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Research Article

Antidiabetic activity of *Peristrophe bicalyculata* Leaf Extract in Streptozotocin and Alloxan-induced diabetic rats

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Abstract
The present study was designed to investigate the antidiabetic and antihyperlipidemic effect of *Peristrophe bicalyculata* leaves extract in Wistar rats. Streptozotocin and alloxan were used to induce type 1 diabetes or chemically-induced diabetes. In each experiment, forty-nine albino rats (120 – 150 g) were divided into 7 groups (n=7). Rats in group A (Control) and B (Diabetic control) were administered 0.2ml/day of distilled water. Group C rats were administered Glibenclamide (5 mg/kg, oral). Rats in group D (non-diabetic rats), E, F and G were administered *P. bicalyculata* methanol extract (400, 100, 200 and 400 mg/kg body weight) orally respectively for 1 week. Evaluation of fasting blood glucose level, lipid profiling, and adiponectin levels were carried out. Fasting blood glucose levels and plasma lipid profiles of diabetic control rats were significantly higher than those of normal control rats. Administration of 100, 200 and 400 mg/kg methanol extract of *P. bicalyculata* significantly reduced blood glucose level when compared to diabetic control after one week (168 hours). At 100 mg/kg of *P. bicalyculata* extract (specifically), the serum level of low density lipoprotein cholesterol was reduced and that of high density lipoprotein cholesterol was enhanced compared to diabetic control ($p<0.05$). The serum level of triglyceride and very low density lipoprotein was reduced. At 400 mg/kg concentration, there was a significant reduction in serum total cholesterol level. Results also revealed that 100 mg/kg leaves extract significantly increased adiponectin levels in pre-treated diabetic rats compared to non-treated diabetic rats.

Key Words: *Diabetes, Adiponectin, Perisrophe. bicalyculata, Lipid profiles*

INTRODUCTION

Diabetes mellitus (DM) is a complex metabolic disorder involving many organs and can devastate the lives of affected individuals (Kodl and Seaquist, 2008). The International Diabetes Federation (IDF) estimates that in 2013 there were 382 million people with diabetes and 316 million people suffer from impaired glucose tolerance and increased risk of diabetes. These results are expected to increase to 471 million at 2035 and predicted less than 25 years there would be 592 million people suffering from diabetes without quick and precise prevention (International Diabetic Federation, 2013). Diabetes can be classified into five clinical categories, type 1 diabetes (due to autoimmune destruction of the β-cells, usually leading to absolute insulin deficiency), type 2 diabetes (due to a progressive insulin secretory defect in the background of insulin resistance), type 3 is gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes), and other specific types of diabetes due to other causes, for example, type 4 from genetic defects in β-cell function or insulin action, drug or chemical induced alterations (such as in the treatment of HIV/AIDS or after organ transplantation), and type 5 resulting from any disease of the exocrine pancreas characterized by a progress that diffusely injures the pancreas can cause diabetes (Racheal, 2018). The blood glucose level of a healthy human is about 100 mg/dL on fasting and up to 160 mg/dL in the postprandial state. Diabetes is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating a fasting blood glucose level at or above 126 mg/dL or 7.0 mmol/L, plasma glucose level at or above 200 mg/dL or 11.1 mmol/L two hours after a 75 g oral anhydrous glucose in water indicates diabetes mellitus and also a glycated haemoglobin level ($HbA1_c$) level greater than 7% (American Diabetes Association, 2016). Diabetes, if left untreated over period to time increase the risk of cardiovascular system-like hypertension, heart attack, stroke and other chronic disease like peripheral neuropathy, diabetic retinopathy, kidney failure, erectile dysfunction and poor healing process (Dresden and Danielle, 2017).

