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Anti-hypercholesterolemic effect of *Pistacia lentiscus* fatty oil in egg yolk-fed rabbits: a comparative study with simvastatin

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[ABSTRACT]

AIM: The current study was undertaken to assess anti-hyperlipidemic activity of *Pistacia lentiscus* fatty oil (PLFO) in rabbits following a hyperlipidemic diet.

METHOD: Twenty healthy female (WNZ) rabbits were divided into four groups of five animals each: (a) normal control (NC group) receiving standard diet, (b) hyperlipidemic control (EY) group receiving standard diet and gavaged daily with egg yolk (10 mL), (c) hyperlipidemic + PLFO (EY + PLFO) group receiving as the EY group and treated daily with PLFO (2 mL/kg BW, (d) hyperlipidemic + simvastatin (EY + SVS) group receiving as the EY group and treated once daily with 2.5 mg/kg BW of simvastatin. At the end of the six-week experimental period, the lipidemic profiles of the different groups were investigated.

RESULTS: In the EY group, the egg yolk resulted in a significant increase of total cholesterol (TC), triglycerides (TG), HDL-C, LDL-C, and the LDL-C/HDL-C ratio. Both the EY + PLFO and EY + SVS groups, when compared to the EY group, showed a significant decrease of TC, TG, LDL-C, and the LDL-C/HDL-C ratio. However, with respect to HDL-C the differences were not significant. The TGs were significantly lower ($P < 0.001$) in the simvastatin-treated group when compared to rabbits treated in the PLFO group.

CONCLUSION: The study concludes that *P. lentiscus* fatty oil (PLFO) possesses anti-hyperlipidemic properties at least in reducing total cholesterol, LDL-cholesterol and triglycerides.

[KEY WORDS] *Pistacia lentiscus*; Fatty oil; Anti-hperlipidemic activity; Rabbits

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Introduction

Hypercholesterolemia is an important risk factor of cardiovascular disease. It has been estimated that a 10% decrease in blood cholesterol levels reduces this risk by between 19% and 54%, depending on a person's age [1]. Lipid management has typically focused on control of LDL-cholesterol. Several drugs are currently available for the treatment of hyperlipidemia, and the most potent agents are known as HMG CoA reductase inhibitors or statins. All these agents lower LDL in a dose-dependent manner, approximately 20%−38% with initial doses, and by 35%−61% with maximal doses [2]. Although statins represent the gold standard for the treatment of dyslipidemia, pharmacologic therapies can also effectively raise HDL-cholesterol and reduce triglycerides, and include fibrates and niacin. Fibrate therapy has been shown to significantly raise HDL-cholesterol levels by 10% to 35% and reduce triglycerides by 20% to 50% [3]. A meta-analysis by Birjmohun *et al.* [4] indicated that fibrates had beneficial effects on patients' lipid profile, decreasing triglycerides by 36%, LDL by 8%, and total cholesterol by 11%, and increasing HDL by 10%. Niacin modifies all elements of the lipid profile favorably; it lowers triglycerides by 20%−35%, LDL by 5%−25%, and increases HDL by 15%−35%. The consumption of plant sterols has been shown to decrease plasma concentrations of cholesterol, without adverse effects in humans [5]. It is important to indicate that drug therapy to inhibit cholesterol biosynthesis is effective, but has some potential negative consequences. Some adverse effects associated with statin therapy were reported: asymptomatic elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) [6-7], muscle symptoms or signs (pain, soreness, weakness, and/or cramps, and creatine kinase elevations [8-11], rhabdomyolysis with renal failure [10,12], polyneuropathy, memory loss, sleep disturbances, impotence, gyne-

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comastia, lupus-like syndrome, and pancreatitis [7,13]. Pascual-Cruz *et al*. [14] have observed a high percentage of oral symptoms in patients undergoing treatment with statins (dryness, cough, bitterness, and itchiness in tongue and lips, insomnia). Combination therapy to treat dyslipidemia has become popular in patients with coronary heart disease; however, it can also increase the risk of serious adverse effects, like myalgias and rhabdomyolysis [15]. Concerns about the safety of fibrate-statin combinations have focused on the incidence of myositis or rhabdomyolysis; primarily associated with cerivastatin and gemfibrozil combination therapy [16-18]. The variable reported side effects of niacin formulations included flushing, cardiac arrhythmias, dry skin, rashes, glucose intolerance, dyspepsia, thrombocytopenia, hepatic necrosis, and leg cramps [19]. In addition, some extracts of plant origin are beneficial in lipid management, but they need a complex purification process, particularly to extract certain toxic components such as canavanin of luzern [20]. Therefore, efforts are underway to develop potent and better HDL elevators and LDL-lowering agents with no adverse effects for the prevention of cardiovascular diseases.

