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Original article

Efficacy of the traditional use of Olive Leaves decoction as Anti-diabetic Agent in Geriatrics.

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Abstract :

Background: Several studies focused the light on the antidiabetic effect of Olive Leaves extract especially on the geriatrics. **Aim** : The current study was conducted to evaluate the anti-diabetic effect of olive leaves decoction on elder patients. **Methods**: The elderly subjects were randomized into 4 groups: Group I: Normal control group , Group II (gp2): hypertensive group, Group III: diabetic group & Group IV : diabetic hypertensive group. Each group included 20 subjects who was taken a specific dose of Olive leaves tea for 8 weeks treatment twice daily with a meal. Blood glucose level was measured at baseline screening and after each week until the end of the study. **Results**: During the study period, blood sugar and glycosylated hemoglobin changed significantly. The mean fasting blood glucose (F. BL. G.) difference reached up to 11.35 mg/dL for group I ,up to 10.55 mg/dL for Gp. II, up to 96.70 mg/dL for the Gp. III and up to 78.50 mg/dL for Gp.IV . After 8 weeks of treatment, the mean blood sugar had significantly decreased in group II and group IV ($p < 0.001$; $n = 20$). **Conclusion**: the results of this study suggest that olive leaves extract is beneficial to the diabetic patients to control plasma glucose level.

Keywords: Olive leaves, geriatrics, diabetic patients, glycemic control

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Introduction:

In eastern countries and around the world, complementary and alternative therapies are widely used (1). When conventional therapy fails to cure chronic diseases symptoms, people prefer to use unconventional therapies such as herbal medicine (2-4). Medicinal plants are a significant source of economic value all over the world, where nature has provided us with a vast botanical wealth and a wide range of plant species (6,7). The medicinal value of plants is found in chemical substances that have a specific

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physiological action on the human body, the most important of which are alkaloids, flavonoids, tannins, terpenoids, and phenolics (7,8). They may be act as antioxidants, anti-inflammatory, hypocholesterolemic, antihypertensive, and hypoglycemic agents (5).

Hyperglycemia in type 2 diabetes mellitus (T2DM) is regarded as a major clinical risk factor for a variety of disorders, including cardiovascular and renal disease, retinopathy, and poor blood flow (9-10). Disturbances in insulin secretion, sensitivity to tissue insulin actions, or both are thought to be the most common causes of T2DM pathophysiology, diseases primarily caused by tissue insulin resistance that progresses to complete loss of secretory activity of pancreatic -cells (11). As a result, there is a great urgency to find better treatment and novel prevention strategies for these global health problems. However, due to the side effects associated with insulin and oral hypoglycemic agents, there is an increasing demand by patients to use natural products (12,13).

Among the plants used to treat diabetes, the olive tree (Olea europeae) is the most important. Olive leaves (Olea europea L.) have traditionally been used as natural remedies in European and Mediterranean countries (14). They have been used in the human diet as extracts, herbal teas, and powders, and contain a number of potentially bioactive compounds. (5,14). The antioxidant and phenolic components oleuropein, hydroxytyrosol, oleuropein aglycone, and tyrosol appear to be responsible for the bioactivity of olive tree byproduct extracts (15-17).

Several studies have shown that oleuropein (in leaves) has a wide range of pharmacological and health-promoting properties, including lowering the risk of coronary heart disease (18, 19), anti-inflammatory (20-24), antitumor, anti-proliferative (25, 26), antidiabetic [27-30], antibacterial and antifungal properties (31-34). Many of these properties have been attributed to polyphenols' antioxidant properties (35), as well as oleuropein, which has been linked to improved glucose metabolism and normalised cardiovascular signs. Then Olive leaf extract may be a promising alternative to control diabetes and its cardiovascular complications.

So, the aim of the current study is to evaluate the effect of olive leaves' extract on blood glucose level in diabetic and hypertensive geriatrics.

Subjects and Methods:

Source of Olive leaves: During the pruning process, the ripe olive leaves (Olea europaea) Koronkii variety were gathered from a farm in ‘Beni- Suef’ governorate.

