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Evaluation of antidiabetic effect and hematotological profile of methanol extract of *Ceiba pentandra* G (Malvaceae) stem bark on alloxan-induced diabetic rats

Odoh, U. E.*, Onugha, V. O. and Chukwube, V. O.

Department of Pharmacognosy and Environmental Medicines, Faculty of Pharmaceutical Sciences, University of Nigeria, Nsukkka, Nigeria.

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The anti-diabetic effect of methanol extract of stem bark of *Ceiba pentandra* and its beneficial/ toxicological effect on hematological parameters in normal and alloxan-induced-diabetic rats were studied. The acute toxicity (LD_{50}) test and phytochemical analysis were also carried studied. The diabetic rats were divided into five groups of 5 animals each given oral administration of the extract daily for 14 days. The antidiabetic study was carried out using 200, 400, and 800 mg/kg body weight of *C. pentandra* extract. The methanol extract of *C. pentandra* significantly ($p < 0.05$) reduced the blood glucose level in diabetic and norm glycemic rats in comparison with glibenclamide (standard drug). The effect of *C. pentandra* at 800 mg/kg (33.6%) was more effective compared to glibenclamide (23.0%) in lowering blood glucose with the added benefit of restoring reduced hematological parameters in diabetic rats to near normal level in norm glycemic rats. The acute toxicity (LD_{50}) test of the methanol extract was found to be greater than 5000 mg/kg. This showed the extract is relatively safe. The plant is also rich in flavonoids, saponins, resins, terpenoids, glycosides, and tannins. The result of this study shows that *C. pentandra* does possess anti-diabetic activity, beneficial effect and hence can ameliorate hyperglycemia and anemia in alloxan-induced diabetic rats establishing its potential as a source for isolation of new oral antihyperglycaemic agents.

Key words: *Ceiba pentandra*, hyperglycemia, hematology, diabetes.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration caused by insulin deficiency. It is a major cause of disability and hospitalization and results in significant financial burden (Vats et al., 2002). World Health Organization has reported that about 171 million people worldwide were suffering from diabetes mellitus in the year 2000, while predicting that this figure will double come the year 2030 (WHO, 2002). This report was corroborated by Wild et al. (2004). Regions with

*Corresponding author. E-mail: estellamaris5@yahoo.com, uchenna.odoh@unn.edu.ng.

approximately 140 million people worldwide suffer from diabetes (WHO, 1999) with the greatest interests in Asia and Africa where diabetes rate could rise to 2 to 3 folds than the present rates (ADA, 1997). Glucose plays a vital role in the regulation of β-cell insulin secretion (Hunt, 1995).

Among individuals with diabetes mellitus, three types are recognized; patients with insulin dependent or type 1 are ketosis prone and have increased or decreased frequency of certain histocompability antigens (HLA) on chromosome 6 and islet-cell antibodies (Silver and Loraine, 1986). This type has been termed juvenile onset diabetes. Type II patients are non-ketosis prone. Both type I and type II lead to hyperglycemia which largely causes the acute signs of diabetes; excessive urine (polyuria), resulting in compensatory thirst (Polydipsia) and increased hunger (polyphagia), blurred vision, unexplained weight loss, lethargy and changes in energy metabolism. Other examples of impaired glucose tolerance are insulinoma or reactive hyperglycemia (Goodman and Gilman, 2006).

Long-term hyperglycemic condition is associated with damage and failure of many organs such as eyes, kidney, nerves, heart and blood vessels (Kumar et al., 2008). Recently, it is suggested that formation of free radicals involved in the pathogenesis of diabetes and the development of diabetic complications, because a prolonged exposure to hyperglycemia increases the generation of free radicals and reduces capacities of the antioxidant defense system (Sanders et al., 2008). High levels of reactive oxygen have been found to play a role in the pathogenesis of several diseases including non-insulin dependent diabetes mellitus. Diabetic patients, both type I and type II exhibit abnormal antioxidant status, auto-xidation of glucose and excess glycosylated proteins (Young et al., 1992). Oxidative stress in diabetes mellitus leads to tissue damage, with lipid peroxidation, inactivation of proteins, and protein glycosylation as intermediate mechanisms for complications including retinopathy, nephropathy and coronary heart diseases. The underlying causes of diabetic complications have been attributed to hyperglycemia, which results in oxidative stress, alterations in enzyme activities, protein glycosylation and several structural changes (Wolfe et al., 1991).