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Molecular mechanisms of diabetes are diverse and unknown especially in genetically induced complicated disease. The more reason in this study why type 3 models/chemicals (streptozotocin, alloxan) which can also mimic type 1 model experimentally was used to induce diabetes. Clinically, insulin is the mainstay therapy for the treatment of type 1 diabetes, although sulfonylurea (most especially second generation) can also be used. Insulin and sulfonylureas aside their main mechanism of actions has also been shown to exert indirect effects to increase insulin sensitivity. Among the therapies for type 2 diabetes are troglitazone and metformin which are said to function as insulin sensitizers. Troglitazone, a ligand for the peroxisome proliferator-activated receptor-γ and is thought to act directly upon adipose tissue, thereby exerting indirect effects to increase insulin sensitivity in skeletal muscle (Simeon, 1999). Metformin exerts its principal action to suppress hepatic glucose production (Natali and Ferrannini, 2006). Metformin does not improve peripheral insulin sensitivity but the reduction of adipose tissue mass and weight loss which are important side effect of metformin was shown to increase insulin sensitivity (Natali and Ferrannini, 2006). Despite the wide variety of medication combination for glycemic control, most of the antidiabetic drugs are associated with very poor glycemic control which reflect the limitation of current antidiabetic drugs and necessitate the search for newer agents with better blood glucose control.

Peristrophe bicalyculate (Rets.) Nees. (*Acanthaceae*) is an erect, hispid herb or under shrub about 60–120 cm in height which is found in forest undergrowth, hedges and waste land almost throughout Nigeria (Gaudani *et al*., 2010). *Peristrophe bicalyculata* belongs to the kingdom: plantae, phylum: Mangnoliophyta, class Magnoliopsida, order Lamiales, family Acanthaceae and to the genus Peristrophe. It is called "tuban dawaki" by Hausas in Northern Nigeria, meaning floor of the horse. *Peritrophe bicalyculata* has been reported to possess anti-bacterial properties (antituberculostatic), used as snake poison antidote, and in the treatment of bone fracture and sprain (Gaudani *et al*., 2010). Hoda *et al* (2006) carried out the pharmacological studies on this plant in relation to psychomotor disorders and showed the antidepressant effect of the aqueous extract of the plant. The plant was also reported to possess beneficial effects against hyperlipidemia (Abdulazeez, 2011). Phytochemical screening of this plant revealed the presence of flavonoids, alkaloids, terpenoids, sterols, saponins and tannins (Hoda *et al.*, 2006) which has been reported in previous studies to reverse hyperglycemia and hyperlipidemia (Okey *et al*., 2016) but with no scientific information on the mechanism of its antidiabetic effect, hence this study.

MATERIALS AND METHODS

Plant material: The fresh leaves of *P. bicalyculata* were obtained from Staff Quarters, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria. They were authenticated by a staff in the Forestry Research Institute of Nigeria, Ibadan, Oyo-State, Nigeria.

Antidiabetic testing materials*:* Glucometer and glucose test strips (infopia Co., Ltd. Korea).

Animal treatments*:* Forty-nine Wistar rats (120-150 g) were obtained from a private breeder at Ile-Ife, Osun State. The animals were housed and they had access to food and water ad labium. The rats were fed with commercial pelletized feed and water freely and kept in a clean and well ventilated rat cage. The animals were also exposed to normal 12 hour light and darkness cycle. The study was generally conducted in accordance with recommendations from the declaration of Helsinki guiding principles in the care and use of animals.

Preparation of methanolic extract of P. bicalyculata*:* The leaves of *P. bicalyculata* were shade-dried and reduced to a powdery form by grinding. 64.73g of powdered sample was soaked in 70% methanol for 72 hours, after which it was decanted. The filtrate was then evaporated in rotary evaporator to obtain a solid extract which weighed 18 g. The extract was then dissolved in distilled water and used for the study.

Preparation of Stock Solution: 1g of the solid extract was dissolved in 10 ml of distilled water to obtain a stock solution with a concentration of 100 mg/ml. The dose administered to each rat from the stock solution was determined using the weight of individual rat.

Table 1
Experimental design

Streptozotocin-Induced Diabetes Study	
Group (n = 7)	Treatment
A	Oral administration of 0.2ml distilled water/day (Control)
B	Oral administration of 0.2ml distilled water/day (Diabetic control)
C	Oral administration of Glibenclamide; 5mg/kg body weight
D	Oral administration of *P. bicalyculata*; 400 mg/kg (non-diabetic, 1 week)
E	Oral administration of *P. bicalyculata*; 100 mg/kg body weight (1 week)
F	Oral administration of *P. bicalyculata*; 200 mg/kg body weight (1 week)
G	Oral administration of *P. bicalyculata*; 400 mg/kg body weight (1 week)

