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Review

Olive Oil Polyphenols in Cancer: Molecular Mechanisms and Therapeutic Promise

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Abstract

Olive oil, a cornerstone of the Mediterranean diet, is increasingly recognized not only for its cardiovascular benefits but also for its potential role in cancer prevention and therapy. Among its bioactive constituents, several phenolic compounds—tyrosol, hydroxytyrosol, oleuropein, oleacein, and oleocanthal—have demonstrated promising anticancer activities in various experimental models. These compounds act synergistically through diverse mechanisms, including antioxidant, anti-inflammatory, and immunomodulatory effects, as well as modulation of cell proliferation, apoptosis, angiogenesis, and metastasis. Notably, oleocanthal selectively induces cancer cell death via lysosomal membrane permeabilization, while hydroxytyrosol and oleuropein exhibit potent radical-scavenging and anti-proliferative properties. This review synthesizes findings from in vitro, in vivo, and clinical studies on the anticancer potential of these polyphenols, with emphasis on their mechanisms of action and possible applications in cancer prevention and adjunctive therapy. Given the established link between obesity and cancer development, clinical studies examining the metabolic, anti-inflammatory, and immunomodulatory effects of olive polyphenols in populations with obesity or prediabetes provide valuable insights into their potential to influence cancer-related pathways indirectly. However, direct clinical evidence in cancer patients remains limited and preliminary, underscoring the need for focused, well-controlled trials with cancer-specific endpoints. Furthermore, it critically evaluates the translational relevance of these findings, highlighting gaps in clinical research and future directions. Literature was retrieved from Google Scholar, PubMed, and ScienceDirect using keywords such as cancer, immunomodulatory, anti-inflammatory, olive, tyrosol, hydroxytyrosol, oleuropein, oleacein, and oleocanthal. Given the rising global cancer burden and the favorable safety profiles of these natural molecules, elucidating their molecular actions may support the development of novel integrative therapeutic strategies.

Keywords: olive oil; polyphenols; immunomodulatory; anti-inflammatory; apoptosis

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1. Introduction

Cancer remains a major global health burden, ranking as the second leading cause of death worldwide after cardiovascular diseases [1]. To date, over 130 distinct cancer types have been identified, with breast, lung, colorectal, prostate, and stomach cancers among the most prevalent [1]. The etiology of cancer is multifactorial, involving inherited genetic mutations and diverse environmental exposures that disrupt normal cellular homeostasis [2]. Lifestyle factors such as poor dietary habits, obesity, excessive alcohol

consumption, smoking, and micronutrient deficiencies (e.g., vitamin B_{12}) further contribute to cancer risk [3]. Alarmingly, global cancer incidence is projected to rise, with new cases expected to increase from 19.3 million in 2024 to nearly 28.4 million by 2040 [1,4,5].

At the molecular level, carcinogenesis is driven by accumulated genetic alterations that dysregulate cell growth and apoptosis. These changes may be inherited or acquired through exposure to carcinogens, including chemical agents, ionizing radiation, and oncogenic viruses [6]. Although conventional cancer treatments—such as surgery, chemotherapy, radiotherapy, and targeted molecular therapies—have improved survival rates, they are often associated with severe adverse effects, including immunosuppression and increased susceptibility to secondary malignancies [7]. Moreover, the high cost and complexity of these treatments pose significant barriers to healthcare access, particularly in low-resource settings [8]. Socioeconomic and ethnic disparities exacerbate these challenges, as minority populations frequently encounter systemic barriers to adequate care [9,10]. These limitations underscore the pressing need for alternative, accessible, and effective approaches to cancer prevention and therapy.

Herbal medicine is widely used by cancer patients globally, particularly in low- and middle-income countries [11–13]. A systematic review and meta-analysis of 155 studies involving over 800,000 participants reported a global prevalence of 22% for herbal medicine use among cancer patients, with notably higher rates in Africa (40%) and Asia (28%) [13]. Cross-sectional studies from Iran and Malawi revealed that over 80% of cancer patients used herbal or traditional medicines during treatment, often without informing their healthcare providers [11,12]. In Morocco, 70% of breast cancer patients reported using complementary and alternative medicine, with phytotherapy being the most common modality [14,15]. Similarly, a survey of 339 oncology healthcare professionals across 16 Middle Eastern countries highlighted widespread herbal use among cancer patients, with 80.3% of respondents reporting encounters with patients using at least one herbal product—raising concerns about potential herb–drug interactions and toxicity [15].

Among various dietary-based preventive approaches, the Mediterranean diet has attracted considerable attention for its protective effects against cancer, inflammatory diseases, and neurodegenerative disorders [16]. A central component of this diet is extra virgin olive oil (EVOO), derived from the olive tree (Olea europaea), which has been used for centuries in Mediterranean and Arab-Islamic traditional medicine to treat wounds, gastrointestinal disorders, and other health conditions [17–19]. Modern scientific studies have validated many of these traditional uses, showing that olive polyphenols—including oleocanthal and oleuropein—exhibit potent antioxidant, immunomodulatory, anti-inflammatory, and anticancer effects [20,21]. For instance, oleocanthal has been shown to induce apoptosis and inhibit proliferation in multiple cancer cell lines, highlighting its potential as a natural anticancer agent [21] (Figure 1).

Polyphenols are a diverse class of plant-derived secondary metabolites abundant in olives, fruits, vegetables, and teas. These compounds modulate critical cellular processes—including immunomodulation, anti-inflammatory responses, cell proliferation, apoptosis, angiogenesis, and metastasis—that contribute to cancer chemoprevention and therapeutic strategies [22–25]. Specifically, olive polyphenols such as hydroxytyrosol and oleuropein have demonstrated efficacy in inhibiting tumor cell proliferation, enhancing chemotherapy effectiveness, and reducing treatment-associated toxicities [26–28]. Their widespread dietary presence and broad spectrum of biological activities make them promising candidates for integrative oncology.