Olive leaves tea preparation: Each dose of green olive leaves, that were collected, dried and stored until use, were cut into small pieces and packed in a bag contains 10

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gram dried olive leaves. To be ready for use each tea bag was boiled for 5 to 10 minutes in drinking water.

Experimental design: This was a prospective, observational study. All subjects were selected from Beni-Suef University Hospital suffering from hypertensions with age above 50 years old and classified into 4 groups: Group I(gp1): Normal control group consists of healthy volunteers. Group II (gp2): hypertensive group included 20 hypertensive elderly patients (n=20) divided into (male and female) subjects. Group III: diabetic group includes diabetics elderly patients divided into male and female. Group IV : included diabetic hypertensive elderly subjects patients (n=20) divided into (male and female) . In the current study, each group was taken a specific dose of Olive leaves tea for 8 weeks treatment. In the experiment, the four groups , the subjects were given a specific dose of olive leaves tea twice daily with a meal, one in the morning and the other in the evening, and advice on how diabetes may be ameliorated by an adequate lifestyle. Blood glucose level was measured at baseline screening and after each week until the end of the study.

Body weight, body mass index, abdomen circumference, kidney function tests and liver function tests was also measured at baseline screening, and after 8 weeks of treatment. Adverse effects were observed and if present, recorded during the study.

Exclusion criteria:

- Elderly (defined as older than 75).
- Diabetic patients with diabetic complications as ketoacidosis, glaucoma or diabetic foot.
- Patients with chronic organ failure

All the patients gave written informed consent prior to the inclusion into the study.

Study population. The study population consisted of 40 subjects aged between >50 and less than 75 years suffering from diabetes. Diabetic patients (the onset of diabetes was after 40 years of age) and Fasting Plasma glucose level FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h according to American Diabetic Association (36).Hypertensive patients' stage II (patients a systolic blood pressure (SBP) ≥ 140 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg according to new ACC and American Heart Association (AHA) guidelines 2017. All the patients gave written informed consent prior to the inclusion into the study. Ethical approval was granted by the Research Ethical Committee at Faculty of Medicine, Beni-Suef University, (FWA#: FWA00015574). The consent forms were obtained from all groups participants.

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Results:

During the study period, blood sugar and glycosylated hemoglobin changed significantly. The mean fasting blood glucose (F. BL. G.) difference reached up to 11.35 mg/dL for the control healthy group (Gp. 1), up to 10.55 mg/dL for the hypertensive group (Gp. 2), up to 96.70 mg/dL for the diabetic group (Gp. 3) and up to 78.50 mg/dL for the hypertensive diabetic patients (Gp. 4) after 8 weeks of treatment (Fig.1A).

Concurrently, the average post prandial blood glucose (PP. BL. G.) difference in these groups also reached a maximum, amounting to 14.65 mg/dL for the control healthy group (Gp. 1), up to 8.25 mg/dL for the hypertensive group (Gp. 2), up to 120.05 mg/dL for the diabetic group (Gp. 3) and up to 90.75 mg/dL for the group containing hypertensive and diabetic patients (Gp. 4) after 8 weeks of treatment (Fig.2 B).

The average glycosylated hemoglobin (HbA1c.) difference in these groups also reached a maximum, amounting to 0.27 for the control healthy group (Gp. 1), up to 0.34 for the hypertensive group (Gp. 2), up to 2.04 for the diabetic group (Gp. 3) and up to 2.00 for the group containing hypertensive and diabetic patients (Gp. 4) after 8 weeks of treatment (Fig.1 C).

