HYDROXYTYROSOL and OLEOCANTHAL: BIOACTIVE COMPOUNDS in OLIVE and OLIVE PRODUCTS with THERAPEUTIC PERSPECTIVES

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PREFACE

Olive is a significant plant species that grows and is cultivated in areas with a Mediterranean climate, processed into products, such as table olives and olive oil varieties, has high commercial and economic value, is effective on human health thanks to the essential nutrients and bioactive compounds it contains, and is considered one of the basic elements of the Mediterranean diet.

In this book, various biological properties and effects on human health of hydroxytyrosol and oleocanthal compounds, which are two crucial secondary metabolites with phenolic characters found in olives and their products, have been investigated and detailed information has been presented in the light of scientific studies.

As can be seen from the datas presented, I believe that these two bioactive compounds can be further evaluated as two substantial herbal natural resources for scientific studies to be conducted in many areas (food, pharmacology, medicine, cosmetics, etc.) in the future, and they will be used as two promising compounds, especially in functional food and neutraceutical uses.

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INTRODUCTION

The Mediterranean diet, which has attracted substantial scientific interest due to its positive implications for health of human (Arangia et al., 2023; Xu et al., 2025), has been linked to a reduced prevalence of oncological disease, cardiac and vascular disorders, and central nervous system degenerative conditions (Gallardo-Fernández et al., 2022a and 2022b). The olive is a highly significant plant species with considerable commercial value, commonly found in regions where the Mediterranean climate prevails worldwide, and a cornerstone of the Mediterranean dietary pattern. Observed in tree and shrub forms, the fruits of the olive, harvested at specific times, are predominantly utilized either as table olives (TOs) or processed into olive oil (OO). Such products substantially enhance the commercial value of the olive. Furthermore, olives contain important bioactive compounds exhibiting diverse biological properties (Rodrigues et al., 2020; Silva and Schmiele, 2021), thereby increasing not only their commercial but also their biological value. These bioactive compounds are present in the olive fruit (OF) and are either directly transferred into the final product or transformed into different components during processing (e.g., OO production). One of the most crucial bioactive compounds formed during the production of OO is oleocanthal (OLC) (Vougogiannopoulou et al., 2014; Rodríguez-Morató et al., 2016; De Medina et al., 2017; Francisco et al., 2019; Di Risola et al., 2025). Besides, olive contains hydroxytyrosol (HT), a prominent phenolic

compound (PhC) found in products and derivatives of *Olea europaea L.* (Prevete et al., 2025; Xu et al., 2025).

HT, typically not present in its free form, is produced through hydrolysis of oleuropein (OLE) by enzymatically or chemically (García-Molina et al., 2024; Messa et al., 2024). HT and other polyphenolic compounds are primarily present in virgin olive oil (VOO), a vital natural olive-derived product (Filardo et al., 2024; Frumuzachi et al., 2024 and 2025; Zodio et al., 2025). In addition, HT, recognized for its established biological activities, is also detected in OFs and TOs (Fernández-Prior et al., 2021; Gallardo-Fernández et al., 2022a and 2022b). Furthermore, this secondary metabolite (SM) represents one of the principal phenolics found in olive leaves (OLs) (Arangia et al., 2023; Georgiou et al., 2025).

The distribution and concentration of HT across various parts and processed forms of the olive significantly affect their biofunctional attributes. This SM is widely acknowledged for its potent antioxidative capacity and extensive range of biological functions, such as angiogenesis-inhibiting, anticarcinogenic, heart-protective, inflammation-suppressing, microbicidal, neuronal-protective, and virucidal activities (Martínez et al., 2019; Gallardo-Fernández et al., 2020 and 2022a, and 2022b; Filardo et al., 2024; Tang et al., 2024; Xu et al., 2025). Moreover, HT leads to the inhibition of microbial growth and cancer cell proliferation while simultaneously supporting cognitive and cardiovascular function (Fernández-Bolaños et al., 2008; Richard et al., 2011; Batarfi et al., 2024; García-Molina et al., 2024). Nevertheless, its considerable hydrophilicity results in

suboptimal pharmacokinetic behavior, thereby limiting its applicability in therapeutic contexts (Prevete et al., 2025).

Besides HT, in relation to health and bioactivity, particular attention has been drawn to OLC, which possesses a secoiridoid structure (Francisco et al., 2019; Marrero et al., 2023). This SM exhibits nutraceutical (Romani et al., 2019; Lozano-Castellón et al., 2020) and anti-inflammatory properties (Lucas et al., 2011; Carpi et al., 2019; Marrero et al., 2023). Additionally, it was reported that OLC demonstrates anti-inflammatory activity comparable to that of ibuprofen, a non-steroidal anti-inflammatory drug (Beauchamp et al., 2005). Moreover, this compound has been associated with anti-cancer effects (LeGendre et al., 2015; Fogli et al., 2016; Di Risola et al., 2025), anti-Alzheimer's effects (Monti et al., 2012; Qosa et al., 2015), protective effects against joint diseases/arthropathy (Scotece et al., 2012), and a cardioprotective role against cardiovascular diseases (CVDs) (Agrawal et al., 2017; Cuffaro et al., 2023). It also exhibits neuroprotective effects (Francioso et al., 2020; Di Risola et al., 2025).

In this book, the bioactive properties and therapeutic potential of HT and OLC, substantial bioactive PhCs found in olive and olive products, are investigated by utilizing scientific studies, and it is emphasized that these phytochemicals can be a promising natural source for future scientific research in various fields, such as medicine, pharmacy and food sciences.

1. THE DEFINITION and CHARACTERISTICS of HYDROXYTYROSOL and OLEOCANTHAL

1.1. Hydroxytyrosol

HT [2-(3,4-dihydroxyphenyl) is a major bioactive component of extra virgin olive oil (EVOO), olives (*Olea europaea L.*), leaves, and even wine (Chatzikonstantinou et al., 2024; Tang et al., 2024). It is primarily present in its esterified form as secoiridoid derivatives (OLE and its aglycone) or in free form (Robles-Almazán et al., 2018). As a catechol group member, HT is classified as a primary alcohol (Arangia et al., 2023).

The enzymatic breakdown of OLE is catalyzed by β-glycosidase and esterase, yielding derivatives such as HT, elenolic acid, and glucose (Figure 1) (Omar, 2010; Grewal et al., 2020; Canbey et al., 2024; García-Molina et al., 2024; Messa et al., 2024). When Figure 1 is examined; OLE is converted into HT and elenolic acid glucoside compounds by esterase enzyme. In addition, OLE is first converted into glucose and OLE aglycone compounds by β-glucosidase enzyme, and then OLE aglycone is turn into HT by esterase enzyme (Charoenprasert & Mitchell, 2012; Britton et al., 2019; Frumuzachi et al., 2024; García-Molina et al., 2024; Soldo et al., 2024).

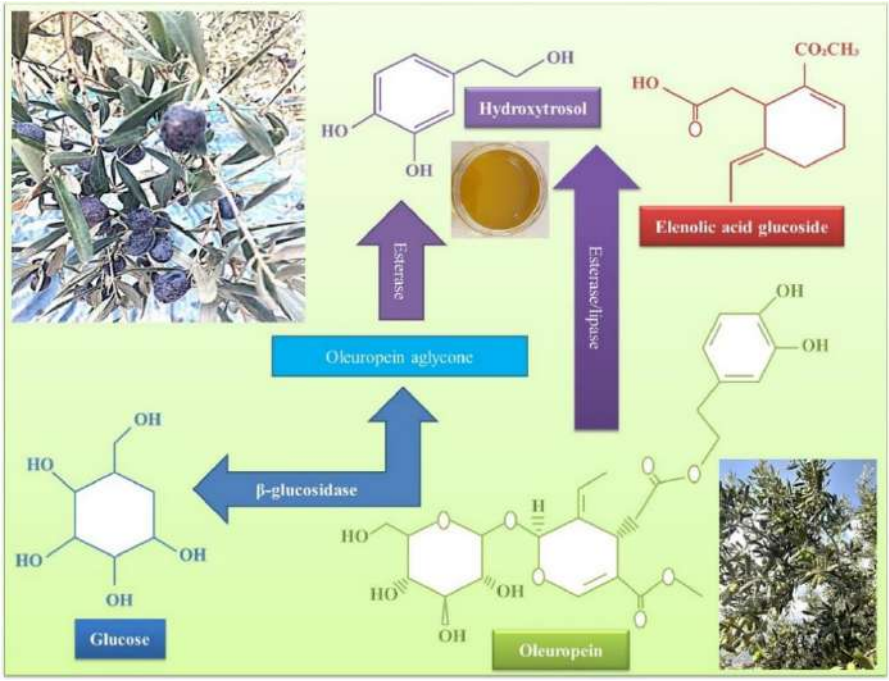


Figure 1: The HT Formation from OLE by β-Glucosidase and Esterase

References: Modified from Grewal et al., 2020; Canbey et al., 2024; García-Molina et al., 2024; Messa et al., 2024.

HT, a low molecular weight phenolic acid, is predominantly found in ripened olive drupes (Russo et al., 2020; Luzi et al., 2021; Marrone et al., 2024). The concentration of free HT increases during olive maturation and OO processing due to β-glucosidase activity, which releases HT from its secoiridoid precursors (Britton et al., 2019; Plastina et al., 2019; Romani et al., 2019; Otero et al., 2021; Hassena et al., 2025). HT is more prevalent in the aqueous by-products of oil extraction, such as pomace and olive mill wastewater, than in OO itself. In addition to enzymatic degradation, acid-catalyzed hydrolysis,

a widely utilized method in laboratory and industrial applications, is another pathway for producing free HT from OLE (De Leonardis et al., 2008; Klen & Vodopivec, 2011; Kalogerakis et al., 2013; Xu et al., 2018; Asghar et al., 2024; Messa et al., 2024).