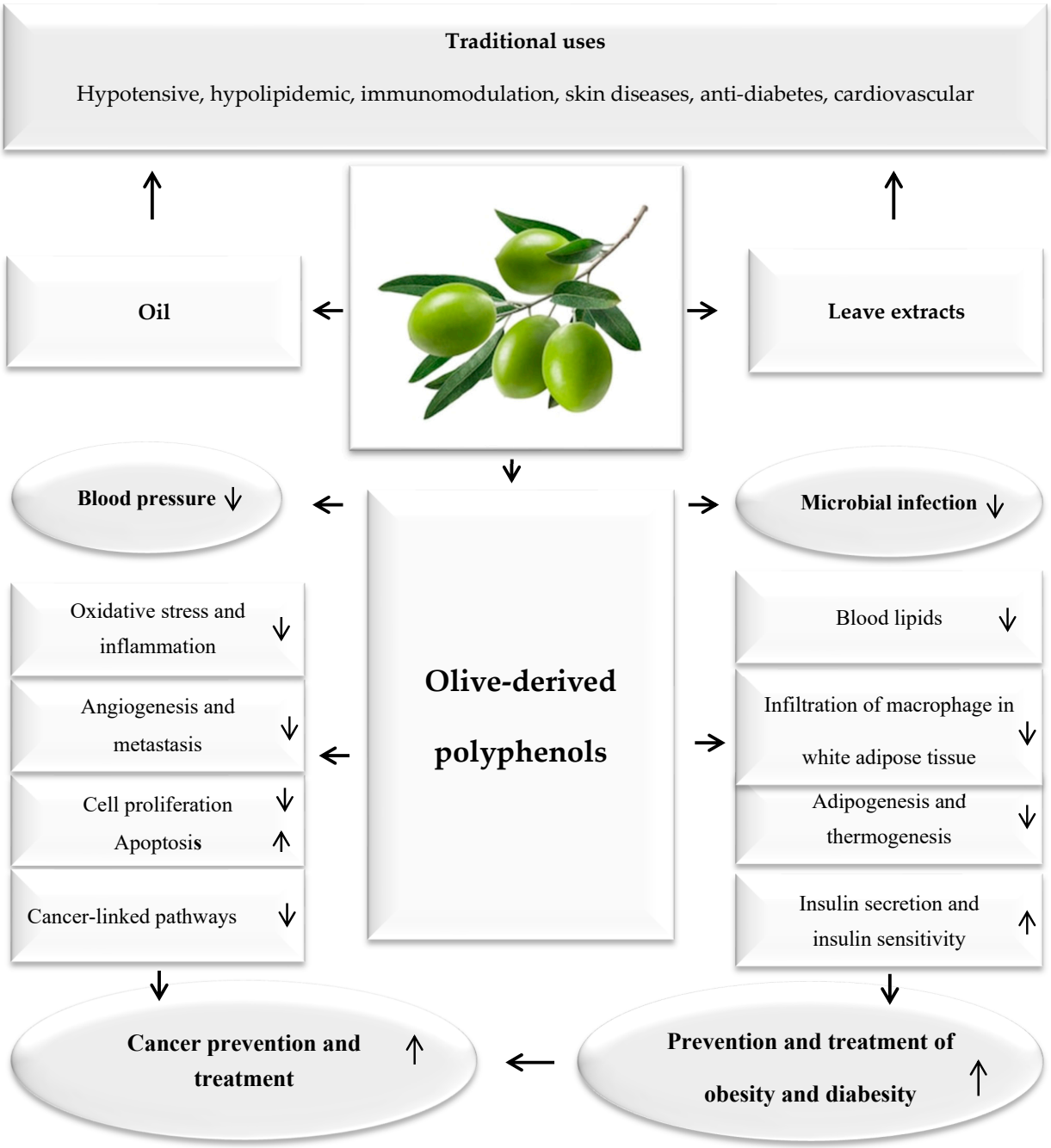


Figure 1. Traditional and evidence-based health beneficial effects of olive and olive-derived polyphenols and related products. These compounds exhibit diverse bioactivities, including antioxidant, anti-inflammatory, immunomodulatory, anticancer, cardioprotective, and metabolic effects. Notably, many of these benefits have been demonstrated in vitro and in vivo, with emerging clinical evidence supporting their role in metabolic health and chronic disease prevention. Given the strong link between obesity and cancer, interventions that improve metabolic and inflammatory status—such as olive polyphenols—may indirectly contribute to cancer risk reduction. However, direct clinical studies in cancer populations are still limited, highlighting an important area for future research. ↑ Activation; ↓ Inhibition.

In addition to polyphenols, EVOO is rich in monounsaturated fatty acids, particularly oleic acid, which confer cardiovascular and neuroprotective benefits [12,13,29]. Regular EVOO consumption is associated with a reduced risk of cognitive decline and up to a 30% decrease in dementia-related mortality [30,31]. Major olive-derived phenolics—

including hydroxytyrosol, oleuropein, oleocanthal, and tyrosol—combine antioxidant and anti-inflammatory properties to counteract oxidative stress and chronic inflammation, two key drivers of aging and disease [31–33]. These bioactives act on multiple molecular targets, ranging from free radical scavenging to inhibition of pro-inflammatory signaling pathways and tumor-promoting mechanisms.

This review explores the anticancer potential of key olive polyphenols, integrating traditional knowledge with modern scientific evidence. Special emphasis is placed on their chemical properties, mechanisms of action, and possible roles in future cancer prevention and therapy.

2. Olive Oil Bioactives: Tyrosol, Hydroxytyrosol, Oleuropein, Oleacein, and Oleocanthal

EVOO is rich in phenolic compounds that exhibit significant biological activities. Among these, tyrosol, hydroxytyrosol, oleuropein, oleacein, and oleocanthal are particularly remarkable for their potent antioxidant, immunomodulatory, anti-inflammatory, and anticancer properties. These bioactives originate primarily from olives and olive leaves and are formed through enzymatic reactions during oil extraction, which enrich the phenolic profile of EVOO (Figure 2) [34–36].

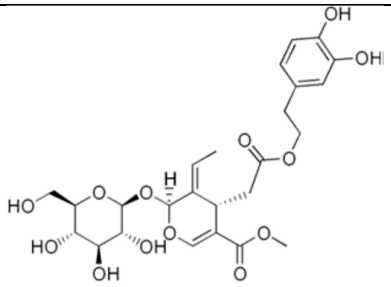
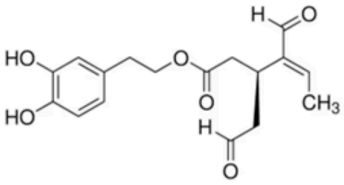
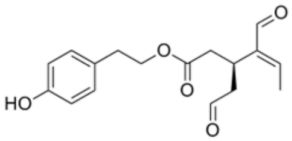
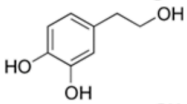
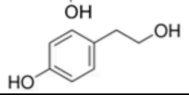
Compound	Chemical structure
Oleuropein	
Oleacein	
Oleocanthal	
Hydroxytyrosol	
Tyrosol	

Figure 2. Chemical structure of oleuropein, oleacein, oleocantha, hydroxytyrosol, and tyrosol.

Bonvino et al. (2018) established the OliveNet™ database, cataloging 676 olive-derived compounds, including 222 phenolics classified into 13 subclasses [34]. Other studies have reported that olive oil contains more than 200 bioactive molecules, including polyphenols, tocopherols, phytosterols, and fatty acids [35,36]. Notably, over 55 of these compounds have demonstrated potential anticancer activity [34,37]. The five phenolics discussed here are central to regulating oxidative stress, immunomodulation, inflammation, and cancer-

related signaling pathways [38–42], underscoring their importance in disease prevention and therapy.

Tyrosol, a simple phenolic alcohol present in EVOO and table olives [39,43,44], represents one of the fundamental phenolic compounds in olive oil. Closely related is hydroxytyrosol, a catechol derivative of tyrosol and one of the most potent natural antioxidants [40,45]. Its ortho-dihydroxy structure enhances radical scavenging and metal chelation capacity. The concentration of hydroxytyrosol in EVOO ranges from 50 to 800 mg/kg, depending on processing methods [46–48]. Oleuropein, a bitter secoiridoid glycoside, predominates in olive leaves and unripe olives [38,43,44]. Its levels range from 12 to 150 mg/kg in EVOO and up to 90 mg/g in olive leaves [49,50]. Over time, oleuropein undergoes hydrolysis, yielding hydroxytyrosol and elenolic acid [42,46,51,52]. Oleacein, a dialdehydic secoiridoid formed from ligstroside during oil processing, is found in EVOO at concentrations of 10–200 mg/kg [39,42,51]. Oleocanthal, another dialdehydic secoiridoid, arises from enzymatic hydrolysis of oleuropein aglycone [41]. Comprising a tyrosol moiety and an elenolic acid derivative, its concentration in EVOO ranges from 10 to 300 mg/kg [53].

3. Polyphenols as Epigenetic and Immunomodulatory Agents in Cancer Prevention

Functional and nutraceutical foods have emerged as valuable tools for enhancing immune responses and supporting disease management. A significant portion of their health-promoting effects is attributed to polyphenols, a broad class of naturally occurring compounds known for their antioxidant, anti-inflammatory, and immune-regulating properties. Traditionally recognized in herbal and natural medicine, polyphenols have been found to influence various immune cells, including dendritic cells, macrophages, and natural killer (NK) cells. They also stimulate the proliferation and function of T and B lymphocytes, while suppressing pro-inflammatory T helper cell subsets such as Th1, Th2, Th17, and Th9 [2,16,22] (Figure 3). These compounds play a critical role in lowering inflammation by decreasing levels of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), and interferon-gamma (IFN-γ). They promote immune balance by inducing regulatory T cells (Tregs), particularly in inflammatory and autoimmune conditions such as inflammatory bowel disease. Additionally, polyphenols help restrain the proliferation of autoreactive T cells and encourage apoptosis, thereby maintaining immune homeostasis and preventing harmful overactivation [2,16].