After 8 weeks of treatment, the mean blood sugar had decreased from baseline in the control healthy group (F. BL. G.: 91.25 ± 9.4 vs. 102.60 ± 8.8, $p < 0.001$; PP. BL. G.: 113.55 ± 7.4 vs. 128.20 ± 6.6, $p < 0.001$; HbA1c 4.98 ± 0.42 vs. 5.26 ± 0.65, $p < 0.001$; $n = 20$), also significantly decreased in the hypertensive group (F. BL. G.: 89.60 ± 6.7 vs. 100.15 ± 11.2, $p < 0.001$; PP. BL. G.: 115.65 ± 3.9 vs. 123.90 ± 8.5, $p < 0.001$; HbA1c 4.99 ± 0.29 vs. 5.33 ± 0.56, $p < 0.001$; $n = 20$), decreased in the diabetic group (F. BL. G.: 106.00 ± 8.7 vs. 202.70 ± 42.9, $p < 0.001$; PP. BL. G.: 131.45 ± 6.9 vs. 251.50 ± 61.5, $p < .001$; HbA1c 7.71 ± 0.7 vs. 9.76 ± 1.4, $p < 0.001$; $n = 20$) and significantly decreased in the group containing hypertensive and diabetic patients (F. BL. G.: 105.05 ± 4.6 vs. 183.55 ± 42.3, $p < 0.001$; PP. BL. G.: 130.70 ± 7 vs. 221.45 ± 50.8, $p < 0.001$; HbA1c 7.53 ± 1.2 vs. 9.53 ± 1.3, $p < 0.001$; $n = 20$). So there is a significant difference in the blood glucose levels measurement before and after treatment for the hypertensive group (table 1).

Table 1. Mean ± SD of blood sugar (mg/dl) during the study

Groups	Measuring Time	F. Bl. G.	Pp. Bl. G.	HbA1c
Gp1 Normal	At week 0 (W0)	102.60 ± 8.8	128.20 ± 6.6	5.26 ± 0.65
	At week 8 (W 8)	91.25 ± 9.4	113.55 ± 7.4	4.98 ± 0.42
Gp2 Diabetic	At week 0 (W0)	202.70 ± 42.9	251.50 ± 61.5	9.76 ± 1.4
	At week 8 (W 8)	106.00 ± 8.7	131.45 ± 6.9	7.71 ± 0.7
Gp3 Hyper. & Diab.	At week 0 (W0)	183.55 ± 42.3	221.45 ± 50.8	9.53 ± 1.3
	At week 8 (W 8)	105.05 ± 4.6	130.70 ± 7	7.53 ± 1.2

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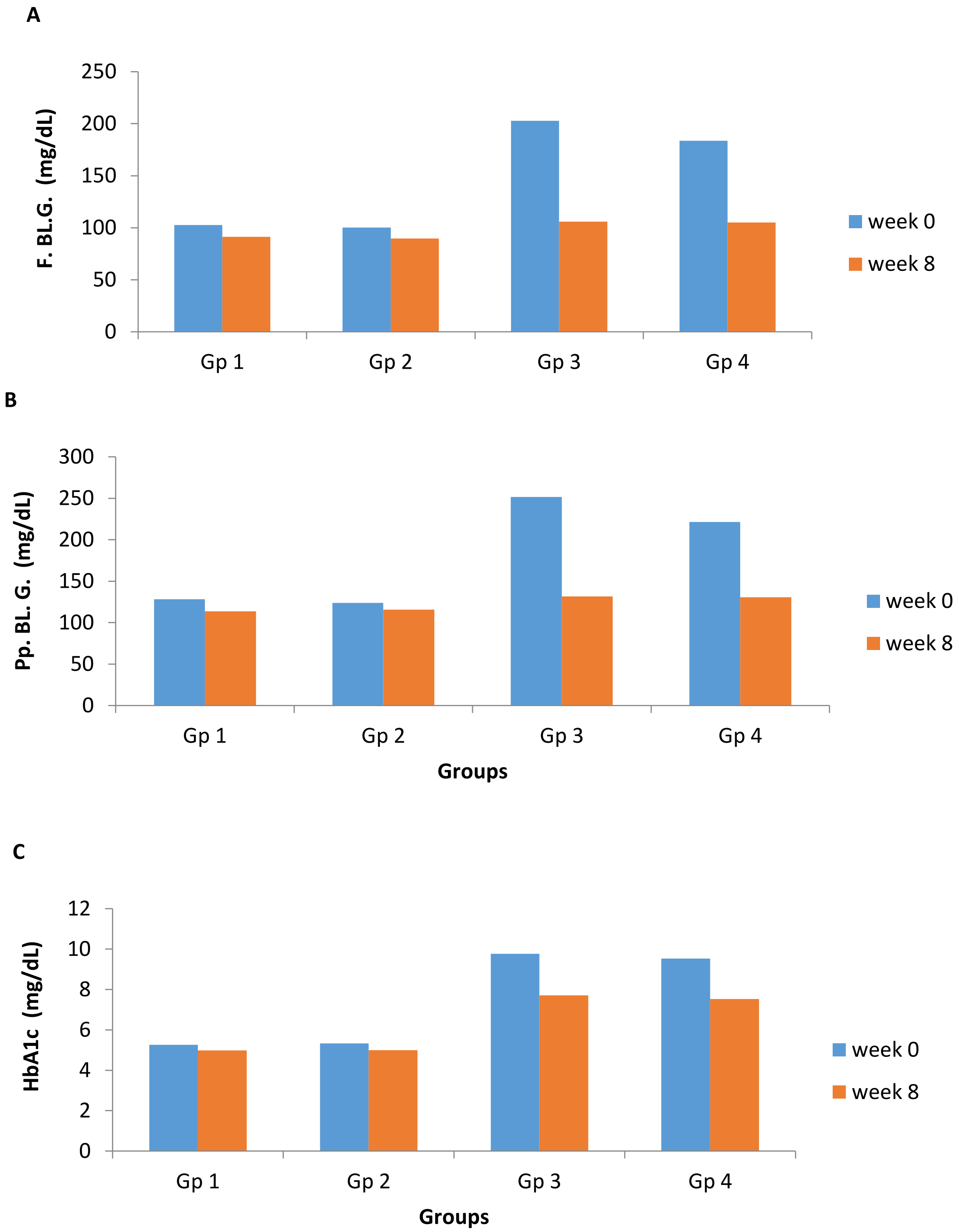

