Olive tree (*Olea europaea*) leaves: potential beneficial effects on human health

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*Olive tree (*Olea europaea *L.) leaves have been widely used in traditional remedies in European and Mediterranean countries such as Greece, Spain, Italy, France, Turkey, Israel, Morocco, and Tunisia. They have been used in the human diet as an extract, an herbal tea, and a powder, and they contain many potentially bioactive compounds that may have antioxidant, antihypertensive, antiatherogenic, anti-inflammatory, hypoglycemic, and hypocholesterolemic properties. One of these potentially bioactive compounds is the secoiridoid oleuropein, which can constitute up to 6–9% of dry matter in the leaves. Other bioactive components found in olive leaves include related secoiridoids, flavonoids, and triterpenes. The evidence supporting the potentially beneficial effects of olive leaves on human health are presented in this brief review.*

INTRODUCTION

The olive tree (*Olea europaea*, Oleaceae) is a traditional symbol of abundance, glory, and peace, and its leafy branches were historically used to crown the victorious in friendly games and bloody war. The olive fruit, its oil, and the leaves of the olive tree have a rich history of nutritional, medicinal, and ceremonial uses.[1] In addition to cereals, the olive is an important crop in the Mediterranean Basin, which produces 98% of the world total (approximately 11 million tons)[2], and lends important economic and dietetic benefits to the people of that region.[3] The introduction of olive cultivation coincided with the expansion of the Mediterranean civilizations, and the olive has been used widely in traditional remedies in European Mediterranean islands and countries such as Spain, Italy, France, Greece, Israel, Morocco, Tunisia, and Turkey. Moreover, there are at least nine biblical references citing the medicinal use of the plant in ancient times. Apart from the Mediterranean region, the plant is also cultivated widely in the Arabian Peninsula, the Indian subcontinent, and Asia.[4]

Olive byproducts, including olive oil extractions, are derived from the olive trees. The term "olive leaves" refers to a mixture of leaves and branches from both the pruning of olive trees and the harvesting and cleaning of olives. The production of olive leaves from pruning is ~25 kg per olive tree, and 5% of the weight of harvested olives collected at the oil mill can be added to that weight.[5]

In recent years, there has been great interest in the health effects of various herbal teas. Olive-leaf tea is one of the most common, traditional herbal teas used among Mediterranean people to cure certain diseases. For this reason, interest in the potential health benefits of olive leaves has increased among scientists in various fields. Recently, antioxidant, hypoglycemic, antihypertensive, antimicrobial, and antiatherosclerotic effects of olive leaves have been reported in various studies. In this article, some of these studies on the beneficial health effects of olive leaves are reviewed.

CHEMICAL CHARACTERISTICS OF OLIVE LEAVES

The chemical composition of olive leaves varies depending on several conditions such as origin, proportion of branches on the tree, storage conditions, climatic conditions, moisture content, and degree of contamination

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Key words: antiatherogenic, antihypertensive, antioxidant, hypoglycemic, oleuropein, olive leaves

doi:10.1111/j.1753-4887.2009.00248.x

with soil and oils. In addition, the structural carbohydrates and nitrogen content in olive leaves depends on factors such as the variety of the olive tree, climatic conditions, year, proportion of wood, etc.[5–8]

Polyphenols in olive leaves

Olea europaea L. is widely studied for its alimentary use (the fruits and the oil are important components in the daily diet of a large part of the world's population), whereas the leaves are important for their secondary metabolites such as the secoiridoid compounds oleacein and oleuropein.[3,9–12] Olive tree leaves are well known for their beneficial effects on metabolism when used as a traditional herbal drug. These properties are attributed to the phenolic compounds of olive leaves.