Many traditional plant treatments for diabetes mellitus are used throughout the world (Marles and Transworth, 1995). Alternative strategies to the current modern pharmacotherapy of diabetes mellitus are therefore urgently needed. Many herbs and plant products have been shown to have hypoglycemic action. Many traditional plant treatments for diabetes are used throughout the world.

The hypoglycemic effect of several plant extracts and herbal formulations have been confirmed which are being used as antidiabetic remedies and their therapeutic capabilities are investigated intensively (Sharma et al., 1992). Laboratory studies and ethnobotanical information have shown that extracts of *Vernonia amygdalina, foxglove, pterocarpus, Allium cepa, Allium sativa, Anarcadium occidentale, Acalypha wilkeseria, Bridelia feruginea*, and *African mistoetle* have been found to lower blood sugar levels in experimental animals (Odoh et al., 2014).

Ceiba pentandra, commonly called the silk-cotton or kapok tree belongs to the Malvaceae family. It is an emergent tree of tropical rainforest predominant in South East Asia and often described as majestic, because of its wide application in traditional medicine (Ngounou et al., 1995). Various morphological parts of this plant have been reported to be useful and efficacious remedies against diabetes, hypertension and cardiac reflexology, headache, dizziness, constipation, mental disorder, pyrexia, peptic ulcer, rheumatoid arthritis and leprosy. It is also used as renal fluid mobilizer (Nounou et al., 1995). Folk medicine in Nigeria uses the root bark for the treatment of infections. In India and Malaysia, it is used for bowel complaints and also in the treatment of diarrheas in West Africa (Elumalai et al., 2012). It has been documented that *C. pentandra* possesses anti-inflammatory, antilipidemic, anthelminthic, angiogenesis and hepatoprotective activities (Elumalai et al., 2012).

The hypoglycemic activity of stem bark aqueous extract of *C. pentandra* at high doses (>800 mg/kg/day) on streptozotocin (STZ) induced type I diabetes has already been reported by Olusola et al. (2003). The present study aims at the evaluation of antidiabetic effect and hematological profile of methanol extract of *C. pentandra* stem bark on alloxan-induced diabetic rats.

MATERIALS AND METHODS

Collection and preparation of the plant

Fresh stem bark of *C. pentandra* was collected from Imo State, in the South Eastern part of Nigeria in July, 2014. The plant material was identified and authenticated by Mr. Alfred Ozioko, a plant taxonomist and staff of International Centre for Ethno medicine and Drug Development, Nsukka, Nigeria. The voucher specimen was deposited at the Herbarium of the Department of Pharmacognosy and Environmental Medicines, University of Nigeria, Nsukka. The stem bark was cleaned, air-dried and pulverized using Thomas Wiley Laboratory Mill Model 4.

The powdered plant material was then stored in an air-tight container to keep it moisture free until the time of use.

Extraction of the plant extract

A 1.10 kg of the powdered stem bark was macerated with 4.00 L of 80% methanol for 48 h and then filtered. The filtrate was concentrated in a vacuo. The brownish extract was weighed and stored in the refrigerator for further experiments.

Animal

White albino mice (20 to 30 g) and rats (140 to 170 g) bred in the Animal House of the Department of Pharmacology and Toxicology, University of Nigeria, Nsukka were used for the experiments after

permission had been obtained from the institutional Animal Ethics Committee. They were kept under standard conditions for seven days with access to food and water before the onset of the experiments.

Phytochemical analysis

Preliminary phytochemical analysis was carried out to detect the presence or absence of phytoconstituents using standard method (Harbourne, 1973; Evans, 2002).

Acute toxicity test

The LD_{50} of the extract was determined in the mice intraperitoneal using Lorkes' method (1983).

Antidiabetic evaluation

Effect of methanol extract of C. pentandra on the blood sugar level of norm glycemic rats

Twenty-five animals divided into 5 groups of 5 animals each were used. The fasting blood sugar levels were taken before treatment with the extract. Group I, II and III received 200, 400 and 800 mg/kg of extract, respectively. Group IV received 5 mg/kg of glibenclamide (standard drug), while Group V received 5 ml/kg of normal saline. Blood samples were withdrawn from the animals at 0, 1, 2, and 3 h after treatment with extract and standard drug and blood sugar levels determined using Accu-check glucometer for acute study and at 7 and 14 days for sub-acute study.

