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Laurus nobilis leaves extract protects against high fat diet-induced type 2 Diabetes in rats

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***Laurus nobilis*, commonly known as bay, is used in folk medicine as a remedy for many ailments. The present study investigates the protective effect of *L. nobilis* leaves extract against high fat diet-induced type 2 diabetes in rats. Animals were divided into group 1 (control), groups 2, 3, and 4 (bay leaves aqueous (AQ) extracts; 50, 100, and 250 mg/kg of body weight, respectively), and groups 5, 6, and 7 (bay leaves methanol/acetone (MeAc) extract; 50, 100, and 250 mg/kg of body weight, respectively). Animals were fed an isocaloric high fat diet for four weeks. The intake of bay leaves extracts was associated with a significant decreases in serum levels of glucose (AQ, 100 and 250 mg/kg; MeAc, 50, 100, and 250 mg/kg) and serum triglyceride (AQ, 250 mg/kg; MeAc, 100, and 250 mg/kg) as well as lower abdominal fat (all AQ and MeAc groups) and body weight gain (MeAc groups only). In conclusion, *L. nobilis* leaves extract intake provides a protective remedy against high fat diet-induced type 2 diabetes.**

Key words: *Laurus nobilis*, type 2 diabetes, bay leaves, high fat diet.

INTRODUCTION

Diabetes is a major public health problem worldwide with 425 million cases estimated in 2017 (Karurunga et al., 2017). Its global health care expenditure is expected to reach 802 billion US dollars in 2040 (Ogurtsova et al., 2017). Conventional medicinal treatments prescribed for diabetic patients are overpriced and may cause unfavorable side effects (Choudhury et al., 2018). Newer glycemia controlling agents are therefore needed.

Herbal medicine is a promising alternative that relies on botanical extracts containing pharmacologically active compounds and substances (Atanasov et al., 2015). Extensive studies are being conducted on herbal supplements due to their potential efficacy, low-cost and low-toxicity (Ota and Ulrih, 2017). *Laurus nobilis*, also

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known as bay, is a native evergreen Mediterranean plant that is also cultivated in western Asia, southern Europe, northern Africa and America (Parthasarathy et al., 2008). Bay leaves essential oil has an economic importance in both food (Sharma and Sharma, 2012) and fragrance industry (Surburg and Panten, 2016). However, *L. nobilis* is rarely used in the pharmacy industry although it was believed improve impaired digestion, bloating and other symptoms (Özcan and Chalchat, 2005). Besides these effects on digestive system activity, *L. nobilis* possess antioxidant (Dall'Acqua et al., 2009) and insulin improving activities *in vitro* (Broadhurst et al., 2000). Oral administrations of *L. nobilis* dried leaves to rabbits also demonstrated antioxidant as well as protective effects on cataract development (Casamassima et al., 2017). Oil extract of *L. nobilis* leaves showed a dose dependent anti-inflammatory effect and a significant antinociceptive activity in mice and rats (Sayyah et al., 2003). The polysaccharides and oil extracts of *L. nobilis* growing in Lebanon were also studied and reported to exhibit antimicrobial and antibiofilm activities (Chmit et al., 2014). *L. nobilis* ground leaves ingestion (1-3 g/day; 30 days) was reported to improve insulin function, decrease serum levels of glucose, total cholesterol, low density lipoprotein cholesterol (LDL), and increase high density lipoprotein cholesterol (HDL) in humans with type II diabetes (Khan et al., 2009). Same treatment administered to type I diabetic patients resulted in similar beneficial effects (Aljamal, 2011). Cookies containing bay leaf powder (not less than 6% w/w) exhibited significant benefit on postprandial glucose level in healthy human subjects (Khan et al., 2017). Rabbits fed with fat-enriched diet supplemented with dried bay leaves (1 g/kg body weight; 56 days) showed a significant decrease in their blood lipid and glycemic profiles as well as a reduction in the serum levels of ALT and AST (Casamassima et al., 2017). The active ingredients behind this outcome are yet to be determined. In alloxan induced diabetic rats, Bay leave ethanolic extract displayed a significant reduction in fasting blood glucose and significant increase in fasting insulin level, as well as a significant decrease in triglyceride, total cholesterol, low density lipoprotein, very low density lipoprotein, liver enzymes, blood urea and serum creatinine level (Al Chalabi et al., 2020). In another recent study, *L. nobilis* leave extract exhibited considerable decrease in blood glucose level and restored the altered liver enzymes, urea, creatine kinase, total protein levels, calcium and ferritin to near normal in streptozotocin (STZ)-induced diabetic rats (Mohammed et al., 2021).