Olive polyphenols are a consequence of the reactivity to pathogen attack and the response to insect injuries in the olive tree. The two main sources of olive polyphenols are olive leaves and the waste from the olive oil industry, known as alperujo. Alperujo is a cheap source of natural antioxidants, containing concentrations up to 100-fold higher than those found in olive oil. Olive leaves have the highest antioxidant and scavenging power among the different parts of the olive tree (e.g., oleuropein content in olive oil ranges between 0.005% and 0.12% and that in alperujo reaches up to 0.87%, while that in olive leaves ranges between 1% and 14%).[3] There are five groups of phenolic compounds principally present in olive leaves: oleuropeosides (oleuropein and verbascoside); flavones (luteolin-7-glucoside, apigenin-7-glucoside, diosmetin-7-glucoside, luteolin, and diosmetin); flavonols (rutin); flavan-3-ols (catechin), and substituted phenols (tyrosol, hydroxytyrosol, vanillin, vanillic acid, and caffeic acid). The most abundant compound in olive leaves is oleuropein, followed by hydroxytyrosol, the flavone-7-glucosides of luteolin and apigenin, and verbascoside. Hydroxytyrosol is a precursor of oleuropein, and verbascoside is a conjugated glucoside of hydroxytyrosol and caffeic acid. The chemical structures of these compounds are shown in Figure 1.[13]

The total polyphenol content and the total flavonoid content of olive tree leaves were determined[14] to be 2,058 mg GAE (gallic acid equivalent) per 100 g and 858 mg CTE (catechin equivalent) per 100 g, respectively, reflecting values similar to that of red-grape peel. The bitter compound oleuropein, the predominant secoiridoid in the olive tree, is a potent antioxidant endowed with anti-inflammatory properties. Oleuropein, discovered in 1908 by Bourquelot and Vintilesco, is a heterosidic ester of elenolic acid and dihydroxyphenylethanol.[13] 3, 4-Dihydroxyphenyl ethanol, more commonly known as hydroxytyrosol, is the principal degradation product of oleuropein. Oleuropein is present in high amounts in unprocessed olive fruit and leaves, while hydroxytyrosol is more abundant in the processed olive fruit and olive oil. The decrease in the concentration of oleuropein and the increase in the concentration of hydroxytyrosol occur due to chemical and enzymatic reactions that take place during maturation of the fruit or as a result of olive processing (e.g., oil production).[15] Several studies have investigated the phenolic composition of olive leaves.[11,16–21] Analysis of olive-leaf aqueous extracts identified seven phenolic compounds: caffeic acid, verbascoside, oleuropein, luteolin 7-O-glucoside, rutin, apigenin 7-O-glucoside, and luteolin 4′-O-glucoside. Pereira et al.[9] found higher amounts of phenolic compounds in the aqueous extract of olive leaves than in the hydromethanolic extracts of the same and other olive-leaf cultivars. Furthermore, the major compounds in the hydromethanolic extracts were flavonoids, while the major compound in the aqueous extract was oleuropein, representing ~73% of the total identified compounds. Caffeic acid was found to be a minor compound, corresponding to ~1% of the total phenolic compounds. Phenolic compounds of olive leaves such as rutin, luteolin 7-O-glucoside, luteolin 7-O-rutinoside, luteolin 40-O-glucoside, apigenin 7-O-glucoside, and apigenin 7-O-rutinoside are reported in the literature, but data about their constancy, amounts, or distribution among cultivars are scarce.[16]

BIOAVAILABILITY OF OLIVE-LEAF POLYPHENOLS

The current literature lacks sufficient data to fully understand the bioavailability of polyphenols such as oleuropein, hydroxytyrosol, and tyrosol in olive leaves. However, it is known that oleuropein is poorly absorbed due to its large size and planar configuration. It has also been hypothesized that since oleuropein is a glycoside, it could potentially access a glucose transporter like a sodium-dependent glucose transporter (SGLT1) found on the epithelial cells of the small intestine, thereby permitting its entry into the cells. Conversely, Hollman et al.[17] postulated that the absorption of the quercetin glycoside (a similar polyphenolic compound) involves active sugar transporters.

HEALTH-RELATED EFFECTS OF OLIVE-LEAF POLYPHENOLS

The health effects of virgin olive oil are attributed mainly to the presence of particular polyphenols and have been widely studied in recent decades. Oleuropein, the most abundant polyphenol in olive leaves, prevents cardiac disease by protecting membrane from lipid oxidation,[4,11] by affecting coronary blood vessel dilation,[18] by exerting antiarrhythmic action,[4] by improving lipid metabolism,[5]

