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Review Article

THE BIOLOGICAL ACTIVITIES OF OLEUROPEIN AND HYDROXYTYROSOL

Ibrahim CANBEY[1], Aycan YIGIT CINAR[2], Ozan GURBUZ[3]

Abstract Oleuropein and hydroxytyrosol, two bioactive phenolic compounds predominantly found in olive leaves and olive oil, have garnered significant attention due to their extensive range of biological activities. These compounds exhibit potent antioxidant, anti-inflammatory, and antimicrobial properties, which contribute to their therapeutic potential in preventing and managing various chronic diseases, including cardiovascular disorders, metabolic syndromes, and neurodegenerative conditions. Furthermore, recent studies highlight their role in modulating cellular signaling pathways, promoting apoptosis in cancer cells, and enhancing immune responses. This review aims to provide a comprehensive analysis of the current scientific literature on the biological activities of oleuropein and hydroxytyrosol, with an emphasis on providing scientific data for future scientific studies, applications in clinical and nutraceutical settings.

Keywords: Oleuropein; hydroxytyrosol; biological activities; bioactive phenolic compounds.

TÜBİTAK ULAKBİM

1Bursa Uludag University, Faculty of Agriculture, Department of Food Engineering, 16059, Nilufer, Bursa, Turkiye.
2Bursa Technical University, Faculty of Engineering and Natural Science, Department of Food Engineering, https://orcid.org/0000-0003-2038-725X 16310, Bursa, Turkiye
3Bursa Uludag University, Faculty of Agriculture, Department of Food Engineering, 16059, Nilufer, Bursa, Turkiye.

Introduction

The Mediterranean diet is highly regarded for its role in reducing the risk of numerous chronic illnesses, such as cardiovascular disorders, neurodegenerative diseases, and various types of cancer (1,2,80). A defining characteristic of the this diet type is its abundant use of olive oil and derivatives, renowned for their high biophenol content (3,81). Oleuropein (OLE) and hydroxytyrosol (HT) are two primary polyphenolic compounds found in the olive tree (*Olea europaea*) and its products, particularly in olive oil (80). Derived from tyrosine or phenylalanine, these phytochemicals impart a bitter and sharp flavor to olive oil due to their intricate interplay with the taste receptors (25,82,83). Nevertheless, various genetic and environmental variables influence the levels, profiles, and bioaccessibility of these polyphenols (108). These compounds are widely recognized for their potent biological activities, which contribute to the health benefits associated with olive oil consumption (80).

OLE is a prevalent biophenolic compound found in a range of olive-derived products, including olive leaves, fruits, and oil (4,5). Its content varies significantly depending on the olive cultivar, geographic region, and the method of olive oil production. This compound is also present in olives in their unripe, bitter form, contributing to the bitterness of the fruit (80,81). OLE, the predominant phenolic constituent in olive oil, is distributed across various parts of the olive. Belonging to the secoiridoid class, it undergoes hydrolysis to yield HT and 2-(3,4-dihydroxyphenyl)-ethanol. The abundance of this bioactive compound is greater in the initial phases of fruit maturation, where it is converted into glycosylated derivatives by esterase enzymes (51,85). This secoiridoid has garnered significant interest from researchers owing to its diverse health-promoting effects, such as antioxidative, neural-protective, inflammation-modulating, oncoprotective, heart-protective, etc. (6,7,8).

The other important bioactive phytochemical HT is a smaller phenolic compound, which is the primary metabolite of oleuropein after hydrolysis (81). OLE is broken down through hydrolysis during the ripening of olives and is subsequently transformed into HT upon digestion, facilitated by lipase enzymes (5,9). It is abundant in both olive oil and the olive fruit, and its content increases as the fruit ripens (19). Structurally, hydroxytyrosol is a simple phenolic compound, consisting of a hydroxylated tyrosol structure (80). Hydroxytyrosol is also found in other parts of the olive tree, including the leaves and stems (15). HT, also exhibits biological activities like OLE, such as antioxidative, brain-protective, antimicrobial, heart health-enhancing, cancer-fighting, etc. (5,10-12).

This review examines the biological properties and functions of oleuropein and hydroxytyrosol, which are present in varying concentrations in olives, olive products, and their by-products, focusing on their molecular mechanisms of action, therapeutic potential, and implications for human health, and providing scientific insights that may be essential for future research.

