

Antihyperlipidemic and Antioxidative Properties of *Pistacia atlantica* subsp. *kurdica* in Streptozotocin-Induced Diabetic Mice

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Introduction: *Pistacia atlantica* subsp. *kurdica* is an important food source and a well-known medicinal plant in the Zagros Mountains of Iran. The present study aimed to investigate the effect of *P. atlantica* extract and essential oil in streptozotocin-induced diabetic mice.

Materials and Methods: Different doses of hydroalcoholic extract and essential oil of *P. atlantica* subsp. *kurdica* (50, 100, and 200 mg/kg) were given to streptozotocin-induced diabetic mice in separate groups for three weeks. At the end of treatment, blood samples were collected; then, oxidative stress markers, TNF- α , and lipid profile were determined in its serum samples.

Results: Our findings showed that the administration of *P. atlantica* extract for three consecutive weeks significantly improved the lipid profile, oxidative stress, and inflammation process by reducing lipid peroxidation and increasing total antioxidant capacity.

Conclusion: This study showed that *P. atlantica* subsp. *kurdica* has antioxidant and blood lipid-lowering effects that can be used as a supplement to improve diabetes complications.

Keywords: *Pistacia atlantica* subsp. *kurdica*, phytochemical, diabetes, lipid profile, oxidative stress

Introduction

Diabetes mellitus, as a global main public health concern, is increasing due to urbanization, obesity, and aging.¹ It is anticipated that the number of diabetic patients will reach 366 million in 2030.² Increased oxidative stress and lipid profile alterations are important contributors to the initiation and progression of diabetes as well as its complications.^{3,4} In addition to insulin therapy, diabetes mellitus could be controlled by a combination of fasting, diet control, and plant therapeutics.⁵

It has been estimated that around 80% of the people in some Asian/African regions rely on traditional medicine for their health care.⁶ Commonly the pharmaceutically efficient forms of these plants are their extractions.⁷ In addition, the chemical factors of extracts/essential oils qualify their usage in food industries. Recently, there has been increasing attention on traditional herbs with antioxidant, anti-inflammatory and antidiabetic properties.^{8,9} The efficiency of traditional herbs needs to be confirmed in diabetes; therefore, the World Health Organization (WHO) recommends the assessment of traditional plant treatments for diabetes mellitus.^{5,10}

Pistacia atlantica subsp. *kurdica* is from the Anacardiaceae family and is found in the Zagros Mountains of Iran (west and northwest of Iran with a mild climate).

Oleoresin derived from *P. atlantica* is applied to produce chewing gum. The fruit of *P. atlantica* is consumed by inhabitants as food and the unripe fruit is served in pickles. Its husk and kernel oil is consumed as frying oil by local people. In addition to food consumption, *P. atlantica* has been employed in traditional medicine in the treatment of various diseases including stomach disorders and throat infections.¹¹ It has been shown that *P. atlantica* and its chemical factors induce some pharmacological actions including anticancer, antioxidant, anti-inflammatory, and antimicrobial activities.^{12–15} Therefore, this project was initiated to evaluate the impact of long-term treatment with hydroalcoholic extract (HE) and essential oil (EO) of *P. atlantica* subsp. *kurdica* on glucose, lipid profile, TNF- α and oxidative stress biomarkers in streptozotocin (STZ)-induced diabetic mice.

Materials and Methods

Chemical substances were bought from Merck, Darmstadt, Germany unless otherwise mentioned. 2,4,6-tripyridyl-s-triazine (TPTZ) and STZ were provided from Sigma-Aldrich Company (St Louis, MO, USA). The ripe *P. atlantica* subsp. *kurdica* fruits were gathered in May 2016 from the Awraman region in Marivan, Kurdistan in the west of Iran. A voucher specimen (MPH-11854) is deposited in the Herbarium of the Research Institute of Forests and Range-land Research by Hossein Maroufi, Sanandaj, Iran.

Preparation of the Extract and Essential Oil

The extract and essential oil of *P. atlantica* subsp. *kurdica* were prepared according to our previous study.¹⁵

Animal Experiments

Male albino mice (25–30 g) were bought from the animal house of Hamadan University of Medical Science. The animals were kept under a temperature of 22–25°C, humidity of 50–55%, and 12 h light/dark cycle. Animals were given the standard diet with water ad libitum.

Induction of Experimental Diabetes

The induction of diabetes was done through intraperitoneal administration of STZ in 0.1 M citrate buffer (pH 4.5) at a dose of 60 mg/kg to mice following the estimation of baseline fasting blood sugar concentration. At 72 h following STZ administration, animals with

fasting blood glucose levels over 200 mg/dL were considered to be diabetic.