Effect of methanol extract of C. pentandra on alloxan-induced diabetic rats

The basal blood glucose level of the rats was taken before induction of diabetes by collecting blood sample from the tail vein of the rats and the glucose concentration determined using Accu-check glucometer. Diabetes was induced by intraperitoneal administration of 150 mg/kg body weight of alloxan monohydrate freshly prepared in normal saline. On the 3rd day, the fasting blood sugar levels were determined and animals with fasting blood sugar levels of 200 mg/dl and above were considered diabetic and grouped into five of five animals each based on their blood sugar level range. Groups I, II and III animals were treated daily with 200, 400 and 800 mg/kg body weight of methanol extract of stem bark of *C. pentandra* respectively and Group IV animals received 5 mg/kg of glibenclamide only while group V received 5 ml/kg of normal saline. Blood samples were withdrawn from the animals at 0, 1, 2, and 3 h after treatment with extract and standard drug and blood sugar levels determined using Accu-check glucometer for acute study and at 7 and 14 days for sub-acute study.

Determination of hematological parameters

Blood samples were obtained from the optical plexus of the rats using a heparinized (plain) haematocrit capillary. The determination of the differential leucocyte count, packed cell volume, haemaglobin concentration, red blood cell count, and white blood cell count was done according to Akah et al. (2007).

Statistical analysis

Data obtained from the experiment were subjected to one-way analysis of variance (ANOVA) using the SPSS program (Woodson, 1987). Results were expressed as mean standard error of mean (SEM) of triplicate value. P values of 0.05 were considered to be significant.

RESULTS

Phytochemical analysis

The stem bark extract shows the presence of the following phytoconstituents: alkaloids, carbohydrates, flavonoids, glycosides, saponins, steroids, tannins, reducing sugars, terpernoids.

Acute toxicity test

After intraperitoneal administration of the extract in mice at up to 5000 mg/kg dose, no death was observed. This shows that the extract is safe.

Antidiabetic evaluation

Intraperitoneal administration of alloxan monohydrate into the rats caused significant diabetogenic response in wistar albino rats with significant increase in the levels of blood sugar compared with non-induced rats. The blood glucose levels increased from 80 to 567 mg/dl. Following oral administration of the extract at studied doses, the blood glucose level was significantly reduced ($P<0.05$). The doses of 400 and 800 mg/kg had significant effect on the blood glucose level as compared with diabetic untreated rats in both norm glycemics and alloxan-induced diabetic rats (Tables 1 to 4). Values obtained at 800 mg/kg compared favorably well with that of glibenclamide treated group.

Hematological evaluation

There were some levels of restoration of almost all the hematological parameters after 14 days of treatment with the extract and a standard anti-diabetic drug (glibenclamide) as shown in Table 5. The packed cell volume (PCV), Hb concentration, red blood cell (RBC) count and the mean cell volume (MCV) values were restored to near normal levels in diabetic rats. After treatment, leucopenia (reduced total whitr blood cell (WBC) count) associated with diabetes was significantly restored in rats that were given 200 mg/kg of the extract and glibenclamide. Similarly, RBC count in rats treated with 200 mg/kg extract was also lower ($P < 0.05$) than the RBC count obtained in rats treated with 800 mg/kg of the extract. At 400 and 800 mg/kg of the extract given, RBC, PCV and Hb were better restored while at 200 mg/kg the lymphocytes and neutrophils improved better than at 400 and 800 mg/kg.

Table 1. Results of phytochemical analysis of extract of the stem bark of *C. pentandra*.

Secondary metabolite	Inference
Alkaloids	+
Carbohydrates	+
Flavonoids	+
Glycosides	+
Saponins	+
Steroids	+
Tannins	+
Reducing sugars	+
Terpenoids	+
Fats and oils	–
Protein	–
Resins	+

-= Absent; += present.

DISCUSSION

Diabetes is the world's largest growing metabolic disorder, and as the knowledge on the heterogeneity of this disorder is advanced, the need for more appropriate therapy increases (Bailey et al., 1986). Recent available hypoglycemic agents produce some serious side effects like hypoglycemic coma (Larnner, 1985) and hepatorenal disturbances (Amjad et al., 2013).