Type 2 diabetes is one of the chronic health problems that has long-term consequences but could be preventable. Although the beneficial effect of bay leaves on both types I and type II diabetes was established, its protective effect against type 2 diabetes is not yet clear. The present study was carried out to investigate the protective effects of bay leaves aqueous and methanol-acetone extracts on high fat diet-induced type 2 diabetes in rats and shed light on the potential active ingredients involved.

MATERIALS AND METHODS

Plant

L. nobilis leaves were collected from Mount Lebanon region in September 2017. The plant was identified according to the characteristics described in “Handbook of Medicinal Herbs” (Deshpande, 2006). Leaves were dried in the shade at room temperature, then chopped into small pieces and soaked in either pre-boiled water (30 min) or methanol-acetone (1:1; 72 h). The aqueous extract was added daily to drinking water and administered to animals. The methanol-acetone extract was subjected to rotary evaporation, and the obtained oil was sprayed on food pellets and given to animals.

Animals

Adult male Wistar rats (6 weeks old; 200-225 g) were housed in a temperature and humidity-controlled room under a 12:12 light/dark cycle. All animals were randomly allocated into seven weight-matched groups of 7 rats each and fed an isocaloric high fat diet for 4 weeks to induce type 2 diabetes (Table 1). *L. nobilis* leaves aqueous (AQ) extract (groups 2-3-4) and methanol-acetone (MeAc) extract (groups 5-6-7) were administered at doses of 50, 100 and 250 mg/kg, respectively. All experimental protocols were approved by the Animal Ethical subcommittee of the Lebanese American University, which complies with Guide for the Care and Use of Laboratory Animals.

Blood sampling and analyses

The control group was monitored periodically (days 0, 14 and 28) for its serum glucose level to ensure that the animals have developed type 2 diabetes because of the high fat diet intake. After 4 weeks of isocaloric high fat diet intake, all animal groups were fasted (18 h), anesthetized and then sacrificed to collect serum samples and abdominal fat. Serum samples were used to determine glucose, lipids (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) and creatinine levels as well as liver enzyme (alanine transaminase (ALT) and alkaline phosphatase (ALP) activities (Cobas Integra 400 plus; Roche Diagnostics, USA). All serum samples were run in duplicate and analyzed within the same assay. Furthermore, the intra-abdominal fat samples (epididymal, mesenteric and retroperitoneal) were collected, blotted on a filter paper, and weighed.

Glucose tolerance test

On day 14 of the experiment, an intraperitoneal glucose tolerance test was conducted on fasted animals (18 h) using intraperitoneal injection of 300 g glucose/L in physiologic saline in a dose of 5.83 ml/kg body weight. Blood glucose was measured using Accu-Check glucometer at t_0, and after 30 min, 1 h and 2 h post glucose injection.

Gas chromatography mass spectrometry analysis

The composition of the MeAc was analyzed using gas chromatography-mass spectrometry (Hewlett Packard, HP6890

Table 1. Nutrient composition of the high fat diet administered to animals.