Experimental Design

Animals were divided into 10 groups and each one comprised 6 mice. The groups were 1) normal untreated mice; 2) diabetic untreated mice; 3) normal mice treated with 200 mg/kg of HE; 4, 5, and 6) diabetic mice treated with 50, 100, 200 mg/kg of HE, respectively; 7) normal mice treated with 200 mg/kg of EO; 8, 9, and 10) diabetic mice treated with 50, 100, 200 mg/kg of EO, respectively. Three weeks following intervention, animals were anesthetized with intraperitoneal administration of 40 mg/kg ketamine and 10 mg/kg xylazine mixture, after overnight fasting. Blood specimens were gathered from the heart and centrifuged at 1500 g for 10 min for preparing serum.

Determination of Glucose and Lipid Profile

Serum levels of glucose, triglyceride (TG), total cholesterol (TC), HDL-C and LDL-C were measured using commercial kits (Pars Azmoon, Tehran, Iran). In addition, the Atherogenic Index (AI) and Coronary Risk Index (CRI) were estimated by the following formulas:

$$AI = \frac{LDL - Cholesterol}{HDL - Cholesterol} \quad CRI = \frac{Total\ Cholesterol}{HDL - Cholesterol}$$

Lipid Peroxidation (LPO) Assay

LPO was determined in serum samples by the use of thiobarbituric acid reactive substances (TBARS) method as described by Navaei-Nigjeh et al.¹⁶ Briefly, a reaction mixture was provided containing 0.2% TBA in 0.05 M H₂SO₄. The specimens were read by a microplate reader (Synergy HTX, BioTek Instruments Inc., Winooski, VT, USA) set at 532 nm against malondialdehyde (MDA) as the standard provided at several concentrations (1, 2, 4 and 8 μ M). Finally, results were expressed as nmol/mL.

Ferric Reducing/Antioxidant Power Assay

Total antioxidant capacity (TAC), called FRAP, in serum samples was measured according to the reduction of Fe³⁺ to Fe²⁺. In this experiment, the complex between Fe²⁺ and TPTZ, as an indicator, results in a blue color with an absorbance maximum at 593 nm as previously described Navaei-Nigjeh et al.¹⁶ Results were expressed as μ mol/mL.

Table 1 HE/EO Effects on Glucose Level and Lipid Profile in the Serum of Diabetic Mice

Group	Glucose	TG (mg/dL)	TC (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	VLDL (mg/dL)	Atherogenic Index (AI)	Coronary Risk Index (CRI)
Control	129±10	64.1±7.3	92.8±6.4	41±5.2	35±4.7	12.8±1.4	0.8±0.1	1.5±0.2
STZ	363±36 ^{aaa}	125.1±16.7 ^{aaa}	134.4±5.9 ^{aaa}	25±3.1 ^a	58.7±6.4 ^a	25.0±3.3 ^{aaa}	2.3±0.3 ^{aaa}	5.1±0.7 ^{aaa}
HE (200 mg/kg)	144±11	80.1±14.1	95.6±7.6	37±6.4	28.8±8.1	16.1±2.8	0.7±0.2	2.2±0.4
STZ+HE (50 mg/kg)	338±35	78.3±9.1 ^{bbb}	93.6±4.8 ^{bbb}	26±4.4	52.3±7.9	15.6±1.8 ^{bbb}	2.1±0.4	3.1±0.5 ^{bb}
STZ+HE (100 mg/kg)	398±23	67.9±9.8 ^{bbb}	103.5±6.8 ^{bbb}	28±3.6	48.1±9.1	13.5±1.9 ^{bbb}	1.7±0.3	2.4±0.4 ^{bbb}
STZ+HE (200 mg/kg)	392±38	76.7±6.0 ^{bbb}	86.2±12.8 ^{bbb}	28±5.5	39.8±2.8 ^b	15.3±1.2 ^{bbb}	1.4±0.3	2.8±0.5 ^{bbb}
EO (200 mg/kg)	219±17	97.6±15.3	106.8±13.2	44±6.1	43.1±3.2	19.5±5.1	0.9±0.1	2.2±0.4
STZ+EO (50 mg/kg)	392±18	101.7±9.2	130.8±10.8	26±4.8	59.2±11.2	20.3±1.8	2.3±0.5	3.9±0.7
STZ+EO (100 mg/kg)	370±25	108.6±9.4	121.6±17.6	24±4.1	64.8±8.7	21.7±1.8	2.7±0.5	4.6±0.8
STZ+EO (200 mg/kg)	355±31	88.6±11 ^{bbb}	122±18.1	21±3.6	61.9±12.3	17.7±2.2 ^{bbb}	2.9±0.6	4.3±0.7

Notes: Statistical analysis used one-way ANOVA with Tukey's test. Values are expressed as mean±SEM, n=6 for each group. Significantly different from the control group: ^aP<0.05, ^{aa}P<0.01, and ^{aaa}P<0.001. Significantly different from the diabetic group: ^b(P<0.05), ^{bb}(P<0.01) and ^{bbb}(P<0.001).