HT exhibits a broad spectrum of health benefits, such as anticancer, anti-inflammatory, antimicrobial, antioxidative, cardio- and neuro-protectives, wound-healing effects, etc. (Plastina et al., 2019; Fernández-Prior et al., 2021; Chatzikonstantinou et al., 2024). Its potent antioxidant activity is attributed to the o-dihydroxyphenyl moiety, which facilitates free radical scavenging through quinone formation. Additionally, HT can donate hydrogen ions, enhancing its iron-chelating efficacy compared to tyrosol (Tyr) (Karković Marković et al., 2019; Ricelli et al., 2020; Bucciantini et al., 2021; Arangia et al., 2023).

1.2. Oleocanthal

OLC ($C_{17}H_{20}O_5$) (Figure 2) is an important Tyr ester that exhibits a chemical structure closely resembling that of OLE (Kotsiou & Tesseromatis, 2017), and it is also known as deacetoxy-ligstroside aglycone (El Haouari et al., 2020). OLC was first documented in the literature in 1992 as a PhC present in EVOO, and the chemical structure of this compound was subsequently elucidated by Montedoro and colleagues in 1993 (Montedoro et al., 1992a, 1992b, and 1993; El Haouari et al., 2020; Leo et al., 2025).

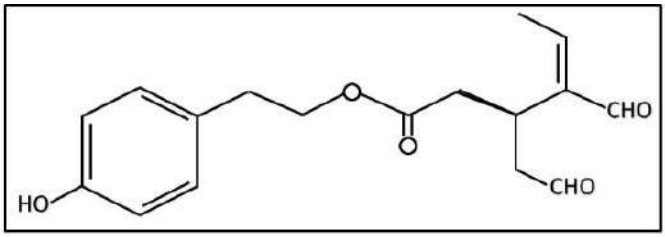


Figure 2: The chemical structure of OLC

Reference: Modified from Infante et al., 2023.

In 2003, OLC was reported to be the sole PhC responsible for the throat irritation, burning sensation, and bitterness characteristic of EVOO (Andrewes et al., 2003). The name "oleocanthal" is derived from the combination of “oleo-” (referring to olive), “canth-” (indicating a stinging or burning sensation), and “-al” (denoting an aldehyde group) (Beauchamp et al., 2005; Cicerale et al., 2009). Subsequently, various laboratory studies attempted the chemical synthesis of OLC (English & Williams, 2009; Valli et al., 2013), leading to the development of several analog compounds through Tyr esterification and carbamoylation reactions (El Haouari et al., 2020). Naturally occurring OLC possesses an S-configuration at its chiral carbon center, whereas its synthetic counterpart predominantly exhibits the R-configuration (Beauchamp et al., 2005; Cicerale et al., 2009).

In the literature, OLC has been referred to by various alternative names, including deacetoxy-dialdehydic ligstroside aglycone (Peyrot des Gachons et al., 2011), decarboxymethyl ligstroside aglycone (Cicerale et al., 2009), dialdehydic form of deacetoxy ligstroside

glucoside (Abuznait et al., 2013), deacetoxy ligstroside aglycone (Garcia-Villalba et al., 2010), and p-hydroxyphenylethanol-elenolic acid dialdehyde (Fini et al., 2008; Casamenti & Stefani, 2017; El Haouari et al., 2020).

1.2.1. Oleocanthal concentration in olive oil

Among the different types of OO, EVOO is characterized by its extraction through mechanical or other physical means under specific thermal conditions that do not induce chemical alterations. Furthermore, it undergoes no treatments beyond washing, decantation, centrifugation, or filtration. This high-quality oil is never produced through re-esterification processes involving solvents or chemically active adjuvants, nor is it blended with oils of other types. The processing methods employed ensure the preservation of health-related properties, which are primarily attributed to minor bioactive constituents like PhCs (Ambra et al., 2017; Jimenez-Lopez et al., 2020; Di Risola et al., 2025).

EVOO (Figure 3) is a product of high biological value, a characteristic largely conferred by its rich polyphenolic composition. In most EVOO varieties, PhCs are typically found in concentrations ranging from 100 mg/kg to 300 mg/kg of oil (Andrewes et al., 2003); however, higher amounts, between 500 mg/kg and 1000 mg/kg, have also been reported (Monti et al., 2001). In this context, the amount of OLC in EVOO has been documented to exhibit considerable variation, with concentrations spanning from 0.2 mg/kg to as high as 498 mg/kg (Gomez-Rico et al., 2006). These concentrations correspond to

approximately 10% of the total phenolic content (Fogliano & Sacchi, 2006; Cardeno et al., 2013). Nevertheless, higher relative concentrations of OLC, exceeding 10% of total phenolics, have also been observed (Karkoula et al., 2012 and 2014). The rate of OLC in natural OOs is significantly influenced by a multitude of factors, including the olive cultivar and species, the geographical region of cultivation, producing techniques, harvest ripeness, fruit extraction methods, the age of the olive tree (OT), storage conditions, and culinary processing methods (El Haouari et al., 2020; Silva & Schmiele, 2021; Kahraman et al., 2023).

Figure 3: An example of EVOO

The ripening stage of the OF at the time of harvest significantly influences the OLC concentration in EVOO (Morello et al., 2004; Gomez-Rico et al., 2006; Cicerale et al., 2011). In one study, the OLC concentrations in EVOO were reported as 123.24 ± 6.48 mg/kg, 114.20 ± 17.42 mg/kg, and 152.22 ± 10.54 mg/kg for early, normal,

and late harvest periods, respectively (Cicerale et al., 2011). Additionally, another investigation revealed that over a short two-month period, during which the maturity of the OF increased and the harvest was delayed, the OLC concentration in EVOO decreased by approximately 43% (Morello et al., 2004). Moreover, a study examining oils produced from olives harvested at various time points between October 2006 and January 2007 demonstrated that the highest OLC concentration (13.9 mg/kg) was attained during the second harvest date (Giuffrè et al., 2010).

Cultivar and geographical region are also critical factors influencing the OLC concentration in OO (Beauchamp et al., 2005; Franconi et al., 2006; Bajoub et al., 2015; Negro et al., 2019). In a study conducted within this context, the data indicated that EVOO produced in Italy exhibited significantly higher OLC concentrations (up to 191.8 ± 2.7 mg/kg), while olives cultivated in the US demonstrated substantially lower OLC levels (22.6 ± 0.6 mg/kg) (Beauchamp et al., 2005). In another investigation, the OLC concentrations in EVOOs derived from Taggiasca and Seggianese cultivars were reported as 8.3 ± 4.0 mg/kg and 53.0 ± 12.0 mg/kg, respectively (Franconi et al., 2006). Furthermore, high OLC concentrations were identified in certain Italian EVOOs, specifically in the Colozzese and Oliva Grossa varieties, with measured levels of 75.4 mg/kg and 103.4 mg/kg of oil, respectively (Negro et al., 2019).

The OLC concentration in OO is also influenced through cultivation practices or farming methods like irrigation applied during the growth

or production of OFs (Gomez-Rico et al., 2006). For example, the study has indicated that enhanced water supply administered to OTs results in a reduction in OLC concentration (Tovar et al., 2001). Indeed, EVOOs produced from olives grown under high irrigation conditions exhibited lower OLC concentrations (23.1 ± 1.3 mg/kg). In contrast, higher OLC concentrations were observed in EVOO produced from olives cultivated with minimal irrigation (50.9 ± 6.5 mg/kg). Another study reported a reduction of approximately 37%-38% in OLC concentration in EVOO derived from olives grown under high irrigation (Servili et al., 2007).

Another parameter influencing OLC concentration is the storage conditions of OO. The impact of storage conditions on OLC concentration has been highlighted in several studies. In one study, it was observed that OLC proportion in OO reduced by a maximum of 37% over a 10-month period when exposed to light and O_2. However, when light and O_2 exposure were restricted, the decrease in OLC was found to be 15%. In oils stored under conditions of either O_2 or light exposure, similar degradation rates of OLC were observed over 10 months, with reductions of 28% and 25%, respectively (Cicerale et al., 2013). In a separate study, it was reported that OLC concentration in EVOO remained unchanged after being stored at room temperature for 12 months (Sicari et al., 2010).

Finally, a study on cooking procedures observed that OLC concentration decreased by 20% after two hours of frying at 180°C (Gomez-Alonso et al., 2003). Furthermore, it was found that this SM

remained relatively stable when heated at 240°C for 90 minutes (Cicerale et al., 2009).

In addition to OO, olive pomace (OP) (by-product) is currently recognized as a source of biologically active molecules, such as PhCs (Obied et al., 2005; Akar et al., 2009). The use of pomace, particularly as a source of OLC and other PhCs, may offer a supplementary approach to mitigating the ecological impact associated with this type of waste. Moreover, it would further promote the utilization of this by-product. In a related study, the OLC concentration in OP obtained after OO production was reported to be 128.25 ± 11.33 mg/kg in early harvest, 112.15 ± 1.51 mg/kg in normal harvest, and 62.35 ± 8.00 mg/kg in late harvest (Cicerale et al., 2011). In light of these findings, OP waste is considered a valuable by-product containing OLC (El Haouari et al., 2020).