Nutrient	High fat diet
Protein (%w/w)	16.2
Carbohydrates (%w/w)	55.5
Sugars	7.8
Fat (%w/w)	23.2
Saturated fat	58.1%
Mono unsaturated fat	15.7%
Poly unsaturated fat	20.5%
Fiber (%w/w)	3.65
Metabolizable energy (Kj/g)	20.7
Protein	13%
Carbohydrates	44.8%
Fat	42.1%

series) fitted with a fused silica HP5-MS 5% phenyl methyl siloxane cap column (30 m × 0.25 mm i.d., film thickness 0.25) and directly coupled to the MS. The carrier gas was helium with splitless injection, and the flow rate of 1.2 ml/min was applied. The temperature program was 2.0 min at 70°C, from 70 to 130°C at 8°C/min, from 130 to 180°C at 2°C/min, from 130 to 180°C at 2°C/min and then from 180to 220°C at 15°C/min. Identification of the components was performed by comparing their mass spectra with literature (NIST11 and Wiley9). Percentage composition was computed from GC peak areas. The dried aqueous extract was dissolved in methanol, filtered, and then subjected to GC-MS analysis as described earlier.

Total flavonoid content determination

Flavonoid content was estimated using the aluminium chloride colorimetric technique (Chang et al., 2002). Briefly, 0.5 ml of the extract sample (ranging from 0.2 to 5 mg/ml) was separately mixed with 1.5 ml of methanol, 0.1 ml of 10% aluminum chloride, 0.1 ml of 1 M potassium acetate and 2.8 ml of distilled water. The reaction mixture absorbance was then measured spectrophotometrically at 415 nm. A standard curve was constructed using various concentrations of quercetin (12.5 to 200 mg/ml) in methanol.

Total phenolic content determination

The total phenolic content of the extract was determined according to the method by Rossi et al. (2007). Briefly, 0.3 ml of the extract (0.5 to 5 mg) was mixed with Folin Ciocalteu reagent (2.5 ml, 1:10 diluted with distilled water) for 5 min. Then, 2 ml of aqueous Na_2CO_3 (7.5% w/v) was added and the mixture allowed to stand for 30 min at 25°C. Absorbance was measured at 760 nm and the total phenolic content was estimated using a gallic acid calibration curve. Results were presented as mg gallic acid equivalent (GAE)/g of extract or leaves.

Statistical analysis

Data are reported as Mean ± SEM. Results were analyzed by one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test. All data were analyzed with the statistical package SPSS 18 and statistical significance was defined as $p < 0.05$.

RESULTS

Blood analyses

Biweekly check-up of blood glucose level of control group revealed that after 28 days animals fed a high fat diet showed a significant increase in fasting blood glucose level (Figure 1), hence confirming the relevance of the model. Treatment with *L. nobilis* leaves extract for 4 weeks significantly decreased serum triglyceride levels in AQ250, MeAc100 and MeAc250 groups (Table 2). However, no effect was observed on HDL, LDL, and total cholesterol levels (Table 2). Determination of fasting serum glucose levels revealed significant decrease in all treated groups except for AQ50 (Figure 2). A mild but significant increase in serum ALT level was observed in AQ50, AQ100 and MeAc100, but no significant effect on ALP serum level was observed in all treated groups. Similarly, there was no significant change in the fasting serum creatinine level (Table 3). The effect of *L. nobilis* extract on body weight gain was assessed (Figure 3). Results have shown that all treated animals had less weight gain compared with the control where significant difference was reached in all MeAc treated groups. Data also revealed that both the AQ and MeAc extract intake at all doses caused a significant decrease in the abdominal fat mass (Figure 4).

Glucose tolerance test

The glucose tolerance test was conducted two weeks after extract intake. Results presented in Figure 5 showed that neither AQ nor MeAc extract has any

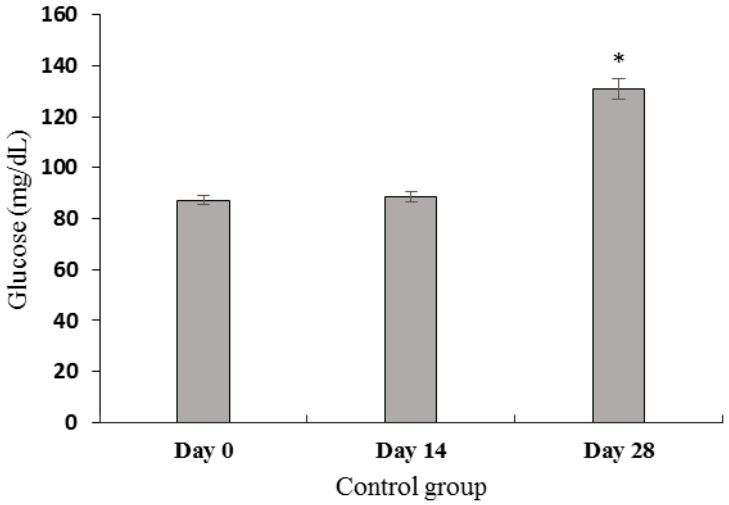

Figure 1. Control fasting serum glucose level (mg/dL) at days 0, 14 and 28. Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

