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Original Research

Properties and uses of *Olea europaea*

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Abstract

The olive tree (*Olea europaea* L.) is rich in polyphenols and has been used since ancient times as a source of food. Olives, its fruits, are used for the extraction of olive oil and, to a lesser extent, for direct use as food. In addition, the olive pomace, a byproduct of the olive oil extraction process made up of husks, pulp residue and pits, is an interesting source of phenolic compounds, in particular oleuropein and ligstroside derivatives, flavonoids, phenolic acids and lignans. Olive oil is mainly composed of triacylglycerols (TAG; 98–99%), predominantly with monounsaturated oleic acid (up to 83%) with the remainder being palmitic, linoleic, stearic and palmitoleic acid.

There are also several lipophilic or amphiphilic microconstituents in virgin olive oil, including phytosterols, squalene, tocopherols, phenolic compounds and terpenic acid derivatives. Phenolic compounds, in turn, are present as phenolic acids or alcohols, oleuropein derivatives, lignans and flavonoids. There are many applications of the olive tree in clinical practice and several trials have demonstrated its associated beneficial properties.

Polyphenols are mainly characterized by an antioxidant action; among these, hydroxytyrosol (HT), which derives from the acid hydrolysis of oleuropein, has the greater antioxidant power. In addition, these compounds can prevent cells from initiating neoplastic transformation.

They also seem to be helpful in preventing cardiometabolic derangements, in improvement of the inflammatory response and modulation of bone metabolism.

Keywords: *Olea europaea*, oleuropein, hydroxytyrosol, polyphenols, cardiometabolic prevention, antioxidant action

Introduction

The olive tree (*Olea europaea* L.) belongs to the *Oleaceae* family and *Olea* genus. It is a fruit tree probably originally from Asia Minor and Syria, since in this region the spontaneous wild olive tree is very common, forming forests on the southern coast of Asia Minor.

Here, the Greeks began to cultivate it upon discovering its great properties and they gave it the special name of 'ἔλαια' which the Latins made 'Olea'.

It has been used since ancient times as a source of food. Olives, its fruits, are used for the extraction of olive oil and, to a lesser extent, for direct use as food. As a result of the bitter taste of freshly picked olives, due to the polyphenol content, their use as fruits in the diet requires specific treatments carried out using various methods aimed at olive debittering (reduction of bitter principles).

In addition, the olive pomace, a byproduct of the olive oil extraction process made up of husks, pulp residue and pits, deserves a mention. The pomace is recycled in the agrifood industry for the extraction of an edible oil, thanks to the lipid fraction contained in the olive seeds. The pomace, however, is not to be considered as a waste product only, being an interesting source of phenolic compounds, in particular oleuropein and ligstroside derivatives, flavonoids, phenolic acids and lignans with powerful antioxidant activity [1]. When olives are pressed during oil production, in fact, the polyphenols, due to their hydrophilic nature, are almost completely conveyed into the washing water of the machinery and of the olive paste, namely into the olive oil vegetation waters.

The amount of polyphenols that remains in olive oil is extremely low, approximately 1% of the total. There are many applications of the olive tree in clinical practice (**Table 1**) and several trials have demonstrated its associated beneficial

Table 1 Biological activities and effects of *Olea europaea* compounds

Activity	Mechanism of action	Beneficial effect on human health
Antioxidant	• Free radical and reactive oxygen/nitrogen species scavenging • Inhibition of LDL oxidation • Increase in all mitochondrial respiratory complex expression • Protection from reduction of mitochondrial DNA synthesis • Modulation of transcription factor activity (NRF1, TFAM)	Risk reduction for developing type 2 diabetes mellitus
Antineoplastic	• Inhibition of cancer cell proliferation by inducing apoptosis • Regulation of epigenetic changes • Antiproliferative effect	Prevention of cancer diseases
Cardiovascular protective	• Hypotensive effect by ACE inhibition • Improvement of endothelial function • Antiplatelet aggregation effect	Prevention of cardiovascular diseases
Hypoglycaemic	• Enhancement of glucose-induced insulin release • Increase in peripheral glucose absorption • Reduction of carbohydrate absorption in the intestine	Prevention of carbohydrate metabolism disorders
Lipid-lowering	• Increase in cholesterol excretion by stimulating secretion of bile cholesterol and then increasing its faecal excretion • Decrease in cholesterol biosynthesis by modulating genes involved in its synthesis • Protection of LDL from oxidative damage	Prevention of lipid metabolism disorders
Anti-inflammatory	• Inhibition of 5-lipoxygenase enzyme • Decrease in leukotriene B4 expression and other inflammatory cytokines	Improvement of inflammatory response
Bone metabolism modulation	• Increase in osteoblast activity • Increase in matrix mineralization process • Inhibition of bone resorption	Protection from bone loss