The crucial bioactive compounds: oleuropein and hydroxytyrosol

OLE, the main phenolic compound present in olives belonging to the Oleaceae family, may account for up to 14% of their total mass, equivalent to 140 mg per gram of dry matter (85,98,99). Nonetheless, certain studies report that olive leaves may contain oleuropein at concentrations reaching as high as 19% (w/w) (106). Identified in 1908 by Bourquelot and Vintilesco, it is composed of three distinct subunits: a secoiridoid (elenolic acid), a polyphenol (HT), and a glucose molecule. The synthesis of OLE in olives takes place within the secondary metabolism of terpenes. In this metabolic route, the mevalonic acid pathway is pivotal, with a branching point leading to the production of OLE (95,99). This secoiridoid is an ester derivative of 2-(3,4-

dihydroxyphenyl) ethanol (hydroxytyrosol) and exhibits an oleosidic framework, a common characteristic shared by many secoiridoid glucosides found within the Oleaceae family (7,13,14,81), and this bioactive compound chemically consists of a glucose molecule attached to a secoiridoid aglycone, which contains a phenolic structure. OLE is the primary compound found in olives, contributing to the characteristic bitter flavor of untreated and raw olives (7), and both fruits and leaves of olive are abundant in the OLE (Figure 1), with minimal levels of its metabolite, HT (15). As olives ripen, the level of OLE diminishes, whereas the concentration of HT rises as a result of OLE hydrolysis (5). For example; the levels of HT and OLE in olive oil can differ, with values typically found between 1.4–5.6 mg/kg for HT and 2.3–9.0 mg/kg for OLE (15,16). OLE is renowned for its diverse pharmacological and biological activities, including antioxidative, anti-inflammatory, antiviral, anticancer, antimicrobial, protecting heart health, and hypolipidemic effects. These properties have made oleuropein a central subject of extensive *in vivo* and *in vitro* researches (100,101,102).

The other important biaoctive compound HT, or 3,4-dihydroxyphenylethanol, is a phenolic alcohol with a molecular weight of 154.16 g/mol and a chemical formula of $C_8H_{10}O_3$, which is primarily obtained from olives as a byproduct in the olive oil manufacturing process (17,80). In olive oil and olives, HT is found in both its unbound form and as a conjugate with various other substances, including OLE (18). The formation of HT occurs via the hydrolytic breakdown of oleuropein, which is naturally occurring in olives, and this process happens inherently during the maturation of olives and can also be induced artificially throughout the processing and also storage of table olives (Figure 2) (19). As can be seen in Figure 2, the degradation metabolites of oleuropein arehydroxytyrosol, elenolic acid, and glucose (99,109). Following hydrolysis, HT becomes accessible in a form that allows for extraction and further application (20,21). HT is a low-molecular-weight compound, resulting in a higher bioactivity-to-mass ratio compared to that of OLE. HT demonstrates potent antioxidative properties and is closely linked to positive outcomes in the management of several human diseases (111), exhibiting anti-tumor properties (112,113), heart-protecting (114,115), and neural protection properties (116,117). The surge in global interest in OLE and HT can be attributed to its wide-ranging health functions and biological effects (12,16,22-24).

The biological activities of oleuropein and hydroxytyrosol

Polyphenols are organic, polar compounds that are commonly present in olive oil, playing a significant role in the health benefits associated with the Mediterranean diet (25-27). Nutritional research involving human participants, as well as animal and *in vitro* studies, has shown that OLE and HT derived from olive, olive oil, olive leaves, etc. display distinct biological activities and health-enhancing functions (12,16,28). OLE and its metabolite, HT, have demonstrated anti-cellular proliferation, apoptosis-inhibiting, inflammation-suppressing, and obesity-preventing effects (107). The biological acitvities of OLE and HT are summarized in Figure 3.

OLE and HT have garnered significant interest due to their availability, safety profile, potent antioxidative properties, effective scavenging of oxygen-derived free radicals, and debated inflammation-reducing effects (80,81). The antioxidant activities of these phenolic substituents have been demonstrated to surpass those of vitamin E or butylated hydroxytoluene in terms of potency (25). At elevated concentrations, these bioactive compounds exhibit pro-oxidant activity in cancer cells, a phenomenon that is associated with their anti-growth effects (97). This pro-oxidant activity could also be associated with the cytotoxicity of

OLE and HT at these high concentrations (84).

Over the past two decades, OLE and HT, either individually or in combination, have been the subject of extensive research regarding infective diseases and the prevention/management of chronic non-communicable diseases, such as cancer, yielding promising findings from *in vitro* and *in vivo*. OLE and its metabolite, HT, have demonstrated significant cancer-inhibiting effects across a variety of tumors, including those of the bladder, brain, breast, cervical, colorectal, gastric, hematologic, liver, lung, prostate, skin, and thyroid regions. Additionally, these bioactive phytochemicals are capable of crossing the blood-brain barrier and exhibit no toxic effects, making them potential candidates for the treatment of various types of neoplastic lesions. Given the promising results of OLE and HT as potential therapies for various tumors, it is crucial to investigate the potential of these compounds in the context of neuroblastoma. Investigation into these compounds is ongoing, with numerous researches highlighting the necessity for further in-depth analysis of their mechanisms of action, especially in relation to cancer therapy. The promising results observed in *in vitro*/*in vivo* investigations provide a solid foundation for continued research, particularly in pediatric oncology, where there is an ongoing demand for safer and less toxic treatment options (51,80,81,86,87,88,89,90,91,92).