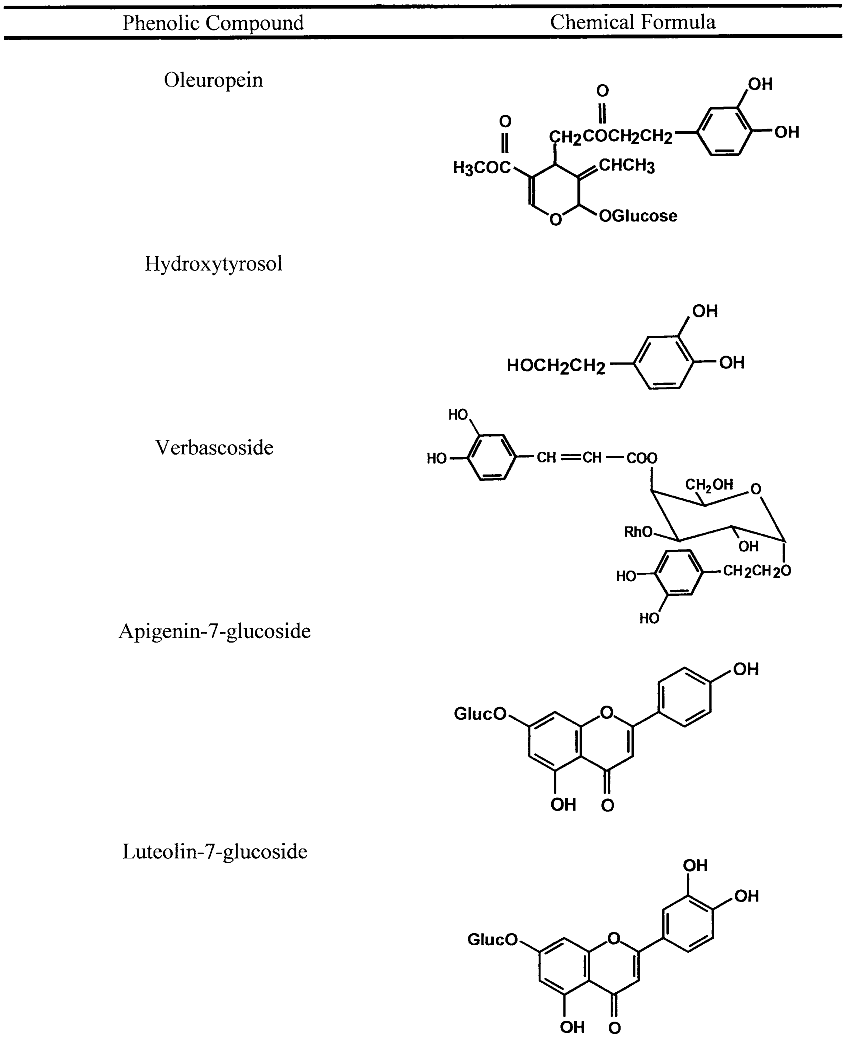

Figure 1 **Chemical structure of the most abundant phenolic compounds in olive-leaf extract.** Reproduced from Benavente-Garcia et al. (2000)[13] with permission.

by protecting enzymes,[4,9–11] by preventing hypertensive cell death in cancer patients,[4] and by its antiviral properties.[1,9] Hydroxytyrosol, an oleuropein derivative, also improves cardiac and tumoral diseases with effects similar to those of oleuropein[4]; in addition, hydroxytyrosol protects against atherosclerosis and prevents diabetic neuropathy.[10] Research on olive polyphenols has also led to the isolation of certain compounds, such as oleocanthal in olive oil, with interesting ibuprofen-like activity.[1,4,9–11]

Antioxidant activity of olive leaves

Phenolic compounds. Reactive oxygen and nitrogen species are essential to energy supply, detoxification, chemical signaling, and immune function. They are continuously produced in the human body and are controlled by endogenous enzymes such as superoxide dismutase, glutathione peroxidase, and catalase. When there is an overproduction of these reactive species, an exposure to external oxidant substances, or a failure in the defense mechanisms, damage to valuable biomolecules (DNA, lipids, proteins) may occur. This damage has been associated with an increased risk of cardiovascular disease, cancer, and other chronic diseases. The antioxidant hypothesis asserts that, as antioxidants can prevent oxidative damage, increased intake of antioxidants from the diet will also reduce the risks of chronic diseases.[19]

There is an increasing interest in natural antioxidants as bioactive components of foods. The protective effects of diets rich in fruit and vegetables against cardiovascular diseases and certain cancers have been attributed partly to antioxidants.[13] The potential importance of antioxidant plant phenols is also seen in the efforts of researchers to 1) increase the content of phenolic com-