Olive oil polyphenols such as hydroxytyrosol, oleuropein, oleacein, and oleocanthal exhibit strong antioxidant activity primarily through three key mechanisms: hydrogen atom transfer (HAT), single electron transfer (SET), and sequential proton loss electron transfer (SPLET). The HAT mechanism involves the direct donation of a hydrogen atom from the phenolic hydroxyl group to reactive oxygen species or free radicals, neutralizing them and forming relatively stable phenoxyl radicals, thus terminating radical chain reactions. The SET mechanism consists of an electron donation from the antioxidant molecule to the radical species, often accompanied by proton transfer, which reduces the oxidizing agents and metal ions responsible for radical generation. Lastly, the SPLET mechanism starts with the loss of a proton from the phenolic hydroxyl group, forming a phenolate anion that subsequently donates an electron to neutralize free radicals. This mechanism is favored in polar environments and contributes significantly to antioxidant capacity. These pathways collectively explain the potent radical scavenging capacity of olive oil polyphenols and support their biological effects in reducing oxidative stress and inflammation, which are critical in cancer prevention and therapy [54–59].

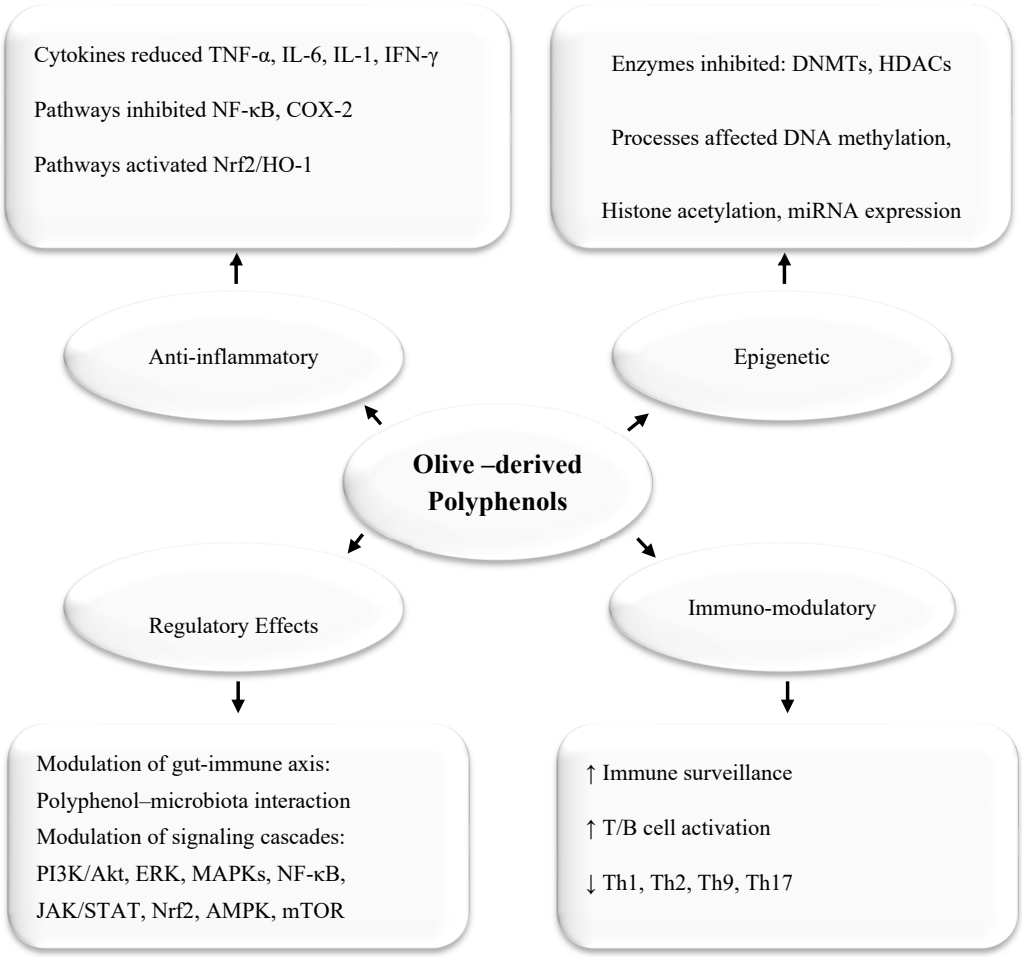


Figure 3. Polyphenols as anti-inflammatory, epigenetic, and immunomodulatory agents. This schematic highlights the diverse biological activities of polyphenols in modulating inflammation, epigenetic regulation, and immune responses. Polyphenols inhibit key enzymes such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), leading to altered DNA methylation, histone acetylation, and microRNA (miRNA) expression. They suppress pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1), and interferon-gamma (IFN-γ), primarily through inhibition of nuclear factor kappa B (NF-κB) and cyclooxygenase-2 (COX-2) pathways, while activating antioxidant pathways such as nuclear factor erythroid 2–related factor 2/heme oxygenase-1 (Nrf2/HO-1). Polyphenols also modulate gut microbiota composition, reinforcing the gut–immune axis and impacting systemic immunity. Signaling cascades such as phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), extracellular signal-regulated kinase (ERK), and mitogen-activated protein kinases (MAPKs) are influenced, resulting in enhanced immune surveillance, increased T and B cell activation, reduced T helper cell subsets (Th1, Th2, Th9, Th17), and promotion of regulatory T cells (Tregs) that mediate immune tolerance. ↑ Activation; ↓ Inhibition.

It is essential to differentiate between immunomodulation and immunostimulation. The former entails a balanced adjustment of immune responses—both enhancing and suppressing activity—to maintain physiological stability. In contrast, immunostimulation refers specifically to the activation or amplification of immune functions. While immunostimulatory effects can be advantageous in fighting infections or cancer, immunomodulation is especially critical in conditions involving chronic inflammation or autoimmunity, where excessive immune activation may cause damage.

Olive oil, a rich source of polyphenols and flavonoids, illustrates these beneficial effects well. Its powerful antioxidant, anti-inflammatory (suppression of pro-inflammatory

mediators, and), and immunemodulation capacities contribute to suppression of carcinogenic (Figure 3). These characteristics make olive oil a promising candidate for preventing and managing chronic inflammatory diseases, including cardiovascular disorders (Figure 1) [60–64]. Beyond their immunological effects, polyphenols exert profound epigenetic influences. They modulate key processes such as DNA methylation, histone acetylation, and microRNA (miRNA) expression, which can lead to the reactivation of tumor suppressor genes and inhibition of cancer-promoting pathways [61,62]. By inhibiting enzymes like DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), polyphenols facilitate apoptosis and halt cell cycle progression [62]. They also regulate immune-related miRNAs, thereby influencing inflammatory signaling and immune cell differentiation [63] (Figure 3).

In cancer, polyphenols contribute to reducing reactive oxygen species (ROS) and modulating signaling cascades, including PI3K/Akt, ERK, NF-κB, and MAPKs [61–65]. These combined effects result in the promotion of programmed cell death, suppression of epithelial–mesenchymal transition (EMT), and inhibition of metastasis [66,67]. Through a combination of immune modulation, epigenetic reprogramming, and anti-inflammatory action, polyphenols provide a comprehensive strategy for cancer prevention and treatment (Figure 3).

Recent research reinforces the immunomodulatory capacity of olive-derived polyphenols. Lee and colleagues showed that antioxidant dietary fiber from olive by-products effectively reshaped gut microbiota and mitigated T cell-driven atopic dermatitis in mice, indicating strong immune regulation via gut–immune interactions [68]. Furthermore, polyphenol-enriched extracts from Sicilian extra virgin olive oil were found to significantly reduce reactive oxygen species and inflammatory cytokines such as TNF-α and IL-1β in peripheral blood mononuclear cells from rheumatoid arthritis patients. This was accompanied by suppression of NF-κB and COX-2 pathways and activation of the antioxidant transcription factor Nrf2, suggesting a dual antioxidant and anti-inflammatory mechanism [69]. Additional preclinical evidence demonstrates that specific olive polyphenols like oleacein provide anti-arthritic and immunomodulatory benefits by activating the Nrf2/HO-1 signaling pathway and inhibiting Th17 cell polarization, supporting their potential role in autoimmune disease management [70]. Collectively, these studies highlight the versatile capacity of olive polyphenols to regulate immune responses both systemically and at the cellular level, largely through redox-sensitive and cytokine-mediated mechanisms.

