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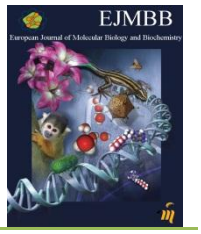

HYPOGLYCAEMIC ACTIVITY OF ETHANOLIC EXTRACT OF *ACTINIOPTERIS DICHOTOMA BEDD* IN NORMAL AND STREPTOZOTOCIN INDUCED DIABETIC RATS

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ABSTRACT
Substantial evidence suggests that ethanolic extracts of *Actiniopteris dichotoma* Bedd increase pancreatic cell viability after STZ (streptozotocin) treatment as a result of their antioxidant properties. In the present study, the hypoglycemic and hypolipidemic activities of *Actiniopteris dichotoma bedd* were studied in normal and STZ-induced diabetic rats, extract orally administrated at doses of 250 and 500 mg/kg once a day for 28 consecutive days. Fasting blood sugar level (FBS), triglyceride, total cholesterol, HDL- and LDL-cholesterol levels were measured. In normal rats, no significant changes were observed in FBS and lipid profiles after orally administration of plant extracts. In diabetic rats, oral administration ethanolic extract at a dose of 250 mg/kg and 250 mg/kg caused significant decreases in glucose level, triglyceride, total cholesterol, LDL-cholesterol levels. However, the ethanolic extract at 500 mg/kg dosage caused a high significant decreases FBS level. The observed effects indicated that *Actiniopteris dichotoma* Bedd could be further developed as a drug to prevent abnormal changes in blood glucose and lipid profile and to attenuate lipid peroxidation in liver and spleen tissues. The aim of this study was to evaluate the hypoglycemic and hypolipidemic activities of *Actiniopteris dichotoma* Bedd in normal and STZ induced diabetic rats.

INTRODUCTION

Medicinal herbs are moving from fringe to mainstream use with a greater number of people seeking remedies and health approaches free from side effects caused by synthetic chemicals. It is documented that 80% of the world's population has faith in traditional medicine, particularly plant drugs for their primary healthcare. India is sitting on a gold mine of well-recorded and traditionally well-practiced knowledge of herbal medicine [1].

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Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia) which is due to insulin deficiency and /or insulin resistance. Diabetes mellitus is syndrome, initially characterized by a loss of glucose homeostasis resulting from defects in insulin secretion, insulin action both resulting impaired metabolism of glucose and other energy-yielding fuels such as lipids and protein [2]. Chronic hyperglycemia in diabetes is associated with long term damage, dysfunction and eventually the failure of organs, especially the kidneys, nerves, eyes and cardiovascular system, which has a significant impact on the health, quality of life, and expectancy of patients as well as on the health care system [3].

The world health organization (WHO) has recently defined traditional medicine (including herbal drugs) as comprising therapeutic practices that have been in existence, often for hundreds of years, before the development and spread of modern medicine and are still in use today [4].

Hyperglycemia occurs because the liver and skeletal muscle cannot store glycogen and the tissues are unable to take up and utilize glucose. In folklore, a variety of plant extracts have been used to treat diabetic patients for centuries. Folklore has given the field of medicine many useful drugs. Obviously evaluation of plants and their active constituents has proven a very useful way of obtaining several useful therapeutic agents. Hence, a logical review of plant constituents having hypoglycemic activity could provide useful clues for obtaining new hypoglycemic agents [5]. The title plant *Actiniopteris dichotoma* is used in folk medicine for treatment of various types of diseases. Chitrakoot is rich in ethnic and biological diversity since ancient times. Several tribal communities like Kol, Gond and Mawasi inhabit Chitrakoot region, and utilize wide variety of plant resources for food, fodder, fibre, medicine. The tribals are familiar about the medicinal uses of *Actiniopteris dichotoma* plant found in their village surroundings and forest areas. This plant has been used as folk and traditional medicine by tribal communities in the treatment of various hazardous diseases.

MATERIAL AND METHODS

COLLECTION OF DRUG MATERIAL

The fresh whole plant was collected from Chitrakoot region, District Satana, Madhya Pradesh in the season of July and August. The plant material to be investigated can be selected on the basis of some specific traditional uses (ethnobotanical bioprospecting approach). The plant was authenticated by Dr. H.B. Singh, H.O.D. of National Institute of Science Communication and Information Resources (NISCAIR), near Pusa gate, New Delhi, India. Reference No. NISCAIR/ RHMD /Consult/2010-11/1408/06.

