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OREOCNIDE INTEGRIFOLIA (GAUD.)MIQ EXHIBITS HYPOGLYCEMIC AND HYPOLIPIDEMIC POTENTIALS ON STREPTOZOTOCIN DIABETIC RATS: A PRELIMINARY DOSE AND DURATION DEPENDENT STUDY

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ABSTRACT

*Oreocnide integrifolia (Gaud.)*Miq (Urticaceae) leaves are used to alleviate diabetic symptoms in folk medicine in northeast India. In the present study, dose and duration dependent hypoglycemic potentials were evaluated in streptozotocin induced diabetic rats. Administration of aqueous leaf extract (100, 250, 500 and 750 mg/kg body weight orally once daily) to diabetic rats reduced glycemic levels by 56 % by 4 weeks of treatment and was comparable to standard reference drug Metformin. The experimental data also revealed significant improvement in lowering lipid profile, Urea, Creatinine, Hb, HbA1c and insulin levels. The present study clearly demonstrates hypoglycemic and hypolipidemic potential of *Oreocnide integrifolia* leaf extract.

Keywords: Insulin, *Oreocnide integrifolia*, Streptozotocin

INTRODUCTION

Diabetes mellitus is characterized by an initial loss of glucose homeostasis resulting from defects in insulin secretion and/or insulin action or leading to impaired metabolism of glucose and other energy-yielding metabolites (Scheen, 1997). It is also accompanied by hyperglycaemia, dyslipidaemia, hypertension, decreased fibrinolytic activity, increased platelet aggregation, and severe atherosclerosis, all of which are potential risk factors.

Though several drugs targeting carbohydrate hydrolyzing enzymes (pseudosaccharides), release of insulin from pancreatic β-cells (sulphonylurea), glucose utilization (biguanides), insulin sensitization and PPARγ agonists (glitazones) are in clinical practice, there is a growing market for antidiabetic agents. Many of these oral antidiabetic agents have been reported to show serious adverse effects (Zhang and Moller, 2000). The multifactorial etiology and multiple pathogenic manifestation of diabetes demands multi-modal therapeutic approach and, future therapeutic strategies require evaluation of efficacy of combination of drugs.

Management of diabetes sans side effects is still a challenge for the pharmaceutical world. Traditional knowledge of medicinal plants has become a recognized tool in research for the search of new sources of drugs and neutraceuticals (Sharma and Mu-

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jundar, 2003). In fact, metformin, one of the most prescribed glucose-lowering medicines currently used, is derived from a chemical isolated from a plant (Witters, 2001).

The World Health Organization has infact recommended the use of herbal medicine especially in developing countries (WHO, 2002).Because of their perceived effectiveness, minimal side effects in clinical experience and effectiveness, herbal drugs are prescribed widely even when their biologically active compounds are not known (Valiathian, 1998).

The local communities residing in the biodiversity-rich areas of the north eastern region of India have traditionally used and relied on herbs for treating various ailments. In many cases, local knowledge of medicinal plants remains poorly documented in scientific literature. These plants have found a prime place in the indigenous system of medicine and are in focus for evaluation of their active ingredients.

*Oreocnide integrifolia (Gaud.)*Miq (family Urticaceae) are trees of 5-20 m height having reddish brown branchlets and simple, alternate, spiral and clustered leaves at twig end, found in wet evergreen forests at 300-1400 m height. They are mainly distributed in India, China, Bhutan, Indonesia, Laos, Myanmar, Sikkim and Thailand (Chen et al., 2003). The roots of *Oreocnide integrifolia* are mixed with ginger powder and applied for treatment of rashes by Khasi and Jayantia tribes of Meghalaya (Begum and Nath, 2000; Kharkongor and Joseph, 1981). In north eastern states of India it is popularly known as ukhajing (manipuri), bonrhea (assamese), gingsining (garo) and dieng teingbah (khasi), and an infusion prepared from the leaves is used as a decoction to alleviate diabetic symptoms. Based on our literature survey till date, there are no scientific reports and hence the present study in this behest was undertaken to evaluate the hypoglycemic and hypolipidemic potential of *Oreocnide integrifolia* leaf extract on streptozotocin induced experimental diabetes.