(Fig. 1): The change in blood sugar during the study
A: The change in fasting blood glucose.
B: The change in post prandial blood glucose.
C: The change in HbA1c.

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Discussion:

Our study is in agreement with a randomized placebo-controlled trial that had previously investigated the effects of OLE on glucose metabolism in subjects with type 2 diabetes, finding an improvement in glycated haemoglobin (HbA1c) after 14 weeks of supplementation (37)..

However, that study did not measure or discuss possible variations in diet or levels of physical activity among participants (37), so that the independent effect of OLE cannot be determined.

Hence, our study is aiming to show the independent effects of OLE on glucose homeostasis in humans, corroborating previous findings in vitro and in animal models (38).

Our results showed that OLE had significant hypoglycemic, hypolipidemic effects. In agreement with the study results, (Jemai, El Feki *et al*. 2009) reveled that, the administration of oleuropein- and hydroxytyrosol-rich extracts significantly decreased the serum glucose and cholesterols (39).

The eventual mechanism responsible of the hypoglycemic activity of OLE may result from a potentiation of glucose induced insulin release or increased peripheral uptake of glucose (40).

Infusion and/or decoction of olive leaves have long been used in the treatment of diabetes(41) . This study represent the anti-diabetic effect of oleuropein, main phenolic component of olive leaf, in agreement with other studies that shown in cell culture or animal models and limited number of studies conducted on humans (42-44).

Mechanisms correlated with the effects on glycemia are many. The first mechanism suggested on the anti-diabetic effect of olive leaf and extract is that they cause hypoglycemia. In a study with diabetic rabbits, it was found that ethanol extract of olive leaf decreased blood glucose (42).. Potential mechanism in this result is the increase in peripheral intake of glucose and insulin secretion induced by glucose (42,43).

It was reported that olive leaf extract may increase glucagon-like peptide-1 secretion in in vivo and in vitro environment and thus can be used for nutrition treatment in Type 2 diabetes (44).

Another study examined the effect of 500 mg olive leaf extract on both diabetic patients and streptozotocin-induced diabetic rats for 1 week (45).