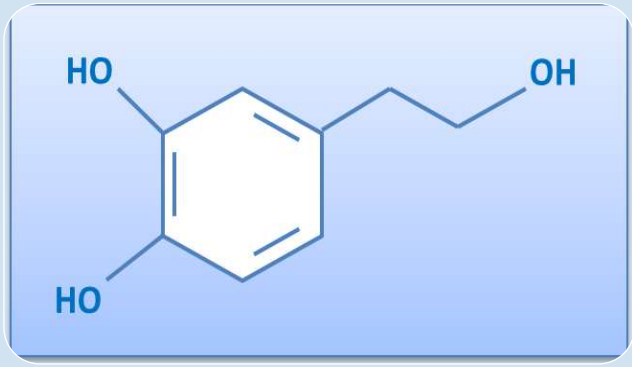
2. THE BIOLOGICAL PERSPECTIVES of HYDROXYTYROSOL and OLEOCANTHAL

2.1. Important Biological Effects and Properties of Hydroxytyrosol

HT is a PhC derived from the olive tree (*Olea europaea* L.), garnering substantial attention in the food, feed, nutraceutical, and pharmaceutical industries (Wang et al., 2024). This SM represents a critical bioactive component, originating as a derivative of OLE. Its concentration in OFs increases significantly as OLE undergoes degradation, particularly during the maturation process

(Charoenprasert & Mitchell, 2012). Furthermore, elevated levels of HT are observed during OO production (Vijakumaran et al., 2021; Arangia et al., 2023; Gervasi & Pojero, 2024). In OO and olives, HT exists in both free and conjugated forms, with conjugates including OLE and other related compounds (Hu et al., 2014). The precursor of HT is Tyr, which undergoes enzymatic conversion into HT within the liver (Rodríguez-Morató et al., 2017; Karković Marković et al., 2019; Marrero et al., 2024).

HT is renowned for its extensive bioactive properties and critical role in biological functions. As a SM, it exhibits higher bioactivity per unit mass compared to OLE. HT is particularly noted for its potent antioxidant activity, contributing to favorable outcomes in the management of various human disorders, including its anticancer properties (Ramírez-Expósito et al., 2018; Hormozi et al., 2020), cardiovascular protection (Wu et al., 2018; Vijakumaran et al., 2023), and neuroprotective benefits (Nardi et al., 2023; Wang et al., 2024; Achour et al., 2025). In addition, HT displays a broad range of biological functions, such as anti-inflammatory and antithrombotic effects, cholesterol-lowering actions, and the ability to suppress excessive immune responses. Its antioxidant properties protect various cell types against oxidative damage caused by reactive oxygen species, resulting in decreased cellular mortality and extended cellular lifespan (Yonezawa et at., 2018; Bertelli et al., 2020; Peñalver et al., 2024; Wang et al., 2024; Hou et al., 2025). The some important biological activities and functions of HT are summarized in Figure 4.



Antimicrobial (Yonezawa et at., 2018; Košćak et al., 2025; Nasr et al., 2025; Zandona et al., 2025); **antioxidant and reactive oxygen species scavenger** (Ricelli et al., 2020; Pérez-Barrón et al., 2021; Terracina et al., 2022; Batarfi et al., 2023; Georgiou et al., 2025; Achour et al., 2025); **anti-inflammatory** (Chen et al., 2019 and 2021; Alblihed, 2021; Elmaksoud et al., 2021; Achour et al., 2025); **anti-fibrogenesis, preventing osteoporosis, positive impacts on obesity, hypercholesterolemia, insulin resistance** (Cao et al., 2014; Efentakis et al., 2015; Poudyal et al., 2017; Illesca et al., 2019); **cardioprotective** (Kamil et al., 2020; Pérez-Barrón et al., 2021; Yu et al., 2022; Batarfi et al., 2023; Razali et al., 2023; Vijakumaran et al., 2023); **neuroprotective** (Robles-Almazan et al., 2018; Kamil et al., 2020; Yu et al., 2022; Razali et al., 2023; Vijakumaran et al., 2023; Achour et al., 2025); **anticancer and anti-apoptotic** (Calabriso et al., 2018; Robles-Almazan et al., 2018; Chen et al., 2019 and 2021; Kamil et al., 2020; Alblihed, 2021; Elmaksoud et al., 2021; Razali et al., 2023; Gervasi & Pojero, 2024).

Figure 4: The biological functions of HT

References: Asghariazar et al., 2022; Batarfi et al., 2024; Canbey et al., 2024; Christodoulou et al., 2024; Frumuzachi et al., 2024; Goncalves et al., 2024.

Numerous studies have highlighted the health-promoting effects of HT, emphasizing its inflammation-reducing, atheroprotective, and anticoagulant activities. Additionally, HT is recognized for its ability to improve vascular endothelial function and mitigate hepatic steatosis (Stefanon & Colitti, 2016). These attributes have established HT as a neurosafeguarding, cardiopreventive, and chemodefensive compound (Schaffer et al., 2007; Visioli, 2012; Yeste et al., 2024). Evidence further proposes that HT interacts with proteins involved in cell cycle regulation and gene expression modulation, thereby displaying oncopreventive potential (Serreli & Deiana, 2018). HT also exhibits notable antimicrobial and antiviral properties (Bedoya et al., 2016; Liu et al., 2025). As a result, it has been categorized as a dietary complement for the prevention and management of various pathological conditions (Wang et al., 2024).

2.1.1. The cardioprotective impacts of hydroxytyrosol

Extensive research has demonstrated a positive association between adherence to the Mediterranean diet and a reduced prevalence of cardiovascular disorders. CVDs remain the leading cause of mortality worldwide, with their incidence strongly associated with risk factors, such as hypertension, hyperlipidemia, diabetes, and obesity. The cardioprotective effects of HT can be attributed to its multifaceted mechanisms of action, including free radical scavenging, activation of antioxidant transcription pathways, and enhancement of detoxification systems (Grosso et al., 2017; Ramic-Catak et al., 2023; Guzowski et al., 2024; Marrero et al., 2024).

Additionally, HT exhibits potent metal-chelating properties, regulates gene expression associated with the development and progression of atherosclerosis, and provides overall cardiovascular protection. It mitigates homocysteine-induced endothelial dysfunction, improves cell adhesion, optimizes lipid profiles, and reduces inflammatory markers, including interleukin-6 (IL-6), thromboxane, and leukotriene. Consequently, diets rich in olive-derived products, particularly EVOO, are advantageous in preventing cardiovascular disorders (De la Torre-Carbot et al., 2010; Yüksel Aydar et al., 2017). Recent findings also highlight novel molecular pathways through which HT mitigates the harmful effects of mercury exposure on cardiac health. These studies emphasize its therapeutic potential in reducing cardiovascular risks associated with heavy metal exposure (Perrone et al., 2024).

Moreover, research involving rats administered HT has shown a marked reduction in serum levels of C-reactive protein (CRP), IL-6, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) (D'Angelo et al., 2020). Both TNF-α and IL-1β directly stimulate the synthesis of IL-6, while IL-1β upregulates the expression of cyclooxygenase-2 (COX-2), a key enzyme in prostaglandin synthesis. This upregulation leads to increased production of prostaglandin E2 (PGE2) and prostaglandin D2 (PCD2), metabolites that serve as critical mediators in inflammatory pathways (Mahboubi Rabbani et al., 2019; Alvarez et al., 2020).

Persistent inflammatory responses are a significant contributor to the progression of CVDs and their outcomes, making inflammation a

critical target for therapeutic strategies. As evidenced by these studies, the consumption of EVOO demonstrates a crucial function in regulating inflammatory reactions and offers substantial cardioprotective benefits (Tune et al., 2017).

2.1.2. The anti-inflammatory influences of hydroxytyrosol

HT, a significant SM, shows anti-inflammatory activity, and this bioactivity has been stated in the various fields, such as food, medical, pharmaceutical, etc (Jeon & Choi, 2018; Yonezawa et at., 2018; Hou et al., 2025). This bioactive compound in OO has been shown to modulate inflammation through its effects on intracellular signaling pathways, particularly those involving the NF-κB (Nuclear Factor kappa B) and Nrf2 pathways. HT primarily promotes the activation of Nrf2 while simultaneously suppressing NF-κB activity (Serreli & Deiana, 2020). Nrf2 functions as a critical regulator of the xenobiotic-activated receptor, initiating the activation of the antioxidant response element (Sivandzade et al., 2019). This activity is upregulated during redox homeostasis imbalances and inflammatory conditions. Additionally, Nrf2 influences processes such as apoptosis, metabolic pathways, and cellular growth (Morales-González et al., 2015).

HT has also demonstrated therapeutic potential across various health conditions, with encouraging results in addressing *Diabetes mellitus*, inflammation, neurological disorders, angiogenesis, cancer, oxidative damage, heavy metal toxicity, hemolysis, LDL oxidation, muscle injury, and kidney toxicity. Furthermore, HT intake has been linked to the modulation of specific microRNAs (miRNAs) in both rodent

models and human studies, highlighting its role in regulating gene expression (Wani et al., 2018; Achour et al., 2025).

In one study, the effects of EVOO and HT on wound healing in diabetic conditions were explored. Diabetic mice with streptozotocin-induced skin wounds were treated topically with HT, while another group was provided a diet enriched with EVOO. The results indicated that both dietary supplementation with EVOO and topical application of HT improved wound healing, underscoring their therapeutic potential in managing diabetic lesions (Duarte et al., 2024).

Similarly, the defensive properties of HT on the skin and its wound-healing potential were investigated using various experimental models, including melanoma-derived cells, HUVECs exposed to pulsed electromagnetic fields, and blood vessel endothelial cells. The findings revealed reduced oxidative damage caused by UV exposure, enhanced cellular proliferation, suppressed apoptosis, and increased heme oxygenase-1 (HO-1) levels through stabilization and nuclear translocation of Nrf2 (Zrelli et al., 2015; Landén et al., 2016; Cheng et al., 2017; Dunnill et al., 2017; Jindam et al., 2017; Krzyszczyk et al., 2018; Szabo et al., 2018).