MATERIALS AND METHODS

Plant material and extraction

Fresh green leaves were collected during the month of October from Imphal district (Manipur) and authenticated by botanist Dr. Hemchand Singh, D.M. College of Science, Manipur University. A voucher specimen (#344) of the herbarium has been deposited at the same department for future reference. The leaves were collected during the month of Sep-Oct, washed thoroughly and shade dried at room temperature. The dried leaves were subjected to size reduction to a coarse powder by using dry grinder and passed through (# 400) sieve. Two hundred grams of powder was mixed with 1 litre of Milli Q water (Millipore, Billerica, MA) and boiled for 30 min and then left to cool down to room temperature. The decoction was filtered (Whatmann # 01) using a suction apparatus and the filtrate was lyophilized and stored in a freezer at −20 °C. The extractive value of the aqueous extract in terms of yield was about 16.9 % (w/w).

Experimental animals

Female *Charles foster* rats (200–230 g) were housed in clean polypropylene cages under controlled room temperature (21 ± 2 ºC).They were fed with comercially available rat chow (M/s Pranav Agro Ltd., Baroda) and provided with water *ad libitum.* The experiment was carried out according to the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India and approved by the Animal Ethical Committee of Department of Zoology, The M.S. University of Baroda, Vadodara (Approval No. 827/ac/04/ CPCSEA).

Induction of Type I diabetes

Rats were rendered diabetic by single intraperitoneal administration of streptozotocin (60 mg/kg) dissolved in 0.1 M Citrate buffer, pH 4.5. Seven days later, blood samples were collected and blood glucose levels determined to confirm induction of diabetes. Only those animals which showed

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fasting blood glucose levels higher than 250 mg/dl were used for the experiment.

Experimental procedure

Sixty-six rats (30 normal and 36 diabetic rats) were divided into eleven groups of six animals each. Group I consisted of normoglycemic rats (NC) administered with vehicle alone while, Groups II, III, IV, and V (NOI100, NOI250, NOI500, NOI750) consisted of normoglycemic rats treated 100, 250, 500 and 750 mg/kg body weight of *OI* (*Oreocnide integrifolia*) extract respectively. Group VI comprised of diabetic rats (DC) which received vehicle only while Groups VII, VIII, IX and X (DOI100, DOI250, DOI500 ,DOI750) consisted of diabetic rats treated with 100, 250, 500 and 750 mg/kg body weight of *OI* extract respectively. Group XI (DMet) consisted of diabetic rats treated with metformin, an antidiabetic drug (50 mg/kg). All animals received their respective drugs in 0.5 % Sodium carboxymethylcellulose orally via gastric intubation for a period of 28 days.

Biochemical determinations

After overnight fasting, blood samples were collected by retro-orbital sinus puncture from experimental animals on 0, 7th, 14th, 21st and 28th day of experimentation (Table 1). Plasma was separated by centrifugation at 3000 rpm for 10 min at 4 °C. Plasma glucose levels were estimated by an analytical Kit (Biogamma, Labkit, Italy). At the end of experimentation on 28th day, plasma high density lipoprotein (HDL), triglycerides (TG), total cholesterol (TC), phospholipids (PHL), creatinine, urea and haemoglobin (Hb) were estimated by specific analytical kits (Merck Diagnostics, Mumbai) while, glycosylated haemoglobin (HbA1c) was estimated by cation-exchange resin method kit (Monozyme Pvt. Ltd., Secunderabad, India). Plasma insulin levels were assayed using rat insulin ELISA kit (Mercodia Diagnostics, Sweden). Low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated by Friedwald's formula (Friedwald et al., 1972).

Table 1: Effect of *OI* extract on fasting blood glucose levels at 0, 7th, 14t^{h}, 21st and 28th day of treatment