ANIMALS

Healthy adult wistar rats of either sex weighing 200-250 g for hypoglycaemic activity and swiss albino mice weighing 22-25 g for determination of toxicity study. They were maintained at standard environmental condition (R.H. - 55-65%, room temperature 25±2°C and 12 h light/ dark cycle) and were fed standard pellet diet and water *ad libitum*. The care and maintenance of the animals were as per the approved guideline of the committee for the purpose of control and supervision of experiment on animal (CPCSEA) 891/AC/05/CPCSEA. All experiments on animals were conducted according to the guideline of establishment's ethical committee on animal experimentation.

PREPARATION OF EXTRACT

Soxhlet extraction is used widely in the extraction of plant. The whole plant was dried and powdered. A fine coarse powder was obtained which was sieved through #40 to obtain uniformity. The powered obtained was extracted in ethanol and distilled water. Continues soxhlet extraction method was used, the powder of crude drug was packed in a thimble made whatman filter paper and then inserted in to the extractor. Each batch extracted for about 35 cycles. The extracts were then made to powder by using rotary evaporator under reduced pressure. When the extraction was completed, the extractant concentrated under vacuum, for large volumes and by heating at low temperature.

DETERMINATION OF LD_{50} OF ACTINIOPTERIS DICHOTOMA

OECD (Organization for Economic Co- operation and Development) guideline 423 was followed for acute oral toxicity and LD_{50} determination.

PROCEDURE OF ACUTE ORAL TOXICITY TEST[6]

The acute oral toxicity of the crude ethanolic extracts of *Actiniopteris dichotoma* was evaluated in mice using the procedures described by Organization for Economic Co-operation and Development 423 guidelines. Results were recorded for the first 30 minutes and at hourly intervals for the next 24 hours and thereafter for a total of 14 days. Body weight was recorded on Day 0 (before dosing), Day 7 and Day 14.

INDUCTION OF EXPERIMENTAL DIABETES BY STREPTOZOTOCIN(STZ)[7]

Male Wistar-albino rats (180–220 g) were rendered diabetic by two intraperitoneal (i.p.) injections of streptozotocin (STZ) freshly dissolved in 0.1 M citrate buffer (pH 4.5) at a dose of 60 mg/kg to 16 h fasted rats with an interval of 5 days. Aged matched normal animals receiving an injection of an equivalent volume of 0.1 M citrate buffer (pH 4.5) comprised a non-diabetic control group. Diabetes was confirmed by the presence of hyperglycemia, polyphagia, polydipsia, polyuria and body weight loss. Seven days afterwards, fasting blood glucose levels were measured and animals with blood glucose concentration above 250 mg/dL were considered to be diabetic and selected for the subsequent experiments.

EFFECTS OF *ACTINIOPTERIS DICHOTOMA* ON DIABETIC AND NORMAL RATS

STZ-induced diabetic rats were randomly allocated and similarly grouped into four groups of six animals: diabetic group (treated with normal saline, 5 mL/kg body wt., *p.o.*), 100 mg/kg body wt. (*p.o.*) tolbutamide treated diabetic group, 250 mg/kg body wt. (*p.o.*) *Actiniopteris dichotoma* treated diabetic group, 500 mg/kg body wt. (*p.o.*) *Actiniopteris dichotoma* treated diabetic group. Body weight matched normal rats were also randomly allocated into three groups of six animals

each: normal control group (treated with normal saline, 5 mL/kg body wt., *p.o.*), 250 mg/kg body wt. (*p.o.*) *Actiniopteris dichotoma* treated normal group, and 500 mg/kg body wt. (*p.o.*) *Actiniopteris dichotoma* treated normal group. Test samples of *Actiniopteris dichotoma* were orally administrated once a day for 28 consecutive days. Fasting blood glucose levels were determined on the 0, 7^{th}, 14^{th}, 21^{th} and 28^{th} day after and before (1st day) the administration of the test samples. The effect of each sample on body weight was also monitored at the same time.

IN NORMAL RATS

Group I: Served as untreated control rats. Received normal saline (5 mL/kg body wt., *p.o*)

Group II: Normal rats received ethanolic extract at the dose of 250mg/kg.b.wt. p.o.

Group III: Normal rats received ethanolic extract at the dose of 500mg/kg.b.wt.p.o.