Additionally, HT inhibits macrophage activation and prevents endothelial injury, thereby reducing cholesterol LDL oxidation, long-term inflammation, and platelet aggregation (Guzowski et al., 2024). Its anti-inflammatory properties have been examined in clinical studies using in vivo glioma models and a systemic lupus erythematosus pristane-induced model in BALB/c mice. These studies

demonstrated that HT inhibits the inducible nitric oxide synthase (iNOS)/nitric oxide (NO) and cyclooxygenase (COX)/prostaglandin E2 (PGE2) pathways. It also downregulates pro-inflammatory cytokines, such as TNF-α and IL-1β and reduces the activity and expression of matrix metalloproteinase-9 (MMP-9) and COX-2 enzymes in activated human macrophages. Furthermore, HT has been shown to lower levels of the pro-inflammatory cytokine IL-6 (Kapoor et al. 2014; Borrie & Kim 2017; Ramírez-Expósito & Martínez-Martos, 2018; Martínez et al., 2019; Tavenier et al., 2020; García-García et al., 2021)

2.1.3. The biological effects on gastrointestinal tract

HT has been shown to regulate oxidative stress and inflammation in various chronic conditions, including those affecting the intestines and gastrointestinal (GI) tract (Arangia et al., 2023). Its preservative and immunoregulatory properties have been highlighted in mitigating intestinal inflammation, as evidenced by numerous in vivo and in vitro experimental studies (Reddy & Naidu, 2016; Lee et al., 2018; Karković Marković et al., 2019). Specifically, HT appears to exert its effects through the modulation of the NF-κB signaling pathway, regulation of pro-inflammatory cytokine production, and modulation of downstream inflammatory mediators, such as COX-2 and iNOS (Reddy & Naidu, 2016; Vezza et al., 2017; Serreli et al., 2019; Morvaridi et al., 2020; Wark et al., 2021; Vrdoljak et al., 2022).

In particular, HT has demonstrated promising effects in mitigating inflammation associated with DSS-induced ulcerative colitis. This is

achieved through the suppression of NLRP3 inflammasome activation and modulation of gut microbiota composition, as observed in vivo (Miao, 2022). Multiple investigations have also validated the antioxidant properties of HT, which contribute to its efficacy against ulcerative colitis. These benefits are largely attributed to HT's facilitation of Nrf2 nuclear translocation (Fuccelli et al., 2018; Wang et al., 2022). Similarly, *in vitro* experiments using human intestinal Caco-2 cells have confirmed the antioxidative properties of HT (Atzeri et al., 2016; Reddy & Naidu, 2016; Vezza et al., 2017).

In the context of Crohn's disease, the mechanisms underlying HT's inflammation-preventing effects include suppression of the p38/MAPK and NF-κB signaling pathways, downregulation of iNOS synthesis, and attenuation of NO production (Guina et al., 2015; Serra et al., 2017; Gu & Feagins, 2022).

HT has also exhibited antimicrobial properties that contribute to its protective effects against gastric ulcers. *In vitro* experiments have demonstrated its ability to inhibit the growth of *Helicobacter pylori* and reduce ulcer size (Castro et al., 2012; Arismendi Sosa et al., 2022; Vrdoljak et al., 2022). Additionally, HT has been shown to suppress NF-κB transcriptional activity, leading to decreased release of pro-inflammatory cytokines, including TNF-α (Sangiovanni et al., 2012). *In vivo* investigations have further highlighted HT's antioxidative and antimicrobial properties, alongside its ability to promote gastric mucosal integrity recovery (Arismendi Sosa et al., 2022).

Several clinical studies are currently underway to explore HT's inflammation-suppressing and antimicrobial properties in the context of gastric ulcers (Reis et al., 2018). A double-blind, randomized controlled trial evaluating olive leaf extracts rich in HT and Tyr demonstrated significant reductions in symptoms of GI discomfort, such as abdominal bloating, acid reflux, and eructation. These benefits are attributed to the biologically active substances in the extract, which provide protection to the gastric mucosa, reduce oxidative stress, and modulate inflammatory responses (Romani et al., 2019; Acar-Tek & Agagunduz, 2020; Malfa et al., 2021).

Moreover, HT's immunomodulatory and antimicrobial properties, along with its programmed cell death-enhancing properties and cell growth-inhibiting effects, suggest a potential role in combating colonic carcinoma. These characteristics highlight HT's multifaceted therapeutic potential against complex, multifactorial diseases. Considering its favorable safety profile and broad spectrum of preventive effects, further research is warranted to fully explore HT's applications in clinical settings (Arangia et al., 2023).

2.1.4. The antioxidant functions of hydroxytyrosol

HT, a widely studied bioactive component of the olive tree, is recognized for its extensive biological functions, particularly its potent antioxidant properties (Martínez et al., 2018; Ventura et al., 2024; Achour et al., 2025; Hassena et al., 2025). As the second most potent antioxidant after gallic acid, HT stands out as one of the strongest antioxidants among PhCs derived from olive tree derivatives,

surpassed only by OLE, caffeic acid, and Tyr (Martínez et al., 2018; Karković Marković et al., 2019). This compound demonstrates antioxidant activity that is ten times more effective than that of green tea and twice as potent as coenzyme Q10 (Lee Richard, 2014). Moreover, HT's radical-scavenging capacity is comparable to that of catechol and OLE. The antioxidant properties of HT are primarily attributed to its molecular structure, which features a phenolic ring, specifically with an ortho-dihydroxy configuration within the aromatic ring, a catechol compound, and three hydroxyl groups. This unique molecular arrangement is largely responsible for its protective effects (Cabrerizo et al., 2013; Martínez et al., 2018; Bertelli et al., 2020; Bucciantini et al., 2021; Peñalver et al., 2024). As a by-product of the olive tree, HT-enriched substances have gained increasing attention due to the rising consumer demand for products fortified with natural antioxidants (Kourti et al., 2024; Peñalver et al., 2024).

The antioxidant properties of HT have been elucidated through various molecular and biological investigations (Yüksel Aydar et al., 2017). These mechanisms include scavenging free radicals (Rietjens et al., 2007a and 2007b), chelating iron (Kitsati et al., 2016), and supporting antioxidant systems such as Nrf2 (Zrelli et al., 2011a; Zou et al., 2012; Mahmoudi et al., 2018; Elmaksoud et al., 2021). In addition, HT serves as a dietary antioxidant and free radical scavenger, with the potential to reduce the risk of atherosclerotic heart disorders by diminishing oxidative damage to LDL. Another study evaluated the impact of HT on sperm viability after cooling and freezing, finding

that HT significantly improved the quality of thawed spermatozoa, DNA integrity, and cell vitality (Alharbi et al., 2024). Similarly, a study on equine erythrocyte membranes demonstrated that HT protects these membranes from peroxidation (Ventura et al., 2024). Additionally, HT has been found to display a pivotal function in modulating molecular pathways associated with inflammatory bowel diseases and GI disorders. Its antioxidant properties contribute to neutralizing free radicals, enhancing antioxidant enzyme activity, and restoring oxidative homeostasis. Furthermore, HT's anti-inflammatory activity, achieved through the suppression of the NF-κB signaling pathway and reduction in pro-inflammatory cytokine release, further complements its antioxidative effects (Arangia et al., 2023).

While HT exhibits potent antioxidant effects, its strong aroma and flavor pose challenges in food applications, particularly in meat products. To overcome these limitations, researchers have focused on encapsulating HT and developing emulsion gels to mitigate sensory changes in meat products. However, the organoleptic properties of these products remain inconclusive. Therefore, the most effective strategies for utilizing HT’s benefits in meat may involve its dietary inclusion in animals or incorporation into innovative packaging solutions (Martínez et al., 2018). Additionally, HT is efficiently absorbed in the GI tract and transported into the bloodstream, where it mitigates oxidative damage caused by reactive oxygen species in tissues. Furthermore, it inhibits the oxidative modification of low-density lipoproteins (García-Molina et al., 2024). Recent studies are

also exploring HT's potential in addressing mitochondrial dysfunction associated with Alzheimer's disease (AD) (Visioli et al., 2022). Given its broad range of positive health effects, HT is increasingly sought after for use in food preservatives, nutritional supplements, and anti-aging formulations (Ciriminna et al., 2016). Experimental models involving C57BL/6 mice, rats, and retinal pigment epithelial cells have demonstrated that HT reduces the GSSG/GSH ratio in adipocytes, enhances electron transport chain functionality, and promotes the nuclear migration of Nrf2, which boosts the expression and activity of key antioxidant enzymes such as GCL, catalase, HO-1, GSH reductase, GSH peroxidase, and NQO1. Additionally, the activation of FOXO3a (Forkhead box O3a) transport factor was observed (Zhu et al., 2010; Zrelli et al., 2011a, 2011b; Forman et al., 2014; Giordano et al., 2014; Granados-Principal et al., 2014; Fuccelli et al., 2018)

2.1.5. The anti-angiogenic and anti-atherogenic effects of hydroxytyrosol

In addition to its well-documented antioxidant activities, HT also demonstrates significant anti-angiogenic and anti-atherogenic properties (Carluccio et al., 2003; Fortes et al., 2012; Marrero et al., 2024; Hou et al., 2025). Angiogenesis, the mechanism through which novel blood vessels are generated from existing vasculature, is a key factor in the progression of various disorders, like cancer (Eelen et al., 2020). This process not only has a vital function in tumor development and spread but also in the survival of the tumor, as it

provides the necessary nutrients and oxygen through an expanded blood supply (Folkman, 2007). In this context, the concept of angioprevention emerges, which involves the prevention of cancer through the inhibition or stabilization of tumor-induced angiogenesis (Albini et al., 2012).

HT has been shown to regulate several angiogenesis-related pathways, thereby limiting the induction of neovascularization within the tumor microenvironment. These regulatory effects of HT on angiogenesis are detailed in Table 1. By modulating key signaling pathways associated with angiogenesis, HT exerts a protective role, not only in cancer but also in a variety of other pathophysiological conditions where angiogenesis is a contributing factor (Marrero et al., 2024).