3.1. Olive Polyphenols, Immune Modulation, and the Tumor Microenvironment

The tumor microenvironment (TME) consists of a complex interplay between cancer cells and surrounding immune and stromal cells, which together influence tumor development, immune evasion, and therapeutic resistance. Among the immune cells present, tumor-associated macrophages (TAMs) are particularly influential, often promoting tumor growth and immunosuppression when polarized toward the M2 phenotype. In contrast, M1-like macrophages exhibit anti-tumor properties by enhancing inflammatory responses and antigen presentation.

Altering the balance between M1 and M2 macrophage states in favor of the M1 phenotype has been proposed as a strategy to improve responses to immunotherapies, particularly immune checkpoint inhibitors such as anti-PD-1/PD-L1 or anti-CTLA-4 antibodies [71,72]. Various plant polyphenols have shown potential to influence macrophage activity, though direct evidence specifically linking olive polyphenols to TAM repolarization in tumor models is still limited. Nevertheless, studies on hydroxytyrosol and oleuropein suggest that these compounds can modulate macrophage responses and suppress inflammatory pathways in non-cancerous models [73,74].

In addition to their potential effects on macrophages, olive-derived compounds may also influence other immune components. For example, oleuropein has been reported to reduce regulatory T cell (Treg) populations and enhance cytotoxic T lymphocyte responses in animal studies, although these findings have not yet been validated in cancer settings. Another promising but underexplored area involves the interaction of olive polyphenols with immune checkpoint pathways. While compounds such as oleocanthal have demonstrated the ability to induce cancer cell death and modulate antigen presentation in vitro [75], research exploring their combination with checkpoint blockade therapies remains lacking.

Given their multifaceted bioactivity and low toxicity, olive oil polyphenols may offer value as adjuncts to existing immunotherapies. However, more focused investigations are needed to assess their impact on immune cell behavior within the TME, particularly regarding TAM polarization, T cell activation, and synergy with checkpoint inhibitors. Addressing these questions could help bridge nutritional approaches with cutting-edge cancer immunotherapy.

3.2. Molecular Mechanisms Underlying the Anticancer Effects of Olive-Derived Polyphenols

Oleocanthal and oleacein, essential phenolic compounds found in EVOO, are preserved solely in unrefined oils. Recent in vivo and clinical research indicates that high-phenolic EVOO can reduce inflammation and oxidative stress markers, aiding in the management of prediabetes and obesity [76–78]. In addition to these metabolic advantages, olive-derived polyphenols demonstrate anticancer effects, such as the capacity to hinder cancer cell growth, trigger apoptosis, and reduce angiogenesis and metastasis [79,80]. These impacts underscore the therapeutic promise of EVOO polyphenols in cancer prevention and therapy (Figure 4).

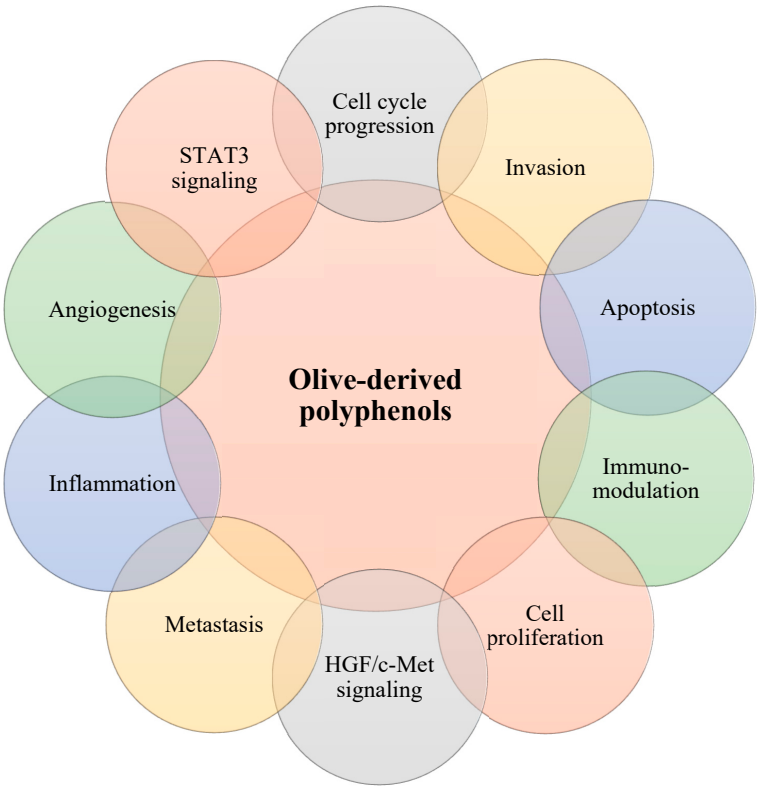


Figure 4. Olive-derived polyphenols target key cancer-related pathways, modulating cell proliferation, apoptosis, invasion, metastasis, angiogenesis, inflammation, and immune responses. STAT3: signal transducer and activator of transcription 3; HGF/c-Met: hepatocyte growth factor/mesenchymal-epithelial transition factor.

3.2.1. Oleocanthal

Inflammation is pivotal in cancer progression, as it encourages DNA damage, facilitates angiogenesis, and increases metastatic dissemination [81]. Consequently, anti-inflammatory compounds such as oleocanthal are highly valued for cancer prevention and treatment. Structurally characterized in 1993 as a 2-(p-hydroxyphenyl)ethyl ester of (3S)-4-formyl-3-(2-oxoethyl)hex-4-enoic acid [82], oleocanthal exhibits both anti-inflammatory and anticancer properties. Research conducted both in vitro and in vivo indicates that oleocanthal can hinder cancer cell growth, induce apoptosis, and interfere with angiogenesis [42,53,83]. It can additionally improve the effectiveness of chemotherapy and radiotherapy while reducing their adverse effects. These actions are facilitated by its disruption of various molecular signaling pathways that play a role in cancer initiation and progression. A notable property of oleocanthal is its ibuprofen-like stinging sensation in the throat. This led researchers to investigate its NSAID-like behavior. Oleocanthal inhibits COX-1 and COX-2 enzymes in a dose-dependent manner, often more effectively than ibuprofen [84]. Given COX-2's role in promoting tumor growth, oleocanthal's inhibition of this enzyme supports its anticancer relevance [81,85].

Clinical studies further confirm the advantages of oleocanthal. In the APRIL study, a randomized, controlled crossover trial, participants with obesity and prediabetes exhibited notable decreases in systemic inflammation markers and enhancements in metabolic and oxidative profiles after one month of consuming high-oleocanthal EVOO [86]. Animal models further demonstrate its effectiveness. In a model of systemic lupus erythematosus (SLE), a diet rich in oleocanthal lowered inflammatory cytokines, enhanced kidney function, and restored endothelial dysfunction by influencing the NF-κB, MAPKs, and STAT3 pathways [87]. In a collagen-induced arthritis model, oleocanthal from diet inhibited the expression of IL-6, IL-1β, TNF-α, COX-2, and iNOS through the Nrf2/HO-1, JAK-STAT, and NF-κB pathways [88]. In vitro research involving osteoarthritis chondrocytes indicates that oleocanthal may reduce PAR-2-mediated inflammation, implying wider use in joint health [89].

Table 1 summarizes key mechanisms through which olive-derived oleocanthal [89–91], oleacein, oleuropein [27], and tyrosol [73,74] exert anticancer effects, based on in vitro and in vivo studies. Data were extracted from peer-reviewed publications and represent consistent findings across multiple models. Due to space limitations and variability across studies, specific concentrations, cell types, and experimental conditions are detailed in the main text and reference list. The table is intended as a focused overview of frequently reported molecular and cellular targets, rather than a comprehensive compilation of all available data.

Table 1. Anticancer molecular and cellular targets olive-derived polyphenols. ↑ Activation; ↓ Inhibition.

