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REVIEW ARTICLE

Phytocontent and Biological Effects of *Olea europaea* L. : A Review

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ABSTRACT

Olive tree (*Olea europaea* L., 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 com-pounds that may have hypoglycemic and hypolipidemic properties. Olea europaea is commonly known as Zaitoon. The ancient Egyptians, Greeks, Romans and other Mediterranean nations cultivated olives for its edible fruits and to obtain oil from them. Leaves of the tree became important when olive leaf extract was reported to be potent in reducing incidence of degenerative diseases, particularly coronary heart disease (CHD) and cancers of the breast, skin, and colon. Olive leaves have the highest antioxidant power among the different parts of the olive tree. While in olive fruit, phenols (e.g.,TYR) and terpenoid hydrocarbon (Squalene) are the major components found in the oil. Much research has been carried out on the medical applications of olive. The choice of the plant was based on the good previous biological study of Olea europaea. Interest to choose this plant, may have been due to the widespread use of olive species medicinally, food industry and cosmetics.

Keywords: *Olea europaea* L., Chemical compounds, Plants, Bioactivities

INTRODUCTION

Plants have been an important source in cancer drug discovery. The medicinal values of plants lie in their phytochemicals, which makes specific physiological actions on the human body. Phytochemicals are compounds found in plants that are utilized as food and medicine top reserve against illness and to ensure human health.

The olive tree is a member of the Oleaceae family Crisosto *et al.*, 2011). The ancient Egyptians, Greeks, Romans and other Mediterranean nations cultivated olives for its edible fruits and to obtain oil from them (Crisosto *et al.*, 2011). Olive trees are normally distributed in the coastal areas of the eastern Mediterranean basin, the contiguous coastal areas of southeastern Europe, northern Iran at the south end of the Caspian Sea, western Asia, and northern Africa (Ryan and Robards, 1998). Olive tree and its fruit are also important in context of religion. Olives are narrated several times in the Bible, both in the New and Old Testaments (Ryan and Robards, 1998). Olive has also been praised as a blessed tree and fruit in the Holy Quran. Olives are not used as a natural fruit because of their extremely bitter taste but are rather consumed either as olive oil or table olives (Kanakis, *et al.*, 2013). Olive oil market is very significant in the olive industry as approximately 90%of annually produced olives go for oil processing (Sibbett *et al.*, 2005).

The therapeutic utilities of *O. europaea* have been indicated in traditional medicine. It has been known to reduce blood sugar, cholesterol, and uric acid. It has also been used to treat diabetes, hypertension, inflammation, diarrhea, respiratory and urinary tract infections, stomach and intestinal diseases, asthma, hemorrhoids, rheumatism, laxative, mouth cleanser, and as a vasodilator. Many phenolic compounds, especially secoiridoids and iridoids (Bendini *et al.*, 2007), and their pharmacological activities have been the focus of attraction for scientists in the last decade (Ghisalberti, *et al.*, 1998).

Oleuropein, a major constituent of *O. europaea*, has got much attention and a lot of work has been done on its pharmacological properties (Soler-Rivas *et al.*, 2000, Omar *et al.*, 2010). Olive has widely been explored as a functional food (Erbay *et al.*, 2010, Galanakis *et al.*, 2011) with various biophenol (Obied *et al.*, 2005, Saija and Uccella, 2000) and other bioactive constituents (El-Abd-Halim and Karakaya, 2009). Volatile constituents from olive oil and their applications in favor development have also been a hot area of the current research (Kalua, *et al.*, 2007). This review have been done on the phytochemistry and bioactivities of olive.

PHYTOCHEMICALS

Phytochemical research carried out on *O. europaea* had led to the isolation of lavonoids, lavone glycosides, lavanones, iridoids, iridane glycosides, secoiridoids, secoiridoid glycosides, triterpenes, biophenols (Obied, 2013), benzoic acid derivatives, xylitol, sterols, isochromans, sugars, and a few other types of secondary metabolites from its different parts .Phenolic compounds, lavonoids, secoiridoids, and secoiridoid glycosides (Jerman, *et al.*, 2010) are present in almost all the parts of O. europaea.