Abbreviations: HE, hydroalcoholic extract; EO, essential oil; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; VLDL, very-low-density lipoprotein; AI, atherogenic index; CRI, coronary risk index.

TNF α Assay

The serum level of TNF- α was measured using the ELISA kit (Crystal day Biotech Co., Shanghai, China). The optical density of the produced color was assessed at 450 nm. Data were expressed as ng/L.

Statistical Analyses

Data were indicated as means \pm SEM and compared by ANOVA. Tukey-Kramer was used as a post hoc test. A *P*-value of less than 0.05 was statistically significant.

Results

HE/EO Effects on Glucose and Lipid Profile

As shown in Table 1, administration of STZ significantly increased serum levels of glucose ($P<0.001$), TG ($P<0.001$), TC ($P<0.001$), VLDL ($P<0.001$), and LDL-C ($P<0.001$); and decreased HDL-C serum level in comparison to the control group. No significant changes were observed in glucose level and HDL-C in diabetic mice during HE and/or EO therapy when compared with the STZ group. HE treatment at the doses of 50, 100, and 200 mg/kg inhibited the rise of TG and TC in diabetic mice. In addition, LDL-C level was remarkably decreased in diabetic mice treated with HE (200 mg/kg). No significant changes were observed in TC and LDL-C levels during EO therapy when compared with the STZ group. Only a significant decrease was observed in TG levels in diabetic mice treated with EO (200 mg/kg) in comparison to the STZ group.

HE/EO Effects on TNF- α Levels

TNF- α levels significantly increased in diabetic in comparison to normal mice ($P<0.05$). Following HE therapy, TNF- α concentration significantly decreased in the dose of 200 mg/kg in comparison to diabetic mice ($P<0.01$). No significant alteration was found in the TNF- α level in diabetic mice during EO therapy when compared with the STZ group (Table 2).

HE/EO Effects on Oxidative Stress Biomarkers

As indicated in Table 2, in the diabetic mice group, serum TAC significantly decreased ($P<0.01$), but returned to normal after usage of HE (200 mg/kg; $P<0.05$), 50 and 100 mg/kg of EO ($P<0.001$ and $P<0.001$, respectively). No significant alteration was seen following administration

Table 2 HE/EO Effects on TNF- α Level and Oxidative Stress Biomarkers in the Serum of Diabetic Mice

Groups	TNF- α (ng/L)	TAC (μ mol/mL)	LPO (nmol/mL)
Control	5.8 \pm 1.1	1.4 \pm 0.15	1.8 \pm 0.36
STZ	8.1 \pm 0.91 ^{aa}	0.8 \pm 0.07 ^{aa}	2.1 \pm 0.49 ^{aaa}
HE (200 mg/kg)	6.1 \pm 0.82	1.25 \pm 0.17	4.9 \pm 0.94
STZ+HE (50 mg/kg)	6.8 \pm 0.49	0.94 \pm 0.08	4.4 \pm 0.50
STZ+HE (100 mg/kg)	7.2 \pm 0.65	1.07 \pm 0.05	3.8 \pm 0.36 ^b
STZ+HE (200 mg/kg)	6.2 \pm 0.37 ^b	1.3 \pm 0.13 ^{bb}	2.9 \pm 0.31 ^{bbb}
EO (200 mg/kg)	6.4 \pm 1.2	1.3 \pm 0.08	2.5 \pm 0.53
STZ+EO (50 mg/kg)	7.8 \pm 0.97	0.9 \pm 0.21	3.1 \pm 0.94
STZ+EO (100 mg/kg)	7.4 \pm 0.38	1.1 \pm 0.25	2.9 \pm 0.54
STZ+EO (200 mg/kg)	6.9 \pm 0.41	1.2 \pm 0.09	3.6 \pm 0.63

Notes: Analysis used one-way ANOVA with Tukey's test. Values are expressed as means \pm SEM, n=6 for each group. Significantly different from the control group; ^{aa}P<0.01 and ^{aaa}P<0.001. Significantly different from the diabetic group ^bP<0.05, ^{bb}P<0.01, and ^{bbb}P<0.001.

Abbreviations: HE, hydroalcoholic extract; EO, essential oil; STZ, streptozotocin; TNF- α , tumor necrosis factor- α ; TAC, total antioxidant capacity; LPO, lipid peroxidation.

of HE (50 and 100 mg/kg) and EO (200 mg/kg). There was a remarkable increase in the level of LPO in diabetic mice when compared to control (P <0.001). Following HE therapy, LPO decreased at the dosage of 200 mg/kg in comparison to the diabetic group (P <0.01). EO suppressed increment of LPO at the dosages of 50 (P <0.05) and 100 (P <0.01) mg/kg.