LDL = low-density lipoprotein; **NRF1** = nuclear respiratory factor 1; **TFAM** = mitochondrial transcription factor A; **ACE** = angiotensin-converting enzyme

properties. The olive tree is rich in polyphenols, and more than 8000 structures are known, including several hundred isolated from edible plants with different biological actions.

Olive oil is mainly composed of triacylglycerols (TAG; 98–99%), a diverse group of glycerol esters with different fatty acids, the predominant one in the TAG of olive oil being monounsaturated oleic acid (up to 83%). Palmitic, linoleic, stearic and palmitoleic acid make up the rest of the TAG of olive oil. There are also several lipophilic or amphiphilic microconstituents in virgin olive oil, including phytosterols, squalene, tocopherols, phenolic compounds and terpenic acid derivatives. Phenolic compounds, in turn, are present as phenolic acids or alcohols, oleuropein derivatives, lignans and flavonoids [2, 3].

Polyphenols appear to reduce morbidity and/or slow down the progression of cardiovascular, neurodegenerative and cancer diseases. The mechanism of action of polyphenols is strongly related to their antioxidant activity. It is known that polyphenols reduce the levels of reactive oxygen species in the human body. In addition, the health-benefitting properties of vegetable polyphenols comprise anti-inflammatory, antiallergic, antiatherogenic, antithrombotic and antimutagenic actions [4].

There is also a body of research that underlines their ability to modulate the human immune system by affecting the proliferation and activity of white blood cells, as well as the production of cytokines or other factors that participate in immunological defence [5].

Daily polyphenol intake ranges from 0.1 to 1.0 g per day [6] and the main dietary sources are fruits and vegetables, together with herbs, spices, seasonings, coffee, tea or wine [7].

Olive oil polyphenols are particularly interesting for their well-established beneficial effects on human health and metabolism, as well as for the popularity of olive oil in many different diets, and specifically, the Mediterranean cuisine.

Oleuropein, on the other hand, belongs to the secoiridoids, a group of coumarin derivatives [8]. It has been shown to be effective against various strains of bacteria, viruses, fungi, moulds and parasites. It also inhibits platelet aggregation [9]. Moreover, it is an important component of a patented formulation of an endothelial proliferation inhibitor.

Oral treatment with oleuropein results in a decreased number of blood vessels, demonstrating strong antiangiogenic properties [10].

Phenolic compounds (oleuropein, protocatechuic acid) within virgin olive oil have also been shown to inhibit the oxidation of low-density lipoprotein (LDL) mediated by macrophages [11].

Olive leaf and fruit extracts containing oleuropein protect the insulin-producing cell line (INS-1) from the deleterious effects of cytokines [12].

The European Food Safety Authority (EFSA) pronounced in 2011, through a group of experts, on olive polyphenols standardized for their hydroxytyrosol (HT) content and its derivatives [13].

Antioxidant action

The peculiarity of polyphenols is their antioxidant activity; several studies conducted on subjects affected by inflammatory disease both at the vascular and skin level (for example, psoriasis) have highlighted the soothing and curative effects of polyphenolic compounds, and in particular, of those recovered from oil waste. These phenolic substances from the olive tree act very quickly, are non-toxic and offer a number of human health benefits. Considering that polyphenols act with an antioxidant and anti-inflammatory mechanism, and that inflammation is the cause of many diseases, the intake of vegetable polyphenols administered with the diet or applied directly to the skin contributes significantly to both prevention and cure. The polyphenol that better characterizes the olive tree

is oleuropein: it is found both in olives (2% on dry matter) and in leaves and stems (1% on dry matter). HT, which derives from the acid hydrolysis of oleuropein, is the polyphenol with the greater antioxidant power. Its beneficial properties for human health are strongly linked to this molecule's ability to scavenge free radicals and reactive oxygen/nitrogen species, as well as to activate endogenous antioxidant systems in the body. The free radical-reducing properties of HT have been convincingly confirmed in rats in the context of diabetes mellitus studies [14].

