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The Ethanolic Leaf Extract of *Alchornea cordifolia* (Schum. & Thonn.) Muell. Arg Inhibits the Development of Dyslipidaemia and Hyperglycaemia in Dexamethasone-Induced Diabetic Rats

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ABSTRACT

Poor lipid and glucose regulation increases the risk for the development of major cardiovascular diseases and other organ damage. The study evaluated the serum glucose and lipid lowering effects of the 70% ($^{v}/_{v}$) ethanolic leaf extract of *Alchornea cordifolia* (ALC) using the dexamethasone-induced diabetic rat model. Thirty six female Sprague-Dawley rats (180-200g; n=6) were rendered hyperglycaemic with dexamethasone (10 mg/kg, sc) once daily for 8 days except the normal control. Each group received either normal saline 0.5 ml/rat, ALC (250 mg/kg, p.o. or 500 mg/kg, p.o.), glibenclamide (5 mg/kg, p.o.) or atorvastatin (5mg/kg, p.o.) as treatment once daily for 8 days. Fasting blood glucose (FBS) readings were recorded at baseline, day 4, 6 and 9. Blood was collected for the estimation of serum triglycerides (TG), total cholesterol (TC), low density lipoproteins (LDL), very low density lipoproteins (VLDL) and high density lipoprotein (HDL) on day 9. The diabetic control group had significantly raised FBS levels (8.20 ± 1.04 mmol/l; ****p<0.001*). Glibenclamide (5.20 ± 0.29; ****p<0.001*) and the extracts [(ALC 250 mg/kg, p.o.; (5.35 ± 0.95 mmol/l); *$p<0.05$); ALC 500 mg/kg, p.o.; (5.98 ± 1.12 mmol/l); *$p<0.05$)] prevented an increase in FBS level. The herbal extracts also reduced the level of serum lipids of rats treated. The 70% ($^{v}/_{v}$) ethanolic leaf extract of *Alchornea cordifolia* has some potential for use in lipid and glucose control.

INTRODUCTION

Diabetes Mellitus is a chronic disease of uncontrolled hyperglycaemia, secondary to defects in insulin secretion or the action of insulin leading to a rise in blood glucose, depression of glucose metabolism in the tissues, an increase in glycogenolysis, and stimulation of gluconeogenesis (Shrivastava *et al.*, 2013). The number of people living with the condition is estimated to reach 300 million by 2025. A major contributor to this trend is the increasing case of obesity the general population (Wild *et al.*, 2007). In the management of Diabetes Mellitus, treatment goals do not only comprise the control of blood glucose but also the regulation of the lipids. The control of the lipids is very critical because of their direct influence on disease outcomes and prognosis (Solano and Goldberg, 2006). Although multiple mechanism have been proposed for this action, an increase in cholesterol level increases the cardiovascular risk due to the microvascular changes while high levels of triglycerides also reduce the sensitivity of cells to insulin activity (Holman *et al.*, 2008; Subramanian and Hirsch, 2014). The latter may be associated with treatment failures and even the progression of patients to Type I Diabetes. Hence the maintenance of an optimum glycaemia and lipidaemia cannot be compromised. The plant *Alchornea cordifolia* (Euphorbiaceae) is very common in the West African sub region with its traditional use principally involving its anti-inflammatory activity in conditions such as dermatitis, asthma, hepatitis, splenomegaly, vaginitis and colitis (Olaleye *et al.*, 2004). Other authors have also reported on the antidiabetic activity of the plant (Mohammed *et al.*, 2012). In this report the anti-diabetic and lipid lowering activity of *Alchornea cordifolia* was studied with the view of exploring the potential use of the plant as a monotherapy for diabetics with poor lipid control and also for

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individuals with poor lipid control who are also at risk of developing Diabetes Mellitus. The 70% ($^{v}/_{v}$) ethanolic leaf extract of *Alchornea cordifolia* (ALC) was tested using the dexamethasone-induced diabetic rat model.

METHODS

Animals

Forty two Sprague-Dawley rats (180-200g) were obtained from the animal experimentation unit of the Centre for Plant Medicine Research (CPMR), Mampong-Akwapem, Ghana. The rats were housed under standard conditions with a 12hr light-dark cycle and given access to water and feed *ad libitum*. The protocol for the study was approved by the institution's committee for animal research.

Chemicals

All chemicals used: Glibenclamide (5 mg/kg, p.o.), dexamethasone (10 mg/kg, sc), Kits for the estimation of Triglycerides (TG), Total Cholesterol (TC), Low Density Lipoproteins (LDL), High Density Lipoproteins (HDL) and Very Low Density Lipoproteins (VLDL) were all obtained from Sigma Aldrich, Germany.

Preparation of Herbal Extracts

The dried leaves of *Alchornea cordifolia* (Schum. & Thonn.) Muell.Arg. (Euphorbiaceae) were dried under shade for two weeks at an ambient temperature after authentication by a taxonomist at the CPMR, Mampong-Akwapem. Hydro-ethanolic extracts of the materials were obtained by macerating 1.0 kg of the powdered plant material in 5.0 litres of 70% ($^{v}/_{v}$) ethanol for 3 days and then filtering. Ethanol was recovered using the Rotary evaporator and the remaining fluid extract lyophilised to obtain a dry powder.