IN DIABETIC RATS

Group I: Served as diabetic control rats ((5 mL/kg body wt., *p.o*)).

Group II: Served as standard received Tolbutamide at the dose of 100 mg/kg.b.wt.p.o.

Group III: Diabetic rats received ethanolic extract at the dose of 250mg/kg.b.wt.p.o.

Group VI : Diabetic rats received ethanolic extract at the dose of 500mg/kg.b.wt.p.o.

BIOCHEMICAL ANALYSIS

Blood samples were collected from retro-orbital plexus. Fasting blood glucose was measured at different time intervals to check the hypoglycaemic state. Serum cholesterol, triglyceride, HDL and LDL were measured using kits.

Statistical Analysis

Results were reported as mean ±SEM for determination of significant inter group difference was analyzed separately and one-way analysis of variance (ANOVA) was carried out [8] Dunnet's test was used for individual comparisons [9].

RESULTS AND DISCUSSION

ACUTE ORAL TOXICITY

Dose of the extract was selected on the basis of screening of toxicity. LD50 was done as per the OECD guidelines for fixing the dose for biological evaluation. There were no signs of acute toxicity. The biological evaluation was carried out at 250 mg/kg. and 500 mg/kg. dose.

STUDY IN NORMAL RATS

The ethanolic extract of plant at the dose of 250mg/kg and 500mg/kg not significantly reduced the Fasting blood sugar (FBS) levels.

STUDY IN DIABETIC RATS

STZ induce type I diabetes in animal models and it has been widely used intravenously or intraperitoneally (i.p.) to, especially rats and mice.[10] Single administration by the route of i.p. STZ at a dose of 60 mg/kg the fasting blood glucose level of experimental rats showed a slight elevation, but a diabetic model could not be successfully established [11,12]. Therefore, another injection of STZ at a dose of 60 mg/kg was given 5 days after the first one according to the literature [13]. After one week of the second injection, almost all experimental animals showed significantly elevated fasting blood glucose levels Streptozotocin was given to animals which showed a stable hyperglycaemia then they were used in the study and divided into various groups as per the experimental protocol. Different strains of animals are known to respond differently to STZ injection and different doses are needed for successful induction [14].

STUDY OF BODY WEIGHT AND FLUID INTAKE

The bodyweight and liquid intake were determined in experimental animals. There was a significant decrease ($p < 0.05$) in the body weight of the diabetic controls compared with the normal controls. Administration of ethanolic extract at the dose of 250mg/kg and 500mg/kg of *Actiniopteris Dichotoma* Bedd to diabetic rats than increased body weight significantly, comparable to the increase in the body weight of normal rats. Diabetic controls had a high intake of food and liquids, while the food and liquid intake was decreased in the ethanolic extract of *Actiniopteris Dichotoma* Bedd - treated groups in comparison to that in the diabetic controls.

ACUTE EFFECT OF PLANT EXTRACT ON BLOOD GLUCOSE LEVEL

STZ- induced diabetic rats exhibiting persistent hyperglycaemia (Blood Glucose>250 mg\dl) were selected for assessing the effect of two different extract of *Actiniopteris Dichotoma* Bedd. The result showed the fasting blood glucose level at various time intervals to observed acute effect of two different doses of ethanolic extract of *Actiniopteris Dichotoma* Bedd. Tolbutamide drug was taken as standard. Data showed that ethanolic extract at the dose of 250 mg/kg and 500 mg/kg significant decrease fasting blood glucose level ($p < 0.05$) compared to diabetic control.

SUBACUTE EFFECT OF PLANT EXTRACT ON BLOOD GLUCOSE LEVEL

Ethanolic extract of Actiniopteris dichotoma bedd at the dose of (500 mg/ kg) showed highly significant ($p < 0.01$) reduce glucose level compared to diabetic control while ethanolic extract at the dose of (250 mg/kg) also showed significant ($P < 0.05$) reduce glucose level.

STUDY OF LIPID PROFILE

Ethanolic extract of Actiniopteris dichotoma Bedd at the dose of 500 mg/kg showed significantly decrease the serum triglyceride ($p < 0.01$), total cholesterol ($p<0.05$) and LDL cholesterol ($p<0.05$) levels compared to diabetic control groups and also showed significant elevation ($p <0.01$) of HDL-cholesterol levels in diabetic rats compared to diabetic control.