Mechanism	Compound	Molecular/Cellular Targets
Inhibition of cell proliferation	Oleocanthal	CDK6↓, cyclin D1↓, TRPC6↓, P21↑, P27↑
	Oleacein	CDK2↓
	Oleuropein	Cyclin D1↓, p21↑, p53↑, CDK↓
	Tyrosol	Cyclin D1↓, PCNA↓, CDK4↓, CDK6↓, p21↑, p27↑
Induction of apoptosis	Oleocanthal	caspase 3, 8, 9↑, Bcl-xL↓, Bcl-2↓, Mcl-1↓, survivin↓
	Oleacein	Bcl-2↓, Mcl-1↓, BAX↑

Table 1. *Cont.*

Mechanism	Compound	Molecular/Cellular Targets
Induction of apoptosis	Oleuropein	Bax↑, Bid↑, Bad↑, Bcl-2↓, p62↓, p70S6K↓, mGlo2↑, LC3-II/LC3-I↑, Beclin-1↑
	Tyrosol	Bax↑, Bcl-2↓, caspase-3↑, PARP cleavage↑, ROS↑
Inhibition of angiogenesis	Oleocanthal	AKT↓, ERK1/2↓, c-Met↓
	Oleuropein	MMP-2, -9↓, uPA↓, VEGF-A↓, D↓, HIF-1α↓
	Tyrosol	VEGF↓, HIF-1α↓, MMP-2↓
Inhibition of metastasis	Oleocanthal	E-cadherin↑, N-cadherin↓, vimentin↓, STAT3↓, Brk/paxillin/Rac1↓, c-Met↓
	Oleuropein	SIRT-1↓, HDAC4↓, miR-194↑, PD-L1↓, XIST↑
	Tyrosol	MMP-2↓, MMP-9↓, N-cadherin↓, vimentin↓, E-cadherin↑
Modulation of cancer-linked pathways	Oleocanthal	ERK1/2↓, AKT↓, STAT3↓, SMYD2↓, Brk↓
	Oleacein	c-KIT↓, K-RAS↓, PIK3R3↓, STAT3↓
	Oleuropein	NF-κB↓, cyclin D1↓, ERK p44/42↓, ERK1/2↓, AKT↓
	Tyrosol	NF-κB↓, AKT↓, ERK1/2↓, JNK↓, PI3K↓, MAPK↓

CDKs: cyclin-dependent kinases (**CDK2**, **CDK4**, **CDK6**); **cyclin D1**: G1 phase regulatory protein; **TRPC6**: transient receptor potential cation channel subfamily C member 6; **P21** (**CDKN1A**), **P27** (**CDKN1B**): cyclin-dependent kinase inhibitors; **p53**: tumor protein p53; **PCNA**: proliferating cell nuclear antigen; **caspases 3, 8, 9**: cysteine-dependent aspartate-directed proteases; **Bcl-xL**, **Bcl-2**, **Mcl-1**: anti-apoptotic Bcl-2 family proteins; **Bax**, **Bad**, **Bid**: pro-apoptotic Bcl-2 family proteins; **survivin**: baculoviral IAP repeat-containing protein 5; **cathepsins D, B**: lysosomal proteases; **p62**: sequestosome 1; **p70S6K**: 70 kDa ribosomal protein S6 kinase; **mGlo2**: mitochondrial glyoxalase 2; **LC3-I/II**: microtubule-associated protein 1A/1B-light chain 3; **Beclin-1**: autophagy-related protein; **PARP**: poly (ADP-ribose) polymerase; **ROS**: reactive oxygen species; **AKT**: protein kinase B; **ERK1/2**: extracellular signal-regulated kinases 1 and 2; **JNK**: c-Jun N-terminal kinase; **c-Met**: hepatocyte growth factor receptor; **MMP-2**, **MMP-9**: matrix metalloproteinases; **uPA**: urokinase-type plasminogen activator; **VEGF-A**, **VEGF-D**: vascular endothelial growth factors; **HIF-1α**: hypoxia-inducible factor 1-alpha; **E-cadherin**, **N-cadherin**: cell adhesion molecules; **vimentin**: intermediate filament protein; **STAT3**: signal transducer and activator of transcription 3; **Brk**: breast tumor kinase; **paxillin**: focal adhesion adaptor protein; **Rac1**: Ras-related C3 botulinum toxin substrate 1; **SIRT-1**: sirtuin 1; **HDAC4**: histone deacetylase 4; **miR-194**: microRNA-194; **PD-L1**: programmed death-ligand 1; **XIST**: X-inactive specific transcript; **SMYD2**: SET and MYND domain-containing protein 2; **c-KIT**: CD117 proto-oncogene receptor tyrosine kinase; **K-RAS**: Kirsten rat sarcoma viral oncogene; **PIK3R3**: phosphoinositide 3-kinase regulatory subunit 3; **NF-κB**: nuclear factor kappa-light-chain-enhancer of activated B cells; **PI3K**: phosphoinositide 3-kinase; **MAPK**: mitogen-activated protein kinase.

3.2.2. Oleocanthal as a Multi-Targeted Natural Agent in Cancer Therapy

Oleocanthal gained prominence in 2011 for its capacity to impede the proliferation, migration, and metastasis of cells from human breast (MCF-7, MDA-MB-231) and prostate (PC-3) cancer cell lines [87]. Initial studies emphasized oleocanthal's potential to combat aggressive triple-negative breast cancer (TNBC), demonstrating its ability to hinder cell proliferation and reduce levels of CA 15-3, a recurrence marker [88]. Mechanistically,

oleocanthal interferes with the hepatocyte growth factor (HGF)/c-Met pathway, often elevated in tumors to promote cytoskeletal rearrangement, angiogenesis, survival, and invasion, by inhibiting c-Met phosphorylation and subsequent signaling [89–91]. Improvements in formulation, like xylitol-based solid dispersions, have increased oleocanthal's solubility and bioavailability, boosting its antiproliferative and pro-apoptotic actions in breast cancer models [42,83]. Simultaneously, oleocanthal has been demonstrated to affect several survival pathways. It attaches to mTOR with an IC_{50} of 708 nM, decreasing mTOR phosphorylation and consequently limiting cell growth mediated by the PI3K/Akt/mTOR pathway in metastatic breast cancer cell lines [92]. Oleocanthal additionally inhibits STAT3 activation in melanoma and liver cancer cells, reducing tumor growth and promoting apoptosis [93,94]. In cutaneous melanoma, oleocanthal effectively inhibits the phosphorylation of ERK1/2 and Akt and reduces the levels of the anti-apoptotic protein Bcl-2 more efficiently than similar secoiridoids [95,96]

Recent preclinical research has broadened oleocanthal's anticancer profile to include more tumors. In colorectal cancer, oleocanthal was shown to suppress the SMYD2–EZH2 epigenetic pathway and block c-Met activation, leading to a marked decrease in tumor weight and a thwarting of relapse in mouse models [97]. Its anti-angiogenic capacity was shown when oleocanthal (both alone and in conjunction with oleacein) hindered endothelial cell invasion and tube development, indicating a function in blocking tumor vascularization [82]. In gastric cancer cells, oleocanthal increased levels of reactive oxygen species (ROS), activated p53, caused cell-cycle arrest, and worked in synergy with chemotherapeutics like 5-fluorouracil, paclitaxel, and cisplatin to improve cytotoxic effects [98]. Additionally, the precise delivery of oleocanthal using anti-CD44-conjugated olive oil nanocapsules specifically eliminated pancreatic cancer stem cells, enhancing absorption and anticancer effectiveness in contrast to non-targeted formulations [99].

Although there is substantial evidence that oleocanthal targets multiple cancer-related pathways—such as c-Met, mTOR, STAT3, and ERK/Akt—most supporting data remain confined to preclinical models. These findings underscore oleocanthal's broad anticancer potential and possible synergy with conventional chemotherapeutics. However, significant barriers still hinder its clinical translation. Challenges such as poor water solubility, rapid metabolism, and limited bioavailability constrain its therapeutic application, though recent advances in formulation and nanodelivery offer promising solutions. Moreover, standardized protocols are needed to evaluate efficacy across various tumor types, given the variability in dosing regimens and tumor-specific responses. Another critical gap is the lack of data on the long-term safety and interaction profile of oleocanthal in humans, particularly in combination therapies. Future research should also explore its effects on cancer stem cell dynamics, the tumor microenvironment, and immunomodulation under clinically relevant conditions. Rigorous clinical trials—especially phase I and II studies—are essential to confirm preclinical findings and to establish optimal delivery methods and dosing strategies. Addressing these issues will be pivotal in advancing oleocanthal from an experimental agent to a viable therapeutic or adjuvant in cancer treatment.