Grouping of Animals

Animals were divided into 6 groups. Group I was the normal control and received no intervention except normal saline (0.5 ml/rat, p.o.). Animals in Group II received dexamethasone 10 mg/kg, sc and served as the diabetic control. Groups III & IV were treated with the standard drug glibenclamide 5 mg/kg, p.o. & atorvastatin 10 mg/kg, p.o. Group V & VI received *Alchornea cordifolia* (ALC) 250 & 500 mg/kg, p.o.

Dexamethasone-induced hyperglycaemia and hyperlipidaemia

The protocol for this study was as described by Munna and Saleem (2013) with some modifications.

Day 1-8

After an overnight fast, the baseline Fasting Blood Sugar (FBS) was recorded for each rat (and on day 4 & 6) followed by dexamethasone 10 mg/kg, sc. daily. Rats in each group then receive their respective assigned treatment daily throughout the experimental period.

Day 9-Termination

After an overnight fast, FBS readings were recorded. Blood samples collected from the tail vein were centrifuged at 4000 rpm for 10 mins and the resultant serum from each sample analysed for lipids (Triglycerides (TG), Total Cholesterol (TC), High Density Lipoproteins (HDL), Low Density Lipoproteins (LDL) and Low Density Lipoproteins (LDL) and Very Low Density Lipoproteins (VLDL) .

Statistical Analysis:

Data is expressed as Mean ± SEM and analysed by One and Two-way Analyses of Variance (ANOVA) followed by Newman-Keuls multiple comparison post test using the GraphPad Prism version 5.0 software. *p*-values <0.05 were be considered as significant.

RESULTS AND DISCUSSION

Effect of Dexamethasone on Glucose and Lipid of Rats

Dexamethasone caused significant hyperglycaemia in the animals treated. This change was characterised by the raised mean FBS (8.20 ± 1.04 mmol/l; ****p<0.001*) of the animals that received only dexamethasone throughout the experiment. Significant hyperlipidaemia was also induced in these animals treated: TG (2.13 ± 0.30 mg/dl; ****p<0.001*), TC (3.58 ± 0.41 mg/dl; ****p<0.001*), LDL (1.36 ± 1.23 mg/dl; ****p<0.001*) and VLDL (0.55 ± 0.04 mg/dl; ***p<0.001*) when compared with the normal control.

Effect of *Alchornea cordifolia* on Serum Glucose

The ethanolic extract of *Alchornea cordifolia* demonstrated potential antidiabetic activity preventing a significant increase in the FBS of rats at the end of 9 days: [(ALC 250 mg/kg, p.o.; (5.35 ± 0.95 mmol/l); **p*<0.05); ALC 500 mg/kg, p.o.; (5.98 ± 1.12 mmol/l); **p*<0.05)]. Glibenclamide the standard antidiabetic agent also had significant antidiabetic activity [FBS (5.20 ± 0.29 mmol/l) (****p<0.001*)] compared to the diabetic control group (Figure 1).

Effect of *Alchornea cordifolia* on Serum Lipids

Alchornea cordifolia at the 2 dose levels prevented an increase in the serum lipids. Triglycerides and total cholesterol levels of rats treated with the herbal extracts were significantly different from animals in dexamethasone group. The serum LDL of animals in was also decreased significantly for the ALC 500 mg/kg, p.o. group. No difference was recorded for serum VLDL for Atorvastatin and ALC 250 mg/kg, p.o (Table 1). HDL levels were also not significantly different from the dexamethasone group. The pathophysiology underlying the development of type 2 diabetes mellitus is complex, multifactorial and develops over a long time (Mooradian, 2009). The resistance of peripheral tissues to the action of insulin is the first step in this process. Hyperglycaemia occurs later, as pancreatic insulin secretion eventually fails to provide sufficient insulin for the metabolic needs of the body (Shoelson *et al.*, 2006).