Table 1. Effect of chronic dose administration of the ethanolic extract of *Actiniopteris Dichotoma* Bedd in normal rats.

GROUPS	DOSE (mg/kg)	BLOOD GLUCOSE (mg\dl)				
		0-DAY	7-DAY	14-DAY	21-DAY	28-DAY
Normal Control	5ml	93 ± 1.9	93 ± 2.7	95 ± 1.2	94 ± 3.1	92 ± 2.4
Ethanolic Extract	250	95 ± 2.7	94 ± 2.6	90 ± 2.4	98 ± 2.9	94 ± 4.8
Ethanolic Extract	500	94 ± 1.4	98± 2.3	91 ± 4.1	97 ± 2.4	92± 2.8

Table 2. Body weight and Fluid intake

Group	DOSE (mg/kg)	Body weight (g)		Fluid intake mL/animal/day
		Before treatment	After treatment	
Normal control	5 ml	198.6± 0.16	237 ± 1.42	34.53 ± 0.12
Diabetic control	5 ml	208.7± 0.08	171.6 ± 0.05 **a**	79.5 ± 0.14 **a**
Diabetic + Tolbutamide	100	212.4 ± 0.07	228.7±0.07**b**	39.65 ± 0.06 **b**
Diabetic + Ethanolic Extract	250	196.6 ±0.09	200.7 ± 0.07**b**	37.66 ± 0.07 **b**
Diabetic + Ethanolic Extract	500	197.7 ± 0.08	215.6± 0.12 **b,c**	36.46 ± 0.28 **b,c**

All values are expressed as mean ± SEM (n=6), One-way ANOVA followed by Dunnet's comparison test. a= compared to untreated control ($P < 0.05$), b= compared to diabetic control ($P < 0.05$), c= Actiniopteris dichotoma Bedd (500mg/kg compared to 250 mg/kg) ($P < 0.05$).

Table 3. Acute effect of ethanolic extract of Actiniopteris dichotoma Bedd on blood glucose level in STZ induced diabetic rats.

Groups	DOSE (mg/kg)	Blood Glucose (mg\dl)				
		0 hr	2 hr	4 hr	6 hr	24 hr
Normal Control	5 ml	93 ± 1.9	93 ± 2.7	95 ± 1.2	94 ± 3.1	91 ± 1.4
Diabetic Control	5 ml	230 ± 2.4	237 ± 1.6	239 ± 3.2	244 ± 2.1	254 ± 4.1
Diabetic+Tolbutamide	100	247 ± 2.3	174 ± 2.7*	147 ± 1.8**	124 ± 1.1**	183 ± 3.6
Ethanolic Extract	250	222 ± 3.7	193 ± 2.4*	164 ± 2.3*	144 ± 1.9*	198 ± 2.8
Ethanolic Extract	500	220 ± 2.4	185 ± 4.3*	158 ± 3.1*	135 ± 2.7*	190 ± 3.8

All values are expressed as mean ± S.E.M (n=5). *P<0.05, ** P<0.01 as compared to diabetic control. One-way ANOVA followed by Dunnet's multiple comparison test.

Table 4. Sub acute effect of ethanolic extract of Actiniopteris dichotoma Bedd on blood glucose level in STZ induced diabetic rats.

GROUPS	DOSE (mg/kg)	BLOOD GLUCOSE LEVEL (mg\dl)				
		0 -DAY	7-DAY	14-DAY	24 -DAY	28- DAY
Normal Control	5 ml	91 ± 2.5	97 ± 2.1	100 ± 2.5	98 ± 1.4	96 ± 3.2
Diabetic Control	5 ml	239 ± 2.5	247 ± 2.3	259 ± 3.4	264 ± 2.5	290 ± 4.2
Diabetic+Tolbutamide	100	241 ± 1.9	198 ± 2.9**	140 ± 1.2**	122 ± 4.3**	88 ± 3.7**
Ethanolic Extract	250	232 ± 2.4	204 ± 3.2*	184 ± 3.7*	151 ± 1.2*	120 ± 3.9*
Ethanolic Extract	500	222 ± 3.2	207 ± 2.8	152 ± 2.4*	134 ± 4.4**	105 ± 1.8**

All values are expressed as mean ± S.E.M (n=5). *P<0.05, **P<0.01 as compared to diabetic control. One-way ANOVA followed by Dunnet's multiple comparison test.

Table 5. Effects of Ethanolic Extract of Actiniopteris dichotoma on lipid profiles of normal and STZ induced diabetic rats.

