

## Anti-hyperglycaemic and Hypolipidemic Effects of *Ocimum basilicum* Aqueous Extract in Diabetic Rats

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**Abstract:** The hypoglycaemic and hypolipidemic effects of the aqueous extract of *Ocimum basilicum* (OB) whole plant were investigated in normal and streptozotocin (STZ) diabetic rats. After a single oral administration, OB significantly reduced blood glucose levels in normal ( $p < 0.01$ ) and diabetic rats ( $p < 0.001$ ). After 15 days of repeated oral administration, OB produced a potent reduction on blood glucose levels ( $p < 0.001$ ) in diabetic rats and a less reduction in normal rats ( $p < 0.05$ ). Total plasma cholesterol and triglycerides levels were significantly reduced after repeated oral administration in diabetic rats ( $p < 0.001$ ) and ( $p < 0.05$ ) respectively. However, no change was observed in total plasma cholesterol and triglycerides levels in normal rats after both single and repeated oral administration. In addition, plasma insulin levels and body weight remained unchanged over 15 days of oral administration in normal and diabetic rats. We conclude that the aqueous extract of OB exhibits potent anti-hyperglycaemic and hypolipidemic activities in diabetic rats without affecting basal plasma insulin concentrations.

**Key words:** *Ocimum basilicum*, aqueous extract, oral administration, anti-hyperglycaemic

### INTRODUCTION

Diabetes mellitus is now taking place as serious disease with burden financial cost<sup>[1]</sup>. The number of people suffering from diabetes is actually estimated to 151 millions and this number is projected to double in the next decade<sup>[2]</sup>. Surely, current diabetes pharmacotherapy gives sharp and good control of blood glucose levels but the efficiency became strictly reduced after long term use<sup>[3]</sup>. In addition to elevated blood glucose levels, diabetes is generally accompanied with lipid metabolism abnormality communally known as diabetic dyslipidemia<sup>[4]</sup>. Unfortunately, the control of diabetic dyslipidemia did not always accompany the control of blood glucose levels<sup>[5]</sup>.

More than 1200 plants species are world wild used in diabetes phytotherapy and experimental studies support the hypoglycaemic activity of a large number of these plants<sup>[6]</sup>. In addition to correction of blood glucose levels, several hypoglycaemic plants are potential in ameliorating lipid metabolism abnormalities of diabetes mellitus<sup>[7]</sup>. Thus, the study of plant hypoglycaemic and hypolipidemic activities may give new pharmacological approach in the treatment of diabetes mellitus<sup>[8]</sup>.

*Ocimum basilicum* (OB) is a plant belonging to Lamiacea family locally known as "Lahbak albaldi".

According to the ethnopharmacological survey in the Tafilalet region, OB is used on the local phototherapy in the treatment of diabetes and cardiovascular diseases<sup>[9]</sup>.

The present study was undertaken to evaluate the hypoglycaemic and hypolipidemic activities of a single and repeated oral administration of the aqueous OB extract at a dose of 20 mg kg<sup>-1</sup> body weight in normal and streptozotocin-induced diabetic rats. Vanadate, a hypoglycaemic and hypolipidemic agent<sup>[10, 11]</sup> was used as a reference drug.

### MATERIALS AND METHODS

**Plant material:** Specimens of *Ocimum basilicum* were collected from the Tafilalet region (semi-arid area) of Morocco in May-June 2001 and air-dried at 40°C. The plant was previously identified and authenticated by Pr. M. Rejdali (Agronomy and Veterinary Institute, Rabat) and a voucher specimen (EM15) was deposited at the herbarium of the Faculty of Sciences and Techniques Errachidia.