Table 2. Fasting serum triglyceride, HDL, LDL, and total cholesterol levels (mg/dL) after 4 weeks of extract treatment.

Parameter (mg/dl)	Control	AQ50	AQ100	AQ250	MeAc50	MeAc100	MeAc250
TRIGL	139 ± 15	113 ± 10	104 ± 10	75.3 ± 5.7*	102 ± 9.4	90.0 ± 8.6*	96.0 ±8.0*
HDL CHOL	46.9 ± 0.8	47.9 ± 1.6	45.9 ± 3.3	36.6 ± 2.5*	48.0 ± 4.4	48.2 ± 2.4	46.0 ± 2.4
LDL CHOL	12.2 ± 0.7	13.6 ± 0.6	15.0 ± 1.4	14.4 ± 1.0	16.1 ± 0.9*	12.4 ± 1.1	10.6 ± 1.1
T. CHOL	62.4 ± 1.5	68.3 ± 2.6	65.3 ± 4.3	56.3 ± 2.9	69.7 ± 4.8	65.7 ± 2.9	63.1 ± 2.9

Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

significant effect on postprandial glucose levels after 30 min, 1 h, and 2 h of glucose IP injection.

Gas chromatography mass spectrometry analysis

GC-MS analysis of the MeAc extract (Table 4) showed that 1,8-cineole, commonly known as eucalyptol, was by far the most abundant (48.3%) compound followed by 5,8-epoxy-15-nor-labdane (19%). Other major constituents include α-terpinene (7.14%), eremanthin (3%), vitamin E (3.29%) and other compounds. GC-MS analysis of the sample that resulted from solubilizing the dried aqueous extract in methanol revealed 5-(Hydroxymethyl) furfural (24.72%) and eremanthin (3.94%) as major components (Table 5).

Phenolic and flavonoid content

Total phenolic and flavonoid content in the *L. nobilis* leaves AQ and MeAc extract are summarized in Table 6. Total phenols were measured by the Folin Ciocalteu reagent in term of Gallic acid equivalent and it was found to be higher in AQ extract (148 mg/g) compared with MeAc extract (46 mg/g). The total flavonoid, however, was higher in the MeAc extract (16.3 mg/g) with respect to the AQ extract (12.6 mg/g).

DISCUSSION

This is the first reported study to assess the preventive effect of the Lebanese *L. nobilis* aqueous (AQ) and methanol-acetone (MeAc) leaves extracts against high fat diet-induced type 2 diabetes in rats. The current study revealed that 4 weeks of bay leaves AQ or MeAc extracts supplementation improved plasma glucose, and significantly decreased serum triglyceride levels, abdominal fat, as well as weight gain.

Since the biological activity of both extracts is highly dictated by the sum of their components, it was essential to analyze their chemical composition by GC-GC/MS. Chemical analysis of the MeAc extract revealed that 1,8-cineole, an oxygenated monoterpene, was the major constituent followed by 5,8-Epoxy-15-nor-labdane and α-