Constituents of the Bark

Lignans like (−)-olivil, (+)-cycloolivil, (+)-1-acetoxypinoresinol, (+)-1-hydroxypinoresinol, (+)-1-acetoxypinoresinol-4-O-methyl ether, and (+)-1-hydroxypinoresinol-4-O-methyl ether have been isolated from the ether extract of the bark of *O. europaea* (Tsukamoto *et al.*, 1984, Perez-Bonilla *et al.*, 2006). Three lignan glucosides, that is, (+)-1-acetoxypinoresinol-4-methyl ether-4-D-glucopyranoside, (+)-1-hydroxypinoresinol-4-D-glucopyranoside, (+)-1-acetoxypinoresinol-4-glucopyranoside. as well as esculin, and oleuropein were isolated from the bark of *O. europaea* and *O. europaea* ssp. *Africana*. The bark of *O. europaea* has (+)-fraxiresinol-1D-glucopyranoside, (+)-1-acetoxypinoresinol-4-D-glucopyranoside, the coumarin sesculetin, scopoletin, and scopolin (Tsukamoto *et al.*, 1985, Tsukamoto, *et al.*, 1984).

Constituents of the Fruits and Seeds.

O. europaea fruits has considerable amount of flavonoids, secoiridoids, secoiridoids glycosides, and phenolics such as tyrosol, hydroxytyrosol, and their derivatives (Esti *et al.*, 1998, Bianco and Uccella, 2000; Owen *et al.*, 2003). Some of hydroxytyrosol derivatives like hydroxytyrosol rhamnoside (Peralbo-Molina *et al.*, 2012), hydroxytyrosol glucoside, and methyl malate-hydroxytyrosol ester were isolated from olive fruit for the irst time. Isolation of new tyrosol derivatives, tyrosol glucoside salidroside, and 1-oleyltyrosol (Savarese *et al.*, 2007; Bianco *et al.*, 2006), along with cornoside, 2(3,4-dihydroxy-phenyl)ethanol (Bianco *et al.*, 2004), halleridone, and hydroxytyrosol-elenolate (Maestroduran, *et al.*, 1994; Bastoni, *et al.*, 2001) ha salso been reported from the fruits of O. europaea. An important and major phenolic compound present in natural table olives is 3,4-dihydroxyphenylglycol (DHPG) which is reported from natural as well as different cultivated olive samples (Maestroduran, *et al.*, 1994; Bastoni, *et al.*, 2001). Galactolipids, triacylglycerols, and fatty acids were isolated from the fruits of *O. europaea* (Bianco *et al.*, 2003; Bianchi and Pozzi 1994). The isolation of a diacylglycerol from olive pulp showing an oleic as well as an oleanolic acid residue (Vlahov *et al.*, 1999). Secoiridoids constitute a major portion of the leaves and fruits of *O. europaea*. Oleuropein is the most abundantly found secoiridoid glycoside in the fruits of O. europaea. Alot of work has been done on isolation, characterization, synthesis, and in silico studies of oleuropein (Bianco, *et al.*, 1998; Sakouhi *et al.*, 2010). Oleuropein may also be used for chemical standardization of the plant and its extracts of medicinal interest (Marra *et al.*, 2005). Aouidi *et al.* developed a method for rapid quantitative determination of oleuropein in *O. europaea* leaves using mid-infrared spectroscopy combined with chemometric analyses (Procopio *et al.*, 2009). A study of the distribution of phenolic compounds in different parts of the olive fruit showed the presence of oleuropein, demethyloleuropein (Nenadis *et al.*, 2009), and verbascoside in all parts of the fruit whereas n¨ uzhenide was found to be the most concentrated phenolic compound in the seeds of olives (Haloui, *et al.*, 2011). The seeds have Secoiridoids and their glycosides are found in olive fruits and seeds. 3,4-Dihydroxyphenylethyl-((2,6-dimethoxy-3-ethylidene) tetrahydropyran-4-yl) acetate has been reported from the olive fruit (Cardoso *et al.*, 2011; Aouidi *et al.