

Olive Leaf Extract as a Hypoglycemic Agent in Both Human Diabetic Subjects and in Rats

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ABSTRACT Olive tree (*Olea europaea* L.) leaves have been widely used in traditional remedies in European and Mediterranean countries as extracts, herbal teas, and powder. They contain several potentially bioactive compounds that may have hypoglycemic properties. To examine the efficacy of 500 mg oral olive leaf extract taken once daily in tablet form versus matching placebo in improving glucose homeostasis in adults with type 2 diabetes (T2DM). In this controlled clinical trial, 79 adults with T2DM were randomized to treatment with 500 mg olive leaf extract tablet taken orally once daily or matching placebo. The study duration was 14 weeks. Measures of glucose homeostasis including HbA1c and plasma insulin were measured and compared by treatment assignment. In a series of animal models, normal, streptozotocin (STZ) diabetic, and sand rats were used in the inverted sac model to determine the mechanism through which olive leaf extract affected starch digestion and absorption. In the randomized clinical trial, the subjects treated with olive leaf extract exhibited significantly lower HbA1c and fasting plasma insulin levels; however, postprandial plasma insulin levels did not differ significantly by treatment group. In the animal models, normal and STZ diabetic rats exhibited significantly reduced starch digestion and absorption after treatment with olive leaf extract compared with intestine without olive leaf treatment. Reduced digestion and absorption was observed in both the mucosal and serosal sides of the intestine. Though reduced, the decline in starch digestion and absorption did not reach statistical significance in the sand rats. Olive leaf extract is associated with improved glucose homeostasis in humans. Animal models indicate that this may be facilitated through the reduction of starch digestion and absorption. Olive leaf extract may represent an effective adjunct therapy that normalizes glucose homeostasis in individuals with diabetes.

KEY WORDS: • animal study • clinical trial • olive leaf extract

INTRODUCTION

LONG USED IN EASTERN CULTURES, complementary and alternative therapies are increasingly employed throughout the world.¹ In the west, individuals may seek out “unconventional” therapies such as herbal medicine when conventional medicine fails to cure chronic diseases and conditions.^{2–4} Olive tree (*Olea europaea* L.) leaves have been widely used in traditional remedies in European and Mediterranean countries. They have been used in the human diet as extracts, herbal teas, and powder and contain several potentially bioactive compounds that may have antioxidant, antihypertensive, antiatherogenic, anti-inflammatory, hypoglycemic, and hypocholesterolemic properties.⁵

The number of randomized trials on complementary therapies has doubled every five years, and the Cochrane library includes 100 systematic reviews of unconventional interventions^{2–4}; however, none of these studies specifically addresses the efficacy of olive tree leaves and its extract materials in metabolic disorders.^{1,6} Olive leaf tea and chewing olive leaves are folk remedies for the treatment of diabetes. The bioactivity of olive tree byproduct extracts appears to be attributable to antioxidant and phenolic components such as oleuropein, hydroxytyrosol, oleuropein aglycone, and tyrosol.⁷

Studies indicate that biologically active compounds in olive leaf products are effective in treating disorders.^{8,9} Several studies have shown that oleuropein (up to 6%–9% of dry matter in the leaves), for example, possesses a wide range of pharmacologic and health-promoting properties.¹⁰ Specifically, oleuropein has been associated with improved glucose metabolism. Oleuropein has been reported to have

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an antihyperglycemic effect in diabetic rats.^{11,12} The hypoglycemic and antioxidant effects of oleuropein have been reported in alloxan-diabetic rabbits.¹³ In streptozotocin (STZ)-induced diabetic rats, olive leaf extract decreases serum concentrations of glucose, lipids, uric acid, creatinine, and liver enzymes,¹⁴ implying that olive leaf extract is more effective than glibenclamide and may be of use as an antidiabetic agent. Rats fed a high-carbohydrate, high-fat diet with olive leaf extract for 16 weeks expressed improved or normalized cardiovascular, hepatic, and metabolic signs than rats fed an identical diet without olive leaf extract. A treatment benefit on blood pressure was not observed.¹⁵

The mechanism through which olive leaf extract attenuates hyperglycemia is still not well recognized.¹³ In the present study, we tested the effect of olive leaf extract on glucose metabolism in human subjects with diabetes. Additionally, we explore the mechanism in a series of animal models.