Apart from the side effects, their costs are high for management of diabetic patients and as such alternatives are needed for better management of diabetes. Hence, the search for safer and more effective anti-diabetic agents has continued. Also, there is WHO's recommendation for search on the beneficial use of medicinal plants in the management of diabetes mellitus (WHO, 1980). Investigation on hypoglycemic agents derived from medicinal plants also gained relevance. Compounds from plants at the other hand can provide an alternative treatment for diabetes (Rashid et al., 1989)

The phytochemical studies of the methanol extract revealed the presence of glycosides, saponins, terpenoids, reducing sugars, fats and oil, alkaloids, carbohydrates, flavonoids and proteins. These secondary metabolites have been reported to have anti-hyperglycaemic effect. Saponin extract of *Citrullus colocynthis* fruit has been reported to cause marked hypoglycemic effect in alloxan- induced diabetic rats (Abdel-Hassan et al., 2000). Steroidal saponins isolated from *Balanites aegyptiaca* Delile exhibited prominent hypoglycemic activity in streptozocin-induced diabetic mice (Kamel et al., 1991). Saponins isolated from the leaves of *Acanthopanax senticosus* injected to mice (100 and 200 mg/kg,) decreased experimental hyperglycemia induced by infecting of adrenaline, glucose, and alloxan, without affecting the levels of blood sugar in untreated mice (Maliehe et al., 2015). An unsaturated triterpene acid isolated from an ethanolic extract of *Bumelia sartorum* root bark produced a hypoglycaemic effect in alloxan-induced diabetic rats (Naik et al., 1991*).* It increased glucose uptake and glycogen synthesis on isolated rat diaphragm and plasma insulin level (Naik, 1991). It appears that this effect was mediated by an insulin secretaguogue effect in pancreatic β-cell. Senegin II, a triterpenoid glycoside isolated from rhizomes of *P. Senega* had been reported to have anti-diabetic effect on mice (Kako et al., 1996). Glycoside of leucopelargonidin isolated from the bark of *Ficus bengalensis* demonstrated significant hypoglycemic, hyppolipidemic and serum insulin raising effects in moderately diabetic rats (Cherian et al., 1993). Also from phytochemical study of *C. pentandra* revealed the presence of epicatechin (Noreen et al., 1998) and flavonoids (Noreen et al., 1998; Ngounou et al., 2000).

Epicatechin, isolated from other plants had been found to stimulate β-cells regeneration, increased insulin secretion or possessed an insulin like effect (Marles and Farnsworth, 1995; Kameswara et al., 2001). Some flavonoids were reported to possess hypoglycaemic activity (Lamba et al., 2000; Cetto et al., 2000).

In both stages of acute toxicity studies, no animal died thus, the LD_{50} is greater than 5000 mg/kg body weight of the extract. This shows it is within nontoxic range and that the extract is relatively safe (Loomis, 1996).

Alloxan-induced hyperglycemia has been a useful experimental model to study activity of hypoglycemic agents (Szkudelski, 2001). Alloxan is well known for its selective pancreatic islet β- cell cytotoxicity and has been used to induce diabetes mellitus in animals. It interferes with cellular metabolic oxidative mechanisms forming highly reactive superoxide radicals which destroy the insulin producing beta-cells in the pancreas. Intraperitoneal administration of alloxan (150 mg/kg) effectively induced diabetes in normal rats as reflected by glycosuria, hyperglycemia, polyphagia and polydipsia compared with normal rats.

The crude methanol extract of the stem bark of *C. pentandra* showed marked anti-diabetic activity on alloxan-induced diabetic rats and at doses of 200, 400 and 800 mg/kg body weight of the extract, it exhibited significant ($p < 0.05$) anti-diabetic activity after 14 days. When compared with 5 mg/kg of glibenclamide used as positive control. The dose of 800 mg/kg body weight of the extract was found to be more effective in giving higher percentage reduction of blood glucose level in alloxan-induced diabetic rats than 5 mg/kg glibenclamide. Also 400 mg/kg dose of the extract have similar anti-diabetic activity to 5 mg/kg doses of glibenclamide.