**Preparation of the aqueous extract:** Plant material was prepared according to the traditional method used in Morocco (decoction): 1 g of powdered whole plant mixed with 100 mL distilled water were boiled for 10

min and then cooled for 15 min. Thereafter, the aqueous extract was filtered using a Millipore filter (Millipore 0.2 mm, St Quentin en Yvelines, France) to remove particulate matter. The filtrate was then freeze-dried and the desired dose (mg of lyophilized aqueous extract of per kg body weight) was then prepared and reconstituted in 1.5 mL of distilled water. The aqueous extracts were prepared daily, just before administration. The extracts obtained were then given orally to different groups at a dose of 20 mg kg<sup>-1</sup> body weight. aqueous OB extract was maroon coloured with a percent yield of 12% with an average osmolarity of 50 mOsm kg<sup>-1</sup> H<sub>2</sub>O and pH 6.1.

**Experimental design:** Experiments were performed in adult male Wistar rats weighing from 200-250 g. Animals were housed under standard environmental conditions (23±1°C, 55±5% humidity and a 12 h light/dark cycle) and maintained with free access to water and a standard laboratory diet (carbohydrates; 30%, proteins; 22%, lipids; 12%, vitamins; 3%) *ad libitum*.

Diabetes was induced by intravenous injection of streptozotocin (Sigma, St Louis, Mo, USA) into the tail vein at a dose of 65 mg kg<sup>-1</sup> body weight. STZ was extemporaneously dissolved in 0.1 M cold sodium citrate buffer, pH 4.5. After 18 h, animals with fasting blood glucose levels greater than 22 mmol L<sup>-1</sup> were considered diabetic and then included in this study.

Normal and diabetic rats were randomly assigned to three different groups (n = 6 for each group). The control group received distilled water; treated groups received aqueous extracts of OB at a dose of 20 mg kg<sup>-1</sup> or sodium-vanadate (Fluka, Chemica, Switzerland) at a dose of 0.8 mg kg<sup>-1</sup>. All experiments were performed in overnight fasted rats.

**Single administration:** The drug solutions or vehicle were administered orally by gastric intubation using a syringe once daily at 09 h a.m. Blood glucose levels were determined in fasted rats, 1, 2, 4 and 6 h after a single oral administration. Total plasma cholesterol and triglycerides levels were determined before and 6 h after OB administration.

**Repeated oral administration:** Rats were treated once daily for two weeks. Blood glucose levels, plasma triglycerides levels, plasma cholesterol levels and body weight were determined after two, four days, one and two weeks of once daily repeated oral administration.

**Determination of parameters:** Blood samples were retrieved from the retro-orbital plexus in fasted and

anesthetized rats using ether solution inhalation. Blood glucose levels were determined by the glucose oxidase method using a reflective glucometer (Model GX, Ames Miles, Bayer Diagnostics, Genome Biotechnologies, Casablanca, Morocco). Plasma triglycerides and total cholesterol levels were measured using colorimetric method with commercially available kits (Randox, UK). Absorbance was measured at 500 nm. Basal plasma insulin concentrations were determined by radioimmunoassay kit (Pharmacia, Uppsala, Sweden) with a Beta matic counter (Cronex, Dupont, France). The kit included human insulin as standard and 125I-labelled human insulin antibody, which cross reacts with rat insulin.

**Statistical analysis:** All the data reported are expressed as mean±SEM. Statistical analysis was performed using the analysis of variance (ANOVA) followed by Bonferroni post tests. The values were considered to be significantly different when the p value was less than 0.05 compared to the respective control group.

## RESULTS

### **Effects of OB aqueous extract administration on blood glucose levels; single oral administration:**

Figure 1 shows change in blood glucose levels after a single oral administration of aqueous OB extract at a dose of 20 mg kg<sup>-1</sup>. In normal treated rats, a significant decrease in blood glucose levels was observed since from the second hour after a single administration (p<0.001) and a further decrease was noticed at the fourth hour (p<0.001). Afterwards, blood glucose levels remained stable. Vanadate treatment at a dose of 0.8 mg kg<sup>-1</sup> produced a slight decrease in blood glucose levels two (p<0.01) and 4 h (p<0.01) after oral administration. In STZ rats, the aqueous OB extract induced a significant decrease in blood glucose levels 4 h after oral administration (p<0.001). However, vanadate caused a significant drop in blood glucose levels 4 h after a single administration (p<0.001).