Extract and Drug	Dose (mg/kg)	Triglyceride (mg/dL)	Cholesterol (mg/dL)	HDL-cholesterol (mg/dL)	LDL-cholesterol (mg/dL)
Diabetic Control	5 ml	78.92 ± 6.57 ##	68.49 ± 7.90 ##	24.42 ± 2.26 #	38.34 ± 2.54 ##
Diabetic+ Tolbutamide	100	76.10 ± 7.54	59.21 ± 2.48 *	26.76 ± 4.32	36.16 ± 4.21

Diabetic+ Ethanolic Extract	250	59.24 ± 1.54 *	55.22 ± 4.21 *	27.46 ± 1.57	23.21 ± 2.44 *
Diabetic+ Ethanolic Extract	500	49.24 ± 8.74 **	52.27 ± 6.41 *	28.26 ± 2.47	24.21 ± 1.34 **
Normal Control		58.41 ± 6.20	55.20 ± 2.64	28.54 ± 4.16	28.15 ± 2.41
Normal+ Ethanolic Extract	250	58.12 ± 2.20	54.23 ± 1.64	30.03 ± 2.81	27.54 ± 4.26
Normal+ Ethanolic Extract	500	59.14 ± 5.21	53.61 ± 1.22	29.03 ± 1.72	27.14 ± 2.16

All values are expressed as mean ± S.E.M (n=5) (standard error of the mean). * $p < 0.05$, **$p < 0.01$ significant from diabetic controls. $^{\#}p<0.05$, $^{\#\#}$ $p < 0.01$ significant from normal controls. One-way ANOVA followed by Dunnet multiple comparison test.

Figure 1. Acute effect of ethanolic extract of Actiniopteris dichotoma Bedd on blood glucose level in STZ induced diabetic rats

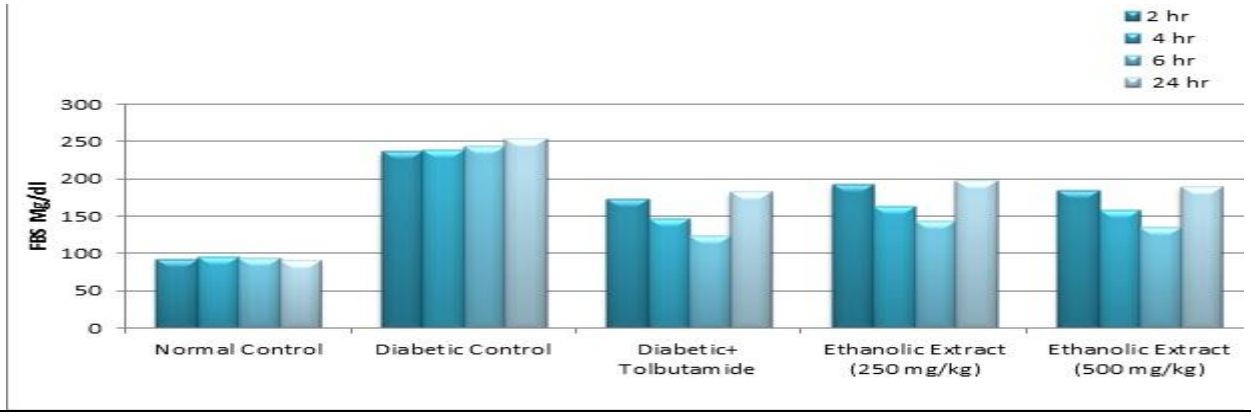
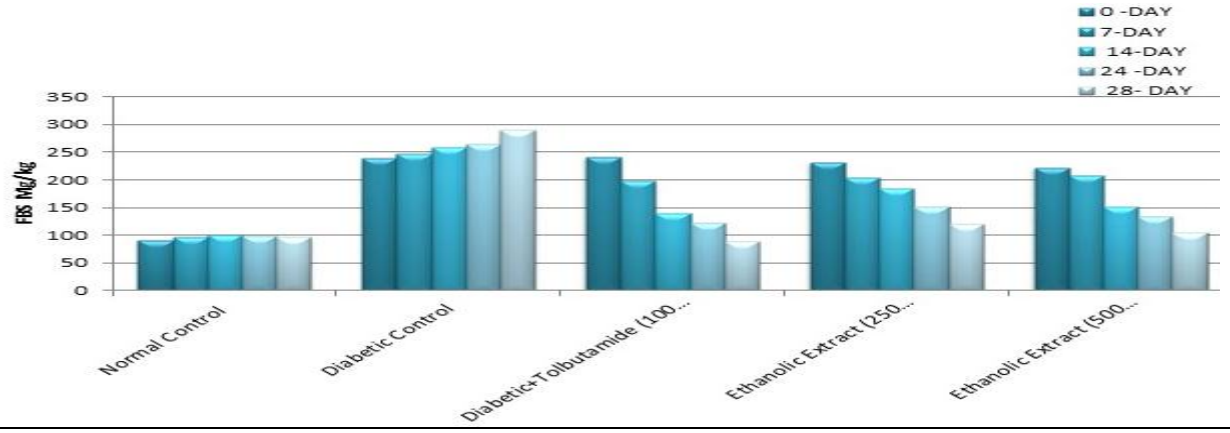