Results of the study showed that diabetic patients had lower HbA1c and fasting plasma insulin level, while there was no difference in postprandial plasma insulin

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level. In addition, there was a decrease in digestion and absorption of starch in intestines of animal model.

According to these results, it is recommended that olive leaf extract can be used as an adjunct treatment for the normalization of glucose homeostasis in diabetic patients (45).In another study, Wistar male rats were given olive leaf powder (6.25%) with standard diet orally for 6 weeks, and it was found at the end of this period that serum glucose level decreased significantly (46)..

A systematic review and meta-analysis examined 8 clinical studies including 162 rats, and it was found that olive leaf extract increased insulin level significantly (4.83 μIU/mL) and decreased blood glucose level (4.21 mg/dL) in diabetic rats (47).

Hydrolysis products of olive leaf polyphenols can also affect glycemia separately. It was reported that although there are limited number of studies about the effect of hydroxytyrosol, which is one of the most important hydrolysis products, on carbohydrate metabolism, it may have positive effects.

Studies that conducted hydroxytyrosol application (50 mg/kg/day × 17 weeks, 20 mg/kg × 8 weeks, and 0.04% × 8 weeks) decreased plasma glucose concentrations and treated insulin resistance .In another study, application of hydroxytyrosol (10 g/kg/day) for 5 weeks decreased homeostatic model assessment-insulin resistance (48).

It is also suggested that olive leaf and its extracts may prevent some complications related to Type 2 diabetes. A study reported that methanolic extract of olive leaf inhibited protein glycation and decreased advanced glycation end products formation (49)..

Another study demonstrated that olive leaf extract was able to cure glucose metabolism in liver and kidneys of rats by minimizing oxidative stress in rats (50).

Similarly, in a study conducted on rats, it was reported that 8 and 16 mg/kg doses of olive leaf extract rich in oleuropein and hydroxytyrosol decreased serum glucose level, cured antioxidant perturbations, and may, by this means, restrain oxidative stress correlated with diabetes pathology and its complications (39).

It was found in a study conducted with overweight men that supplementation of olive leaf (51.1 mg oleuropein, 9.7 mg hydroxytyrosol per day) in capsule form for 12 weeks increased fasting interleukin (IL)-6 and insulin-like growth factor-binding protein-1 and -2 concentrations. However, it did not change IL-8 and tumor necrosis factor-α levels. Moreover, 12-week supplementation increased insulin sensitivity by 15% and pancreatic β-cell capacity by 28% (37).

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The study examining the effect of olive leaf and fruit extracts and oleuropein on β-cell toxicity induced by cytokine concluded that both extracts and oleuropein significantly decreased reactive oxygen species (ROS) induced by cytokine, enhanced abnormal antioxidant defense, and provided redox homeostasis (51).

In addition to this, in a study examining the effect of olive leaf extract on neuropathic pain in streptozotocin-induced diabetic rats and glucose-induced cells, it was found that 200, 400, and 600 µg/mL of extract decreased cell damage (52).

Application of the extract at the doses of 300 and 500 mg/kg/day cured hyperalgesia, inhibited Caspase-3 activation, and decreased Bax (an apoptosis promoter)/Bcl2 (an apoptosis inhibitory) ratio.

These results showed that the extract inhibited neural damage induced by high glucose level/diabetes, suppressed thermal hyperalgesia, decreased neuronal apoptosis, and cured diabetic neuropathic pain (52).

It was also found that oleanolic acid, another component of olive leaf, also increased Na(+) excretion rate without affecting K(+) and Cl(–) rates, decreased plasma creatinine concentration, and enhanced renal profile in streptozotocin-induced diabetic rats (53).

These results imply that olive leaf extract may have a potential effect in the treatment of Type 2 diabetes and prevention of its complications.

Conclusion:

In conclusion, the results of this study suggest that olive leaves extract is beneficial to the diabetic patients to control plasma glucose level.

More clinical trials have to be investigated on humans, and future studies trying powdered or dried leaves

More clinical trials on humans are required as most studies to date were involving animals. Powdered or dried leaves should also be of interest to future studies.

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