### **Effects of OB aqueous extract administration on blood glucose levels, repeated oral administration:**

Change in blood glucose levels in normal and diabetic rats over 15 days of daily OB aqueous extract administration is shown in Fig. 2. In normal rats, a significant reduction in blood glucose levels was observed only after 15 days of repeated oral administration (p<0.01). There was no change in blood glucose levels in vanadate-treated rats. Relating to STZ rats, significant reduction in blood glucose levels was observed from the fourth day of treatment (p<0.001),

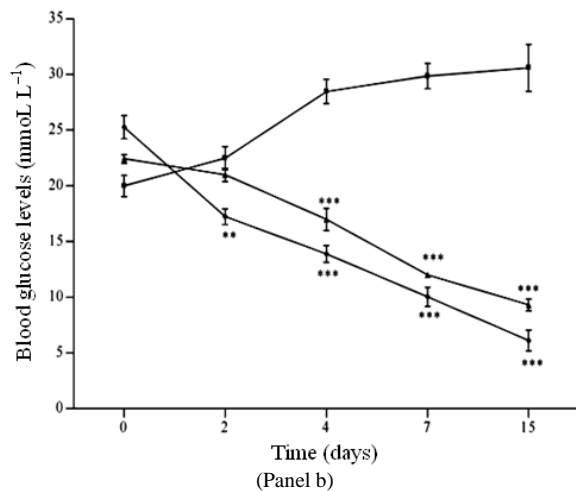
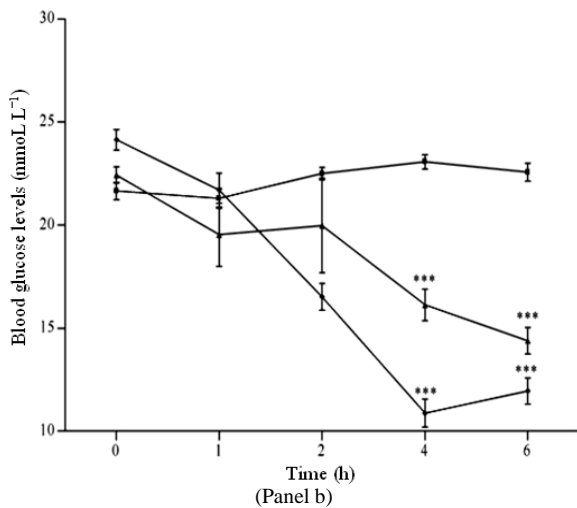
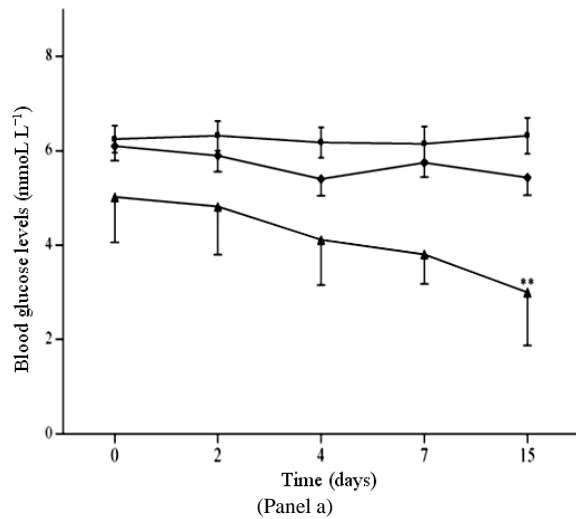
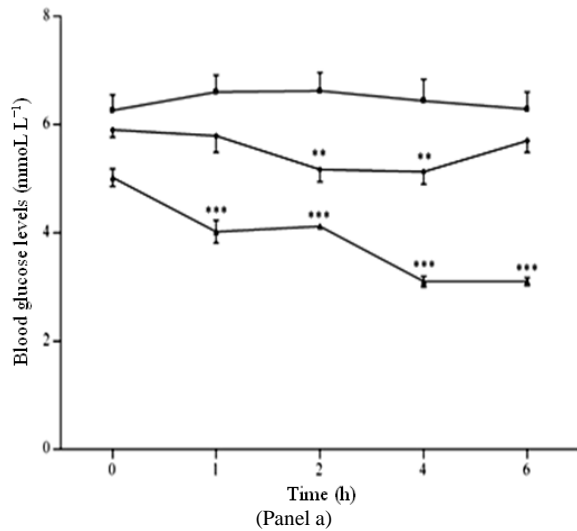