Groups	Treatments	Blood Glucose*				
		0th Day	7th Day	14th Day	21st Day	28th Day
I	NC	105.4±11.74	102.3± 6.00	103.9± 9.70	97.25±12.05	104.9± 8.30
II	NC + O.I 100	102.9± 4.37	106.4±12.05	99.9± 3.70	109.5±15.15	98.25±11.95
III	NC + O.I 250	110.6± 9.34	107.5±11.15	104.1± 3.80	102.7± 6.40	110.3± 5.35
IV	NC + O.I 500	105.7± 9.30	106.6±15.95	106.7± 6.25	103.0± 6.05	110.6± 5.35
V	NC + O.I 750	106.1± 3.50	110.4±13.15	100.4± 7.20	111.6± 9.70	100.6± 4.70
VI	DC	432.4±23.26	456.2±27.05	412.8±16.15	423.1±13.15	429.3±23.10
VII	DC + O.I 100	427.7±16.51	415.8±13.85	400.8±13.65	381.2±19.00	367.4±17.20
VIII	DC + O.I 250	433.3±12.99	412.6±19.35	394.6±16.40	366.5±20.70	351.3±16.10
IX	DC + O.I 500	441.6±24.27	337.7±15.80^{a}	289.6±13.65^{b}	232.6±12.35^{c}	207.2±10.85^{c}
X	DC + O.I 750	439.4±16.30	316.8±12.20^{b}	277.3±17.25^{c}	236.2±15.90^{c}	186.6±17.35^{c}
XI	DC+ Metformin	427.6±20.75	318.7±12.45^{b}	241.4±19.90^{c}	186.5±15.85^{c}	147.6±14.70^{c}

Group I was compared with Group II, III, IV and V
Group VI was compared with Group VII, VIII, IX, X and XI
where a =p<0.05, b=p< 0.01and c= p<0.001
where * = mg/dl

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Statistical analysis

Statistical evaluation of the data was done by one way ANOVA followed by Bonferroni's Multiple comparison test. The results are expressed as mean ± S.E.M using Graph Pad Prism version 3.0 for Windows, Graph Pad Software, San Diego, CA/USA.

RESULTS

Plasma glucose

DC group recorded significantly elevated plasma blood glucose levels throughout the study period ($p<0.001$). Administration of extract to diabetic rats showed significant reduction in blood glucose levels. Low doses of extract (DOI100 and DOI250 mg/kg) had no significant effect on plasma blood glucose throughout study period (Table 2). Higher doses of extract (DOI500 and DOI750 mg/kg) proved to be very potent as glycemic indices were significantly reduced especially between 7^{th} and 28^{th} days of study.

Plasma lipid profile

Diabetic animals recorded significant increase in plasma TC ($p<0.05$), TG ($p<0.05$), FFA ($p<0.05$) and PHL ($p<0.05$), while HDL levels recorded a significant decrement ($p<0.05$). Low doses of extract (DOI100 and DOI250 mg/kg of body weight) did not have any significant effect in decreasing in plasma lipid profile, but higher doses of extract (DOI500 and DOI750 mg/kg of body weight) showed lowered plasma lipid profile significantly while increasing HDL levels (Table 3). These results were comparable with metformin treated diabetic rats. *OI* extract did not have any significant effect on plasma lipid profile in control rats (Table 3).

Plasma Hb, urea, creatinine, HbA1c and insulin levels

Diabetic rats recorded significant decrement in haemoglobin content and increase in glycosylated haemoglobin along with increase in urea and creatinine levels. Low doses of extract (DOI100 and DOI250 mg/kg of body weight) were not able to induce significant changes in levels of haemoglobin and urea contents (Table 4) though, glycosylated haemoglobin recorded a significant decrement.

Table 2: Effect of *OI* extract on plasma total cholesterol (TC), triglycerides (TG), free fatty acids (FFA) and phospholipids (PHL) levels after 28 days of treatment

Groups	Treatments	TC *	TG *	FFA *	PHL *
I	NC	38.1±2.58	44.3±3.98	40.4±2.15	101.5±2.85
II	NC+ O.I 100	35.7±2.45	42.8±2.82	40.1±1.14	103.4±1.21
III	NC + O.I 250	41.7±3.45	48.2±2.90	42.9±1.62	99.83±3.50
IV	NC + O.I 500	40.5±2.20	42.0±3.68	43.0±2.00	100.5±3.51
V	NC + O.I 750	41.0±1.33	43.2±3.13	41.2±1.47	102.3±3.01
VI	DC	71.0±2.95	83.7±3.31	76.6±2.35	134.6±3.38
VII	DC + O.I 100	71.7±1.30	74.8±2.58	72.2±1.84	128.0±2.66
VIII	DC + O.I 250	66.8±1.85	67.2±2.11	67.9±1.49	120.0±1.36
IX	DC + O.I 500	54.2±1.83[a]	53.6±3.38[a]	51.2±1.18[c]	107.8±2.49[b]
X	DC + O.I 750	47.0±1.31[b]	43.5±1.52[b]	43.5±1.46[c]	99.35±3.01[c]
XI	DC+Metformin	47.3±1.97[b]	42.7±2.41[b]	44.9±1.00[c]	94.83±3.49[c]

