Olive Leaf (Olea europaea L. folium): Potential Effects on Glycemia and Lipidemia

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Abstract
Background: Olive tree (Olea europaea, Oleaceae) leaves have been widely used in traditional herbal medicine to prevent and treat various diseases especially in Mediterranean countries. They contain several potentially bioactive compounds that may have hypoglycemic and hypolipidemic properties. Summary: The literature has recently been attempting to define the relationship between olive leaf (Olea europaea L. folium) polyphenols and a number of health problems. Oleuropein, the basic phenolic compound of olive leaf and its extract, is responsible for the characteristic bitter taste and unique aroma of olive fruits. Furthermore, it is shown that oleuropein and its hydrolyzed products have many beneficial effects on human health because of its antioxidant characters. A number of studies report that olive leaf has potentially positive effects on the parameters related to diabetes and cardiovascular diseases by various mechanisms. Besides, toxicity studies suggest that olive leaf is generally safe even at high doses. Key messages: Although current results obtained until today seem promising, the studies in this subject are usually on cell culture and animal trials. Moreover, mostly the extract forms of olive leaves are used in the studies. More randomized controlled human clinical trials with extensive toxicity studies are needed to evaluate potential health effects and safety.

Introduction
Olive tree (Olea europaea, Oleaceae) leaves have an extensive use in traditional herbal medicine with the aim of preventing and treating several diseases particularly in Mediterranean region. The related literature aims to identify the relationship between olive cultivars and diabetes, cardiovascular disease, cancer, and a number of health problems [1, 2].

Nowadays, there has been a considerable interest in natural antioxidants from plant materials to replace synthetic ones [3]. Among natural antioxidants, the olive tree has been widely accepted as one of the species with the highest antioxidant activity via its oil, fruits, and leaves [4]. It is well known that the activity of the olive tree by product extracts in medicine and food industry is due to the presence of some important antioxidant and phenolic components to prevent oxidative damage [5]. The olive tree has long been recognized as having antioxidant molecules, such as oleuropein, hydroxytyrosol, and tyrosol; caffeic acid; and ligstroside associated with the prevention of certain diseases [6, 7].
The main active component in olive leaf and its extract is oleuropein, a natural product of the secoiridoid group. Several studies have shown that oleuropein possesses a wide range of pharmacologic and health-promoting properties including antiarrhythmic, spasmylic, immune-stimulant, cardioprotective, hypotensive, anti-inflammatory, antioxidant, and anti-thrombic effects [2, 8]. Many of these properties have been described as resulting from the antioxidant characters of oleuropein [2]. Previously, oleuropein was reported to have an antihyperglycemic, lipid-regulating, and cardioprotective effects especially in cell culture and animal models [9–13]. Furthermore, with regard to the antioxidant properties of oleuropein, its mechanism in attenuating hyperglycemia and cardiovascular risk parameters is still not well recognized. In this review, the effects of olive leaf and its extract on glycemia, lipidemia, and cardiovascular parameters were examined.

**Methods**

Literature in the PubMed, ScienceDirect, Google Scholar, Cochrane Library, SciELO, and MEDLINE databases for publications in English with the descriptors “Olea europaea”, “olive leaves”, “olive leaf”, “olive leaves extracts”, “olive leaf extracts”, “phenolic compounds”, “polyphenols”, “oleuropein”, “hydroxyl-tyrosol”, “chemical composition”, “health”, “glycemia”, “diabetes”, “hypo-lipidemic effects”, “cardiovascular effects”, “pharmacological effects”, “safety”, and “toxicology” was searched. Publications in languages other than English (which at least have an abstract in English or other languages available) were also included in the review.

**Olive Leaf and its Chemical Structure**

Literature on olive polyphenols principally has focused on olive oil consumption as a main dietary source. However, phenolic compounds are found more in olive leaves. For this reason, olive leaf (Olea europaea L. folium) is used in many fields including pharmacetics, cosmetics, and food industry [14].

Olive tree includes secoiridoids, carbohydrates, sugar alcohols, and terpenoids as biochemicals [15]. Basic components in olive leaf are secoiridoids such as oleuropein, ligrostoside, I methyloleuropine, and oleoside; flavonoids such as apigenin, kaempferol, luteolin, and chrysoeriol; and phenolic compounds such as caffeic acid, tyrosol, and hydroxytyrosol [7, 16, 17].

Secoiridoids, chemical components of leaf, are glycosidically bound and produced by secondary metabolisms of terpenes as the pioneers of various indole alkaloids. Secoiridoids are generally derived from an oleoside type of glucoside oleosides that are characterized with the combination of elenolic acid and glucoside residues [18].