Table 1 **Antioxidant activity of phenolic compounds from olive leaves.**

Phenolic compound	TEAC (mmol/L)
Olive-leaf extract	1.58 ± 0.06
Rutin	2.75 ± 0.05
Catechin	2.28 ± 0.04
Luteolin	2.25 ± 0.11
Hydroxytyrosol	1.57 ± 0.12
Diosmetin	1.42 ± 0.07
Caffeic acid	1.37 ± 0.08
Verbascoside	1.02 ± 0.07
Oleuropein	0.88 ± 0.09
Luteolin-7-glucoside	0.71 ± 0.04
Vanillic acid	0.67 ± 0.09
Diosmetin-7-glucoside	0.64 ± 0.09
Apigenin-7-glucoside	0.42 ± 0.03
Tyrosol	0.35 ± 0.05
Vanillin	0.13 ± 0.01

Abbreviation: TEAC, Trolox equivalent antioxidant capacity. Reproduced from Benavente-Garcia et al. (2000)[13] with permission.

pounds in plants; 2) produce less hydrophilic derivatives by enzymic modification of their structure with improved pharmacological characteristics; 3) explore novel effects; and 4) elucidate the quantitative structure–activity relationships of various phenol classes.[18]

The bitter compound oleuropein, the major constituent of the secoiridoid family of compounds in the olive tree, has been shown to be a potent antioxidant endowed with anti-inflammatory properties. Benavente-Garcia et al.[13] aimed to identify the main phenolic compounds present in olive-leaf extracts to delineate the differential antioxidant activities of these compounds. The antioxidant activities of phenolic compounds from olive-leaf extracts are shown in Table 1. Whole olive-leaf extract showed a TEAC value of 1.58 mM, increasing 72% with respect to the theoretical value obtained from the pooled average of individual TEAC values. This finding suggests that olive phenols may exhibit synergistic behavior in their radical scavenging capacity when mixed, as occurs in the olive-leaf extract. Benavente-Garcia et al.[13] also concluded that flavonols, flavans-3-ols, and flavones with catechol structures were the most efficient olive phenolic compound quenchers for the 2,2′-azinobis (3-ethylbenzothizoline-6-sulfonic acid) ($ABTS^{+}$) radical cation, and this ability was greater as more free hydroxyl groups were present in the flavonoid structure. Moreover, the flavonoids, oleuropeosides, and substituted phenols showed synergistic behavior in mixed form, as occurred in olive-leaf extract with a high content of oleuropein and these active polyphenols. Prevention of free radical formation by oleuropein may be due to its ability to chelate metal ions, such as Cu and Fe, which catalyze free radical generation reactions,[20] as well as its ability to inhibit several inflammatory enzymes, such as lipoxygenases, without affecting the cyclo-oxygenase pathway.[21] In addition, it was found that hydroxytyrosol, oleuropein, caffeic acid, and tyrosol were capable of preventing the generation of reactive oxygen species by intact leukocytes, without evidence of toxicity.[21] Oleuropein and its metabolite hydroxytyrosol both possess the structural requirement (a catechol group) needed for optimum antioxidant and/or scavenging activity. Both oleuropein and hydroxytyrosol have been shown to be scavengers of superoxide anion as well as inhibitors of the respiratory burst of neutrophils and hypochlorous acid-derived radicals.[22] Both compounds also scavenged hydroxyl radicals, with oleuropein showing greater activity.[23] Hydroxytyrosol and oleuropein were also reported to be effective scavengers of the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical.[24]

Buyukbalci and El[25] determined the antioxidant effect of tea prepared from olive leaves against DPPH and hydrogen peroxide radicals. The antioxidant activity of oleuropein was studied using in vivo methods. One of the studies investigated the effect of oleuropein obtained from olive leaves on oxidative stress and enzymatic and nonenzymatic antioxidants in alloxan-induced diabetic rabbits.[26] In a study by Bouaziz et al.,[27] enrichment of refined olive and husk oils with olive leaves and their hydrolysate extract resulted in an appreciable resistance to oxidative deterioration due to the phenolic antioxidant content of the leaves and extract. Oleuropein and hydroxytyrosol were the major compounds in olive-leaf extract and hydrolysate solution, respectively.