Group I was compared with Group II, III, IV and V
Group VI was compared with Group VII, VIII, IX, X and XI
where a =$p<0.05$, b=$p< 0.01$and c= $p<0.001$.
where * = mg/dl

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Table 3: Effect of FEOI extract on plasma lipoproteins levels and atherogenic index after 28 days of treatment

Groups	Treatments	Plasma lipoprotein levels			Atherogenic index
		LDL-C*	VLDL-C*	HDL-C*	
I	NC	25.86±1.20	8.86±0.80	21.10±0.80	1.81
II	NC+ O.I 100	22.66±1.63	8.56±0.56	21.60±0.70	1.65
III	NC + O.I 250	31.24±1.59	9.64±0.58	20.10±1.20	2.07
IV	NC + O.I 500	26.99±1.96	8.40±0.74	21.95±0.35	1.85
V	NC + O.I 750	30.06±1.83	8.64±0.63	19.60±1.70	2.09
VI	DC	74.14±2.00	16.74±0.66	13.60±1.30	5.22
VII	DC + O.I 100	72.26±1.33	14.96±0.52	14.40±1.20	4.98
VIII	DC + O.I 250	64.99±2.01	13.44±0.42	15.25±1.05	4.38
IX	DC + O.I 500	45.52±1.45^{c}	10.72±0.68^{b}	20.40±1.10	2.66
X	DC + O.I 750	34.00±1.77^{c}	8.70±0.31^{c}	21.70±1.50^{a}	2.17
XI	DC+Metformin	34.24±1.98^{c}	8.54±0.48^{c}	21.60±0.70^{a}	2.19

Group I was compared with Group II, III, IV and V
Group VI was compared with Group VII, VIII, IX, X and XI
where a =p<0.05, b=p< 0.01and c= p<0.001
where * = mg/dl

Table 4: Effect of *OI* extract on hemoglobin (Hb), glycosylated hemoglobin (HbA1c), insulin, urea and creatinine levels after 28 days of treatment

Groups	Treatments	Hb$^{@}$	HbA1c$^{\#}$	Insulin$^{\$}$	Urea*	Creatinine*
I	NC	13.20±0.20	6.40±0.20	25.61±0.21	25.60±3.20	24.50±2.30
II	NC+ O.I 100	13.50±0.20	6.40±0.10	24.57±0.18	24.80±2.10	26.25±1.05
III	NC + O.I250	12.90±0.30	6.60±0.10	24.81±0.61	25.60±1.40	24.30±2.10
IV	NC + O.I500	13.20±0.20	6.20±0.10	25.06±0.20	25.25±1.95	23.70±2.20
V	NC + O.I750	12.90±0.50	6.40±0.20	24.28±0.13	26.60±1.60	24.30±0.80
VI	DC	8.90±0.10	12.90±0.20	6.18±0.21	43.20±2.10	46.20±3.40
VII	DC + O.I100	8.90±0.40	10.35±0.25^{c}	8.08±0.24	40.90±2.20	42.10±0.70
VIII	DC + O.I250	9.70±0.20	9.85±0.15^{c}	11.51±0.19^{a}	33.70±3.10	32.46±2.10^{a}
IX	DC + O.I500	9.40±0.30	8.60±0.30^{c}	14.16±0.27^{b}	27.75±1.05^{b}	27.85±1.51^{b}
X	DC + O.I750	10.30±0.20	8.20±0.20	15.64±0.18^{c}	26.43±1.07^{b}	29.81±1.44^{b}
XI	DC+Metformin	12.40±0.20^{c}	8.70±0.20^{c}	18.64±0.30^{c}	26.12±1.11^{b}	34.34±1.01^{a}