*, 2012). Oleoside was isolated from the seeds of olive fruit. Elenolic acid glucoside was isolated from olive pulp and was characterized on the basis of LC-MS. Glucopyranosyl oleoside, 6-rhamnopyranosyl oleoside, and ligstroside were identified in peel, pulp, and fruits of *O. europaea* by electrospray ionization mass spectrometry. Ligstroside aglycone methyl acetal was reported from the olives of Hojiblanca cultivar. A large number of lavonoids such as quercetin (Scalzo and Scarpati; 1993), quercetin-7-O-glucoside, luteolin-7-O-rutinoside (Servili *et al.*, 1999), apigenin-7-O-rutinoside, rutin (Gentile and. Uccella, 2014; Paiva-Martins *et al.*, 2014), vicenin-2, chrysoeriol, chrysoeriol-7-O-glucoside, luteolin-7-O-glucoside, quercetin-3-rhamnoside, apigenin, and quercitrin have been reported from the fruits and pulp of the olives. Oleuropein has been reported from the methanolic extract of boron deficient leaves, peel, pulp, seeds, and wood of *O. europaea* (Ryan *et al.*, 1984; Savournin *et al.*, 2001- Charoenprasert and Mitchell, 2012). Oleuropein and other secoiridoids such as secologanoside, oleoside, 6-E-p-coumaroyl-secologanoside (comselogoside), and 6-O-((2E)-2,6-dimethyl-8-hydroxy-2-octenoyloxy)-secologanoside have been isolated from the methanolic extract of boron deficient leaves (Kuwajima, *et al.*, 1988). Oleoside has also been isolated from water extract of O.europaea leaves (Karioti *et al.*, 2006). Oleoside, reported from fruits, is also present in leaves. hydroxytyrosol-elenolate, elenolic acid methyl ester, and ligstroside were isolated from the chloroform soluble fraction of *O. europaea* leaves (Gariboldi *et al.*, 1986). he ethyl acetate extract of olive leaves yielded two new secoiridoid glycosides oleuricine A and oleu-ricine B (Hansen *et al.*, 1996). Oleuroside and 3,4-DHPEA-EDA (oleacein) were isolated from the aqueous extract of the leaves of *O. europaea* (Mussini *et al.*, 1975, Movsumov and Aliev, 1985). Isolation from ethyl acetate soluble fraction of *O. europaea* leaves yielded different triterpenoids like -amyrin (Sultana and Ata, 2008; Komaki *et al.*, 2003), -sitosterol, oleanolic acid (Duquesnoy et al., 2007; Romero *et al.*, 2010; . Movsumov *et al.*, 1994), erythrodiol (Bianchi, *et al.*, 1994; Schumacher et al., 2002), and urs-2,3-dihydroxy-12-en-28-oic acid. Other triterpene acids isolated from *O. europaea* leaves include betulinic acid, uviol, ursolic acid, andmaslinicacid (Campeol *et al.*, 2004). Flavonoids also constitute some portion of *O. europaea* leaves. Apigenin-7-O-rutinoside, rutin, and luteolin-7-O-glucoside were isolated from the leaves of *O. europaea* . Analysis and quantification of leaves of *O. europaea* from different cultivators showed the presence of lavone glycosides, that is, luteolin-7,4-O-diglucoside, diosmetin, and apigenin-7-O-glucoside. Alignan,4-O--D-glucosyl-9-O-(6-deoxysaccharo-syl) olivil, was reported from the leaves of *O. europaea* (Campeol *et al.*, 2004). A compound never found previously in the vegetal kingdom, that is, 1,5-anhydroxylitol , was isolated from *O. europaea* leaves. Two new compounds 3, 4-dihy droxyphenylethanol-elenolic acid dialdehyde (3,4-DHPEA-EDA) and hydroxytyrosol-elenolate which are the hydrolysis products of oleuropein were isolated from the leaves of *O. europaea* (Paiva-Martins and Gordon, 2001). Besides, hydrocarbons, esters, waxes, triglycerides, tocopherols, esterols, lineal, terpenic alcohols, and terpenic dialcohols have also been reported from the hexane extract of *O. europaea* leaves (Guinda and Lanz, 2002).