Fig. 1: Plasma glucose levels over 6 h of a single oral administration of aqueous OB extract ( $20 \text{ mg kg}^{-1}$ ) in normal (Panel a) and diabetic rats (Panel b). Data are expressed as means $\pm$ SEM, n = 6 rats per group. \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ , when compared to respective control group. ■: Control; ▲: OB extract; ◆: Vanadate

Fig. 2: Plasma glucose levels after once daily repeated oral administration of OB aqueous extract ( $20 \text{ mg kg}^{-1}$ ) for 15 days in normal (Panel a) and diabetic rats (Panel b). Data are expressed as means $\pm$ SEM, n = 6 rats per group. \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ , when compared to respective control group. ■: Control; ▲: OB extract; ◆: Vanadate

this reduction was more pronounced thereafter reaching an average of  $9.32 \pm 0.52 \text{ mM}$  at the end of the treatment ( $p < 0.001$ ). Treatment with vanadate resulted in a reduction in blood glucose levels from the second day ( $p < 0.01$ ). This reduction was maintained until the fifteenth day of treatment ( $p < 0.001$ ). In contrast, the plasma glucose levels of untreated diabetic rats were dramatically increased during four days of experiments reaching the value of  $30.60 \pm 2.10 \text{ mM}$  at the 15th day.

**Effect of OB aqueous extract on body weight:** Body weight of normal and diabetic rats was measured during the study (Fig. 3). As shown in Fig. 3, aqueous OB extract did not cause any significant change in body weight after two weeks of treatment in normal rats while treatment with vanadate caused a decrease in body weight at the end of treatment period ( $p < 0.01$ ).

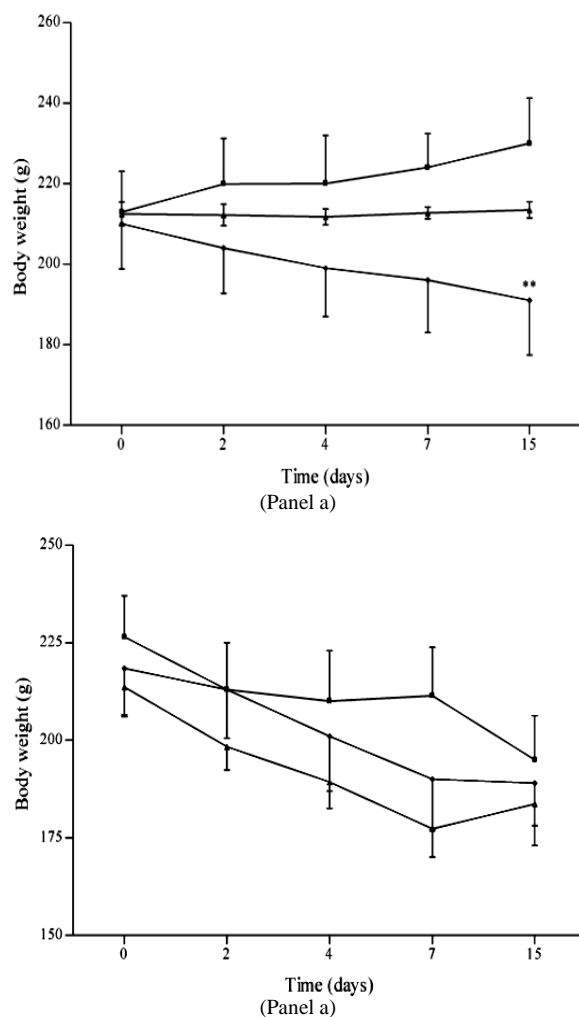


Fig. 3: Body weight change after once daily repeated oral administration of an aqueous OB extract ( $20 \text{ mg kg}^{-1}$ ) for 15 days in normal (Panel a) and diabetic rats (Panel b). Data are expressed as mean $\pm$ SEM, n = 6 rats per group. \*:  $p < 0.05$ ; \*\*:  $p < 0.01$ ; \*\*\*:  $p < 0.001$ , when compared to respective control group.  $\blacksquare$ —: Control;  $\blacktriangle$ —: OB extract;  $\blacklozenge$ —: Vanadate