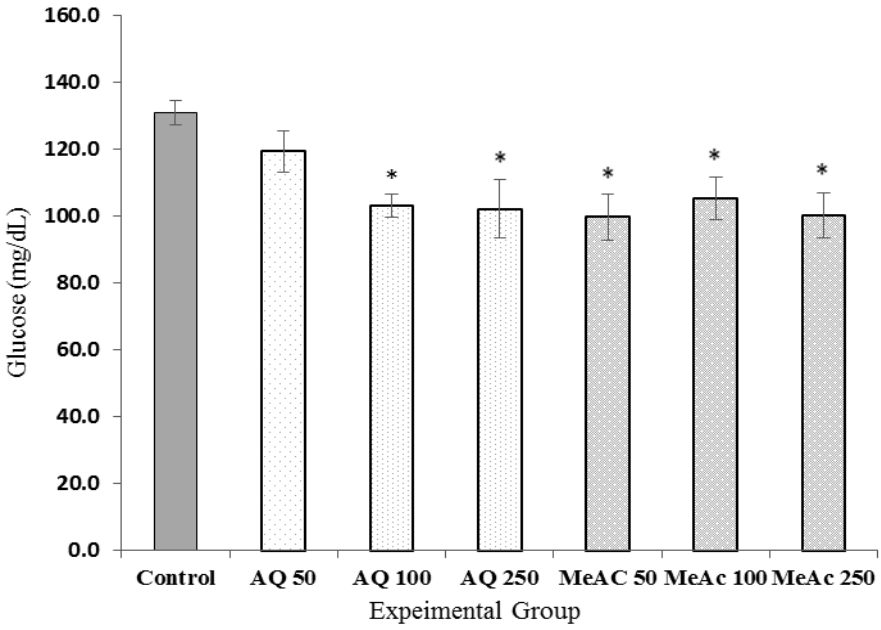

Figure 2. Fasting serum glucose level (mg/dL) after 4 weeks of extract treatment. Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

Table 3. Fasting serum ALT, ALP and creatinine levels after 4 weeks of extract treatment.

Parameter	Control	AQ50	AQ100	AQ250	MeAc50	MeAc100	MeAc250
ALT (U/L)	38.2 ± 1.11	51.4 ± 4.71*	44.5 ± 1.65*	57.0 ± 9.45	43.9 ± 2.72	48.0 ± 2.40*	45.6 ± 3.08
ALP (U/L)	166 ± 21.9	178 ± 11.5	180.4 ± 23.7	214.4 ± 17.3	199.3 ± 8.71	210.6 ± 5.62	225.6 ± 10.7
Creatinine (mg/dL)	0.33 ± 0.01	0.34 ± 0.01	0.31 ± 0.01	0.36 ± 0.02	0.33 ± 0.01	0.31 ± 0.01	0.32 ± 0.01

Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

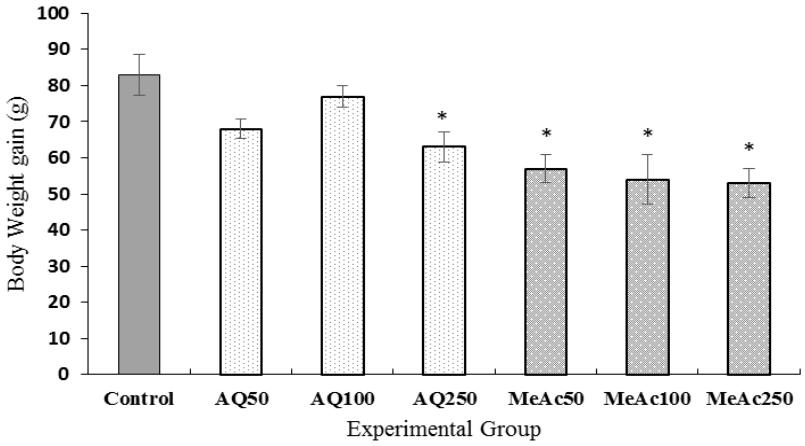

Figure 3. Body weight gain after 4 weeks of extract treatment. Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

Terpinene. In accordance to the present findings, 1,8-cineole is the major component present in most of leaf oil and other parts of the *L. nobilis* plant harvested from different world locations (Abu-Dahab et al., 2014; Said and Hussein, 2014). Surprisingly, the second major constituent in the MeAc extract, 5,8-Epoxy-15-nor-