BIOLOGICAL ACTIVITIES

Antidiabetic Potential

The ethnomedical use of *O. europaea* in treatment of diabetes has been validated in several experimental studies. It has been used by the folk medical practitioners to treat diabetes. Al-Azzawie and Alhamdani proposed that antidiabetic patients may be treated with good antioxidants as the relief in oxidative stress reduces the blood glucose levels. So, they treated hypoglycemic alloxan-diabetic rabbits with oleuropein, a powerful antioxidant agent presents abundantly in olive leaves and fruit, to reduce their oxidative stress. The diabetic rabbits were treated with oleuropein (20mg/Kg body weight) for up to 16 weeks. After treatment it was observed that the blood glucose levels along with most of the antioxidants were restored to the values near to the normal control rabbits. The study proved the effects of oleuropeinas antihyperglycemic and antioxidative agent (Al-Azzawie and Alhamdani, 2006).

Anticancer Effect

Constituents of *O. europaea* have shown very good anticancer activities on various types of cancers (Casaburi *et al.*, 2013). Juan *et al.* investigated the antiproliferative and apoptotic activities of erythrodiol in human colorectal carcinoma HT-29 cells (Juan *et al.*, 2008). It inhibited the cell growth without any toxicity in a concentration range of 100 µM in colon adenocarcinoma cells. Similarly, studies have been conducted on water and methanolic extracts of olive leaves against cancer and endothelial cells. These crude extracts were found to inhibit cell proliferation of human breast adenocarcinoma (MCF-7), human urinary bladder carcinoma (T-24), and bovine brain capillary endothelial (BBCE). Upon phytochemical analysis of these extracts oleuropein was found to be the most abundant compound along with other phenolics and flavonoids. Then the isolated pure compounds luteolin 7-O-glucoside, oleuropein, hydroxytyrosol, and hydroxytyrosol acetate were also subjected to cell proliferation assays. It was concluded that in pure form, these compounds were active in low concentrations (Goulas *et al.*, 2009).

Antimicrobial Potential

The plant has been used as a folk remedy for the cure of numerous infectious disorders of bacterial, fungal, and viral origin. Several studies have been carried out in the past validating the antimicrobial and antiviral potential of *O. europaea* (Adnan *et al.*, 2014). Kubo *et al.* characterized a series of long-chain unsaturated aldehydes from *O. europaea* fruit and its oil lavor for their antimicrobial activities and found them active against abroad spectrum of microbes (Kubo *et al.*, 1995). Pereira *et al.* tested the extracts of various table olives from different cultivators of Portugal for their antimicrobial potential and found that besides having good antioxidant potential, olive phenolics possess good antimicrobial activity suggesting that these table olives may be good candidates against bacteria responsible for human gastrointestinal and respiratory tract infections (Pereira *et al.*, 2007)

Antioxidant potential

Antioxidant activity of oleuropein, hydroxytyrosol, and tyrosol from the leaves of *O. europaea* in comparison with vitamin E and BHT. Oleuropein and hydroxytyrosol showed high antioxidant activity while tyrosol showed neither antioxidant nor prooxidant activity (Le Tutour and Guedon, 1992). Oleuropein was also evaluated for its antioxidant activity in vitro using chemilumine scence assay and was found to have remarkable antioxidant activity (Speroni *et al.*, 1998). Later on, Fogliano *et al.* evaluated the antioxidant activities of two virgin olive oils obtained from same olive batch but processed with different hammer crushing conditions and found that the efficacy of the olive oil which was processed under higher hammer crushing rate was higher than the other (Fogliano *et al.*, 1999). In another study, antioxidant activity of different phenolic compounds isolated from the leaves of *O. europaea* was determined. These compounds included oleuropein, verbascoside, luteolin-7-glucoside, apigenin-7-glucoside, diosmetin-7-glucoside, luteolin, diosmetin, rutin, catechin, tyrosol, hydroxytyrosol, vanillin, vanillic acid, and caffeic acid. Among these, the flavonoids rutin, luteolin, and catechin showed the highest activity against ABTS radicals (Benavente-Garc *et al.*, 2000).