**Effect of OB aqueous extract on basal plasma insulin concentrations:** Basal plasma insulin concentrations did not differ significantly in the OB-treated groups when compared to untreated group in both normal and diabetic rats (Table 1). In addition, vanadate treatment did not affect insulin secretion in both normal and STZ rats.

**Effect of aqueous OB extract on total plasma cholesterol and triglycerides levels:** Single administration: Streptozotocin injection caused a significant increase in the total plasma cholesterol and

Table 1: Basal plasma insulin concentrations ( $\mu\text{U mL}^{-1}$ ) after repeated oral administration of the aqueous OB extract at a dose of  $20 \text{ mg kg}^{-1}$  in normal and diabetic rats. Data are expressed as mean $\pm$ SEM, n = 6 rats in each group

Experimental groups	Plasma insulin concentrations ( $\mu\text{U mL}^{-1}$ )	
	Day 0	Day 15
<b>Normal rats</b>		
Control	35.40 $\pm$ 2.17	36.45 $\pm$ 4.12
OB	33.78 $\pm$ 0.33	33.86 $\pm$ 1.24 <sup>NS</sup>
Vanadate	31.81 $\pm$ 3.15	32.71 $\pm$ 3.00 <sup>NS</sup>
<b>Diabetic rats</b>		
Control	7.08 $\pm$ 0.39	6.75 $\pm$ 0.15
OB	5.06 $\pm$ 0.32	4.12 $\pm$ 0.23 <sup>NS</sup>
Vanadate	6.05 $\pm$ 0.52	5.72 $\pm$ 0.82 <sup>NS</sup>

Table 2: Total plasma cholesterol and plasma triglycerides levels after a single oral administration of OB aqueous extract ( $20 \text{ mg kg}^{-1}$ ) in normal and diabetic rats. Data are expressed as mean $\pm$ SEM, n = 6 rats per group. NS: Not significant compared to the respective control group. #:  $p < 0.001$  when compared to normal rats

Time (h)	Total plasma cholesterol levels ( $\text{mmol L}^{-1}$ )			
	Normal rats		Diabetic rats	
	0	6	0	6
Control	3.27 $\pm$ 0.06	3.20 $\pm$ 0.19	4.2 $\pm$ 0.06 <sup>#</sup>	4.16 $\pm$ 0.19
Vana-date	3.03 $\pm$ 0.1	3.09 $\pm$ 0.6 <sup>NS</sup>	3.03 $\pm$ 0.1 <sup>#</sup>	3.06 $\pm$ 0.23 <sup>NS</sup>
OB	3.10 $\pm$ 0.3	3.03 $\pm$ 0.03 <sup>NS</sup>	4.4 $\pm$ 0.02 <sup>#</sup>	3.8 $\pm$ 0.23 <sup>NS</sup>
<b>Plasma triglycerides levels (<math>\text{mmol L}^{-1}</math>)</b>				
Control	2.06 $\pm$ 0.06	2.1 $\pm$ 0.09	3.0 $\pm$ 0.04 <sup>#</sup>	3.01 $\pm$ 0.19
Vana-date	1.98 $\pm$ 0.03	2.03 $\pm$ 0.2 <sup>NS</sup>	3.17 $\pm$ 0.24 <sup>#</sup>	3.15 $\pm$ 0.09 <sup>NS</sup>
OB	2.12 $\pm$ 0.03	2.01 $\pm$ 0.02 <sup>NS</sup>	3.32 $\pm$ 0.03 <sup>#</sup>	3.25 $\pm$ 0.12

triglyceride levels ( $p < 0.001$ ) when compared to normal rats (Table 2). OB aqueous extract failed to reduce plasma triglycerides and cholesterol levels 6 h after oral administration. No significant change in total plasma cholesterol and triglyceride levels was observed after single oral administration of vanadate in normal and diabetic rats.