Studies on the 3T3-L1 adipocyte cell line have shown that HT stimulates mitochondrial biosynthesis, which is reduced in patients with diabetes mellitus. Relatively low concentrations of HT in adipocytes increase the expression of all mitochondrial respiratory chain complexes, including ATP synthase.

HT protects mitochondria from the reduction of mitochondrial DNA synthesis and modulates the activity of key transcription factors, such as NRF1 (nuclear respiratory factor 1) and TFAM (mitochondrial transcription factor A).

Therefore, HT may contribute to reducing the risk of developing type 2 diabetes mellitus thanks to all these unique properties [15].

The EFSA pronounced on the antioxidant action of HT, oleuropein and its compounds, approving the terms 'reduces oxidative stress', 'has anti-oxidant properties' and 'has anti-oxidant activity' [13].

Antineoplastic action

It has been shown that some plant-derived polyphenols can directly or indirectly prevent cells from initiating neoplastic transformation due to xenobiotics and carcinogenic factors, thus contributing to a lower risk of developing cancer. Carcinogenesis is characterized by a change in the transcriptional activity of many genes, and consequently, in the biological function of the proteins encoded by those genes. Many studies have emphasized an essential role for polyphenolic compounds derived from vegetables, fruits or herbs in the regulation of epigenetic changes, resulting in antiproliferative protection [16].

Experimental studies have proven the protective role of dietary lipids especially in the development of colon cancer. In fact, epidemiological data have reported a lower incidence of colon cancer in the countries of the Mediterranean area, where olive oil (rich in oleic acid and polyphenols) is widely consumed, despite its caloric content [17, 18].

Cardiovascular protective action

It has been shown that oleuropein specifically targets arterial resistance and vessel stiffness, improving endothelial function and normalizing blood pressure (BP) values.

The olive leaf extract exerts a hypotensive action through a direct activity on the smooth muscle of blood vessels, modulating the flow through calcium channels [19], and on endothelium [20], with an excellent tolerability profile.

A double-blind, randomized, parallel and active-controlled trial conducted on 232 subjects aged between 25 and 60 years of age with stage 1 hypertension confirmed the antihypertensive effects and safety of olive leaf extract in comparison with the angiotensin-converting enzyme (ACE) inhibitor captopril [21].

The patients were divided into two groups treated with 500 mg of olive leaf extract or with dosages from 12.5 to 25 mg of captopril, based on the subject's response to therapy, twice daily. After eight weeks of treatment, a decrease in BP was observed in both groups.

The average systolic blood pressure (SBP) reduction from baseline to the end of the

study was 11.5 and 13.7 mmHg in the olive leaf extract group and captopril group, respectively, while the average reduction in diastolic blood pressure (DBP) was 4.8 and 6.4 mmHg, respectively. Since such reductions were not significantly different between groups, the olive leaf extract showed a similar efficacy to captopril in lowering SBP and DBP in subjects with stage 1 hypertension [21]. The authors also suggested that the constituents of olive leaf extract could inhibit ACE, an effect that helps relax artery walls.

Hypoglycaemic action

In recent years, *in vivo* animal model studies have increased in number, especially in rats, in which it has been shown that oral administration of olive leaf extract and, in particular, oleuropein, can lower blood glucose levels *via* a mechanism that would seem to act on insulin release from the pancreas.

The hypoglycaemic activity of this compound may in fact depend on two mechanisms: (a) enhancement of glucose-induced insulin release and (b) an increase in peripheral glucose absorption; moreover, oleuropein and the tannins of the leaves are able to act as β-glucosidase inhibitors, reducing the absorption of carbohydrates in the intestine. In the epithelial cells of the small intestine, they could access a glucose transporter, such as a sodium-dependent glucose transporter (SGLT1), thus allowing the direct entry of glucose into the cells. Human studies have shown that olive leaf extract is able to improve insulin sensitivity and increase pancreatic β-cell activity by 28%. A decrease in the insulin and glucose area under the curve (AUC) has also been observed, demonstrating a better control comparable to that observed with pharmaceutical drugs. Furthermore, the results are independent of lifestyle factors, such as diet or physical activity, body mass index and fat distribution. Certainly, treatment with olive leaf extract is associated with a beneficial hypoglycaemic effect in diabetic patients, although further studies are needed to investigate the mechanisms of action and possible contraindications [22–24].