Table 1. Regulation of angiogenesis-associated pathways by HT derived from VOO (Marrero et al. 2024).

Biological functions	Mechanistic pathways at the molecular level	References
Downregulation of pathways promoting angiogenesis	Suppression of cyclooxygenase-2 activity	Scoditti et al., 2012
	Downregulation of the AKT signaling pathway associated with cell survival	Zhao et al., 2014; Gallardo-Fernández et al., 2022a and 2022b
	Suppression of vascular endothelial growth factor receptor-mediated signaling	Gallardo-Fernández et al., 2022a and 2022b

	Downregulation of NF-κB signaling pathways	Zhao et al., 2014
Reduction in the ability to remodel the extracellular matrix	Downregulation of matrix metalloproteinase expression	Fortes et al., 2012; Scoditti et al., 2012; García-Vilas et al., 2017

HT also exhibit anti-atherogenic funtions (Marrero et al. 2024). Atherosclerosis, defined by the buildup of lipid-enriched plaques within the arterial walls (a condition characterized by the thickening and hardening of the arterial walls), serves as a significant contributor to the pathogenesis of cardiovascular disorders and associated mortality (Wolf & Ley, 2019). Once thought to be primarily a disorder of cholesterol deposition, atherosclerosis is now understood as a syndrome driven by inflammatory processes (Kong et al., 2022). In this regard, the vascular endothelium exerts a pivotal influence on the advancement of atherosclerosis by mediating endothelial dysfunction (Marrero et al. 2024). The anti-atherosclerotic activities of HT is shown in Table 2.

Table 2. Atheroprotective activities of HT derived from VOO (Marrero et al. 2024).

Biological functions	Mechanistic pathways at the molecular level	References
	Suppression of NF-κB signaling pathways	Richard et al., 2011; Mahmoudi et al., 2018

	Suppression of cyclooxygenase-2 activity	Maiuri et al., 2005; Zhang et al., 2009
Inflammation-suppressing	Suppression of inducible NO synthase expression and NO production	González-Correa et al., 2008; Zhang et al., 2009; Richard et al., 2011
	Downregulation of proinflammatory cytokines (e.g., TNF-α) and chemokines (e.g., CCL2, CXCL10) expression	Richard et al., 2011; Mahmoudi et al., 2018
	Decreased expression of adhesion molecules (e.g., ICAM-1, VCAM-1, E-selectin)	Dell'Agli et al., 2006; Manna et al., 2009; Catalán et al., 2015

The anti-atherogenic effects of HT exert a critical function in hindering the onset of atherosclerosis. This is achieved through HT's ability to modulate lipid profiles, reduce inflammation, and inhibit endothelial cell dysfunction, all of which facilitate the inhibition of plaque formation and the maintenance of vascular integrity (Carluccio et al., 2003; Marrero et al., 2024).

2.1.6. The anticancer effects of hydroxytyrosol

Moreover, studies (both in vivo and in vitro) have indicated that HT exhibits significant anticancer activity (Table 3) (Kumar et al., 2024; León-González et al., 2024). Numerous investigations have been conducted to explore the anticancer effects of HT. For instance,

experiments utilizing the human promyelocytic leukemia HL60 cell line demonstrated that HT inhibited cell proliferation, induced cell cycle arrest at the G0/G1 phase, and led to a corresponding reduction in the proportion of cells in the S and G2/M phases. Based on these findings, the authors proposed that HT exerts a protective effect against cancer (Fabiani et al., 2002 and 2008; Marrero et al., 2024).

Table 3. The anticancer functions of HT (Marrero et al. 2024).

Biological functions	Mechanistic pathways at the molecular level	References
Decreasing proliferation of tumor cells	Suppression of ERK1/2 signaling pathway	Corona et al., 2009; Sirianni et al., 2010
	Suppression of EGFR signaling pathway	Terzuoli et al., 2016
	Regulation of the Wnt signaling pathway	Granados-Principal et al., 2011
	Induction of cell cycle blockade	Zhao et al., 2014; Fabiani, 2016; López de las Hazas et al., 2017; Goldsmith et al., 2018
Cellular toxicity	Targeted pro-oxidant activity	Fabiani et al., 2012; Sun et al., 2014; Rosignoli et al., 2016
	Regulation of the Wnt	Granados-Principal et al.,

	signaling cascade	2011
Decreasing viability of tumor cells	Suppression of the pro-survival AKT signaling pathway	Zhao et al., 2014
	Initiation of apoptosis through caspase activation and the mitochondrial pathway	Fabiani, 2016; López de las Hazas et al., 2017; Goldsmith et al., 2018

Additionally, the effects of HT on cell growth inhibition and programmed cell death were further investigated in human colon carcinoma HT-29 cells. HT was found to alter mitochondrial membrane permeability, activate caspase 3, induce endoplasmic reticulum (ER) stress, disrupt ER Ca2+ homeostasis, and activate c-Jun NH2-terminal kinase (JNK) along with the activator protein-1 (AP-1) transcription factor. Furthermore, HT inhibited tumor necrosis factor-α (TNF-α)-induced NF-κB activity and enhanced serine/threonine phosphatase 2A activity. These findings led the authors to conclude that HT plays a significant chemopreventive role by targeting specific transcription factors, tumor suppressors, and tumor promoter-induced protein kinases, while inducing Regulated cell death (Guichard et al., 2006).

Moreover, HT was shown to inhibit tumor growth in the HT-29 cell line. *In vivo* studies revealed that HT suppressed the expression of hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and microsomal prostaglandin-E synthase-1 (mPGES-1). *In vitro* findings demonstrated that HT reduced the phosphorylation of extracellular signal-regulated kinase 1/2 (ERK1/2),

thus inhibiting the PGE-2/ERK1/2/HIF-1α signaling pathway (Terzuoli et al., 2010).

In addition, it was shown that HT exhibited inhibitory effect on tumor growth in Wistar rats implanted with C6 glioma cells. Moreover, HT reduced levels of oxidation in protein and peroxidation lipid (Martínez-Martos et al., 2014). In human colon cancer SW620 cells, it was demonstrated that HT displayed inhibitory effect on cell proliferation by downregulating the expression and activity of enzyme of fatty acid synthase. It has been noted that elevated levels of fatty acid synthase expression are commonly observed in colorectal cancer (Notarnicola et al., 2011). It was reported that HT decreased viability of cell, triggered apoptosis, and exhibited inhibitory effect on proliferation in breast cancer MCF-7 cells of human. Besides, HT induced cell cycle arrest at the transition from the G1 to the S phase (Han et al., 2009).

In addition, the potential anti-tumor effects of HT on breast adenocarcinoma MCF-7 cells of human were investigated, and it was demonstrated that HT induced a G1 phase cell cycle arrest by suppressing the expression of the peptidyl-prolyl cis–trans isomerase Pin1, leading to a reduction in cyclin D1 levels (Bouallagui et al., 2011). Moreover, increased intake of OO, which is abundant in polyphenols like HT, has been linked to a reduced occurrence and frequency of various cancers, including bowel cancer (Bernini et al., 2017; Xie et al., 2021; Mattioli et al., 2022; Sain et al., 2022).

The therapeutic effects of HT have been assessed through studies (*in vitro*) using epithelial and umor cell lines. These investigations have shown that HT can influence genes associated with programmed cell death, including Bax, Bcl-2, Caspase-3, and p53 (Hormozi et al., 2020; Santarelli et al., 2022). Moreover, recent research has demonstrated that HT suppresses the expansion of colorectal cancer cells through the activation of estrogen receptor-β (Terzuoli et al., 2016). Indeed, it has been established that the progression of malignancy in mucosa of human colon is associated with a downregulation of estrogen receptor-β production (Bernini et al., 2017).

Ultimately, it was shown that HT enhances antioxidative function in the colon carcinoma cell line by significantly elevating the levels of antioxidant enzymes (Hormozi et al., 2020). Nevertheless, investigations (*in vivo*) into the health-promoting impact of HT on colon cancer in models based on animals could yield more conclusive results. Moreover, clinical trials have demonstrated the influence of HT on the mechanisms underlying the development of this cancer type (Imran et al., 2018). Besides, experimental frameworks utilized MCF-7 mammary carcinoma cells as well as pancreatic, colorectal, prostate, thyroid, and hematologic malignancy cells. The findings demonstrated that HT facilitates programmed cell death and exerts its cancer-preventing potential by suppressing the Akt, NF-κB, STAT3, and EGFR signaling cascades (Chimento et al., 2014; Sun et al., 2014; Terzuoli et al., 2016; Toteda et al., 2017; Zubair et al., 2017; Goldsmith et al., 2018; Sani et al., 2022).

2.1.7. The antimicrobial effects of hydroxytyrosol

In addition to antioxidant and anticancer activities, HT displays also antimicrobial activities (Ghalandari et al., 2018; Mangana et al., 2025). The antibacterial properties of olive-derived products are attributed to various formations of decarboxymethyl elenoic acid, including its free form, dialdehydic structure, and those conjugated with Tyr and HT (Yüksel Aydar et al, 2017). Antimicrobial research has been conducted with applications in both health of human and the management of agricultural pest (Talhaoui et al., 2015).

In the context of investigating the antimicrobial properties of HT, experimental models included fungal isolates (e.g., *Aspergillus flavus*, *A. nidulans*, *A. fumigatus*, *Candida albicans*, *C. dubliniensis*, and *Fusarium oxysporum*), bacterial isolates (e.g., *B. subtilis*, *E. coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, *P. fluorescens*, *S. enterica*, *Shigella sonnei*, *S. aureus*, and *Yersinia* species), and viral agents (e.g., SARS-CoV-2 and HIV-1). The findings demonstrated remarkable efficacy in disrupting membranes of fungal cells, exhibiting potent antifungal properties. Additionally, HT was shown to facilitate efficient permeation through the cellular membranes of both Gram (-) and (+) bacteria (Bedoya et al., 2016; Crisante et al., 2016; Zorić et al., 2016; Diallinas et al., 2018; Ergoren et al., 2020).