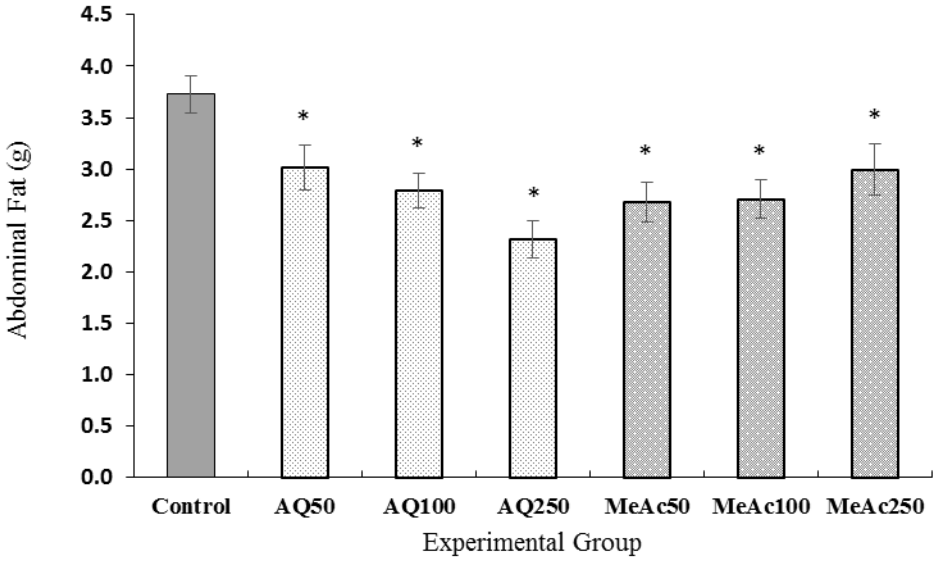

Figure 4. Total Abdominal fat after 4 weeks of extract treatment. Data are presented as mean ± SEM (n=7 per group). *p<0.05 with respect to control.

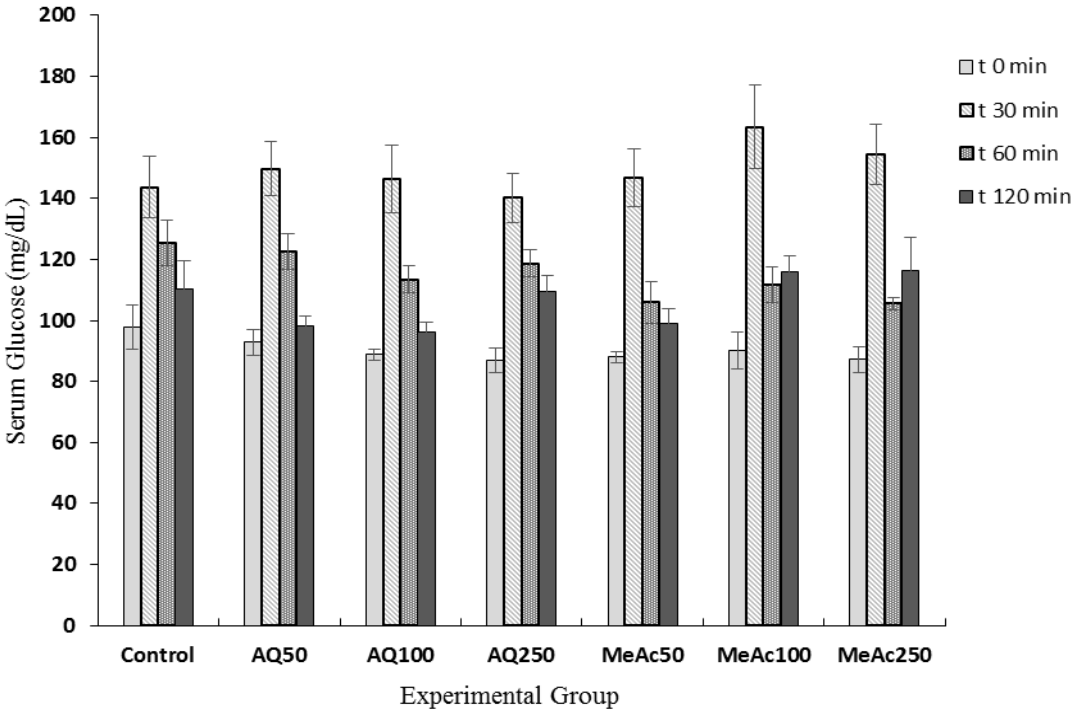

Figure 5. Glucose tolerance test. Serum glucose 30 min, 1 h and 2 h after IP injection of glucose on day 14 of the experiment. Data are presented as mean ± SEM (n=7 per group).

labdane, was not present in any of the Bay leaf oil composition reported in the literature. These variations in oil composition may be attributed to several factors including extraction methods, different geographic origins, developmental stage, season during which the plants are collected, genetic variability, type of soil and the environmental conditions (Al-Jaber et al., 2012).