Alloxan-induced Diabetes Study	
Group (n = 7)	Treatment
1	normoglycemic rats, untreated control rats that were given normal saline alone
2	hyperglycemic rats without extract (alloxan alone)
3	hyperglycemic rats treated with 100 mg/kg extract
4	hyperglycemic rats treated with 200 mg/kg extract
5	hyperglycemic rats treated with 400 mg/kg extract
6	hyperglycemic rats treated with 5 mg/kg Glibenclamide

Induction of diabetes: For the experimental design 1, diabetes was induced in the rats by intraperitoneal administration of 60 mg/kg Streptozotocin dissolved in 0.1M Citrate buffer (pH 4.5) after which the rats were treated with extract and glibenclamide for 7 days. Experimental design 2 involved single intraperitoneal administration of 135 mg/kg alloxan monohydrate (Sigma Chemicals Company, St. Louis, Mo, USA) dissolved in normal saline to induce diabetes, followed by treatment with the extract and glibenclamide for seven days. 4 hours after alloxan injection, rats were orally

infused with 10 g/kg of D-glucose so as to prevent the onset of fatal hypoglycemia which often accompanies administration of alloxan as a result of acute massive pancreatic release of insulin (Stanley and Venugopal, 2001). Diabetic state was established using glucometer (FINE-TEST) on blood from the tail vein of the rats and blood glucose above 250 mg/dL was considered diabetic.

Acute extract treatment in Glucose induced Hyperglycaemia modelling for Type 2 Diabetes mellitus in rats: In high oral glucose hyperglycaemia model, rats were fasted for 12 hours and randomly allotted to six (6) groups of five (5) rats in each group. Group 1 rats which served as the untreated control were orally infused with distilled water. Groups 2 – 6 served as the model control and were pretreated with 15g/kg of D-glucose (Analar). After 45minutes, they were found to be hyperglycaemic and different doses of the extract together with 5mg/kg Glibenclamide were administered just like in alloxan induced model. Blood glucose level was determined at 0.5, 1, 2 and 4 h after oral administration.

Biochemical Analysis: Total Cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C) and adiponectin assays were carried out using Randox kit. Very low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C) were evaluated using the method described by Friedwald *et al*., (1972).

Statistical analysis:
Data obtained were expressed as mean± standard deviation (mean ± SD). The data were analysed with GraphPad Prism version 7.02 and one way analysis of variance (ANOVA) with Tukey's post hoc test used for comparism within the group. The values were considered to be significantly different at $p<0.05$

RESULTS

Phytochemical components of methanol extract of *Peristrophe bicalyculata* aerial parts showed the presence of alkaloids and glycosides, however, there is clear indication that saponin, flavonoids, tannins, anthraquinones and Phlobatannins were absent.

From Table 2, the fasting blood glucose levels of diabetic control rats were significantly higher than those of normal control rats. The result showed a significant increase in blood glucose level of diabetic control rats (from 0 to 180 hours) compared to the normal control rats. Pre-treatment with 100 mg/kg, 200 mg/kg and 400 mg/kg *P. bicalyculata* extract and 5 mg/kg glibenclamide significantly reduced the blood glucose at 168hours.

From Table 3, 100 mg/kg of *P. bicalyculata* extract administration, there was a significant reduction in LDL-C levels and a significant increase in HDL-C levels when compared to the diabetic control. Reductions were also observed in TC, TG and VLDL levels but it was not statistically significant. At 200 mg/kg of *P. bicalyculata* extract administration, there was a significant reduction in TC and LDL-C levels and a significant increase in HDL-C levels when compared with the diabetic control. Reductions were also observed in TG and VLDL levels but it was not statistically significant. At 400 mg/kg of *P. bicalyculata* extract administration, there was a significant reduction in TC levels.

From the result obtained in the alloxan-induced diabetes model, 100 mg/kg, 200 mg/kg, 400 mg/kg and glibenclamide extract did not show significant effect on blood glucose level after 0.5, 1, 2 and 4 hours of post-treatment until the rats were post-treated at 192 and 160 hours respectively.Figure 1 showed a significant reduction in plasma level of adioponectin in the diabetic control rats compared to the normal control rats. There was a significant increase in the plasma level of adiponectin of 100 mg/kg, 200 mg/kg and 400 mg/kg extract treatment groups compared to the diabetic control.