Triterpenoids. Leaf extracts of *Olea europaea* yielded, in addition to oleuropein as a main constituent, tetracyclic and pentacyclic triterpenes, sterols, erythrodiol, uvaol, and oleanolic acid.[4] Somova et al.[4] reported that the main component of the African olive-leaf extract was a 1:1 mixture of oleanolic acid and its isomer ursolic acid. However, these researchers found that Greek olive leaves and European olive leaves contained 0.71% and 2.47% oleanolic acid, respectively. Ursolic acid was not determined in the extracts of Greek olive leaves and European olive leaves. Antioxidant potential of the extracts was measured by monitoring the level of the enzymes glutathione peroxidase and superoxide dismutase were monitored in the blood of both Dahl salt-sensitive and Dahl salt-resistant Sprague Dawley rats. Compared with the control normotensive rats, untreated Dahl hypertensive rats showed a compromised antioxidant status with significantly decreased blood glutathione peroxidase by 22% and red blood cells superoxide dismutase by 24%.

Antiatherosclerotic effect of olive leaves

The phenolic compounds of olive leaves and olive oils in the Mediterranean diet have been associated with a reduced incidence of heart disease. Accordingly, these antioxidant-rich diets might prevent the deleterious effects of oxidative metabolism by scavenging free radicals, thus inhibiting oxidation and delaying atherosclerosis. The process may involve phospholipase C activation and arachidonic acid metabolism, and is thought to reduce hydrogen peroxide.[18] The cardiovascular effects of olive-leaf extracts have been well studied and attributed to the main components of the European leaves, oleuropein and oleacein.[28]

In a study by Somova et al.[4] the antihypertensive, diuretic, antiatherosclerotic, antioxidant, and hypoglycemic effects of oleanolic acid, ursolic acid, and the extracts of olive leaves obtained from African olive leaves (AO), Greek olive leaves (GO), and Cape Town (CT) species were investigated by using a Dahl salt-sensitive (DSS), insulin-resistant rat genetic model of hypertension. DSS-untreated rats developed hypertension spontaneously with significantly increased heart rate. The insulin-resistant rats displayed significantly increased blood glucose by 26% and were prone to develop early atherosclerosis with significantly increased total cholesterol by 108%, along with a more than fourfold increase in low-density lipoprotein (LDL) cholesterol and triglycerides. Biochemical parameters were normalized almost completely after 6 weeks of treatment with oleanolic acid, ursolic acid, and the extracts of AO, GO, and CT. All of the samples showed a potent hypoglycemic, antihyperlipidemic (antiatherosclerotic), and antioxidant activity. It was emphasized that GO and CT with a high level of pure oleanolic acid (2.47%) displayed the best antihypertensive, diuretic/natriuretic, antihyperlipidemic, hypoglycemic, and antioxidant activities.

In a study by Pignatelli et al.,[29] oleuropein and hydroxytyrosol inhibited the phorbol 12-myristate 13-acetate-induced respiratory burst of human neutrophils in a dose-dependant fashion. It was suggested that the effect was due to their capacity to scavenge H_2O_2, which is produced during the arachidonic acid metabolism cascade and leads to platelet aggregation.

Singh et al.[18] studied the effect of olive leaves on platelet function in 11 healthy male volunteers, 18–54 years of age. Food records of the volunteers were obtained by using a food frequency questionnaire over a 7-day period. The results showed that polyphenols found in olive leaves were capable of in vitro platelet activation in healthy, nonsmoking males. There is a need to follow-up on this in vivo study to validate its findings and to establish the bioavailability of these polyphenols.

Cardioprotective effects of olive-leaf polyphenols

Oleuropein, which is completely nontoxic in several animal species, has antitumoral activity.[30]

Doxorubicin (DXR), an anthracycline antibiotic clinically known as adriamycin, is an antineoplastic drug that is highly effective against many malignant diseases. It was reported that the clinical use of DXR is often limited because of its undesirable serious cardiotoxic side effects, which frequently lead to congestive heart failure.[31] The effect of oleuropein on cardiotoxicity induced by acute DXR treatment in rats has been investigated. Andreadou et al.[31] found that all groups treated with oleuropein had very low cytoplasmic vacuolization in cardiomyocytes compared to the DXR group, indicating that oleuropein protects against DXR-induced cardiotoxicity. Oleuropein successfully treated DXR-induced cardiotoxicity by inhibiting lipid peroxidation products, by decreasing oxidative stress, and by reducing nitric oxide species in cardiomyocytes. For this reason, acute DXR cardiotoxicity might be successfully treated with oleuropein.