Lipid-lowering action

In the study of Susalit *et al*. [21], where an olive leaf extract was compared with captopril, the authors reported an average reduction of 7.8, 2.8 and 2.9% in TAG, total cholesterol (TC) and LDL levels, respectively, only in the group treated with olive leaf extract.

At the cellular level, the phenols of olives could reduce blood cholesterol through a dual mechanism:
(1) increasing excretion (by stimulating secretion of bile cholesterol, thereby increasing its faecal excretion) and (**2**) lowering biosynthesis (by modulating genes involved in cholesterol synthesis). The EFSA has made a pronouncement on the action of olive leaf extract on lipid metabolism, declaring and underlining the protective action on LDL from oxidative damage by HT, oleuropein and its compounds [13].

Anti-inflammatory action

The anti-inflammatory activity of oleuropein, observed in numerous experimental models, would seem to be mediated through the inhibition of 5-lipoxygenase enzyme.
This mechanism would result in the reduction of leukotriene B4 expression and of other inflammatory cytokines involved in the molecular events underlying the inflammatory process.
Although still to be confirmed, this property could certainly be an added value to the clinical efficacy of oleuropein. A study performed on Wistar rats subjected to two different diets,

containing extra virgin olive oil (EVOO) (rich in monounsaturated oleic acid) or sunflower oil (rich in polyunsaturated linoleic acid) evaluated, *in vivo*, the effects of different sources of fatty acids [25]. Regarding the lipid profile, plasma levels of TAG, TC, phospholipids, total lipids and polyunsaturated fatty acids were lower in rats that had followed a diet based on EVOO, while lipid peroxidation was higher in rats with a sunflower oil-based diet in which greater oxidative stress was observed [25].

The confirmation of this property occurred with the observation that the introduction of olive oil into the diet inhibited the formation of inflammatory foci in the crypts and in the intestinal mucosa [26], as well as blocking the stages of carcinogenesis *in vitro* [27–29].

These beneficial effects linked to the consumption of olive oil may be due both to the high MUFA (monounsaturated fatty acid) content and to the health-promoting properties of its minor bioactive compounds.

For HT, for example, abundantly present in EVOO, cardioprotective, antioxidant and anti-inflammatory properties, and an antiplatelet aggregation action, have been demonstrated, together with its protective effect on mononuclear cells of peripheral blood against oxidative stress, the inhibition of cancer cell proliferation by inducing apoptosis, the arrest of the cell cycle and an improvement of the inflammatory response.

Bone metabolism modulation action

Oleuropein, a polyphenol present in various parts of the olive tree (fruit and leaves), is effective with respect to the development of osteoblasts and in adipogenesis by acting on the multipotential mesenchymal stem cells (MSCs) of the human bone marrow. It has been shown that oleuropein not only stimulates the development of osteoblasts, but also the process of matrix mineralization and the inhibition of bone resorption [30].

Conclusions

Olive oil, in which the Mediterranean diet is rich, contains polyphenols and lipophilic or amphiphilic microconstituents, including phytosterols, squalene, tocopherols, phenolic compounds and terpenic acid derivatives. Thanks to multiple properties, *Olea europaea* and its derivatives seem to be helpful in the prevention of cardiometabolic derangements, can be added to drugs for the treatment of some chronic diseases and are well tolerated. The polyphenols contained in olive oil, of which pomace is particularly rich, are protective against risk factors for coronary heart disease, especially in subjects with high oxidative stress (such as individuals with hypertension, diabetes or cardiopathy).

Finally, considering that polyphenols, in particular oleuropein, also act with an antioxidant and anti-inflammatory mechanism, and that inflammation is the cause of many diseases, the intake of vegetable polyphenols administered with the diet or in supplements contributes significantly to the prevention of many pathologies or to their treatment synergizing with pharmaceutical drugs.

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