Group I was compared with Group II, III, IV and V
Group VI was compared with Group VII, VIII, IX, X and XI
where a =p<0.05, b=p< 0.01and c= p<0.001
where @ = g/dl, # = Hb%, $ = µIU/ml and * = mg/dl

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Higher dose of extract (DOI500 and DOI750 mg/kg) registered a significant increment in haemoglobin content with a concomitant decrement in glycosylated haemoglobin, urea and creatinine contents ($p<0.05$). These results were comparable to metformin treated rats. *OI* extract administration did not have any significant effect on any of the parameters. Grading of urine sugar level by Benedicts qualitative analysis revealed very high sugar content in DC rats while it was in trace amounts in DOI750 rats. Insulin titre in the animals was significantly lower while there was significant improvement in DOI750 rats. The DCMet animals showed slightly more elevated level compared to DOI750 but still less than the control level (Table 4).

DISCUSSION

Chronic hyperglycemia associated with diabetes is known to induce glycation of body proteins which leads to secondary complications affecting eyes, kidneys, nerves and arteries (Sharma, 1993). Insulin-dependent diabetes mellitus or type 1 diabetes is an autoimmune disorder caused by destruction of insulin producing β-cells when auto aggressive T-lymphocytes infiltrate the islets and leads to hypoinsulinaemia and thus hyperglycemia.

Streptozotocin (STZ) has been proposed to act as a diabetogenic agent due to its ability to destroy pancreatic beta cells by the generation of excessive free radicals (Szkudelski, 2001). Streptozotocin enters the pancreatic β-cell via a glucose transporter-GLUT2 and causes alkylation of DNA and impairment in glucose oxidation (Bolaffi et al., 1987) leading to decreased insulin biosynthesis and secretion (Nakatsuka et al., 1990).

The present study using *OI* extract in type 1 diabetic rats has shown both dosage and duration dependent favorable effects. The attributed anti-hyperglycemic effects of most of the plants is due to their ability to restore islet function by causing an increase in insulin output or by inhibiting the intestinal absorption of glucose or even by facilitation of metabolites in insulin dependent processes. Hence treatment with herbal drugs has an effect on protecting β-cells and smoothening out fluctuation in glucose levels (Jia et al., 2003; Elder, 2004). The antidiabetic efficacy of *OI* extract is clearly indicated by the significant hypoglycemic effect following a 4 week treatment of diabetic rats. The *OI* extract clearly shows a duration as well as dose dependent effect. Both DOI100 and DOI250 mg of *OI* extract treatment had a similar duration dependent effect with 14-18 % decrease in glycemic levels at end of 28 days. Similarly, both DOI500 and DOI750 mg of *OI* extract treatment had similar duration dependent efficacy with a maximal 51-56 % decline in glycemic level by 28 days. The metformin treated diabetic rats at the same time showed a 65 % decrease in glycemic level. However, the absolute glycemic levels of DOI750 and DMet groups of rats are not statistically different. Apparently, though both DOI500 and DOI750 had similar duration dependent decline in glycemic level, the DOI750 effect at the end of 28 days seems to be relatively better and very much similar to the effects of the marketed antidiabetic drug. Apparently, the anti-hyperglycemic effects of both DOI750 and DMet is to a greater extent accreditable to the improvement in insulin level brought about by these agents from the low level seen in DC rats. The lower insulin titre and marked hyperglycemia in DC rats is well reflected in the observed increase in HbA1c level and decrease in Hb content, quite suggestive of glycosylation of proteins, a serious issue of diabetes that is responsible for many secondary complications. It is remarkable that in this context, there is 100 % increase in HbA1c levels in DC rats and treatment with DOI750 reversed this significantly to 30 % of control level very much similar to the result obtained by treatment with DMet. Clearly, the similarly degree of increase in peripheral insulin titre and hypoglycemia are responsible for the observed decrease in HbA1c and increase in haemoglobin in DOI750 and DMet treated

diabetic rats. Similar observations have been made even with other plant products (Bopanna et al., 1997; Venkateswaran and Pari, 2002).