Oleuropein (Oleuropein 1), one of the secoiridoids, is a basic phenolic compound found in olive leaf and the reason of characteristic bitter taste of olive cultivars [18]. Oleuropein is an ester of 2-(3,4-dihydroxyphenyl) ethanol (hydroxytyrosol) and has the oleosidic skeleton that is common to the secoiridoid glucosides of Oleaceae, mainly in its aglycone form, which makes the sugar moiety insoluble in oil [18, 19]. Upon hydrolysis, oleuropein can produce elenolic acid, hydroxytyrosol, tyrosol, and glucose [2]. Oleuropein and hydrolysis products found in olive leaf have important biological characteristics. It is considered that hydroxytyrosol is particularly correlated with health benefits of olive products [20].

Oleuropein content (6–14%) is very high in dry matter of olive leaves [8]. Oleuropein amount in olive leaves may vary depending on harvest season and rise up to 17–23% [21]. However, this complex phenol is found less in olive oil types except extra virgin olive oil, while it is highly available in olive trees and leaves [16, 18]. Table olive production processes increase the transformation of oleuropeins into hydrolysis products such as hydroxytyrosol and tyrosol, and as a result, decrease non-hydrolyzed oleuropein forms [22].

Mannitol, one of the other components of olive leaf, consists of 3% of dry weight of olive leaf and is used as an additive in food and drug industry due to its sweetness ratio and low energy content. The main triterpene from the olive leaf is oleanolic acid, and it consists of 3% of olive leaf’s dry weight and has very important pharmacological features [6].

**Olive Leaf Extract**

There are olive leaf extracts dissolved in dry and various organic solvents. Extracts are produced from olive leaves [16]. Ethanolic extract of olive leaves contains high amount (approximately 20%) of oleuropein. The oleuropein amount in extracts sold in liquid, capsule, or tablet form differs depending on the brand. This amount varies according to extraction method and solvent types. In a study, high amount of oleuropein (37.8 mg/g dried leaf) was extracted through Soxhlet method using methanol, and the value was found to be 14.2 mg/g dried leaf after CO2 modification supercritical fluid extraction method [23]. The study examined the effect of extraction solvent (type, composition, pH, and temperature) and method (maceration and Soxhlet) on oleuropein content of olive leaf extracts. According to study results, extraction with Soxhlet method produced more oleuropein compared to maceration carried out with 80% ethanol and 20% acetonitrile at high temperatures and low pH values (max. = 3) [24]. It is important to note that all olive leaf extracts must comply with Pharmacopoeia monographs and local/national legislations independently of extraction method and solvent type.

**Metabolism and Bioavailability of Olive Leaf and its Extracts Components**

Knowledge on the absorption and disposition of olive oil or olive leaf phenolic components were quite limited [25]. However, it has been reported recently that olive leaf extracts increase in plasma oleuropein and hydroxytyrosol [14]. Studies on the bioavailability of olive leaf extracts show that bioavailability changes individually and depends on gender and dose [14, 25]. In a study, 9 volunteers, including 5 men, were given oleuropein and hydroxytyrosol olive leaf extracts in capsule or liquid form in order to examine their bioavailability amount and mechanisms [14]. Conjugated metabolites of hydroxytyrosol were found as primary metabolites in plasma and urine after extract intake. All conjugated hydroxytyrosol metabolites were found in urine within 8 h after oleuropein. Plasma oleuropein peak concentration was higher after liquid extract intake compared to capsule extract. Moreover, there was a gender effect on the bioavailability of phenolic...
comounds, with males showing greater plasma area under the curve for conjugated hydroxytyrosol [14]. Another study noted that tyrosol and hydroxytyrosol, phenolic compounds of olive oil, are absorbed in humans dose-dependently and excreted as glucuronide conjugates. Additionally, it was reported that increase in the dose of phenolic compounds also increased glucuronide conjugation rate [25].

**Effects of Olive Leaf on Health**

**Glycemia**

Infusion and/or decoction of olive leaves have long been used in the treatment of diabetes [26]. Antidiabetic effect of oleuropein, main phenolic component of olive leaf, is shown in cell culture or animal models and limited number of studies conducted on humans [9–11]. Mechanisms correlated with the effects on glycemia and diabetes are shown in Figure 1.

The first mechanism suggested on the antidiabetic 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 [10]. Potential mechanism in this result is the increase in peripheral intake of glucose and insulin secretion induced by glucose [9, 10]. It was reported that olive leaf extract may increase glucagon-like peptide-1 secretion in vivo and in vitro environment and thus can be used for nutrition treatment in Type 2 diabetes [11]. Another study examined the effect of 500 mg olive leaf extract on both diabetic patients and streptozotocin-induced diabetic rats for 1 week [27]. 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 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 [27]. 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 [28]. 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 [29].

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 [30–32]. In another study, application of hydroxytyrosol (10 mg/kg/day) for 5 weeks decreased homeostatic model assessment-insulin resistance [33].

The effect of olive leaf and its extracts on body weight, which is one of the important parameters of glycemia and diabetes, is controversial. However, it is considered that limited number of studies share a common result that olive leaf extracts do not affect body weight [12, 34, 35]. A systematic review and meta-analysis study reported that there was not a significant change in body weight of rats after extract application [29]. Only one clinical study indicated that in relation to olive leaf extract (51.1 mg/day), hydroxytyrosol (9.67 mg/day) did not affect body weight of overweight men [36].