**Effect of aqueous OB extract on total plasma cholesterol and triglycerides, repeated administration:** Change on total plasma cholesterol and triglycerides levels in normal and diabetic rats during 15 days of oral administration of aqueous OB extract is shown in Table 3. In normal rats, daily oral administrations of aqueous OB extract over 15 days had no effect on total plasma cholesterol and triglycerides levels. However, vanadate administration reduced total plasma cholesterol levels ( $p < 0.001$ ) after 15 days of oral administration. Triglyceride levels were reduced from the fourth day ( $p < 0.01$ ) of treatment and a further reduction was observed in the seventh and fifteenth day of treatment ( $p < 0.001$ ).

Table 3: Total plasma cholesterol and triglycerides levels (mmol L<sup>-1</sup>) after repeated oral administration of aqueous OB extract (20 mg kg<sup>-1</sup>) in normal and diabetic rats. Data are expressed as mean±SEM, n = 6 rats per group

Time (days)	Total plasma cholesterol levels (mmol L <sup>-1</sup> )							
	Normal rats				Diabetic rats			
	0	4	7	15	0	4	7	15
Control group	3.27±0.06	2.73±0.07	2.75±0.01	2.82±0.06	4.2±0.06 <sup>#</sup>	3.85±0.07	4.42±0.01	3.75±0.06
Vanadate treated group	3.03±0.10	2.73±0.05	2.53±0.09	2.16±0.07***	3.03±0.1 <sup>#</sup>	2.73±0.07***	2.53±0.09***	2.16±0.07***
OB treated group	3.10±0.30	2.86±0.04	2.96±0.15	3.02±0.12	4.4±0.02 <sup>#</sup>	3.50±0.4	3.20±0.2***	2.63±0.02***
<b>Plasma triglycerides levels (mmol L<sup>-1</sup>)</b>								
Control group	2.06±0.06	1.93±0.05	1.93±0.08	1.97±0.09	3.00±0.04 <sup>#</sup>	3.03±0.35	2.85±0.42	2.79±0.26
Vanadate treated group	1.98±0.03	1.63±0.03**	1.53±0.03***	1.53±0.05***	3.17±0.24 <sup>#</sup>	2.45±0.3	2.02±0.33*	1.78±0.29**
OB treated group	2.12±0.03	2.10±0.2	2.10±0.03	2.13±0.12	3.32±0.03 <sup>#</sup>	3.02±0.05	2.56±0.12	2.06±0.02*

\*: p<0.05, \*\*: p<0.01, \*\*\*: p<0.001 when compared to untreated diabetic rats. #: p<0.001 when compared to normal controls

In diabetic rats, aqueous OB extract produced a significant reduction on total plasma cholesterol seven days (p<0.01) and fifty days (p<0.01) after once daily oral administration. Triglyceride levels were reduced after 15 days of treatment (p<0.05). Vanadate administration produced earlier reduction in cholesterol levels from the second day of administration (p<0.05), a sustained reduction was observed until the end of treatment period (p<0.001).

## DISCUSSION

Certainly, insulin and oral hypoglycaemic agents i.e., sulphonylurea, alpha-glucosidase inhibitor and thiazolidinediones greatly ameliorate diabetes control<sup>[12]</sup> but efforts remain necessary to discover new hypoglycaemic agents from plants<sup>[13]</sup>. Previous studies have demonstrated that in addition to the hypoglycaemic activity, several plants possess plasma lipid lowering activity in animal model of diabetes mellitus<sup>[14-18]</sup>.