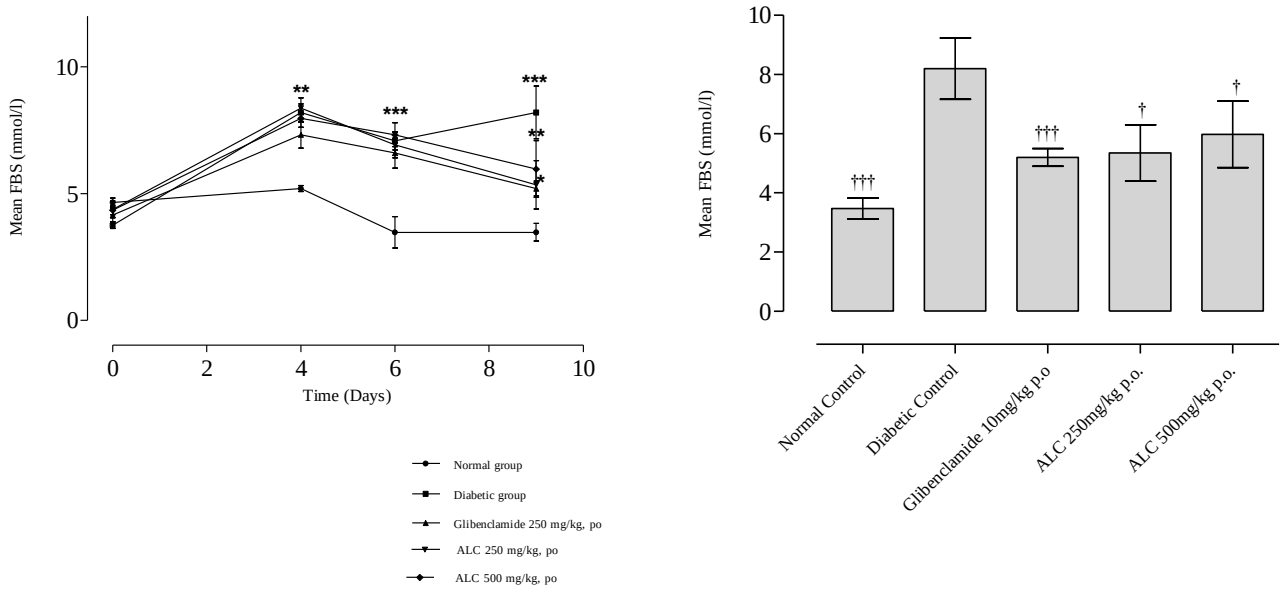

Fig. 1: Effects on the FBS of rats treated with normal saline (0.5 ml/rat), glibenclamide 5mg/kg, p.o. or ALC (250 & 500 mg/kg, p.o.) in the dexamethasone-induced diabetic rat model presented on the time course curve (a). The histogram (b) illustrates the mean FBS at termination of the study. Data is represented as Mean ± SEM, n=6; One and Two-way ANOVA when compared with diabetic control [(*$p<0.05$; **$p<0.01$; ***$p<0.001$). (†P≤ 0.05, ††P≤ 0.01, †††P≤ 0.001)] followed by Newman-Keuls post test.

Table 1: Lipid profile of Rats in the Dexamethasone-Induced Diabetic Rat Model.

GROUP	TG (mg/dl)	TC (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	HDL (mg/dl)
Normal Control	0.60 (±0.05)	2.19 (±0.17)	0.70 (±0.05)	0.27 (±0.02)	0.57 (± 0.04)
Diabetic Control	2.13 (±0.30)	3.58 (0.41)	1.36 (±1.23)	0.55 (±0.04)	0.66 (±0.06)
Standard Atorvastatin (10 mg/kg; p.o.)	1.46 (±0.08)**	1.76(± 0.06)***	1.17 (±0.04)	0.34 (±0.04)	0.13 (± 0.04)
ALC (250 mg/kg; p.o.)	1.06 (±0.17)***	1.86 (±0.36)***	1.07 (±0.20)	0.45 (±0.04)	0.26 (±0.07)
ALC (500 mg/kg; p.o.)	0.60 (±0.03)***	1.37 (±0.11)***	0.69 (±0.09)*	0.27 (±0.01)*	0.41 (±0.06)

All values are expressed as mean ± SEM. One way ANOVA followed by Newman-Keuls post test. *$p<0.05$, **$p<0.01$ and ***$p<0.001$. Normal Control group treated with Normal saline; Diabetic Control group treated with dexamethasone ; Positive control group treated with dexamethasone and Atorvastatin; ALC(250 mg/kg) treated animal group and ALC (500 mg/kg) treated animal group.

The level of serum lipids especially triglyceride is key to this pathological process. In this study the 70% ($^{v}/_{v}$) ethanolic leaf extract of *Alchornea cordifolia* demonstrated significant glucose and lipid lowering activity. Critically, the plant showed the ability to control the serum triglycerides [ALC 250 mg/kg, (1.06 ± 0.17 mg/dl; ***$p<0.001$); ALC 500 mg/kg, (0.60 ± 0.03 mg/dl; ***$p<0.001$)] which is very important in the prevention of insulin resistance that precedes the metabolic syndrome in diabetes. The regulation of total cholesterol and the lipoproteins also decreases the cardiovascular risk that is usually associated with type 2 diabetes mellitus.

Although not specific to *Alchornea cordifolia*, the activity shown by the plant may be attributable to the presence secondary metabolites like the flavonoids; known for their antioxidant and free radical actions. These findings give a good scientific basis for the potential use of the plant in the management of dyslipidaemia and diabetes and also confirms the reasoning behind its traditional use.

CONCLUSION

Results from this report indicates that the 70% ($^{v}/_{v}$) ethanolic leaf extract of *Alchornea cordifolia* has some potential for use in lipid and glucose control with the extracts having hypoglycaemic activity that was comparable to Glibenclamide and hyperlipidaemic activity comparable to Atorvastatin.

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