MATERIALS AND METHODS

Clinical trial

The present study is a randomized, double-blind, placebo-controlled, clinical trial of 14 weeks duration.

The study group ($n=79$) was recruited from a convenience sample of 93 consecutive patients treated at an outpatient clinic, 14 of whom did not meet inclusion criteria.

The eligible patients had been diagnosed with type 2 diabetes (T2DM) at least 1 year before study onset, were 18–79 years of age, had a body mass index <40 kg/m², HbA_{1c} $<10\%$, and were on oral and/or diet therapy for T2DM.

The excluded patients were on insulin therapy; had hepatic or renal dysfunction; history of malignancy; clinically important hematological disorder or severe autoimmune disease; pregnancy, planned pregnancy, or breastfeeding during the trial period; known allergy to olive leaves; drug or alcohol abuse; participation in another clinical trial within the 12 weeks before study onset; or any condition that, in the opinion of the investigator, could interfere with the study compliance or completion.

The patients were randomized to treatment with a tablet of olive leaf extract (500 mg) or matching placebo in a 1:1 ratio using a computer-generated coin toss.

Intervention

Olive leaf extract. Olive leaf extract was prepared from olive leaves as described by Zaslaver *et al.*¹⁶ Briefly, the leaves were randomly picked from the Barnea cultivar in the Jezreel Valley region of Israel and immediately freeze dried on dry ice. After being thoroughly rinsed with sterile distilled water to remove dust, insecticides, and contaminating material, the olive leaves were ground and Soxhlet extracted with hexane for 3 h followed by 80% aqueous ethanol for 6 h. The alcoholic extract was concentrated under reduced pressure at 25°C, and the powder was encapsulated.

The patients were instructed to consume a diet consistent with American Dietetic Association recommendations, and an exercise training program was prescribed. The olive leaf

extract tablet (500 mg) or matching placebo was taken orally once daily throughout the study period, before breakfast. All subjects maintained their usual diabetes therapy, which consisted of the oral hypoglycemic agents sulfonylurea and/or metformin. No patient was treated with insulin.

The study was approved by the institutional review board, and written informed consent was obtained from all the participants before entering the study.

Measures

Weight was measured with patients in light clothing, no shoes, and on a balance scale rounded up to the nearest 0.5 kg. Height was measured in stocking feet using a metal ruler at the apex of the head perpendicular to a wall mounted ruler and recorded rounded up to the nearest 0.2 cm. Blood pressure was measured in all subjects at the beginning and at the end of the study. It was measured using a cuff and analog sphygmomanometer with the patient seated comfortably for not less than 10 min before the first measurement. Blood pressure was measured thrice, and the mean of the three measures was recorded.

Venous blood samples were drawn after an overnight fast of not less than 12 h. Blood samples for the measurement of glucose, insulin, and lipid concentrations were collected in tubes with no additives and allowed to coagulate at room temperature for 30 min. The samples were centrifuged at 600 g for 10 min at 4°C and frozen at -20°C until they were analyzed. Glucose was determined by the glucose oxidase method (Beckman Glucose Analyzer). Serum total cholesterol, HDL cholesterol, and triacylglycerols were enzymatically measured using a Hitachi Cobas-Bio centrifugal analyzer (Roche) using standard enzymatic kits (Roche). Low-density lipoprotein cholesterol was calculated according to the methods described.¹⁷ Plasma insulin was determined by a double antibody RIA (CIS Bio International). Sensitivity was 2.0 $\mu\text{U/mL}$ and the intra- and interassay variability were 4.2% and 8.8%, respectively.