Table 2:
Effect of *P. bicalyculata* leaves extract on fasting blood glucose level in STZ-induced diabetic rats.

Groups	Drugs Administration	0hours	1hours	2hours	4hours	24hours	168hours
A	Control	67±1.7	78±1.5	90±2.1	91.7±3.7	108±5.6	93.3±2.9
B	DC	280±6.6*	314±6.7*	305±5.3*	357.3±8.4*	379±11.1*	530.7±31.2*
C	GLI 5mg/kg	281.3±14.2*	337±23.5*	544.7±13.6*#	584±8.5*#	301.7±26.4	103.7±3.5#
D	400mg/kg PB	98±1.2*#	95.3±6.3#	116.7±4.5#	89.3±2.6#	100±2.6#	100.7±5.7#
E	DM+100mg/kg PB	284±4.6*	364±6.0*#	415.7±2.3*#	445.3±16.2*	398.3±14.7*	115±5.5#
F	DM+200mg/kg PB	365±10.6*#	352.7±6.5*	442.7±27.6*	440.7±12.7*#	340.7±11.5*	236.3±6.3*#
G	DM+400mg/Kg PB	461.7±19.1*#	421.7±6.1*#	415±6.5*#	433.3±8.5*	382.7±8.5*	254±38.1#

Key: DC=Diabetic Control, GLI=Glibenclamide, PB=Peristrophe bicalyculata
**Indicate significantly different from control at p<0.05, # indicate significantly different from Diabetic control at p<0.05.*

Table 3:
Effects of *Peristrophe bicalyculata* leaves extract on plasma lipid profile in Streptozotocin-induced diabetic rats

Groups	Drug Administered (mg/kg)	TC(mg/dl)	TG(mg/dl)	HDL(mg/dl)	LDL(mg/dl)	VLDL(mg/dl)
A	Control	125.7±2.6	85±11.1	61.9±3.4	49.9±2.9	17±2.2
B	DC	243.5±0.3*	89.2±13.3*	51.9±5.9	67.1±8.3*	17.8±2.7*
C	GLI 5	112.8±8.9#	66.9±11.4	52.2±7.9	47.3±10.2#	13.4±2.3
D	400 PB	142.7±19.9	114.8±17.6#	70.3±9.7	49.5±23.1	22.96±3.5#
E	DM+100 PB	105.9±16.2	78.3±13.8	69.1±3.9#	21.2±11.6#	15.7±2.8
F	DM+200 PB	134±5.3#	82.9±7.3	67±1.9#	48.3±5.0#	16.6±1.5
G	DM+400 PB	134±1.3#	80.1±7.4	58.9±4.9	59.1±2.8	16.0±1.5

Key: DC=Diabetic Control, GLI=Glibenclamide, PB=Peristrophe bicalyculata
**Indicate significantly different from control at p<0.05, # indicate significantly different from Diabetic control at p<0.05.*

Table 4:
Effect of acute treatment of methanolic extract of *Peristrophe bicalyculata* aerial parts on blood glucose level in glucose induced diabetic rats.

Group	Treatment	Blood Glucose level (mmol/L)				
		Normal Glucose Level	Acute (hours)			
			0.75hr before treatment	0.5	1	2	4
1	Normal (without glucose)	5.00± 0.42				
2	Diabetic control (Glucose alone)		8.78 ± 0.51	5.60±0.51	4.78 ± 0.69	4.34 ± 0.73	4.08 ± 0.29
3	Diabetic + 100mg/kg extract		8.56 ± 1.31	9.36±1.13	8.64 ± 1.32	5.44 ± 0.37	5.70 ± 0.46
4	Diabetic + 200mg/kg extract		9.00 ± 0.65	8.76±0.30	6.26± 1.11	5.56 ± 0.79	5.12 ± 0.41
5	Diabetic + 400mg/kg extract		12.60 ± 1.13	9.34± 1.81	9.36±1.55	6.48 ±1.12	4.78 ± 0.49
6	Diabetic + 5mg/kg Glibenclamide		8.32 ± 0.84	5.88± 0.55	5.76 ± 0.79	4.42 ± 0.91	2.74 ± 0.55