In addition to HT, a fundamental polyphenol derived from olive brine solutions, demonstrates bactericidal effects against lactic acid bacteria. Both oil mill wastewater and leaf extracts of olive have been shown to possess antimicrobial properties, which are attributed to their PhCs,

such as OLE and HT. These bioactive compounds have exhibited antimicrobial activity against various pathogenic microorganisms like bacteria and viruses (Medina et al., 2013). Indeed, it exhibits strong antioxidative properties against various microorganisms, including *C. albicans*, *Salmonella enterica*, *Clostridium perfringens*, *Streptococcus mutans*, and *Escherichia coli* (Bertelli et al., 2020). Moreover, it has been emphasized that HT functions as an antimicrobial agent, displaying both antibacterial and antiparasitic activities (Robles-Almazan et al., 2018). In addition, HT has been determined to inhibit mycoplasmas at concentrations ranging from 0.03 µg/mL to 0.5 µg/mL. The minimum inhibitory concentrations were determined to be 0.03 µg/mL for *M. hominis*, 0.5 µg/mL for *M. pneumoniae*, and 0.25 µg/mL for *M. fermentans*, respectively (Furneri et al., 2004).

Moreover, HT has been demonstrated to possess bactericidal activity targeting a broad array of bacterial species. Its bactericidal effects were more pronounced against Gram (+) bacteria compared to Gram (-) bacteria. Furthermore, HT exhibited bactericidal properties against both pathogenic bacteria (*Clostridium perfringens* and *Escherichia coli*) and beneficial microorganisms (*Bifidobacterium bifidum* and *Lactobacillus acidophilus*) within the microbiota of intestines (Medina-Martínez et al., 2016). Besides, in a study, it was determined that HT, HT acetate, and HT oleate exhibit antimicrobial effects on *Staphylococcus aureus* and *S. epidermidis* (Ghalandari et al., 2018).

HT, along with its lipophilic derivatives and various biologically significant metabolites, has been synthesized using microbiological,

biotechnological, and other chemical methods (Wani et al., 2018). At present, numerous HT-based products are commercially accessible (Smeriglio et al., 2019; Al Saqr et al., 2022). As a result of its beneficial effects on human health, HT has recently attracted increasing attention from researchers seeking methods to produce large quantities of the compound, either through enzymatic or chemical processes, or by utilizing mill by-products (Messa et al., 2024).

In summary, HT is a significant PhC present in olive tree parts (olives, OLs, etc.) and its products like OO. As it is readily absorbed by the body of human, it has been more extensively studied compared to other olive-derived constituents. Researches has demonstrated that HT exhibits dose-dependent cancer, antioxidant, inflammation-, microbial growth-preventing properties, as well as a role in preventing osteoporosis.

The Mediterranean diet, known for its association with a diminished risk of various cancer types, osteoporosis, and CVDs, highlights the significance of OO as a key component. Consequently, it is hypothesized that regular consumption of OO may contribute to the prevention of these conditions. However, further research is necessary to elucidate the mechanisms by which HT exerts its beneficial effects. In the future, HT holds promise as a natural therapeutic agent for the preventing and treatment of specific diseases (Yüksel Aydar et al, 2017).

2.2. Significant Biological Effects and Properties of Oleocanthal

OLC contributes to the bioactivity value of olives by exhibiting several significant biological properties. However, the absorption and metabolism processes of this bioactive phytochemical are crucial for understanding its in vivo biological effects. The absorption mechanism of PhCs in OO is still not fully understood. After the consumption of OO, it forms a micelle-based system consisting of lipidic and water-based phases (Singh et al., 2009). Polyphenol glucosides may undergo transformation in the oral cavity due to the hydrolytic action of salivary enzymes. However, a significant portion of these SMs transit the stomach and arrive at the small intestine and colon. Prior to their absorption in the small intestine, enzymatic hydrolysis by intestinal enzymes is required (Vissers et al., 2002). Likewise upon reaching the colon, these phytochemicals are generally subjected to microbial metabolism by the gut microbiota (D'Archivio et al., 2010).

The chemical breakdown of secoiridoids can occur in an acidic environment, such as the stomach (Corona et al., 2006; Lopez et al., 2014), or under the more alkaline conditions of the small intestine (Soler et al., 2010; Pinto et al., 2011). This results in the release of free phenolic alcohols into the aqueous phase, making them suitable for absorption (Muriana et al., 2017). While secoiridoids remain relatively resistant to degradation throughout oral digestion, they experience significant losses in the stomach, duodenum (the first part of the small intestine), and colon. It has been found that the recovery rate in the

duodenum phase ranges from 7% to 34% (Quintero-Florez et al., 2018). Research indicates that secoiridoids, which seem to evade absorption in the small intestine, are predominantly transported to the colon where they undergo degradation by the colonic microbiota (Corona et al., 2006). Some researchers propose that OLC's ester bond is relatively likely to be cleaved by esterases exist under acidic or basic environments, as well as within the small intestine or hepatic tissue (Rubio et al., 2012; Lozano-Castellón et al., 2020).

Studies on the bioavailability of PhCs in OO have predominantly focused on HT, Tyr, and OLE (Rodríguez-Morató et al., 2016). Research evidence indicates that these SMs exhibit significant dose-dependent absorption, ranging from 40% to 95% in humans (Visioli et al., 2000; Tuck and Hayball, 2002; Vissers et al., 2002). However, data regarding the pharmacokinetics and bioavailability of OLC remain limited. In this context, further preclinical and clinical investigations are necessary to better understand the bioavailability of this phytochemical and its biologically beneficial effects. Research conducted on this topic detected OLC and its metabolites in urine, indicating that this SM undergoes metabolism and absorption following digestion in humans (Angeloni et al., 2017). Moreover, another investigation demonstrated the presence of high concentrations of OLC-derived metabolites in human urine (Garcia-Villalba et al., 2010). Furthermore, the results of this study indicated that OLC is primarily biotransformed via hydrogenation, hydroxylation, and hydration processes (Garcia-Villalba et al., 2010).

Additionally, it has been confirmed that OLC remains stable for up to four hours under acidic conditions at 37°C and transitions from the oil phase to the aqueous phase (Romero et al., 2007; Pang & Chin, 2018). Furthermore, when compared to other PhCs in OO, OLC demonstrates notable stability to heat during cooking. This is likely attributable to the compound's molecular composition and antioxidative capacity (Cicerale et al., 2009; El Haouari et al., 2020).

OLC constitutes approximately 10% of the total PhCs in EVOO (Fogliano & Sacchi, 2006). Despite its relatively low concentration, it is estimated that this amount is sufficient to contribute to health benefits (El Haouari et al., 2020). In fact, the potential benefits arising from the pharmacological properties of OLC are believed to be long-term, and achieved through consumption of small quantity. In this regard, the consumption of 25 ml to 50 ml of OO containing 200 mg/kg of OLC delivers approximately 10 mg of OLC daily, which corresponds to nearly 10% of the standard ibuprofen dosage (Beauchamp et al., 2005). Accordingly, the consumption of modest and steady amounts of OLC over the long term through OO consumption may partly account for the reduced prevalence of specific cancers and various other ailments linked to the Mediterranean dietary pattern. Additionally, OLC may reach its therapeutic potential when acting in conjunction with other biologically active compounds present in OO (El Haouari et al., 2020).

Many diseases are linked to chronic inflammatory processes that worsen with aging. Among these diseases are CVDs, inflammatory joint disorders, malignancies, diabetes mellitus, and AD (Lozano-Castellón et al., 2020). The OLC compound exhibits significant biological properties (anti-inflammatory, anti-cancer, neuroprotective, etc.) and has a positive effect on several serious health issues and diseases, including cancer, Alzheimer's, arthropathy, and cardiovascular problems (Pei et al., 2016; Angeloni et al., 2017; Carpi et al., 2019; Cirmi et al., 2020; Marrero et al., 2023; Di Risola et al., 2025).

2.2.1. The anticancer activity of oleocanthal

Epidemiological evidence and numerous case-control studies support the notion that the Mediterranean diet reduces cancer risk, with particular emphasis on the inverse relationship between OO consumption and the prevalence of cancer formation. This effect is thought to stem from the antioxidant, anti-inflammatory, and anti-tumor properties exhibited by the PhCs in OO (Coccia et al., 2016; Spagnuolo et al., 2022).

Figure 5 illustrates the cancer types that are biologically influenced by OLC. Upon reviewing the data presented in Figure 5, it is evident that this SM demonstrates biological properties against melanoma, liver cancer, malignancies including carcinoma of the breast, prostate neoplasm, pulmonary carcinoma, colorectal carcinoma, multiple myeloma, acute promyelocytic leukemia, and chronic lymphocytic leukemia (Infante et al., 2023).

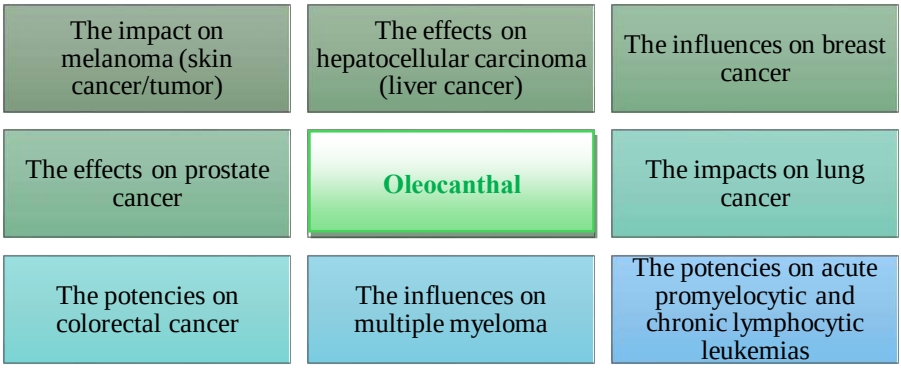


Figure 5: Types of cancer affected by biological properties of OLC
Reference: Infante et al., 2023.