Animal models

Inverted sac method. An *in situ* technique was used for assessing the absorption of nutrients from the small intestine into the body. Absorption occurs on the mucosal side, while the serosal side is in contact with the blood supply. The response of both sides to starch is assessed. Male Sprague-Dawley rats (150–200 g) were anesthetized, and a section of the small intestine was removed. The intestine was cut into 8 mm pieces, and each segment was inverted. The inverted sacs were filled with Krebs–Henseleit buffer containing 1% starch solution + 1% pancreatin or sucrose in the presence and absence of olive leaf extract. The sacs were incubated for 120 min.¹⁸ The amount of glucose absorbed was determined on the mucosal and serosal sides of the inverted sac using an Auto glucose analyzer.

Oral carbohydrate tests. Starch (600 mg starch/100 g body wt) was orally intubated into fasting healthy or diabetic rats. Diabetes was induced by an intramuscular injection of 40 mg streptozotocin/kg body wt (Sigma Chemical)

dissolved in 0.1 mM citric acid pH-4.5. Blood samples were taken from the rat tail tips of rats after an overnight fast and at set time intervals. Glucose levels were determined using a hand-held Elite glucometer (Bayer). Rats were then intubated with 0.6 g starch/100 g body weight with or without the addition of 0.1 g/100 g body weight of the olive leaf extract.¹⁸ The hypoglycemic effect of olive leaf extract was also evaluated in sand rats (*Psammomys obesus*). *P. obesus* of both sexes (age 2.5–3.5 months) from the diabetes-prone line of the Hebrew University colonies were obtained from Harlan Laboratories Ltd. They were kept on a regular artificial light cycle (12-h light, 12-h dark cycle) and used at 10–16 weeks of age as previously described (19). After weaning at 3 weeks, the diabetes-prone *P. obesus* animals were initially fed a nondiabetogenic low-energy diet containing 2.38 kcal/g (Koffolk) *ad libitum* and exhibited normoglycemia. In their natural habitat, sand rats feed exclusively on low-calorie, high-salt succulents and demonstrate normal blood glucose levels. When we feed these animals a regular chow diet with a higher caloric density, they develop obesity and a diabetes including hyperglycemia and hyperinsulinemia. Within a matter of weeks, these animals develop late complications of diabetes, including cataracts.

The proposed hypoglycemic effect of olive leaf extract was determined in sand rats using the standard intubation technique just described.

Statistical analysis

Data were analyzed using SPSS v10.0 (SPSS, Inc.). Continuous data were described as mean \pm standard deviation and compared by treatment assignment using the t-test for independent samples. Associations between continuous variables were described by calculating the Pearson's correlation coefficients. Nominal variables such as sex and treatment assignment are described using frequency counts and compared by treatment assignment using the chi-square test (exact as appropriate). Time-dependent variables were compared using General Linear Model repeated measures analysis followed *post hoc* by Bonferroni's test. All tests are two-sided and considered significant at $P < 0.05$.

TABLE 1. CLINICAL CHARACTERISTICS OF STUDY SUBJECTS

	Olive leaves n=41	Placebo n=38	P-value
Male	27 (66%)	24 (63%)	0.8
Female	14 (34%)	14 (37%)	
Age > 55 years	21 (51%)	20 (53%)	0.9
Age < 55 years	20 (49%)	18 (47%)	
Duration of diabetes			
> 10 years	15 (36%)	16 (42%)	0.6
< 10 years	26 (64%)	22 (58%)	
BMI > 25 kg/m ²	31 (76%)	29 (76%)	0.9
BMI < 25 kg/m ²	10 (24%)	9 (24%)	
Diet only	4 (10%)	4 (11%)	0.9
OHD + diet	37 (90%)	34 (89%)	

BMI, body mass index; OHD, oral hyperglycemic drugs.