Pistacia lentiscus L. is an evergreen shrub belonging to the Anacardiaceae family. It is widely distributed throughout the Mediterranean region, and has been used in traditional medicine by very ancient civilizations, including the Greeks and Egyptians [21]. The aerial parts have been used in the treatment of hypertension and possess stimulant and diuretic properties [22]. According to Ali-Shtayeh *et al*. [23], the leaves are extensively used in traditional medicine for the treatment of eczema, diarrhea, and throat infections, and as a potent antiulcer agent. The essential oil extracted from the aerial parts exhibits antioxidant, anti-inflammatory, antimicrobial [24], antifungal [25, 26], and antiatherogenic activities [27]. The mastic gum has been used for the management of abdominal discomfort, stomachache, dyspepsia, and peptic ulcer [28]. It has been reported by Balan *et al*. [29] that the 50% ethanolic extract of Chios mastic gum of *P. lentiscus* inhibited proliferation and induced apoptosis in human colon cancer cells *in vitro*. Other medicinal virtues of this plant were related to the fixed oil extracted from dark berries of *P. lentiscus*. The fatty oil is known particularly in North African traditional medicine, in the eastern region of Algeria to Tunisia. The people of these regions have used this oil externally to treat sore throats, locally to treat burns and wounds, and internally for respiratory allergies [30]. A few scientific reports published recently focused on the pharmacological and toxicological profiles of this oil. This laboratory has demonstrated a cicatrizing activity of this oil following experimental burns in a rabbit model, by decreasing the inflammatory phase, promoting wound contraction, and reducing the epithelialization period [31]. Tounes *et al*. [32] reported that this oil may partially help in protection against mercury intoxication. Some toxicological aspects of this oil were also investigated [33-34], and the chemical composition of this fixed oil studied [35- 38].

The present study was undertaken to assess, the preventive effect of *Pistacia lentiscus* fatty oil (PLFO) in hypercholesterolamia induced by prolonged feeding of egg yolk in a rabbit model.

Material and Methods

Extraction and phytochemical analysis of Pistacia lentiscus fatty oil

Pistacia lentiscus fruits (85% dark and 15% red berries) were collected from the Tamalous region, in eastern Algeria. A voucher specimen (PL-1210ZD) has been deposited at the Pharmacology and Toxicology Laboratory, Mentouri Constantine University, Algeria. The berries were shade-dried for ten days, and then the oil was extracted by a traditional method in different steps. First the fruits were ground using millstones into a paste, which was then mixed for 30 min. After grinding, the paste was spread on fiber disks and was pressed. Warm water was run down the sides of the disks to increase the filtration of the oil. The liquids were then separated by decantation. At the end of this phase *Pistacia lentiscus* fatty oil (PLFO) was produced. To ascertain the quality of this oil, some physicochemical characteristics (organoleptic parameters, state at 20°C, solubility, density, refractive index, acid content, iodine content, peroxide and saponification values, and the percentage of unsaponifiable matter) were determined in the "Laboratory of Quality Control", Bab El Kantra Constantine, Algeria. The different determinations were carried out according to the methods as recommended in CODEX STAN 210 [39]. The fatty acid composition was determined by gas chromatography coupled to mass spectrometry (GC-MS) analysis and was carried out in triplicate; the obtained percentages were expressed as $\bar{x} \pm s$.

Chemicals and materials

Simvastatin (Zostine®, 20 mg, n°01/06 M 136/035) was obtained from a private pharmacy. Eggs were purchased from the local market. The yolk of the eggs were separated manually, pooled in a clean container and mixed.

Animals and experimental protocols

Healthy female white New-Zealand rabbits (n = 20, 10 weeks old, initial body weight 1.5 to 1.8 kg) were purchased from a local supplier (Hama Bouziane, Constantine, Algeria) and used for these studies. Animals were group housed (three or two/cage) in stainless cages and kept in standardized environment conditions at 22−25 °C in a 12 h light-dark cycle. They had unrestricted access to drinking water and were given twice daily standard rabbit food (Bouzerea, Algiers). Animals were acclimated for 10 days before initiating studies which were conducted in accordance with the Faculty of Science and Life, Mentouri Constantine University, Algeria.

At the end of the acclimatization period, the animals were divided into four groups of five rabbits each with similar body weight:

a) Normal Control (NC): Received standard diet.

b) Hyperlipidemic Control (EY): Received standard diet