Moreover, these significant bioactive compounds exhibits strong antioxidative properties, eliminating free radicals, inhibiting oxidative degradation of lipids, preventing oxidative stress, and protecting cellular integrity which plays a key role in aging and various diseases, including heart and blood vessel-related and neurological degeneration disorders (7,8,12,16,81,96). Besides, the worldwide awareness for naturally antioxidative substances like OLE and HT is growing as consumers become more aware of their health benefits and as there is a shift toward natural substitutes for synthetic additives (12,29,30). Particularly, HT is a extensively researched constituent of the olive tree and a recognized food additive with diverse biological properties. Consequently, the extraction of HT-rich compounds from natural sources has become a focal point of scientific research, driven by the growing market demand for products enriched with naturally occurring antioxidants (110).

Moreover, OLE has been recognized for its ability to lower blood pressure and its wide-ranging pharmacological activity, including heart-guarding, inflammation-suppressing, cancer-preventing, and neural protection properties (93). Indeed, the neural protection properties of OLE have been demonstrated through its ability to trigger apoptosis and autophagy, as well as to suppress the activation of microglia and astrocytes, thereby preventing the excessive release of inflammation-inducing cytokines and, in turn, mitigating central nervous system inflammation. This explains the association between OLE intake and a reduced likelihood of developing Alzheimer's disease, persistent sadness, and other neurological conditions (94). Furthermore, OLE demonstrated a notable inflammation-preventing effect in rats by decreasing levels of TNF, IL-1, COX-2, and NO (103), as well as reducing the mRNA expression of immune-stimulating cytokines in the brains of diabetic rats (104). A study revealed that OLE's gastrointestinal instability was observed under simulated conditions using human digestive enzymes. Additionally, the research demonstrated a potent cell-proliferation blocking and inflammatory-preventing activities of both pure OLE and olive leaf extract. However, to preserve the biological activity of OLE as a dietary supplement, olive leaf extract, or infusion, microencapsulation techniques should be employed due to its gastrointestinal instability (99). In another study, it was found that administering OLE to diabetic rats led to a reduction in serum leptin and an raise in rates of adiponectin, while also significantly inhibiting the elevated expression of COX-2 and TNF-α mRNA in the livers of the STZ-treated group. Consequently,

OLE has demonstrated encouraging outcomes in alleviating high cholesterol, free radical damage, irritation, and biomarkers of hepatic dysfunction in rats with diabetes (105).

Conclusion

In conclusion, OLE and HT emerge as promising natural compounds with a broad spectrum of biological activities that underscore their potential as therapeutic agents. Their antioxidative, anticancer, anti-inflammatory, antimicrobial, and neuroprotective properties, combined with their roles in modulating critical molecular pathways, suggest significant applications in the prevention and management of chronic diseases such as cardiovascular disorders, cancer, and neurodegenerative conditions. Given their potential, these compounds represent valuable targets for further research and may contribute significantly to the development of functional foods and therapeutic agents. However, despite their demonstrated efficacy in preclinical studies, further research is needed to establish their pharmacokinetics, bioavailability, and long-term safety in clinical settings. Future investigations should focus on optimizing their delivery systems and exploring synergistic effects with other bioactive compounds to fully harness their therapeutic potential.

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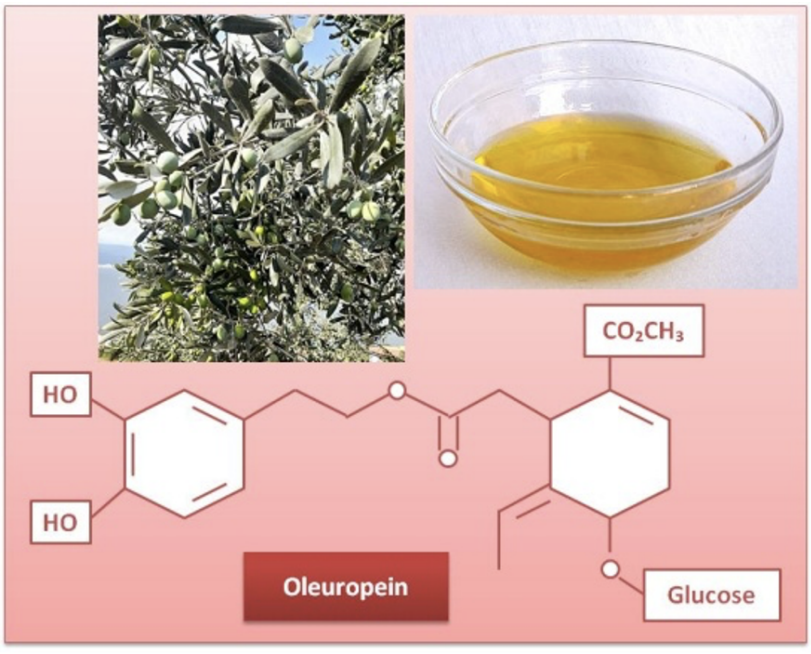