Insulin is a powerful metabolic hormone singularly countering the lipolytic actions of all other hormones like glucagons, catecholamines, growth hormone etc. Essentially, these hormones activate the hormone sensitive lipase in peripheral depots (adipose tissue) bringing about lipolysis contributing to hyperlipidemia and hypercholesterolemia as well as increased loads of hepatic and renal lipids and cholesterol. Insulin deficiency, as it occurs during diabetes, favours the actions of hormone sensitive lipase and increases secondary risk factors in the form of increased plasma lipid fractions. This is clearly validated by the herein, observed significant (2-3 folds) increase in various plasma lipid fractions in STZ induced DC rats. Similar observations are recorded in literature in the many studies on induced diabetes (Gupta et al., 2009; Rajkumar et al., 2005). *OI* extract treatment is found to be effective in lowering the DC specific plasma lipid parameters with DOI750 being the most potent almost normalizing all the lipid values very much similar to the response obtained with Metformin. The *OI* extract effectively lowered cholesterol, triglyceride and LDL-C levels and increased HDL-C levels. There are similar reports on the ability of other medicinal plants also exhibiting potential hypolipidemic and hypocholesterolemic effects (Pari and Latha, 2002; Mitra et al., 1995). The underlying mechanism of lipid lowering activity of *OI* extract may be correlated with this ability to increase insulin level and the consequent mechanism of action as suggested above. Since, diabetes induced hyperlipidaemia is attributable to excess mobilization of fats from adipose tissue, due to under utilization of glucose (Khanna et al., 2002), the regression of diabetic state on *OI* extract administration inferably increases utilization of glucose by the recovered insulin levels, thereby depressing the mobilization of fat. The hypocholesterolemic action of *OI* extract can be associated with a decrease in LDL fraction as cholesterol lowering property can result from rapid catabolism of LDL-C through its hepatic receptor for final elimination in form of bile acids (Krishnakumar et al., 2000).

Postprandial elevation of triglyceride (TG)-rich lipoproteins (TRLs) is also a well-recognized feature of diabetic dyslipidemia and includes the accumulation of intestinally derived apolipoprotein B48 (apoB48)-containing lipoproteins (Lewis et al., 1991; Curtin et al., 1996; Mero et al., 1998). VLDL is normally converted to LDL via the actions of post-heparin lipases. The result from the present study suggests that the *OI* extract is able to restore, at least partially, catabolism of β-lipoproteins and also as hypothesized by many works with other plants (Campillo et al., 1994; Pérez et al., 1999). The restoration of catabolic metabolism of VLDL could be due to an increased stimulation of the lipolytic activity of plasma lipoprotein lipase.

The renoprotective effect of *OI* extract is also very clearly indicated by significantly lowered plasma levels of creatinine and urea produced in higher amounts in DC rats. Apparently, *OI* extract has potent ability to afford protection against renal damage generated in higher amounts under uncontrolled diabetes mellitus (Almdal and Vilstrup, 1988; Hwang et al., 1997).

Several phytomolecules including flavonoids, alkaloids, glycosides, saponins, glycolipids, dietary fibres, polysaccharides, peptidoglycans, carbohydrates, amino acids and others obtained from various plant sources have been reported as potent hypoglycemic agent (Mukherjee et al., 2006). Flavonoids are a heterogeneous group of ubiquitous plant polyphenols, that exhibits a variety of pharmacological activities, including the anti-atherogenesis effect, lipoprotein oxidation, blood platelet aggregation and vascular reactivity (Del Bas et al., 2005; Peluso, 2006). Triterpenoid and steroidal glycosides, referred to collectively as saponins, are bioactive compounds present

naturally in many plants and known to possess potent hypoglycemic activity (Rao and Gurfinkel, 2000). Qualitative phytochemical analysis of *OI* extract from our lab revealed presence of flavanoids, phenolics, saponins, terpenoids, sugars and steroids (Ansarullah; personal communication). Hence, the observed antidiabetogenic effects of *OI* extract principally at the level of carbohydrate metabolism as well as secondary on lipid metabolism could be accredited to the many active compounds present in the extract.

CONCLUSION

Overall, it may be concluded that *OI* extract possesses hypoglycemic and hypolipidemic potential and has been shown to afford significant protection against streptozotocin diabetes. Currently, we are employing activity directed fractionation assays to further isolate and characterize the bioactive compounds responsible for antidiabetic activity.

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