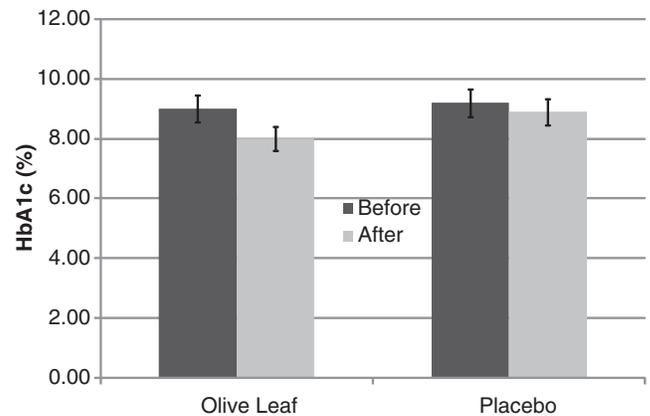


FIG. 1. HbA1c by treatment assignment. Between group, post-treatment comparison, $P = .037$.

RESULTS

Clinical trial

The participants ($n=79$, 28 women, mean age 61 ± 8 years) are described by treatment assignment in Table 1. All the patients were adults with type 2 diabetes. The patients were stable for at least 3 months, meaning that during the last 3 months before study enrolment, they had received constant therapy with no changes in dose or medication before study initiation.

As can be seen in Figure 1, subjects treated with olive leaf extract for 14 weeks had significantly lower HbA1c levels than those treated with placebo ($8.0\% \pm 1.5\%$ vs. $8.9\% \pm 2.25\%$, $P=0.037$). Compared with placebo, olive leaf extract treatment was also associated with a significant decrease in fasting insulin levels: 11.3 ± 4.5 vs. 13.7 ± 4.1 , $P=0.01$, see Fig. 2. Fasting and postprandial insulin and glucose levels did not significantly differ between groups (Fig. 3).

Animal models

Inverted sac model. Olive leaf extract inhibited both digestion and absorption in a concentration-dependent manner. This inhibition was seen in both the serosal and

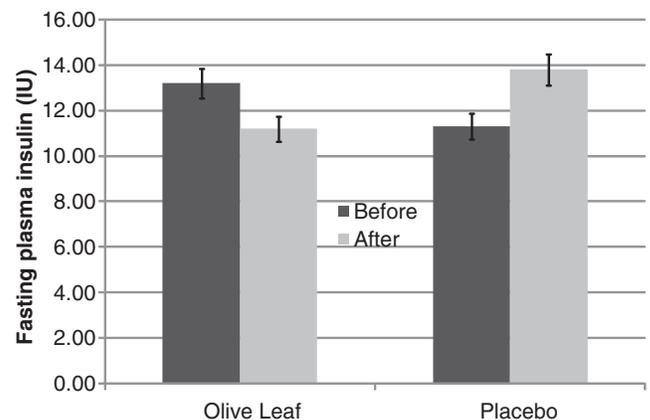


FIG. 2. Fasting plasma insulin by treatment assignment. Between group, post-treatment comparison, $P = .01$.

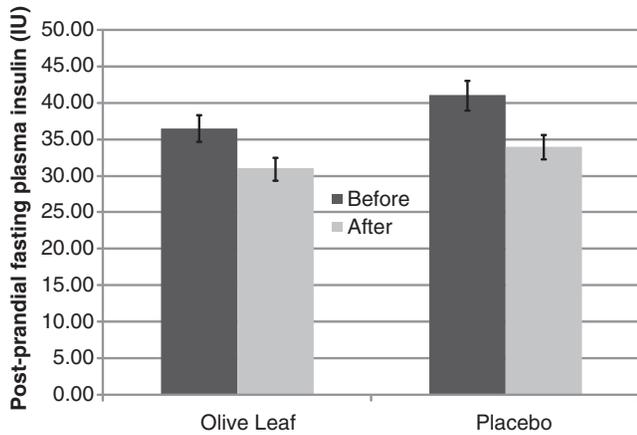


FIG. 3. Postprandial plasma insulin by treatment assignment. Between group, post-treatment comparison, $P = .34$ (not significant).

mucosal sides of the intestine. A distinct dose response was observed at concentrations of 10, 20, and 40 mg. At 40 mg olive leaf extract, 54% and 80% percent inhibition was observed in mucosal and serosal sides of the intestine, respectively. A similar inhibition was observed when sucrose was used (data not shown).