Glibenclamide is a standard anti-diabetic drug that stimulates insulin secretion from β-cell of isles of Langerhans. Also, glibenclamide is ineffective when there is no functional β-cells left in the pancreas and this therefore suggests that alloxan does not cause total destruction of the β-cells. The possible mode of action of the plant extract might be by potentiation of the insulin

Table 2. Effect of methanol extract of *C. pentandra* stem bark on alloxan-induced diabetic rats (acute study).

Treatment	Dose(mg/kg)	Mean fasting blood glucose level (mg/dl)		
		0 h	1 h	2 h
Control (normal saline 5 ml/kg)	-	283.40±0.32	294.90±0.35 (4)	307.90 ± 0.36 (- 8.65)
Extract	200	568.25±1.00	556.25±0.86* (2.1)	529.40±0.31 (6.84)
	400	480.75±0.64	435.20±1.20* (9.5)	426.80±0.20 (11.22)
	800	349.00±1.42	322.00±0.80* (7.7)	310.50±1.03 (11.03)
Glibenclamide	5	355.30±0.58	349.80±0.62* (1.7)	341.30±1.11 (3.94)

Values are ±SEM, n = 5, *P < 0.05, percentage reduction of blood glucose level in parenthesis.

Table 3. Effect of methanol extract of C. *pentandra* on plasma glucose level of normoglcemic rats (subacute study).

Days	Treatment				
	Extract (mg/kg)			Glibenclamide (mg/kg)	Normal saline (ml/kg)
	200	400	800	5	5
0	98.11±0.54	109.20±0.52	105. 8±0.88	100.8±1.31	110.20±0.50
7	89.21±0.45 (9)	100.50±1.36 (7)	90.77±0.61 (14)	91.92±1.05 (8.8)	110.80±1.30
14	78±0.22 (20.5)	86.95±1.44* (21.2)	60.50±0.83* (33.6)	77.44±0.85* (23)	112.13±1.21

Values are ±S.E.M, n = 5, *p < 0.05, percentage reduction of blood glucose level in parenthesis.

Table 4. Effect of methanol extract of C. *pentandra* stem bark on plasma glucose level of alloxan-induced diabetic rats (subacute study).

Day	Treatment group				
	Extract (mg/kg)			Glibenclamide. (mg/kg)	Diabetic control (Normal saline (ml/kg)
	200	400	800	5	5
0	568.25±0.38	480.75±0.42	349.0±1.28	335.30±0.82	283.40±0.18
7	450±13±2.10* (20.82)	*340.14±07 (29.32)	288.01±1.50* (17)	299.666±040* (15.6)	377.80±0.18
14	402.15±0.66 (29.24)*	280.40±0.80* (41.67)	*182.01±0.41 (47.9)	180.90±0.01* (47.3)	483.90±0.52

Values are ±S.E.M, n = 5, *p < 0.05, percentage reduction of blood glucose level in parenthesis.

effect by increasing the pancreatic secretion of insulin from β-cells of islet of Langerhans or its release from the bound form.

The effect of *C. pentandra* could be related to a stimulation of remaining β cells or regeneration of β-cells. It had been reported that β-cells regeneration occurred through both increasing the replication of pre-existing β-cells and neogenesis from the precursor cells located in or by the pancreatic duct (Lei et al., 2004).

The assessment of haematological parameters could be used to reveal the deleterious effect of foreign compounds including plant extracts on the blood constituent of animals. They are used to determine possible alterations in the levels of biomolecules such as enzymes, metabolic products, haematology, normal functioning and histomorphology of the organs (Megalhaes et al., 2008). The occurrence of anaemia in diabetes mellitus has been reported due to increased non-enzymatic glycosylation of RBC membrane proteins (Oyedemi et al., 2011). Oxidation of these proteins and hyperglycemia in diabetes mellitus causes an increase in the production of lipid peroxides that lead to hemolysis of RBC (Arun and Raesh, 2002).

In this study, the red blood cells parameters such as HB, PCV, MCH, MCHC were studied to investigate the beneficial/toxicity effect of *C. pentandra* extract on the anaemic status of the diabetic rats. The levels of RBC, Hb, hematocrit, and MCHC in the diabetic animals were

Table 5. Effect of methanol extract of *Ceiba pentandra* stem bark on the haematological parameters in alloxan-induced diabetic rats after two weeks.