Enzyme Inhibition Effect

The use of olive in folk medicine to treat the inhibition of enzymes involved in various ailments is old. In Mediterranean folk medicine, the preparation of olive leaf has been used as a common tonic for gout. Flemmig *et al.* investigated the possible inhibitory effect of 80% ethanolic dry olive leaf extracts and nine isolated compounds from it against xanthine oxidase (XO), an enzyme which is a cause of gout. All opurinol was used as a reference drug in this study. Olive leaf extract as well as several of its phenolics showed xanthine oxidase inhibitory activity. The flavone apigenin showed the strongest XO inhibitory activity while oleuropein, caffeic acid, luteolin-7-O-D-glucoside, and luteolin also showed significant contribution in XO inhibition. Water extract of the fresh terminal branches of *O. europaea* ssp. *africana* inhibited peptidase and glycosidase enzyme activities which are produced by the periodontopathic bacteria Porphyromonas gingivalis, Bacteroides intermedius, and Treponema denticola (Homer *et al.*, 1992). The aqueous extract of olive leaves was tested for Angiotensin Converting Enzyme (ACE) inhibition activity in vitro. Due to significant activity, a bioguided isolation was performed to isolate the main component responsible for the ACE inhibition which was oleacein while the other isolates did not show ACE inhibitory activity. A series of unsaturated aldehydes, characterized from olive oil flavor, were found to inhibit the enzyme tyrosinase which catalyzes the oxidation of L-3,4-dihydroxy phenylalanine (L-DOPA). these aldehydes were proved to be noncompetitive inhibitors of tyrosinase and showed low toxicity on brine shrimp test (Kubo *et al.*, 1999).

Antihypertensive and Cardioprotective Activities.

Hypertension is the cause of heart diseases and it may cause stroke of the arteries, peripheral arterial diseases, and chronic kidney diseases if not treated. Many natural products have been found effective against hypertension. The cardiotonic effects of three triterpenoids, namely, uvaol , ursolic acid , and oleanolic acid isolate from the leaves of O. europaea, were examined. Oleanolic acid and uvaol showed a significant, dose-response vasodepressor effect; therefore, olive oil was suggested as a natural and cheap source of controlling hypertension (Somova *et al.*, 2004). A random parallel clinical trial was conducted on the patients of stage-1 hypertension to evaluate the antihypertensive effects of olive leaf extract in comparison with the reference drug Captopril. Olive leaf extract was administered at a dose of 500mg twice a day while the control group was treated with 25mg Captopril twice a day until 8 weeks. All the patients showed a significant decrease in their systolic as well as diastolic blood pressure after treatment and the patients treated with olive leaf extract showed better results than Captopril (Susalit, *et al.*, 2008). Ethanolic extract of olive leaf, upon injection intragastrically to mice at a dose of 250mg/Kg body weight, was found active against 11-deoxycorticosterone acetate induced hypertension (Circosta *et al.*, 1990). In another study, the ethanolic or chloroform extract of olive leaves showed a slow decrease in blood pressure in moderate hypertension after prolonged use (Luibl 1958).

Anti-Inflammatory and Antinociceptive Activities.

Extra virgin olive oil has shown remarkable anti-inflammatory activity due to oleocanthal, a compound present in EVOO which has a strikingly similar profile to ibuprofen, a synthetic anti-inflammatory drug (Beauchamp *et al.*, 2005). Studies on anti-inflammatory and antinociceptive effect of OLE on male Wistar rats showed that OLE doses of 50–200mg/Kg produce dose-dependent analgesic effects and intraperitoneal administration of 200mg/Kg OLE caused significant decrease in pain responses in formalin test (Esmaeili-Mahani *et al.*, 2010). The ethanolic and n-hexane extracts of olive fruits were investigated for their in vivo anti-inflammatory and antinociceptive activities. For anti-inflammatory activity the carrageenan-induced hind paw edema model was used and for the antinociceptive activity the hot plate test in mice was used. he results revealed that n-hexane extract showed activity at 400mg/Kg dose while ethanolic extract did not show a significant activity. A study was conducted to evaluate the traditional medicinal uses of olive leaves in Tunisia. Intraperitoneal administration of essential oil of *O. europaea* at doses of 100, 200, and 300mg/Kg caused a significant reduction in acetic acid-induced abdominal constrictions and paw edema in mice. Eidi *et al.* studied the anti-inflammatory and antinociceptive activities of olive oil to scientifically prove the use of olive oil as pain relieving in folk medicine. The antinociceptive activity was studied using hot plate, formalin, and writhing tests while acute anti-inflammatory effects of olive oil in mice were studied using xylene ear edema test (Eidi *et al.*, 2012). Similar set of studies was also conducted to show the effects of maslinic acid in acetic acid-induced writhing, inflammatory phase of formalin-induced pain, and capsaicin-induced mechanical allodynia in mice (Nieto *et al.*, 2013). The results indicated that the olive oil only decreased the second phase of formalin-induced pain while it exhibited antinociceptive activity against writhing-induced pain in mice by acetic acid. In the xylene ear edema test, olive oil showed significant anti-inflammatory activity in the mice while malonic acid also showed antiallodynic effects (Nieto *et al.*, 2013). Ursolic acid, a triterpenoid from olive leaves, has been reviewed for its anti- and proinflammatory activities (Nieto *et al.*, 2013).