In vivo studies. Olive leaf extract was added to starch and given by intubation to healthy rats. Significantly lower blood glucose levels at 30, 60, and 120 min after the intubation (Fig. 4) were observed.

When repeated in STZ-diabetic rats, the addition of olive leaf extract to the starch administered by intubation resulted in significantly lower blood glucose tolerance curves (Fig. 5).

Olive leaf extract was added to starch and administered by intubation to sand rats, resulting in a trend toward normalized glycemic response; however, the response was not as strong as that observed in STZ-diabetic rats (Fig. 6).

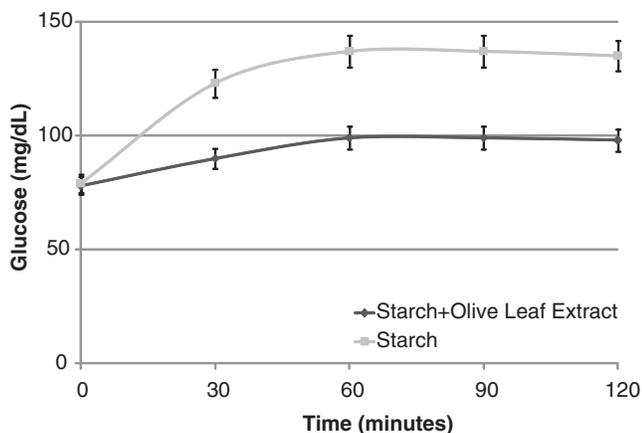


FIG. 4. In normal rats, glucose response at 0, 30, 60, 90, and 120 min in normal rats after starch tolerance test versus without olive leaf extract.

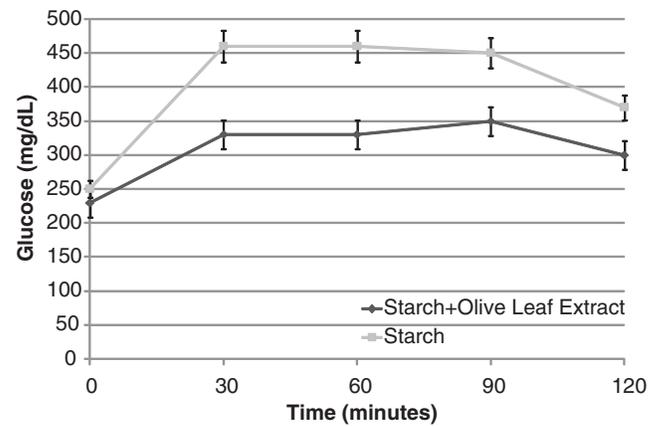


FIG. 5. In streptozotocin rats, glucose response at 0, 30, 60, 90, and 120 min in normal rats after starch tolerance test versus without olive leaf extract.

DISCUSSION

Maintaining glycemic control by treating well-defined HbA1c targets is endorsed by current guidelines.²⁰ In the present study, treatment with olive leaf extract from plants grown in Israel was associated with a significant reduction in HbA1C values. These findings are consistent with a previous report in which four plants used in traditional Arab medicine, with olive leaves among them, were effective in controlling blood glucose in patients with diabetes.^{21,22} Indeed, olive tree leaves have been long recognized as a traditional antidiabetic and antihypertensive herbal intervention and have been used to treat these conditions as well as infectious diseases in Europe.¹¹

Olive leaf-derived polyphenols have been identified as therapeutic agents delaying the progression of advanced glycation end products-mediated inflammatory diseases such as diabetes.²³ Additionally, oleuropein and tannins in olive leaves are reported to act as α -glucosidase inhibitors, reducing the absorption of carbohydrates in the gut.¹² Olive