3.3. Oleuropein

Oleuropein, a key phenolic compound found in olives, has been thoroughly studied for its cancer-fighting attributes. Initial studies showed that in MCF-7 breast cancer cells, oleuropein reduced cell proliferation in a time-dependent way [100]. These in vitro results were reflected in vivo, as dietary supplementation with 125 mg/kg oleuropein diminished pulmonary metastases in mice with MCF-7 xenografts [101]. Mechanistically, oleuropein influences several signaling pathways: in MDA-MB-231 triple-negative breast cancer cells, 100 μM oleuropein inhibited the NF-κB pathway and its downstream targets cyclin D1 and

COX-2 by blocking AKT phosphorylation and IκB expression [102]. A similar inhibition of NF-κB was noted in the seminoma cell lines TCAM-2 and SEM-1 [103], while HT-29 colon cancer cells showed resistance of IκB to oleuropein at concentrations of 400–800 μM, emphasizing cell-type specificity [104].

The anti-inflammatory enzyme COX-2, associated with tumor angiogenesis and growth, is diminished by oleuropein in colon carcinoma via a decrease in CREB transcriptional activity [105]. This effect might be enhanced by oleuropein's suppression of the Wnt/β-catenin signaling pathway, which is inappropriately activated in colorectal, gastric, and endometrial cancers [106–108]; in fact, NSAIDs that focus on this pathway have demonstrated chemopreventive effectiveness [109]. Oleuropein additionally affects nuclear receptors: while PPAR agonists can occasionally be associated with increased colorectal cancer risk, elevated PPAR expression may inhibit tumor growth [110]. In HT-29 cells, hydroxytyrosol (instead of oleuropein) induces PPAR upregulation [104]. Additionally, oleuropein disrupts the epithelial–mesenchymal transition by blocking MAPKs, ERK, and AKT—key activators of NF-κB—thus altering the tumor microenvironment and pre-metastatic niche through the modulation of VEGF, MMPs, and inflammatory cytokines [111–113]. Its anti-metastatic properties are demonstrated by increased apoptosis and reduced invasion in MDA-MB-231 cells at 370 μM, along with lower levels of MMP-2 and MMP-9 in glioma cell lines (U251, A172) and reduced MMP-7 in HepG2 hepatocarcinoma cells [114,115]; as MMPs promote angiogenesis and invasion, their inhibition likely plays a role in oleuropein's anti-metastatic effects [116]. In thyroid carcinoma TPC-1 and BCPAP cells, oleuropein and its peracetylated derivative suppressed proliferation at concentrations below 100 μM while decreasing ERK and AKT phosphorylation [117]. Similarly, prostate cancer cell lines LNCaP and DU145 experienced necrosis when exposed to 100–500 μM oleuropein [118].

At the apoptotic level, oleuropein raises p53 and Bax while reducing Bcl-2 and HIF-1α, aligning with the inhibition of the AKT survival pathway [102], and might also engage with GRB2, MEK, MDM2, RAF, and RTKs. Recent findings suggest that oleuropein enhances the expression of the cannabinoid receptor CB1 in Caco-2 colon cells at 50 μM, which corresponds with decreased tumor growth both in vitro and in vivo [105,119], implying further tumor-suppressing mechanisms. In SH-SY5Y neuroblastoma cells, 350 μM oleuropein impeded migration, although the specific targets are still to be determined [116].

Expanding on this initial research, recent studies have enhanced our knowledge of oleuropein's anticancer properties. To overcome its limited bioavailability, a PEGylated nano-phytosome co-formulation of oleuropein and rutin attained an IC_{50} of 0.14 μM against colon cancer cells, significantly surpassing the potency of free compounds and suggesting the potential for passive tumor targeting [119]. In breast cancer, oleuropein enhances the effectiveness of paclitaxel in MCF-7 cells by decreasing oxidative stress, allowing for reduced chemotherapy doses while preserving the antitumor effect [120]. Individual treatments with oleuropein at concentrations of 1–10 μM likewise suppress proliferation, movement, and viability in hormone receptor-positive (MCF-7) and triple-negative (MDA-MB-231) cell lines, underscoring its widespread anti-metastatic effects [121]. Transcriptomic analysis of triple-negative cells indicated that oleuropein, whether used alone or in conjunction with oleocanthal, modifies gene expression in apoptosis, cell cycle, and inflammation pathways [122]. In models of metastatic castration-resistant prostate cancer, oleuropein affects the PCSK9-LDLR pathway, inhibiting tumor development and recurrence [123]. Ultimately, thorough reviews highlight the necessity for improved delivery systems and dosing approaches to translate these in vitro and in vivo achievements into clinical uses [124].

Although oleuropein demonstrates potential anticancer effects, numerous factors need additional exploration. Its metabolism and bioavailability are inconsistent and not well

understood because of significant first-pass metabolism, which includes de-glycosylation, hydrolysis, oxygenation, and methylation. Additional human research is required to assess how various factors influence its absorption, distribution, and overall effectiveness. Furthermore, the ideal dosage, duration of exposure, and cancer-specific impacts of oleuropein are still not well-defined. Investigations should additionally examine how structural alterations can improve its efficacy and elucidate the mechanisms responsible for its synergistic effects with chemotherapeutic drugs such as doxorubicin. These issues need to be resolved before oleuropein can be included in standard cancer treatment protocols or utilized as a preventive supplement.

3.4. Oleacein

Oleacein is a vital bioactive secoiridoid polyphenol mainly located in EVOO. It is structurally connected to other well-researched olive polyphenols like oleuropein and oleocanthal, yet possesses unique biological activities. Oleacein has garnered growing interest for its strong antioxidant, anti-inflammatory, and anticancer effects [66,76,77]. Its diverse effects enhance the health advantages linked to the Mediterranean diet, establishing it as a potential agent for chemopreventive and therapeutic uses, particularly in cancer treatment. Chemoprevention involves utilizing natural or synthetic substances to avert or postpone the emergence and advancement of diseases, particularly cancer [77,98]. Although the idea generally encompasses disease prevention via dietary or medicinal approaches, it has gained particular significance in the field of oncology. Chemoprevention currently has a significant role in cancer treatment and management, focusing on the prevention of tumor initiation, development, and recurrence [25,125].

The ways in which chemopreventive agents function are varied and intricate. They encompass antioxidant and anti-inflammatory properties, regulation of cell growth, and control of programmed cell death mechanisms, including apoptosis and autophagy. These agents also disrupt necrosis pathways, hinder tumor angiogenesis, and prevent metastatic behavior by modifying crucial signaling cascades [126]. Oleacein has shown significant anti-cancer properties in various in vitro experiments. It greatly diminished the viability of cells from melanoma, neuroblastoma, and multiple myeloma [127–129]. In melanoma cells, oleacein causes cell cycle arrest at the G1/S transition by enhancing the phosphorylation of cyclin-dependent kinase 2 (Cdk2) at Tyr15, which inactivates Cdk2 and stops cell cycle progression [127]. In multiple myeloma, oleacein induces cell cycle arrest by enhancing the expression of p27KIP1 and p21CIP1, resulting in cell accumulation in the G0/G1 phase and an increased percentage of sub-G0 phase (hypodiploid) cells, signifying apoptosis [129].

Apoptotic processes additionally reinforce the anticancer effects of oleacein. It enhances internucleosomal DNA fragmentation and elevates the pro-apoptotic gene BAX while downregulating the anti-apoptotic genes BCL-2 and MCL-1 [127]. Alterations in gene expression are controlled by particular microRNAs (miRNAs): a notable reduction in miR-214-3p, which targets BAX, alongside heightened levels of miR-34a-5p and miR-16-5p, both targeting BCL2, as well as increased miR-193a-3p, which targets MCL-1. In neuroblastoma cells, oleacein promotes apoptosis by increasing BAX and decreasing BCL-2 protein levels [128]. Likewise, in endothelial cells, oleacein causes a rise in the sub-G1 population, alongside the activation of caspases 3 and 7, validating its pro-apoptotic function [126]. Moreover, oleacein disrupts tumor angiogenesis by inhibiting the activation and growth of endothelial cells. It restricts cell movement and the development of capillary-like formations. In vivo models like the chick chorioallantoic membrane (CAM) assay demonstrate that oleacein administration hinders vascularization beneath and surrounding treated disks [130].