Gastroprotective Effect

A study was carried out to check the effect of olive leaf extract on the gastric defense system against experimentally induced gastric lesions by absolute ethanol in mice. The OLE was administered at a dose of 40, 80, and 120mg/Kg while the reference drug ranitidine was given to the positive control at a dose of 50mg/Kg, intragastrically. The protective effect of both the OLE and ranitidine was similar and in conclusion OLE possessed significant gastroprotective activity. It was suggested that the activity may be due to the antioxidants present in OLE (Dekanski, *et al.*, 2009). Arsi´ c *et al.* described the gastroprotective efect of olive oil extract in respect to its quercetin content. he quercetin content of the sample was confirmed by HPLC. Cold-restraint stress (CRS) induced rat gastric mucosa lesions test was applied to observe the gastroprotective effect of the sample.

Neuroprotective Potential

It has been reported that Mediterranean diet has a healthy effect on its people and they have a reduced risk of neurodegenerative (88) and cancer risks including breast and colon cancer (Fehri *et al.*, 1996). Guan *et al.* investigated the effect of maslinic acid, a triterpenoid isolated from olive leaves, on neuroprotection in type 2 diabetic rats. Streptozotocin was injected to induceneuronal death in mice. Maslinic acid showed a significant neuroprotective activity in a dose-dependent manner (Trichopoulou *et al.*, 2000). In another similar study, the efect of maslinic acid was observed on cultures of neurons from cerebral cortex. The results revealed that maslinic acid promoted a dose-dependent neuron survival during glutamate toxicity and may be a lead for natural neuroprotective drugs (Vecchia and Bosetti, 2007). The effect of maslinic acid and its mechanism of action on cortical neurons using oxygen-glucose deprivation and the nreoxygenation of 24 hours. Flow cytometry assay was used to monitor neuronal apoptosis and the results showed that maslinic acid alleviated the neuron injury in a dose-dependent manner (Guan *et al.*, 2010).

CONCLUSION

O. europaea is an important medicinal plant used for the treatment of stomach problems, diabetes, hypertension, diarrhea, respiratory and urinary tract infections, skin diseases, bacterial and fungal infections, hemorrhoids, rheumatism, asthma, and hair loss. Pharmacological studies carried out on the fresh plant materials, crude extracts, and isolated components of *O. europaea* provide a reasonable support for its various traditional uses. Recent studies have been carried out focusing on evaluation of the antidiabetic, anticancer, antimicrobial, antifungal, antiviral, antioxidant, antihypertensive, gastroprotective, anti-inflammatory, antinociceptive, neuroprotective, and cardioprotective activities. Most of the mentioned pharmacological studies were aimed at confirming its traditional uses. It has been found that some of its traditional uses like antioxidant, antidiabetic, anticancer, and so forth have extensively been explored by several researchers. Most of the pharmacological studies carried out on *O. europaea* have been conducted on crude extracts of different parts of the plant and very few pharmacological reports are present for pure compounds isolated from the title plant of which oleuropein, maslinic acid, oleanolic acid, and so forth are the most abundant and notable. Thus, it is somehow difficult to reproduce the results of all the studies and pinpoint the exact bioactive metabolites. Hence, there is a further need of studying the pure isolates for their pharmacological properties.

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