While OLC exerts effects on various cancer types, it also exhibits several significant biological activities as shown in Figure 6 (Infante et al., 2023). Furthermore, the prevention or suppression of such fatal diseases by OLC is attributed to its key anticancer mechanisms as presented in Figure 7.

Melanoma (malignant tumor of melanocytes)	• Inhibition of ERK 1/2 and AKT phosphorylation and modulation of Bcl-2 through its downregulation. • Suppression of STAT3 phosphorylation, reduction in the nuclear localization of STAT3, and decrease in the transcriptional activity of STAT3.
Hepatocellular carcinoma (primary liver cancer)	• Inhibition of EMT and reduction in the nuclear translocation of STAT3, and its DNA binding activity. • Induction of apoptosis and mitochondrial depolarization in HCC cell lines.
Breast cancer	• Dose-dependent inhibition of HGF-induced cell migration, invasion, and G1/S cell cycle progression. • Inhibition of HGF-induced c-Met activation and mTOR signaling pathway. • Inhibition of EMT and reduction of cellular motility.
Prostate cancer	• Suppression of mCRPC cell progression through the inhibition of histone methyltransferase SMYD2 expression.
Lung cancer	• Inhibition of HGF-mediated lung adenocarcinoma cell growth and migration through the reduction of total and activated c-Met levels, and suppression of COX-1 and COX-2 activity. • Suppression of non-small cell lung cancer cell progression and metastasis to the brain, heart, kidneys, and spleen.
Colorectal cancer	• Inhibition of tumor formation through the suppression of COX-2 and activation of AMPK.
Multiple myeloma	• Induction of apoptosis in cancer cells • Inhibition of MIP-1α expression • Downregulation of ERK1/2 and AKT signaling pathways
Acute promyelocytic leukemia	• Inhibition of cancer cell proliferation and induction of apoptosis in cancer cells. • Increased cytotoxic effects (increased percentage of necrotic cancer cells)
Chronic lymphocytic leukemia	• Reduction in white blood cell and lymphocyte counts • Increase in ccK18, Apo1-Fas, and p21 levels • Decrease in Survivin and cyclin D levels

Figure 6: Biological activities of OLC in various cancer types. Abbreviations: AKT, Protein Kinase B; AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma 2; cMet, Mesenchymal-epithelial transition factor; COX-1 and COX-2, Cyclooxygenase-1 and Cyclooxygenase-2; EMT, Epithelial-mesenchymal transition; ERK 1/2, Extracellular signal-regulated kinase 1/2; HCC, Hepatocellular carcinoma; HGF, Hepatocyte growth factor; mCRPC, Metastatic castration-resistant prostate cancer; MIP-1α, Macrophage inflammatory protein-1 alpha; mTOR, Mammalian target of rapamycin; SMYD2, SET and MYND domain containing 2; STAT3, Signal transducer and activator of transcription 3

Reference: Infante et al., 2023.

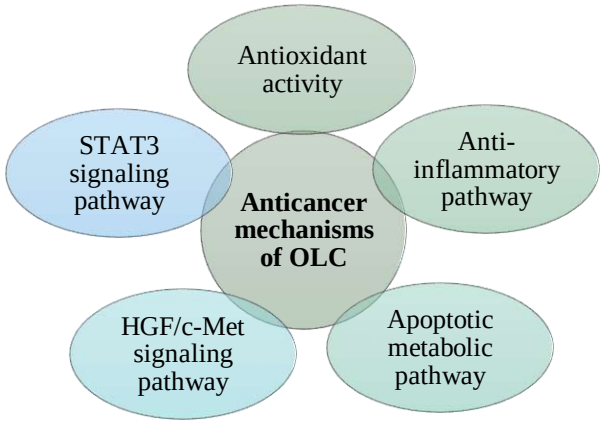


Figure 7: Anticancer mechanisms exhibited by OLC on cancer diseases. Abbreviations: c-Met, Receptor Tyrosine Kinase (Protein coding for hepatocyte growth factor receptor); HGF, Hepatocyte Growth Factor; STAT3, Signal Transducer and Activator of Transcription 3

Reference: El Haouari et al., 2020.

The anticancer mechanisms and the pathways through which OLC affects cancer cells are illustrated in Figure 8 (El Haouari et al., 2020). In addition, recent findings from various in vivo and in vitro

investigations has revealed that components of OO of modulate receptors, signaling kinases, and transcription factors implicated in cellular stress responses and inflammatory processes. These constituents are involved in regulatory pathways governing the cell cycle and demonstrate protective properties against oncogenesis (Markellos et al., 2022). Similarly, in one scientific study, OLC was shown to inhibit the activities of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), enzymes targeted by inflammation-modulating pharmaceuticals like ibuprofen (Beauchamp et al., 2005). Inhibition of cyclooxygenase enzymes, which mediate the production of pro-inflammatory compounds like prostaglandins and thromboxanes (Rosignoli et al., 2013), leads to a reduction in the conversion of arachidonate to eicosanoids, prostaglandins, and thromboxanes in the inflammatory metabolic pathway (Cicerale et al., 2010). Another study reported that OLC demonstrates inflammation preventing properties by dose-dependently inhibiting cyclooxygenase (COX) enzymes, which are integral to the biosynthesis of prostaglandins involved in inflammatory processes. Consequently, it has been proposed that the prolonged consumption of low, chronic doses of OLC may contribute, at least in part, to the reduced prevalence of CVD, specific cancer types, and other degenerative conditions linked to the Mediterranean dietary pattern (Beauchamp et al., 2005). Corroborating the health-promoting effects attributed to this SM, multiple in vitro investigations have shown that OLC potently suppresses the proliferation, migration, and invasion of human breast and prostate carcinoma cell lines (Elnagar et al., 2011).

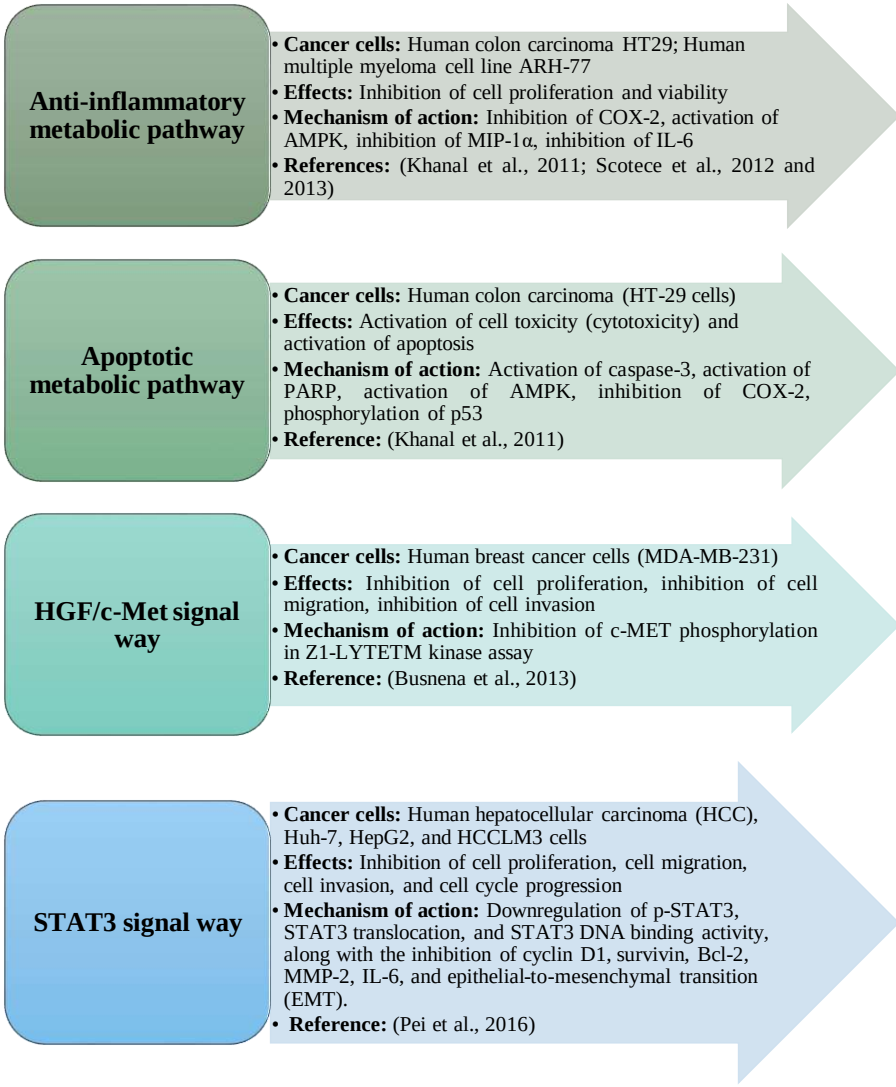


Figure 8: Effects and action mechanisms of OLC in anti-cancer mechanisms. Abbreviations: AMPK, AMP-activated protein kinase; Bcl-2, B-cell lymphoma-xL; cMET, HGF receptor or cellular MET tyrosine kinase; COX-2, Cyclooxygenase-2; EMT, epithelial-to-mesenchymal transition; IL-6, Interleukin-6; MIP-1α, Macrophage inflammatory protein-1 alpha; MMP-2, Mitogen-activated protein kinases; PARP, Poly-adenosine diphosphate-ribose polymerase

Reference: El Haouari et al., 2020.