The genus *Ocimum* comprises some 65 plant species world wide used in the traditional medicine. OB is commonly used in as culinary herbs in the Mediterranean region. Previous studies reveal the antimicrobial<sup>[19]</sup>, insecticidal<sup>[20]</sup> and anti-carcinogenic<sup>[21]</sup> activities of different OB extracts. Furthermore, *Ocimum sanctum* possess anti-hyperglycaemic effect in alloxan-diabetic rats<sup>[22]</sup>. In the current work, we aim to evaluate the hypoglycaemic and lipid lowering activity of aqueous OB extract at a dose of 20 mg kg<sup>-1</sup> in normal and diabetic rats after both a single and 15 days of repeated oral administration. Vanadate was used as a reference drug mimicking several insulin actions *in vivo* such as stimulation of hexose uptake, the stimulation of lipogenesis and the inhibition of lipolysis<sup>[23]</sup>. We have

used streptozotocin-induced rats as a recommended animal model of insulin dependent diabetes mellitus. Intravenous injection of streptozotocin at a dose of 65 mg kg<sup>-1</sup> caused an irreversible pancreatic beta cell destruction leading to hypoinsulinemia and severe hyperglycaemia<sup>[24]</sup> and the increase in blood glucose levels is accompanied by a parallel increase in plasma cholesterol and triglycerides levels<sup>[25]</sup>. Thus, streptozotocin-induced diabetic rat is a valid animal model for the study of hypoglycaemic and hypolipidemic activity of plant extract.

In spite of counter-regulatory factors avoiding the reduction in blood glucose levels by stimulating glucose production and limiting glucose utilization<sup>[26]</sup>, OB caused a significant reduce in blood glucose levels after a single oral administration in normal rats. OB may act rapidly in normal rats after a single oral administration but not chronically indicating that the observed hypoglycaemic effect of OB in normal rats is not cumulative during 15 days of oral administration. However, the hypoglycaemic effect was more apparent and cumulative over 15 days of oral administration in diabetic rats. Thus, aqueous OB extract possess a potent anti-hyperglycaemic effect in diabetic rats. In contrast, in untreated diabetic rats, blood glucose levels increased from the second day, due the insulinopenia and the consequent insulin resistance<sup>[27, 28]</sup>. Plasma insulin levels were not affected by OB administration in normal and diabetic rats. Aqueous OB extract may act via inhibition of hepatic glucose production<sup>[29]</sup> and/or renal glucose reabsorption<sup>[30]</sup>, improving *in vivo* insulin action<sup>[31]</sup> or stimulation of glucose utilization by the peripheral tissues<sup>[32]</sup>.

Elevated plasma cholesterol and triglyceride levels are major risk factors of cardiovascular diseases<sup>[33]</sup>. Current hypoglycaemic agents allow a sharp control of blood glucose levels but insufficient correction of lipid

abnormality is observed especially hypertriglyceridemia<sup>[34]</sup>. Due to hyperglycaemia and insulin resistance, diabetic rats showed elevated plasma cholesterol and triglycerides levels<sup>[4]</sup>. Aqueous OB extract reduced total plasma cholesterol and triglycerides levels only in diabetic rats. Some studies have reported similar hypolipidemic activity in streptozotocin-induced diabetic rats<sup>[14-18]</sup>.

As no change in plasma insulin levels were observed after OB administration in normal and diabetic rats, the observed hypolipidemic effect seems independent of insulin action and may involve the inhibition of the key enzymes on cholesterol and triglycerides synthesis<sup>[35]</sup> or increasing cholesterol excretion throughout bile acid formation<sup>[36]</sup>. However, it is not excluded that the observed hypolipidemic effect is mediated throughout the control of glycemia since the glycemic control is the major determinant of total cholesterol and triglyceride levels<sup>[37]</sup>, the evolution of glycemia was parallel to lipidic parameters in both normal and diabetic rats.

In conclusion, the aqueous extract of OB exhibits potent anti-hyperglycaemic and long term cholesterol and triglycerides lowering activity in STZ diabetic rats independently of insulin secretion. These results support its traditional use in the treatment of diabetes and cardiovascular disease. Finally, the precise mechanism (s) and site (s) of action of this activity and the active constituent (s) involved are still to be determined in addition to toxicological studies.

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