The current study demonstrates that Bay leaf AQ or MeAc extracts supplementation protect from high fat diet-induced type 2 diabetes. Both extracts significantly

Table 4. GC-MS analysis of *L. nobilis* MeAc extract.

S/N	Retention time (min)	Composition (%)	Compound
1	4.402	0.41	Unidentified A
2	4.603	3.23	Unidentified B
3	4.683	0.60	Beta-Phellandrene
4	4.751	48.3	1,8-cineole
5	7.317	0.90	(-)-Terpinen-4-ol
6	7.597	1.35	α-Terpineol
7	9.712	0.37	Unidentified C
8	10.215	0.16	Unidentified D
9	10.307	7.14	α-Terpinene
110	10.484	0.96	Eugenol
11	11.118	0.45	(-)-β-elemene
12	11.787	0.33	Caryophyllene
13	35.615	1.39	Unidentified E
14	36.18	3.02	Eremanthin
15	45.64	3.32	Unidentified F
16	51.812	3.42	Unidentified G
17	61.557	3.29	Vitamin E
18	103.874	19.1	5,8-Epoxy-15-nor-labdane

Table 5. GC-MS analysis of dried *L. nobilis* water extract dissolved in methanol. Identified compounds (≥ 90% match) are reported.

S/N	Retention time (min)	Composition (%)	Compound
1	5.34	0.25	2H-Pyran-2,6(3H)-dione
2	6.97	1.63	Thymine
3	8.259	2.36	4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-
4	9.942	24.72	5-(Hydroxymethyl)furfural
5	16.06	0.63	1-Methyl-4-(1-acetoxy-1-methylethyl)-cyclohex-2-enol
6	16.683	0.24	trans-Isoeugenol
7	22.936	0.29	Butyrovanillone
8	23.617	0.26	Methoxyeugenol
9	26.053	0.36	Benzenepropanol, 4-hydroxy-3-methoxy-
10	28.833	0.21	(E)-2,6-Dimethoxy-4-(prop-1-en-1-yl)phenol
11	30.741	1.09	(E)-4-(3-Hydroxyprop-1-en-1-yl)-2-methoxyphenol
12	43.141	0.4	n-Hexadecanoic acid
13	43.374	1.43	Eremanthin
14	44.093	2.51	Eremanthin
15	52.579	0.34	Methyl stearate
16	54.181	1.13	Reynosin
17	62.725	0.7	Squalene
18	69.125	0.58	Vitamin E

Table 6. Total flavonoid and phenolic content of *L. nobilis* AQ and MeAc extract.

Extract	Flavonoid content		Phenolic content	
	mg/g of extract	mg/g of leaves	mg/g of extract	mg/g of leaves
Aqueous	12.6	0.72	148	8.44
Acetone/Methanol	16.3	0.94	46.0	2.65

improved fasting serum glucose. Previous report indicated that bay leaves consumption in type 2 diabetic patients for 4 weeks caused a reduction in plasma glucose, total cholesterol, and triglycerides (Aljamal, 2011). In another study, administration of capsules containing powdered bay leaves to patients with type 2 diabetes caused a marked decrease in the blood glucose content (Khan et al., 2009). Recent report also indicated that consumption of cookies containing different doses of bay leaves by healthy individuals significantly lowered postprandial blood glucose concentrations (Khan et al., 2017).