Hypoglycemic effect of olive leaves

Olive-tree leaves are well known as a traditional antidiabetic and antihypertensive herbal drug.[12] Olive leaves have also have been used as a medical herb to treat diabetic hyperglycemia, hypertension, and infectious diseases, and they are especially widely recognized as a traditional remedy for diabetes and hypertension in Europe.[32] There have been two mechanisms suggested to explain the hypoglycemic effect of oleuropein in diabetes: 1) the potential to affect glucose-induced insulin release, and 2) an effect to increase peripheral uptake of glucose.[26]

In addition, part of the effect of oleuropein on diabetes and its complications derives from its antioxidant activity.[10] Al-Azzawie and Alhamdani[26] studied the hypoglycemic and antioxidant effects of oleuropein in alloxan-diabetic rabbits. The rabbits were treated with 20 mg/kg body weight of oleuropein during 16 weeks. The levels of blood glucose were significantly decreased in oleuropein-treated rabbits after initiation of treatment, being strictly apparent at week 8 as compared with diabetic control rabbits, who continued to exhibit elevated glucose levels throughout the study period. The results demonstrated that oleuropein may be beneficial in inhibiting hyperglycemia and oxidative stress induced by diabetes, and they suggest that administration of oleuropein may be helpful in the prevention of diabetic complications associated with oxidative stress.

Komaki et al.[32] studied the effect of olive-leaf extract on postprandial blood glucose in diabetic rats. Their findings suggest that both luteolin and oleanolic acid have an inhibitory effect on postprandial blood glucose increase in diabetic rats. They also investigated the effect of olive-leaf extract on the glycemic responses to cooked-rice loading in humans. The subjects were divided into two groups according to their blood glucose levels before loading (normal and borderline groups for diabetes). The change in blood glucose level of the borderline group was decreased significantly after loading olive-leaf extract and cooked rice in comparison with the control group. It was also reported by Gonzalez et al. that oleuropein in olive leaves accelerated the uptake of glucose by the cell.[33]

Oleuropein is an agonist for TGR5, a G-protein-coupled receptor that is activated by bile acids and that mediates some of their various cellular and physiological effects. Sato et al.[10] studied the antihyperglycemic activity of a TGR5 agonist isolated from olive-tree leaves. TGR5 was identified as the first cell-surface receptor activated by bile acids, and this receptor is reported to mediate some of the endocrine functions of bile acids. Bile acids are emerging as important metabolic signaling molecules.[10] They have been shown to increase energy expenditure in part through activation of mitochondrial function, hence preventing the development of obesity and insulin resistance in mice fed a high-fat diet.[10] TGR5 slows the weight increase induced by high levels of fat and has potent antihyperglycemic activity, which may contribute to the antidiabetic effect of olive leaves. Sato et al.[10] reported that oleanolic acid lowered serum glucose and insulin levels in mice fed a high-fat diet, and it enhanced glucose tolerance. The findings of their study suggest that both oleuropein and oleanolic acid are involved in the antidiabetic effect of olive leaves and further emphasize the potential role of TGR5 agonists in improving metabolic disorders.

CONCLUSION

There is traditional and widespread use of olive leaves and olive-leaf tea in the Mediterranean region. Results obtained in animal studies support the idea that olive leaves have potentially beneficial effects on certain health conditions, including hypertension, cardiovascular diseases, diabetes, and hyperlipidemia. These beneficial effects may be due to the antioxidant components of olive leaves, especially oleuropein. Although the health effects of olive leaves in humans are promising, some challenges remain, such as the need to gain a greater understanding of the possible interactions between the bioactive components of olive leaves and other dietary constituents, as well as the need to determine the most effective dose of olive leaves to obtain various beneficial effects in human subjects. Additional clinical work is required to examine the safety profile of various doses of olive leaves, and more basic science studies are needed to improve our understanding of the molecular mechanisms underlying any therapeutic efficacy of olive leaves and their various bioactive constituents.

Acknowledgments

Declaration of interest. The authors have no relevant interests to declare.

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