose (400 mg/kg) of AEPS were very potent in antagonizing dexamethasone induced hyperglycaemia and hypertriglyceridemia. Phytochemical analyses of the leaves of the plant show the presence of saponins, steroids, flavonoids, phenols, triterpenoids, and tannins (Nworu et al., 2009). It is likely that the glucose lowering property could be due to the combined effect of these bioactive constituents. For instance, saponins isolated from the leaves of *Acanthopanax senticosus* decreased experimental hyperglycemia induced by injection of adrenaline, glucose and alloxan (Sui et al., 1994). Flavonoids, saponins, alkaloids and the triterpenoids have been reported by several workers to possess glucose lowering property in diabetic animals (Nojima et al., 1998, Yoshikawa et al., 1998; Kamel et al., 1991). Furthermore, three phenolic constituents (marsupin, pterosupin, and pterostilbene) of a related plant (*Pterocarpus marsupium*) significantly lowered the glycemia of diabetic rats in a manner comparable to that of 1, 1- dimethylbiguanide

(Metformin) (Manickam et al., 1997).

Moreover, glucocorticoid action is mediated by the glucocorticorticoid receptor (GR), a nuclear receptor that regulates physiological events through activation or repression of target *genes* involved in inflammation, gluconeogenesis and adipocyte differentiation (Bamberger et al., 1996; Schacke and Rehwinkel, 2004). It is therefore, probable that the extracts of *P. santalinoides* may contain substances that compete with glucocorticoids for the glucocorticoid receptor (competitive antagonism) or they may contain substances that stimulate the production of repressor elements that inhibit the transcription. That is, they may bind to negative glucocorticoid response elements that mediate the repression of *gene* transcription. In the liver, glucocorticoids increase the activities of enzymes involved in fatty acid synthesis and promote the secretion of lipoproteins (Wang et al., 1995). The hepatic lipogenic effect of glucocorticoids results in accumulation of triglycerides in the liver. This reduces insulin sensitivity in the liver (Samuel et al., 2004). The extract of *P. santalinoides* could also act by inhibiting the expression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.

Furthermore, glucocorticoids antagonize insulin-stimulated translocation of glucose transporters (e.g. Glut-4) from intracellular compartments to the plasma membrane (Carter-su and Okamoto, 1987; Horner et al., 1987; Oda et al., 1995). This results in insulin resistance. The extracts could act by reversing the glucocorticoid mediated translocation of the glucose transporters from the plasma membrane to the intracellular compartment. The leaf extracts of *P. santalinoides,* therefore, appeared to have improved insulin resistance through enhanced insulin sensitivity in peripheral tissues, as was evident from the decreased glucose levels. However, the exact mechanism of action of these extracts were not established in this study. Drugs ameliorating hyperinsulinemia are likely to have greater therapeutic potential as they may also exert beneficial effects on the clinical course of NIDDM, hypertension and coronary heart disease. In conclusion, oral administration of the leaf extracts of *P. santalinoides* reduced glucose and triglyceride concentrations in dexamethasone treated rats. If these results are extrapolated to humans, then *P. santalinoides* might prove useful in the treatment of NIDDM and/or prevention of insulin resistance in non-diabetic states such as obesity and impaired glucose tolerance.

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