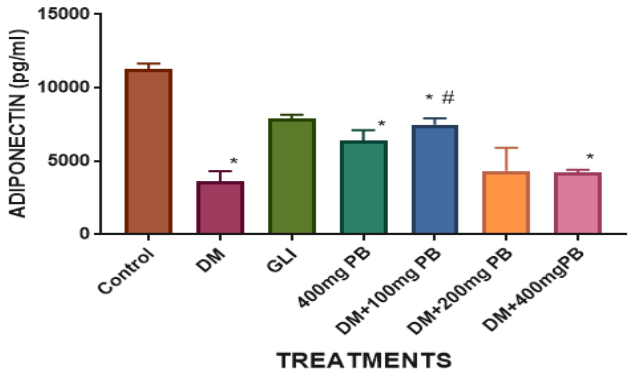

Figure 1:
Plasma Adiponectin concentration (pg/ml) in Control and *Peristrophe bicalyculata* Treated alloxan-induced diabetic Rats. * indicate significantly different from normal control, p <0.05, # indicate significantly different from Diabetic control.

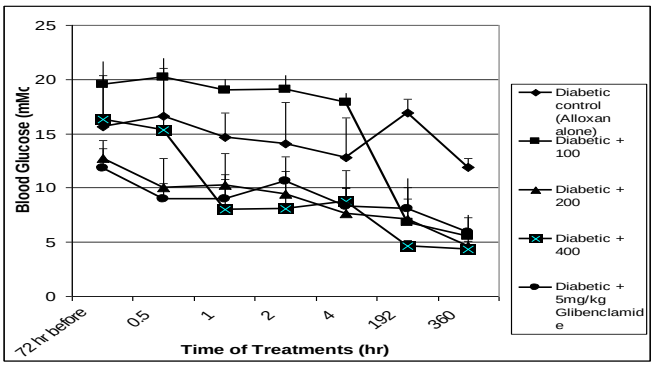

Figure 2:
Change in blood glucose level after acute and sub-acute extract treatment in alloxan-induced diabetic rats.

DISCUSSION

Diabetes treatment and management has been increased tremendeously in the last decade (Tun, *et. al;* 2017). Recently, WHO has approved the use of medicinal plant materials in the management of diabetes (Kooti, *et al;* 2016, Choudhury, *et al;* (2018). In this study, the effect of methanol extract of *P. bicalyculata* leaves on STZ-induced diabetic rats were reported. *P. bicalyculata* treatment in STZ-induced diabetic rats significantly reduced the blood glucose level after a long period of time (168hours). The biochemical mechanism of actions of *P. bicalyculata* extract might be due to an insulin mimetic effect on muscle and adipose tissues either through stimulating glucose uptake and metabolism (Maureen *et al*., 1999), or by inhibiting hepatic gluconeogenesis (Dale *et al*., 2009) and glycogenolysis. This mechanism explained here is buttressed in our study when the extract was treated in glucose loaded hyperglycemic rat model and the blood glucose level reduced with time. It has been found out that most of the oral hypoglyceamic agents in use have multiple mechanism of action (Lorenzati, et al.; 2010). Other suggested mechanism of action could also be by stimulation of regeneration process or increase pancreatic secretion of insulin from existing β-cells and inhibiting activity against α-glucosidase enzymes in small intestine which converts disaccharides into monosaccharides for sake of absorption (Kazeem *et al*., 2013). The action of *P. bicalyculata* leaves extract on blood glucose (especially in STZ-induced diabetic rats pre-treated with 100 mg/kg extract) in diabetic rats is similar to that of glibenclamide (5mg/kg), a potent hypoglycaemic agent, and suggest that *P. bicalyculata* leaf extract contain active components that can reduce blood glucose level during diabetes associated hyperglycemia. Glibenclamide is known to produce effect via selective blockade of adenosine triphosphate (ATP) sensitive K+ (KATP) open-gated channels in the plasma membrane. This leads to closure of K+ (KATP) open-gated channels and polarized membrane becomes depolarized thereby activating voltage gated Ca_2+ channels. A rise in cystolic (Ca_2+) has been shown to trigger the release of endogenous insulin in β-cells of the pancrease (Luzi and Pozza, 1997), this suggest that streptozotocin at 60 mg/kg i.p. might not be sufficient for complete destruction of β-cells and/or few cells remained to have capability to regenerate and secret insulin.