While oleacein shows great promise, it is still among the least researched polyphenols compared to oleocanthal and oleuropein. Recent research indicates that oleacein may be advantageous in dietary supplements aimed at cancer prevention, supported by epidemiological evidence showing a negative relationship between olive oil intake and cancer rates. Nonetheless, its function in regulating oxidative stress and endoplasmic reticulum stress has not been explored. Comprehensive studies and randomized clinical trials are necessary to determine its clinical significance. These will assist in confirming its chemopreventive potential and determining if such compounds can boost therapeutic outcomes or enhance quality of life for cancer patients by hindering tumor growth and aiding conventional treatments.

Furthermore, oleacein has epigenetic impacts, especially in multiple myeloma models, where it acts as a histone deacetylase (HDAC) blocker. This results in heightened acetylation of histones and non-histone proteins and a decrease in the transcription factor Sp1. Furthermore, oleacein regulates tumor-suppressive microRNAs, such as miR-22 and miR-29b, and boosts the effectiveness of chemotherapeutic drugs like bortezomib and carfilzomib [129].

New clinical evidence backs up these results. In a randomized clinical trial with patients with early-stage chronic lymphocytic leukemia, daily intake of EVOO enriched with oleacein and oleocanthal notably elevated apoptotic markers like cleaved cytokeratin-18 and Fas/Apo-1, while lowering the levels of survival markers survivin and cyclin D. These modifications occurred without any adverse effects, suggesting that oleacein is both biologically active and safe for human consumption [131]. Together, this information portrays oleacein as a powerful and insufficiently studied chemopreventive compound whose mechanisms involve cell cycle modulation, promotion of apoptosis, suppression of angiogenesis, and epigenetic regulation. Even with this potential, oleacein is still less researched than its counterparts, like oleocanthal and oleuropein, highlighting the necessity for more preclinical and clinical studies to confirm its therapeutic value.

3.5. Tyrosol

Potentially, tyrosol prevents oxidative damage via the activation of antioxidant enzymes to protect cells from ROS [132]. On the other hand, tyrosol hinders inflammatory responses within the cancer microenvironment by suppressing the induction of HIF-1α/NF-κB pathway, decreasing secretion of pro-inflammatory molecules like TNF-α and IL-6, which act as initiators/promoters in tumorigenesis [133,134]. Furthermore, tyrosol represses the PI3K/Akt/mTOR/S6K signaling, reducing the induction of HIF-1α with the downstream target genes, while tyrosol also infirmly binds to the AhR in the cytoplasm, decreasing its transcriptional ability and thereby mitigating tumor progression under hypoxic conditions [135]. Tyrosol-mediated apoptosis involves alterations to key proteins by increasing p53 and decreasing Bcl-2 expression so as to suppress anti-apoptotic signals and induce apoptosis. Intriguingly, tyrosol also prevents UVB-induced apoptosis in HaCaT keratinocytes, suggesting a protective role for tyrosol in non-malignant epithelial cells [136]. In prostate cancer models (PC-3 and DU145), tyrosol decreased cell viability through ROS-mediated mitochondrial dysfunction, indicating its potential as an anticancer agent [137]. Tyrosol inhibits tumor growth by targeting multiple proliferative signaling pathways [138]. Studies in liver cancer cells have reported that tyrosol induces upregulation of the second phase detoxification enzyme NAD(P)H: quinone oxidoreductase-1 (NQO1) by the antioxidant response element, leading to inhibited augmentation in SMMC-7721 human liver cancer cells [28,139].

3.6. Hydroxytyrosol

Hydroxytyrosol mitigates oxidative stress, lessens the worst side effects of chemotherapy, and improves paclitaxel's anticancer efficacy, thereby promoting better health outcomes for patients [140]. Hydroxytyrosol regulates the levels of ROS and downregulates HIF-1α production in MCF-7 breast cancer cells in vitro, while also binging to bear the aryl hydrocarbon receptor (AhR) [132]. While hydroxytyrosol inhibits the production of NF-κB and COX-2, it reduces mutations caused by inflammation and subsequent cancer progression [133]. Recent investigations have identified ROS scavenging and antioxidant system regulation as the main modes of hydroxytyrosol-mediated antitumor action [141]. Hydroxytyrosol-related inhibition of AKT and NF-κB signaling, induction of G1/S cell cycle arrest, and downregulation of cyclin D1/E and CDK2/4, which subsequently decreases the expression of androgen receptor and prostate-specific antigen (PSA), have also been established, thereby suggesting that hydroxytyrosol can be exploited for therapeutic interventions in prostate cancer [26,132]. Cholangiocarcinoma has a poorer prognosis due to its late detection and chemotherapy resistance. It is also susceptible to hydroxytyrosol-mediated anticancer effects. The administration of hydroxytyrosol leads to cell cycle arrest and apoptosis in both in vitro and in vivo systems, thereby inhibiting the proliferation of various cancer cell lines, including TFK-1, KMBC, and GBS-SD [142]. Treatment of cancer cell lines of the thyroid with high-dose hydroxytyrosol greatly decreased cell viability by downregulating cyclin D1 and upregulating the expression of P21. Annexin V-P1 staining and DNA fragmentation assays confirmed apoptosis induction by hydroxytyrosol in papillary and follicular thyroid carcinoma cells [143]. Hydroxytyrosol also inhibited the production of the CCL5 chemokine in non-cancer human fibroblasts, disrupting ERK1/2-cyclin D1 signaling and, thus, hindering the proliferation of MB231 breast cancer cells. Compared with paclitaxel therapy alone, hydroxytyrosol co-treatment significantly decreased tumor burden and preserved oxidative balance [144]. Besides that, hydroxytyrosol cooperates with cetuximab to downregulate epidermal growth factor receptor (EGFR) and to inhibit proliferation of colon cancer cells [145]. Hydroxytyrosol modulates PI3K/Akt inhibition and MAPK pathway activation by regulating cell division markers such as cyclin D1 and CDK4, causing cytostatic activity to cancer cells [146]. Hydroxytyrosol also influences key genes involved in cell proliferation, apoptosis, and Wnt signaling by upregulating Wnt ligand-related protein 4 (Sfrp4), thus downregulating breast cancer progression [147].

Table 2 provides a simplified overview of converging evidence from the literature; detailed model-specific data, doses, and experimental contexts are discussed in the main text. Hydroxytyrosol has been shown to induce apoptosis, cell cycle arrest, and mitochondrial dysfunction via reactive oxygen species generation in colon cancer cells [148]. Both hydroxytyrosol and oleuropein reduce viability, inhibit migration and invasion, and activate autophagy pathways in estrogen receptor-positive breast cancer cells [149]. Oleuropein has been reported to trigger G_1 cell cycle arrest and apoptosis through p53 and Bax activation and Bcl-2 suppression [150]. Oleacein and oleocanthal demonstrate anti-angiogenic properties by inhibiting endothelial proliferation, migration, and tube formation, as well as by inducing apoptosis [151].

Table 2. Summary of reported anticancer mechanisms of olive-derived polyphenols: tyrosol (Ty), hydroxytyrosol (HT), oleuropein (OP), oleacein (OC), and oleocanthal (OT).

Anticancer Mechanism	Ty	HT	OP	OC	OT
Induction of apoptosis	√	√	√	√	√
Anti-inflammatory	√	√	√	√	√
Anti-oxidant	√	√	√	√	√
Anti-metastasis		√	√		√
Inhibition of cell proliferation	√	√	√		√
Inhibition of angiogenesis		√	√		√
Induction of autophagy		√	√		√
Inhibition of cell migration		√	√		√
Targeting cell signaling pathways	√	√	√		√

√ indicates that the respective mechanism has been consistently reported in at least two independent peer-reviewed studies for the indicated compound.

4. Challenges in Clinical Translation of Olive Oil Polyphenols

Despite extensive preclinical evidence supporting the anticancer potential of olive oil polyphenols such as hydroxytyrosol, tyrosol, oleuropein, oleacein, and oleocanthal, several translational barriers remain unresolved, limiting their application in clinical oncology. These include:

Poor Bioavailability and Rapid Clearance: A critical issue limiting therapeutic effectiveness is the low systemic bioavailability of these compounds. Hydroxytyrosol, while highly hydrophilic, undergoes swift metabolism and elimination, primarily as glucuronide and sulfate conjugates with diminished biological potency [152,153]. Lipophilic polyphenols such as oleocanthal and oleacein exhibit limited solubility in aqueous environments, resulting in variable absorption and inconsistent systemic exposure [154]. Human pharmacokinetic studies report peak plasma levels of hydroxytyrosol within an hour post-ingestion, although these levels are transient and subject to high inter-individual variability [153].