2.2.2. The other biological impacts of oleocanthal on human health

In addition to the biological activities of OLC observed in cancer, it has additionally been demonstrated to exert favorable effects in diminishing or preventing the onset of other diseases, such as neurodegenerative conditions like AD (Iacono et al., 2010; Des Gachons et al., 2011; Lucas et al., 2011; Cicerale et al., 2010 and 2013; Agrawal et al., 2017; Cusimano et al., 2017; Kotsiou & Tesseromatis, 2017; Pang & Chin, 2018; Di Risola et al., 2025). It has been demonstrated that this SM exhibits pharmacological properties that may prove advantageous in the management of AD (Li et al., 2009; Pitt et al., 2009; Pang & Chin, 2018). These findings support research indicating a 40% reduction in AD incidence among individuals following a Mediterranean-style diet (Scarmeas et al., 2009).

OLC displays a role in reducing AD in Mediterranean populations through two mechanisms. First, in AD, a microtubule-associated protein, Tau, which plays a function in promoting microtubule assembly and stability, begins to accumulate in neurofibrillary tangles. A study related to this demonstrated that OLC inhibits Tau aggregation (Li et al., 2009). Second, beta-amyloid (Aβ) oligomers, also known as ADDLs, have been proposed to play a significant role in the development of AD. These ADDLs are believed to bind to postsynaptic regions, leading to synaptic and neuronal loss. In a study, it was shown that OLC has the capacity to alter the oligomerization

state of ADDLs and protect neurons from the synaptopathological effects of ADDLs. Thus, this bioactive SM protects neurons from synaptic disruption caused by ADDLs and promotes the clearance of ADDLs through antibody-mediated mechanisms (Pitt et al., 2009).

Beyond its role in attenuating AD, the dose-dependent anti-inflammatory effects of OLC observed in vitro parallel the dose-dependent oral irritation response (Beauchamp et al., 2005). This correlation establishes oral irritation, as quantified through taste bioassays, as an effective proxy for biological activity (Joshi et al., 2007; Cicerale et al., 2009). Moreover, the transient receptor potential cation channel A1 (TRPA1) has been recognized as a sensory receptor linked to OLC, with its anatomical distribution localized specifically within the oropharyngeal region of the oral cavity (Peyrot des Gachons et al., 2011).

OLC has also demonstrated effects on arthropathy originating from the nervous system. In vitro studies have shown that OLC ameliorates osteoarthritis (OA) and rheumatoid arthritis (RA). OA is distinguished by the presence of mechanical load in the joint structures, but it also contributes to inflammation symptoms and disease progression (Bonnet & Walsh, 2005). In contrast, RA is primarily driven by inflammation, particularly through an autoimmune process. In both conditions, pro-inflammatory cytokines and other mediators create an inflammatory environment, leading to the upregulation of cartilage-degrading factors (Goldring & Otero, 2011). It has been determined

that OLC exerts a downregulatory effect on these cytokines and mediators (Iacono et al., 2010; Scotece et al., 2012).

In an investigation, a chondrogenic cell line was exposed to stimulation both with and without OLC to trigger the synthesis of NO, a key mediator implicated in the pathogenesis of osteoarthritis, using lipopolysaccharide (LPS). Cells treated with OLC produced significantly less NO compared to the untreated control group. This effect was associated with the phosphorylation of p38 kinase, which facilitates the suppression of inducible NO synthase (iNOS), the enzyme primarily responsible for the biosynthesis of NO (Iacono et al., 2010). In further experiments conducted by the same research group, the effects of LPS-induced OLC on pro-inflammatory cytokines, such as macrophage inflammatory protein 1a (MIP-1a), interleukin-6 (IL-6), and NO production were examined in chondrogenic and macrophage cell lines (Scotece et al., 2012). The results demonstrated that this bioactive compound suppressed both the expression and synthesis of these pro-inflammatory cytokines in chondrogenic cells and attenuated their expression and production in macrophages. OLC also decreased the expression of iNOS and the production of pro-inflammatory cytokines such as IL-1b, tumor necrosis factor alpha (TNF-a), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in macrophages (Scotece et al., 2012). Further in vivo studies and human trials are necessary to fully assess the effects of this secoiridoid on arthropathies (Lozano-Castellón et al., 2020).

Another issue that OLC has shown effectiveness in is certain types of CVDs (Lozano-Castellón et al., 2020; Milena & Maurizio, 2025). Atherosclerotic CVD is a chronic inflammatory condition initiated by endothelial damage and driven by various cell types, including platelets (May et al., 2008). The therapeutic focus in reducing the progression and events of CVDs has been on limiting platelet activation through the inhibition of cyclooxygenase, phosphodiesterase, adenosine diphosphate receptors, and the restriction of platelet-platelet interactions via glycoprotein IIb/IIIa (Yousuf & Bhatt, 2011). During platelet activation, significant lipid remodeling occurs, involving the formation of a range of bioactive species that promote clot stabilization and inflammation, as well as increasing shape change, degranulation, and activation (O'Donnell et al., 2014). Oxylipins are a higher class of bioactive lipids produced by the oxidation of polyunsaturated fatty acids. The best-known oxylipin associated with clot formation is thromboxane, the production of which is targeted by aspirin through cyclooxygenase inhibition. Additionally, oxylipins produced by lipoxygenase (LOX) and cytochrome P450 enzymes may also play a role in platelet activation and the modulation of inflammation (Tourdot et al., 2013).

In addition, EVOO, rich in OLC, has been shown to exert various effects against CVDs, including improvements in endothelial function in patients with early atherosclerosis (Widmer et al., 2013) and anti-platelet effects in healthy men (Agrawal et al., 2017). Furthermore, it has been demonstrated to inhibit NF-κB signaling (Brunelleschi et al., 2007). This inhibition leads to a reduction in the expression of

vascular cell adhesion molecule 1 (VCAM-1), thereby decreasing leukocyte adhesion to the endothelium and promoting normal endothelial function (Libby, 2006). Additionally, OLC, a derivative of Tyr, has been included in the health claims authorized by the European Food Safety Authority (EFSA, 2011).

Although extensive investigations have been conducted in this domain, additional empirical evidence is necessary to comprehensively elucidate the properties and health-promoting potential of OLC. In particular, further research is ensured to assess the influence of OLC on the sirtuin family of proteins, which are integral to essential cellular processes such as genomic stability, lifespan regulation, and metabolic control (Milne & Denu, 2008), as well as aging, gene expression, programmed cell death, and inflammatory responses (Preyat & Leo, 2013). Moreover, the prophylactic and therapeutic implications of this SM in the context of type 2 diabetes mellitus represent another promising area of investigation. This pathological condition is marked by insulin resistance, which arises due to a dysfunction in insulin receptor signaling to undergo phosphorylation, a condition often exacerbated by pro-inflammatory molecules like TNF-a (Wellen & Hotamisligil, 2005). Therefore, OLC may have the potential to reduce insulin resistance by inhibiting or decreasing the levels of these pro-inflammatory molecules. Additionally, neuropathic disorders arising from damage to the peripheral nervous system are a common complication of chronic diabetes (Czerwińska et al., 2018).

CONCLUSION and RECOMMENDATIONS

The olive tree (*Olea europaea* L.) is a valuable plant species with high nutritional value, which is processed into different products, like TO varieties and OO, and in the process, different by-products are formed. Olive, which is a very important part of the Mediterranean diet thanks to the significant nutritional elements and bioactive compounds in its composition, is becoming very important in terms of bioactivity, especially owing to the PhCs it contains.

In this context, HT, a phenolic acid, exhibits substantial biological properties, such as antioxidant, antimicrobial, anti-inflammatory, anticarcinogenic, and heart health protective, and contributes to the prevention of many serious diseases, including Alzheimer's disease, *Diabetes mellitus*, many types of cancer, etc. In addition to its positive effect on human health, it is also a great natural source for the natural preservation of foods due to its antioxidant character.

Besides HT, there are substantial bioactive compounds in OF, some of which are transformed during the processing of the fruit into oil. One of the most important of these compounds is the OLC component. This SM has the potential to be used in many diseases thanks to its anti-inflammatory, antioxidant and neuroprotective effects and activities. The most important of these diseases are cancer, AD, cardiovascular problems and joint disorders.

When all these parameters are taken into consideration different parts of the olive (fruit, leaves, etc.), its products, and also

by-products can be evaluated as natural sources of HT. When olive products are consumed by humans, this SM is also taken into the body. The important point here is that olives should be processed into products without damaging this compound or in a way that causes minimal damage. More importantly, by-products obtained during the processing of olive products and not utilized can be transformed into a source of HT with appropriate extraction and processing techniques. These can be offered to consumers in different forms for HT.

In addition to them, considering its essential biological properties on health; in order to benefit more from OLC, it would be beneficial to develop production methods that will damage this phtyochemical the least in OO production. The bioactivity of the OO produced in this way will be improved. Furthermore, the development and production of different OO products (tablets, capsules, etc.) containing this SM will provide access to more consumers. However, the necessary clinical and laboratory studies should be conducted and disseminated to determine appropriate dosages. With such innovative approaches, bioactive compounds will be utilized in a natural way and scientific contributions will be made to the use of natural resources without degradation for future studies (especially in terms of functional foods and pharmaceuticals).

ETHICAL STATEMENT

This book, titled *"Hydroxytyrosol and Oleocanthal: Bioactive Compounds in Olive and Olive Products with Therapeutic Perspectives"*, is based entirely on existing scientific literature. All scientific research and publication ethics have been strictly followed. All procedures were carried out in accordance with academic integrity and scientific ethical standards. Proper citation has been given to all referenced sources. The author declare no conflict of interest.

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