Discussion

In the present project, the administration of STZ for three consecutive weeks gave rise to a remarkable rise in glucose, TC, TG, LDL, and VLDL serum concentration in the mice. In contrast, the HDL level in serum samples significantly decreased in diabetic mice. Hyperglycemia in STZ-induced diabetic mice could be caused by destroying β -cells in Langerhans islets, which has an adverse impact on serum lipid concentration.^{16,17} Secondary elevation of free fatty acid in the blood owing to their mobilization from adipocytes can lead to the clearance of HDL and might be one of the probable mechanisms of hyperlipidemia in diabetes.^{17,18} Therefore, STZ-induced lipid disturbances may be due in part to extra action of lipolytic hormones on adipocytes.¹⁹ In addition, hypertriglyceridemia in diabetic mice could result from an increment in hepatic VLDL overproduction and impaired metabolism of TG-rich particles. It can cause the deposition of fat in ectopic sites such as skeletal muscle (lipotoxicity).²⁰ Lipoprotein lipase (LPL) dysfunction may be another contributor to hypertriglyceridemia. Observed elevation in TC of diabetic mice may be due to a decrease in

HDL-C. These changes may be relevant in explaining the increased predisposition of diabetes to atherosclerosis and coronary heart disease. HE administration for three consecutive weeks resulted in a remarkable decrease in serum concentration of TG, TC, LDL, and VLDL in the diabetic mice. Serum glucose levels had no significant alteration in both normal and STZ diabetic mice after HE and/or EO treatment. It seems that HE/EO changed the serum lipid profile without decreasing blood glucose levels. Phytochemical studies on different subspecies of *P. atlantica* extract indicated the presence of flavonoids and phenolic compounds as major chemical components.^{11,21-23} These compounds may be associated with the therapeutic effects of *P. atlantica*. Previously, Hashemnia et al have reported that N-hexane extract of *P. atlantica* seed produced a potent antihyperglycemic effect in STZ diabetic mice. Unfortunately, the subspecies of *P. atlantica* in this research was not specified; *P. atlantica* comprises three subspecies in Iran, *kurdica*, *mutica*, and *cabulica*.²⁴ This discrepancy may be explained at least in part by the difference in subspecies and extract of *P. atlantica* in the study. Our findings showed that HE may attenuate hypercholesterolemia via modifying the lipoprotein state. On the other hand, enhancement of LDL receptors and/or the lecithin-cholesterol acyltransferase (LCAT) activity may participate in the regulation of lipid profile. LCAT has a critical role in consolidating free cholesterol into HDL and transferring back to VLDL or IDL, which is returned through the liver cells.²⁵ In addition, a decrease of TG in serum diabetic mice is possibly due to the inhibition of lipogenesis in adipose tissue.

Oxidative stress plays a leading part in the progress of diabetes complications such as dyslipidemia and inflammatory process. One of the critical biomarkers of oxidative damages is lipid peroxidation, which is the most explored area of research when it comes to reactive oxygen species (ROS).⁶ In addition, it has been reported that TNF α could affect glucose hemostasis and adipose tissue dysfunction.²⁵ TNF α could suppress tyrosine phosphorylation inside the insulin receptors and may inhibit glucose transporter gene expression.²⁶ In the current study a remarkable rise in LPO biomarker and decrease in TAC of serum were observed, as supported by previous studies, such as Pourkhalili et al.¹ In addition, TNF α was remarkably increased in diabetic mice. Stimulation of oxidative stress signaling pathways and TNF α seems to take part in the stimulation of some redox-sensitive transcription factors such as nuclear factor kappa B (NF- κ B).²⁷ On the other hand, it has been shown that NF- κ B stimulation in hepatocytes has a contributory role in

progressing insulin resistance and the occurrence of diabetes mellitus.^{28,29}

HE administration for three consecutive weeks significantly improved oxidative damage and inflammatory processes through decreasing lipid peroxidation and increasing TAC, as well as modulation of TNF α in the serum of diabetic mice. However, the effects of EO were less than HE in diabetic animals. It seems that phenols and flavonoids, the major constituents of HE, have more potential to remove free radicals and decrease the inflammatory reactions than monoterpene hydrocarbons in EO.

Conclusion

In conclusion, our survey indicated that continued oral intake of HE for three weeks might provide beneficial effects on the hyperlipidemia, oxidative stress, and inflammatory response in diabetic mice. The finding might support its usage by the Iranian population in the management and treatment of diabetes. This suggests that *P. atlantica* subsp. *kurdica* intake may prevent or be helpful in decreasing dyslipidemia related to diabetes. Finally, the exact mechanisms and the active constituents of *P. atlantica* subsp. *kurdica* involved are still to be determined via additional studies.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work and declare that the content has not been published elsewhere.

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Disclosure

The authors have no conflicts of interest to disclose.

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