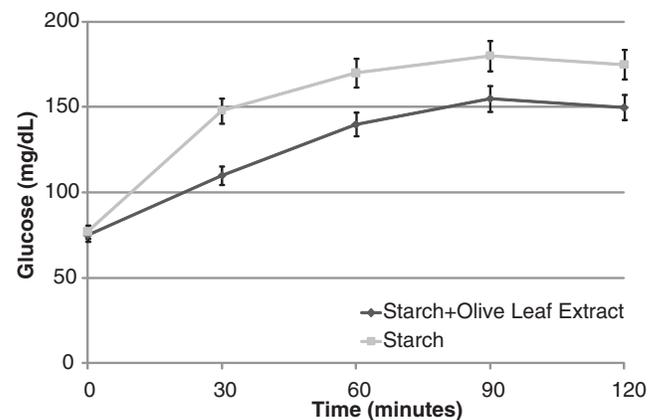


FIG. 6. In sand rats, glucose response at 0, 30, 60, 90, and 120 min in normal rats after starch tolerance test versus without olive leaf extract.

leaf extract was shown to have an inhibitory effect on the postprandial blood increase in glucose in diabetic rats.²⁴ In humans treated with olive leaf extract, blood glucose was significantly decreased after cooked rice loading compared with untreated controls.²⁴

There have been two possible mechanisms suggested to explain the hypoglycemic effect of the olive leaf extract oleuropein: (1) improved glucose-induced insulin release, and (2) increased peripheral uptake of glucose.⁵ The oleuropein in olive leaves has been shown to accelerate the cellular uptake of glucose, leading to reduced plasma glucose.¹¹ Since oleuropein is a glycoside, it could potentially access a glucose transporter such as a sodium-dependent glucose transporter (SGLT1) found in the epithelial cells of the small intestine, thereby permitting its entry into the cells.²⁵ Experimental data point to an interaction between dietary flavonol monoglucosides with the intestinal SGLT1 and inhibited Na-independent glucose uptake.^{26,27}

Another way in which olive leaf extract might exert its hypoglycemic effect is through the inhibition of pancreatic amylase activity.²⁴ Animal studies have shown that olive leaf extract consistently induced a hypoglycemic effect when added to starch intubations in both healthy and diabetic rats,¹² as confirmed by our animal experiments. Olive leaf extract may either inhibit starch digestion and glucose uptake or stimulate hepatic glycogen synthesis, culminating in reduced hyperglycemia. For example, in our *in vitro* inverted sac experiments, serosal free glucose levels were decreased, and overall glucose absorption was significantly diminished by the olive leaf extract, suggesting that starch digestion by intestinal enzymes and the inhibition of disaccharases at the level of the intestinal mucosa may underlie the hypoglycemic effect of the olive leaf extract.

In addition to its hypoglycemic effect and antioxidant properties, olive leaf extract has been shown to exhibit a range of indirect actions that may be beneficial to health, including the inhibition of inflammatory enzymes,^{28,29} platelet aggregation,³⁰ and the metabolic activation of procarcinogens.³¹ We have previously shown that lung cells exposed to polyphenol compounds from olive leaf extract exhibited a dramatic decrease in NO levels, suggesting that this may be beneficial for use in the treatment of lung inflammations.¹⁶

The present study was not designed to identify the active compound or compounds in olive leaf extract responsible for treatment benefit. The discovery of bioactive components would certainly facilitate care of the individual with diabetes and should most definitely be the subject of future research.

In vitro and *ex vivo* experiments in animal models imply the inhibition of starch absorption as a possible mechanism through which olive leaf extract reduces blood glucose-tolerance curves. However, animals were administered much higher doses of olive leaf extract than the human subjects participating in the clinical trial. Generalization of the proposed mechanism of action to humans may be, thus, limited. On the other hand, the reduction of HbA1c in humans receiving only 500 mg/day

doses of olive leaf extract suggests that clinical efficacy requires a relatively low dosage. Furthermore, the high dose delivered to animals was not associated with adverse events, indicating that lower doses of olive leaf extract are safe for human use.

In conclusion, the results of the present study suggest that treatment with olive leaf extract is associated with a beneficial hypoglycemic effect in patients with diabetes. The use of this intervention should be further investigated in a clinical trial large enough to evaluate extract-drug interactions and possible subgroup analyses.

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