Figure 2. Sub acute effect of ethanolic extract of Actiniopteris dichotoma Bedd on blood glucose level in STZ induced diabetic rats



DISCUSSION

Ethanolic extract of *Actiniopteris Dichotoma* Bedd was given to diabetic rats than increased body weight significantly, comparable to the increase in the body weight of normal rats. Diabetic controls had a high intake of food and liquids, while the food and liquid intake was decreased in the ethanolic extract of *Actiniopteris Dichotoma* Bedd -treated groups in comparison to that in the diabetic controls. Study was conducted to assess the hypoglycemic activity on chronic dose administration in normal rats and results showed that ethanolic extract at 250mg/kg and 500mg/kg there were no significantly change occurred in fasting blood sugar (FBS) levels respectively as compare to normal. In acute study, ethanolic extract of *Actiniopteris Dichotoma* Bedd at the dose of 250mg/kg and 500mg/kg significant reduced ($p<0.05$) fasting blood sugar (FBS) level compared to diabetic control. Ethanolic extract at the dose of 500mg/kg were showed highest decrease of FBS level. In sub acute study, ethanolic extract at the dose of (250 mg/ kg) showed significant ($p < 0.05$) reduce glucose level compared to diabetic control while ethanolic extract at the dose of 500 mg/kg) also showed significant ($P < 0.01$) reduce glucose

level. Lipid profile in diabetic rats after 28 days caused significant increases in triglyceride, total cholesterol, LDL cholesterol and a significant reduction in HDL cholesterol concentrations compared to normal animals. In diabetic rats, treated with ethanolic extract of Actiniopteris dichotoma at dose of 250mg/kg and 500 mg/kg for 28 days could significantly decrease the serum triglyceride, total cholesterol and LDL cholesterol levels compared to diabetic control groups. Usually, diabetes is associated with profound alternation in lipid and lipoprotein profiles as illustrated in this study and literature.[15] The results of this study showed that Actiniopteris dichotoma could reverse the hyperlipidemia in experimental diabetic rats, and thus may lead to a decrease in the risk of micro- and macrovascular disease and related complications.[16] The improvement of lipid profile might be directly or indirectly related with the reducing of blood glucose levels in diabetic rats.

CONCLUSIONS

The present study evaluated the hypoglycemic and hypolipidemic effects of ethanolic extracts of *Actiniopteris Dichotoma* Bedd in normal and STZ induced diabetic rats. It illustrated that after oral administration of *Actiniopteris Dichotoma* Bedd at a dose of 250 mg/kg for 28 consecutive days, the fasting glucose levels in STZ-induced diabetic rats were significantly decreased and at a dose of 500 mg/kg, the blood glucose, triglyceride, total cholesterol, LDL-cholesterol levels were also significantly reduced. In normal rats, no significant differences were found in glucose levels, lipid profiles. As a conclusion, the present study confirmed for the first time the *in vivo* hypoglycemic and hypolipidemic effects of *Actiniopteris Dichotoma* Bedd. The observed hypoglycemic and hypolipidemic effects of *Actiniopteris Dichotoma* Bedd on diabetic rats extend our knowledge about the potential bioactivities. It could be used by diabetic patients to decrease the complications of diabetes. However, it was also found that dosage of 500 mg/kg *Actiniopteris Dichotoma* Bedd caused a significant body weight gain loss in both normal and diabetic rats. Therefore, further studies are necessary to determine the exact nature of the active principles, the mechanism of action.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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