Flavonoids and polyphenols present in both AQ and MeAc extracts may have contributed to the regulation of glycemia in our diabetic rat model. According to previous studies, polyphenols present in bay leaves were shown to improve insulin sensitivity, glucose uptake, and antioxidant status of diabetic patients (Anderson, 2008; Khan et al., 2017). One mechanism by which bay leaves may attenuate blood glucose is via the inhibition of carbohydrate hydrolyzing enzymes such as α-amylase and α-glucosidase which are involved in glucose absorption. Studies have shown that bay leaves extracts containing mainly 1,8-cineole and other polyphenols inhibit the activities of both enzymes (Basak and Candan, 2009; Basak and Candan, 2013). Thus, the reduction of plasma glucose in rats treated with AQ or MeAc extracts may be partially due to the inhibition of the activities of α-glucosidase and α-amylase enzymes by the major phytochemicals present in both extracts.

The second major compound present in the MeAc extract is the labdane-type diterpene 5,8-Epoxy-15-nor-labdane. Crude extract obtained from *Opuntia ficus indica* containing 5,8-Epoxy-15-nor-labdane displayed effective capacity to decrease postprandial levels of glycemia in rat model of acute hyperglycemia (Manzano et al., 2017). Other labdane-type diterpenes isolated from tora seeds demonstrated potent α-glucosidase inhibitory activity which is considered an important approach in the treatment of type 2 diabetes (Ghosh and Rangan, 2015).

Previous study on streptozotocin induced diabetic rats showed that oral administration of eremanthin (5, 10, and 20 mg/kg bw) for 60 days significantly reduced plasma glucose level in a dose dependent manner and decreased glycosylated hemoglobin, serum triglyceride, total cholesterol, LDL-cholesterol and markedly increased plasma insulin, tissue glycogen, HDL-cholesterol and serum protein (Eliza et al., 2009). Also, a study on the methanolic extract of *Costus speciosus* leaves containing eremanthin revealed an inhibition of α-glucosidase activity, fructosamine formation, glycation and glycation induced protein cross-linking, hence supporting its hypoglycemic effect and its role in slowing down protein glycation (Perera et al., 2016). Similar anti-hyperglycemic, antihyperlipemic effects were observed with ethanol extract of *C. speciosus* root (Bavarva and Narasimhacharya, 2008). The sesquiterpenoid eremanthin is found in both the AQ and MeAc extracts of bay leaves and thus could have contributed to the observed protection against high fat diet-induced type 2 diabetes.

The present study showed a significant reduction in serum triglyceride levels, abdominal fat, and weight gain upon treatment with AQ or MeAc extracts specifically at high doses. Previous studies have demonstrated that visceral fat accumulation is associated with serum triglyceride (TG) levels and insulin resistance in non-obese Japanese type 2 diabetic patients (Taniguchi et al., 2002; Taniguchi et al., 2001). Khan et al. (2009) have reported a marked decrease in serum triglyceride levels and blood lipid profile in patients with type 2 diabetes after daily consumption of 2 g of dried bay leaves. Also, Aljamal (2011) suggested that bay leaves reduced triglyceride, LDL and total cholesterol and increased HDL levels in people with type 2 diabetes. Furthermore, feeding male rabbits with meals supplemented with dried bay leaves resulted in a marked decrease in blood lipid and glycemic profiles (Casamassima et al., 2017). Based on *in vitro* and *in vivo* studies, the mechanism by which bay leaves may lower lipid concentrations is through the enhancement of insulin sensitivity leading to improvements in blood glucose and lipid profiles (Aljamal, 2011; Casamassima et al., 2017). Treatment with either AQ or MeAc extracts of bay leaves for 4 weeks did not affect fasting serum creatinine level or ALP enzyme activity. However, an inconsistent variation in ALT activity was observed. Previous reports revealed a reduction in the levels of ALT, AST and ALP after treatment with bay leave extract in carbon tetrachloride (Gasparyan et al., 2015) or paracetamol (Ravindran et al., 2013) intoxicated rats.

Conclusion

The present study provides evidence of the protective effect of bay leaves AQ and MeAc extracts against type 2 diabetes induced by a high fat diet in rats. Although, no major adverse effects were noticed after four weeks of treatment, further studies are needed to confirm its long-term safety.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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