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 [37]. 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 [38]. 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 [34]. 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% [36]. 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 [39]. 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 [40]. 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)/Bcl_{2} (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 [40]. It was also found that
Lipid-lowering and cardioprotective effects of oleuropein and olive leaf extracts have been proved in several studies [12, 44, 45]. It was found that 50 and 100 mg/kg/day of olive leaf extract significantly decreased plasma total cholesterol, triglyceride, and LDL cholesterol levels and inhibited lipid peroxidation by increasing catalase and superoxide dismutase activity in rats fed with a diet rich in cholesterol for 16 weeks [12]. In rats fed with a high-fat diet, supplementation of olive leaf extract reversed chronic inflammation and oxidative stress correlated with plasma malondialdehyde [46]. Similar to previous in vivo and animal studies, olive leaf extract (136 mg oleuropein; 6 mg hydroxytyrosol) significantly decreased plasma total cholesterol (–0.32 mmol/L), LDL cholesterol (–0.19 mmol/L), and triglyceride (0.18) levels in 60 pre-hypertensive men after 6 weeks. In addition, IL-8 level also decreased [44].

Potential effects of olive leaf on lipid metabolism and inflammation emerge by means of metabolic pathways and inflammation-related genes [13, 47–50]. In a study supporting these results, it was found that daily 20 mL olive leaf extract supplementation given to 29 healthy male participants changed expression level of early growth response protein 1, cyclooxygenase-2, and inhibitor of DNA binding 3 genes in peripheral blood mononuclear cells [47]. A study conducted with ovariectomized rats showed that olive leaf extract supplementation at the doses of 200 or 400 mg/kg body weight decreased serum triglyceride level particularly at high doses [48]. Furthermore, it was determined that 1–10 µg/mL concentration of oleuropein and hydroxytyrosol extracts inhibited ROS and protected cardiomyocytes against toxicity and carbonyl stress induced by 4-hydroxynonenal [13]. Another study found that oleuropein increased inductive nitric oxide synthase expression and nitric oxide production according to dose in mouse macrophages [50].

There are studies in the literature proving that olive leaf extract decreases endoplasmic reticulum stress, and thus it may also decrease myocardial infarction [51, 52]. A study demonstrated that hydroxytyrosol and oleuropein decreased apoptosis and endoplasmic reticulum stress, induced by acrolein, in cardiomyocyte cells by reducing 78-kDa glucose-regulated protein, the C/EBP homologous protein, and Bax expression levels in rats [52]. Another study supported the claim that hydroxytyrosol and olive leaf extract reversed the increase in C/EBP homologous protein and 78-kDa glucose-regulated protein expression levels induced by isoproterenol, and it may show cardioprotective effect by means of endoplasmic reticulum stress [51].

Safety of Olive Leaf and its Extract

Although there are strong evidence regarding biological activity of olive leaf extract and its components, there is limited knowledge on their systemic toxicity and reliability [53–55]. Toxicity studies show that olive leaf extracts are generally reliable and do not show toxic effect even at high doses [53, 54]. Results of a study showed that supplementation of olive leaf extract in male and female rats at single dose of 2,000 mg/kg (acute toxicity) and 100, 200, and 400 mg/kg doses (subacute toxicity) given for 28 days did not result in any toxicity [54]. Water soluble extract of olive leaf was given at the doses of 360, 600, and 1,000 mg/kg/day for 90 days and did not cause any mortality and toxicity [53]. Only one study reported some histological changes such as fatty cytoplasmic vacuolation, necrosis of the hepatocytes, and a slight hemorrhage in both liver and kidneys of rats after the supplementation of olive leaf extract (0.9%) for 6 weeks [56]. In addition, there is no adequate evidence about its genotoxic effects in the literature [16]. Thus, more studies are needed to fully understand the safety of olive leaf extracts for humans.
Conclusion

One of the natural antioxidant sources, olive leaf has been used in order to prevent and treat some diseases in traditional medicine for ages. Furthermore, olive leaf and its products such as olive oil are important components of Mediterranean diet. A large number of studies in the literature report that olive leaf has positive effects on the parameters related with diabetes and cardiovascular diseases through many mechanisms. It is possible to say that even the current results obtained until today seem promising. However, there are still numerous key points that need to be answered, and these will require further research. According to the literature, the studies in this subject are generally on cell culture and animal trials. Therefore, more randomized controlled human clinical trials are needed. Additionally, mostly the extract forms of olive leaf are used in the studies. So, potential effects of powder or dried olive leaf consumption on health should be taken into consideration in future studies. It should also be considered whether the individuals with diabetes and cardiovascular disease or those who take a routine medication have herb-drug interaction or not. In addition, potential health effects of olive leaf should be evaluated with extensive toxicity studies, and further clinical studies should be carried out in this subject.

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