In addition, alloxan caused irreversible destruction of pancreas β-cells responsible for production of insulin thereby leading to hyperglycemia Similar to the result obtained in streptozotocin-induced diabetes, anti-diabetic effect of *P. bicalyculata* leaves was observed during sub-acute extract pre-treatment. Based on this evidence that *P. bicalyculata* leaves

extract require longer duration (between 170 – 360 hours) to reduce blood glucose level in the streptozotocin and alloxan-induced diabetic model, the active components of this plant may only be a useful agent in the long term treatment of type 1 diabetes.

Adiponectin is a protein hormone secreted from adipose tissue and placenta that modulates a number of metabolic processes, including glucose regulation and fatty acid oxidation. (Díez and Iglesias 2003, Chen et al., 2006). Adiponectin is secreted into the bloodstream where it accounts for approximately 0.01% of all plasma protein. Its concentration is drastically reduced in diabetics compared to non-diabetics and weight reduction significantly increases circulating concentrations. (*Coppola et al., 2009). Principally, adiponectin acts on three main organs in the body: the liver skeletal muscles and blood vessels. (*Arunkumar and Sushil 2017). The reduced level of adiponectin in diabetic rats in this study is similar to findings from other studies where adiponectin production was reported to be negatively correlated with accumulated visceral fat (Anna *et al*., 2009), and knocking out adiponectin resulted in severe insulin resistance and diabetes (Takashi *et al*., 2006). On the other hand, a high adiponectin level is found to be a consistent indicator of lower risk of type 2 diabetes because of its anti-diabetic and anti-atherogenic effects (Ghorban *et al*., 2014). In line with this study, the results revealed that pre-treating the rats with *P. bicalyculata* leaves extract significantly increased adiponectin levels in pre-treated diabetic rats compared to unpretreated diabetic rats.

Several studies have documented the association of diabetes mellitus and abnormalities in lipid metabolism (Klaus, 2015). Diabetes mellitus is associated with an increase in TG and LDL-C (Triglyceride and Low density lipoprotein cholesterol), and decrease in HDL-C (High density lipoprotein cholesterol). The results from this study revealed disturbance in lipid metabolism in diabetic untreated rats. These effects were attenuated when rats were pre-treated with varying concentration of *P. bicalyculata* extract. The rats pre-treated with the extract at varying concentrations revealed decrease in serum level of TC (Total cholesterol), TG and LDL levels when compared with the diabetic control and was associated with increased serum level of HDL-C. The increased level of HDL-C in *P. bicalyculata* leaves extract pre-treated rats could be due to the enhancement of lecithin: cholesterol acyltransferase (LCAT) which has been shown to plays a key role in incorporating the free cholesterol into HDL which is then taken back to the liver (Seth *et al*., 2015). LDL-C reducing effect of *P. bicalyculata* could be attributed to increased expression of low density lipoprotein receptor (LDLR) which enhanced LDL particles uptake in liver from the circulatory system, through the depletion of intracellular cholesterol (Gamaledin *et al*., 2014). In addition, the decreased level of Total Cholesterol by the *P. bicalyculata* leaves extract could be as result of active component with hypocholesterolemic containing property, which is possibly acting as inhibitor of hepatic hydroxyl methyl glutaryl CoA (HMG CoA) reductase in the liver (Said *et al*., 2016), or increasing the fecal components by inhibiting the absorption of cholesterol from intestine (Janine *et al*., 2006).

In conclusion, the present study revealed the blood glucose lowering, anti-hyperlipidaemia and hyper-adiponectoremic property of methanol extract of *P. bicalyculata* leaves during streptozotocin and alloxan-induced type 1 diabetes in Wistar rats. This study also revealed that 60 mg/kg streptozotocin and 135 mg/kg alloxan monohydrate does not completely destroy the pancreatic beta cell during chemical-induced type 1 diabetes. There could be a possible role of the extract in ncreasing the level of adiponectin to explain its anti-diabetic and anti-lipidaemia activities,

Conflict of Interest

All authors attest there is no conflict of interest attached with this manuscript

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