Figure 1. The chemical structure of OLE (7,16)

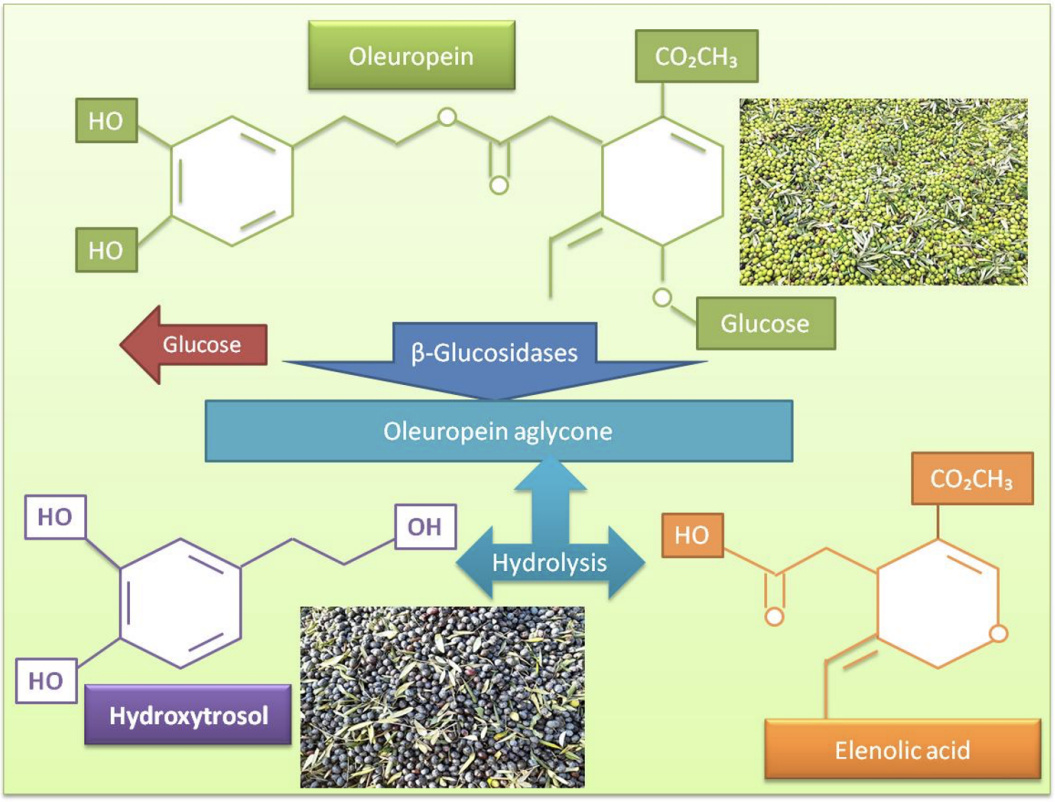

Figure 2. The enzymatic breakdown of OLE results in the formation of hydroxytyrosol (16,19,99)

Oleuropein (secoiridoid)	Hydroxytyrosol (phenylethanoid)
• **Anti-inflammatory** (14,31-33) • **Antimicrobial** (31,34-37) • **Anticancer** (7,9,14,37-40,80) • **Antitumor, pro-apoptotic and anti-proliferative activities against several cancer cell lines in humans** (41-45) • **Antioxidant** (14,33,43,46-49) • **Suppressing reactive oxygen species** (50-53) • **Antihypertensive** (54), **antidiabetic** (14) • **Hypoglycemic** (55,56), **hypolipidemic** (46), **antiobesity** (57) • **Cardioprotective** (14,37,58) • **Wound-healing activity on skin, etc.** (37,48)	• **Antioxidant** (11,24,59-64) • **Reactive oxygen species scavenger** (11, 24,62) • **Cardioprotective** (11,24,61,62,63,65,66, 68-70) • **Anti-inflammatory** (59,63,67,71-75) • **Anti-apoptotic** (67,71-75,80) • **Neuroprotective** (61,65,66,68-70) • **Anticancer, antimicrobial, protecting skin and eye** (61,65,66,69,80) • **Anti-fibrogenesis, preventing osteoporosis, positive impacts on obesity, hypercholesterolemia, insulin resistance** (76-79)

Figure 3. The biological activities of OLE and HT (7,8,12,16,81)