Parameter	Experimental groups				Diabetic control
	Extract (mg/kg)			Glibenclamide (mg/kg)	Normal saline (Mg/ml
	200	400	800	5	5
RBC count per mm^3 blood (N × 10^4 cells)	*4.41±0.06	*4.50±0.12	*4.73±1.35	*4.50±0.18	4.10±0.02
Hb (gldl)	*12.45±0.50	*12.48±0.04	*13.60±1.12	*13.31±1.01	10.92±0.3
PCV (%)	50±1.36	43±1.16	44±2.13	38±0.06	51± 0.18
MCV (fl)	*83.90±0.01	*88.89±0.14	*93.02±0.11	*80.85±1.12	124.39±0.1
MCHC (pg)	33. 65±06	31.20±0.18	30.91±0.08	35.02±1.20	21.41±0.13
MCH (pg)	28.23±1.10	27.73±0.04	28.75±1.11	28.32±0.13	26.63±0.71
(WBC count)per mm^3 blood (N × 10^3 cells)	*7.55±0.07	7.14±0.12	7.02±1.16	8.31± 1.36	5.60±0.09
Neutrophils (%)	18±0.41	25. 78±1.30	26.70±1.18	23.30±1.5	23±2.1
Lymphocytes (%)	*67.40±0.16	60.71±0.13	66.1±0.44	64.13±1.03	51.2 23±0.33

Values are ±S.E.M, n = 5, *p < 0.05.

reduced which may be due to the infections on the normal body system. This observation agrees with report of Baskar et al. (2006) who reported antihyperglycemic activity of aqueous root extract of *Rubia cordifolia* in streptozotocin-induced diabetic rats. The alterations of these parameters are well known to cause anaemic condition in man (Balasubraimamian et al., 2009).

Following the administration of *C. pentandra* extract, the level of RBC and its differential were appreciably improved especially at 400 and 800 mg/kg doses of the extract. This gives an indication that the plant extract may contain some phytochemicals that can stimulate the formation or secretion of erythropoietin in the stem cells of the animals.

Erythropoietin is a glycoprotein hormone which stimulates stem cell in the bone marrow to produce red blood cells (Olilsson et al., 2006). The stimulation of this hormone enhances rapid synthesis of RBC which is supported by the improved level of MCH and mean corpuscular hemoglobin concentration (MCHC) (Abu-Zaition, 2010). These parameters are used mathematically to define the concentration of hemoglobin and to suggest the restoration of oxygen carrying capacity of the blood. Though the mechanism of action of this extract is not investigated in this study, but it may be attributed also to the ability of plant extract to lower lipid peroxidation level that causes hemolysis of erythrocytes (Ashafa et al., 2009). Therefore, it could inhibit peroxidation of polyunsaturated fatty acids in the cells membrane and hemolysis of red blood cells in the diabetic animals as reported by Torell et al. (1986) and Faure et al. (1991).

For normal glycemic rats that received the extracts, there was no significant change in hematological parameters. Anemia following administration of an agent can be because of lysis of blood cells and/or inhibition of blood cells synthesis by the active constituents of the extract and decrease in hematological parameters in experimental animals has been associated with anemia (Lillie, 1965). Significant increase in differential lymphocytes and neutrophils count in the diabetic rat must have resulted from the stress induced by diabetes in accordance with stress induced lymphocytosis and neutrophilia in avian species (Forbes et al., 2002). There was restorative effect in the rats treated with methanol extract of *C. pentandra.* The 400 and 800 mg/kg of the extract produced the highest restorative effects in RBC count, Hb, and MCV that is significantly higher ($P < 0.01$) than the effect of 200 mg/kg of the extract. The 200 mg/kg had more restorative effect in WBC count and lymphocytes than 400 and 800 mg/kg of the extract.

In addition, there was no significant change in hematological parameters in the extracts treated animals compared to the control, which indicates that there is no lysis of blood cells and/or inhibition in blood cells synthesis by the active constituents of *C. pentandra* extract. The above statement suggests the non-toxicity of *C. pentandra* in rats.

Conclusion

The results obtained from this study shows that, the stem bark of *C. pentandra* was effective in reducing blood glucose level in normal and alloxan-induced diabetic animal with the added benefit of restoring reduced hematological parameters. The constituent(s) responsible for this effect requires further investigation.

Conflict of interest

The authors have not declared any conflict of interest.

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