Extensive Metabolic Conversion: Upon ingestion, olive polyphenols are subjected to complex metabolic pathways, including phase I and II reactions such as oxidation, methylation, sulfation, and glucuronidation [155]. These biochemical modifications alter both their structure and biological activity, making it difficult to directly relate in vitro effects to in vivo outcomes. For instance, oleocanthal rapidly transforms into various metabolites, such as oleocanthalic acid, whose biological properties are not yet fully characterized [154].

Limitations of Delivery Systems: The chemical instability of many polyphenols under physiological conditions has prompted the development of advanced delivery technologies. Approaches including nanoemulsions, encapsulation, and lipid-based systems are being explored to improve gastrointestinal stability, enhance solubility, and enable sustained release [155,156]. While such systems have demonstrated efficacy in preclinical models, their translation into clinical settings is still in the early stages, with few having reached clinical trials.

Undefined Dosing Parameters: Many experimental models employ concentrations of polyphenols that are not achievable through regular dietary intake or supplementation. Consequently, the dose–response relationships in humans remain poorly defined, complicating the identification of safe and therapeutically effective dosing regimens for compounds like oleuropein and oleocanthal [155].

Variable Individual Responses and Broad Mechanisms: The multitargeted nature of olive polyphenols—affecting pathways related to inflammation, oxidative stress, angiogenesis,

and epigenetic modulation—contributes to both therapeutic potential and challenges in specificity. Individual variability in genetics, gut microbiota composition, and dietary patterns may also significantly influence therapeutic outcomes, limiting the predictability of responses [152,153].

Scarcity of Robust Clinical Trials: Although some human studies indicate improvements in oxidative and inflammatory biomarkers following hydroxytyrosol consumption, robust, large-scale randomized clinical trials focused on cancer-related outcomes are lacking [153,157]. A recent pilot trial using extra virgin olive oil enriched with oleocanthal and oleacein in patients with early-stage chronic lymphocytic leukemia showed favorable molecular effects and good tolerability. However, larger and more comprehensive clinical trials are needed to confirm these initial findings [158].

5. Concluding Remarks

Cancer remains a leading global health challenge, and the pursuit of safer, more effective strategies for its prevention and treatment continues to be a top priority. Among the emerging approaches, bioactive polyphenols found in extra virgin olive oil (EVOO)—a cornerstone of the Mediterranean diet—have shown considerable promise [17,18,159]. Key compounds such as hydroxytyrosol, tyrosol, oleuropein, oleacein, and oleocanthal have been extensively studied for their anticancer properties (Table 2). These naturally occurring molecules act through multiple mechanisms, including the attenuation of oxidative stress and inflammation, regulation of cancer cell proliferation and apoptosis, and inhibition of angiogenesis and metastasis.

Notably, oleocanthal has demonstrated a unique ability to selectively target cancer cells by disrupting lysosomal membranes. Hydroxytyrosol and oleuropein are also recognized for their potent antioxidant and antiproliferative effects. Furthermore, growing evidence suggests that these polyphenols may modulate epigenetic processes by inhibiting key enzymes such as DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), presenting novel avenues for cancer control.

Despite their broad spectrum of anticancer activities—mediated through epigenetic, inflammatory, oxidative, and metastatic pathways—significant challenges remain in the clinical translation of olive-derived polyphenols such as oleocanthal, oleacein, and tyrosol. Most of the existing evidence stems from in vitro and animal studies, with only limited human data available. Although some clinical trials have yielded promising results, comprehensive, large-scale investigations are lacking. Moreover, the pleiotropic nature of polyphenol action, which involves the modulation of multiple signaling cascades, necessitates more targeted research to elucidate context-dependent effects and potential synergistic or antagonistic interactions with standard therapies. Key issues such as dose–response relationships, bioavailability, and compound stability must also be addressed to facilitate effective clinical application. Future research should prioritize mechanistic studies using clinically relevant models, alongside well-designed, standardized trials to validate the therapeutic utility of these natural agents in cancer prevention and treatment.

It is important to critically evaluate current clinical studies assessing olive polyphenols in cancer-related contexts. For example, some trials report changes in surrogate apoptosis markers rather than definitive clinical outcomes and are often limited by small sample sizes, lack of blinding, or absence of placebo controls, which restrict the strength of conclusions regarding therapeutic efficacy. Such limitations highlight the need for rigorously designed randomized controlled trials with appropriate controls, blinding, sufficient sample sizes, and clinically relevant endpoints to confirm the promising anticancer potential suggested by preclinical data [160,161].

Although preclinical findings are encouraging, rigorous randomized clinical trials are urgently needed to confirm the efficacy of these compounds in human populations and to define optimal dosing regimens and delivery systems. While oleocanthal and hydroxytyrosol have been the subject of substantial investigation, other compounds—especially oleacein—remain underexplored. Further studies should investigate oleacein's role in regulating redox balance and cellular stress responses, areas that have thus far received insufficient attention.

Importantly, the preservation of bioactivity in olive oil polyphenols is influenced by processing and storage conditions. Heat exposure during cooking or industrial extraction, as well as prolonged storage at elevated temperatures, can significantly degrade sensitive compounds such as hydroxytyrosol, oleocanthal, and oleacein. For instance, high malaxation temperatures reduce total phenolic content, while storage above 25 °C accelerates degradation and reduces antioxidant capacity. Therefore, using high-quality EVOO in raw or minimally heated forms may help retain its beneficial properties and enhance its translational impact. This consideration is vital for bridging the gap between experimental data and practical dietary strategies [162,163].

Epidemiological evidence linking high EVOO consumption to reduced cancer incidence further supports the preventive potential of these polyphenols. Given their low toxicity and natural origin, olive oil-derived polyphenols represent promising adjuncts to conventional therapies, with the potential to enhance treatment efficacy while minimizing adverse effects. Going forward, a deeper exploration of their molecular mechanisms, synergistic interactions, and clinical integration may enable more personalized and effective strategies for cancer prevention and therapy.

Future perspectives involve investigating genetic and metabolic factors that influence olive polyphenol efficacy to enable personalized prevention and therapy. Their multitargeted, low-toxicity profiles make them promising adjuncts to conventional cancer treatments, warranting studies on interactions with existing therapies. Standardizing extraction and formulation methods will be essential for clinical translation. Additionally, long-term epidemiological and clinical trials are needed to confirm their preventive benefits across diverse populations.

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References

1. Elhawary, N.A.; Ekram, S.N.; Sembawa, H.A.; Tashkandi, E.; Bannani, S.; Azher, Z.A.; Abumansour, I.S.; Almuqati, R.M.; Attieh, R.; Sindi, I.A.; et al. Descriptive epidemiology of female breast cancer around the world: Incidence, mortality, and sociodemographic risks and disparities. *Int. J. Environ. Health Res.* **2025**, *1*, 5. [CrossRef]
2. Nikolouzakis, T.K.; Chrysos, E.; Docea, A.O.; Fragkiadaki, P.; Souglakos, J.; Tsiaoussis, J.; Tsatsakis, A. Current and future trends of colorectal cancer treatment: Exploring advances in immunotherapy. *Cancers* **2024**, *16*, 1995. [CrossRef]
3. Bultman, S.J. Molecular pathways: Gene–environment interactions regulating dietary fiber induction of proliferation and apoptosis via butyrate for cancer prevention. *Clin. Cancer Res.* **2014**, *20*, 799–803. [CrossRef]

4. Yousef, M.; Yousef, A.; Chowdhury, S.; Fanaeian, M.M.; Knafl, M.; Peterson, J.; Zeineddine, M.; Alfaro, K.; Zeineddine, F.; Goldstein, D.; et al. Molecular, socioeconomic, and clinical factors affecting racial and ethnic disparities in colorectal cancer survival. *JAMA Oncol.* **2024**, *10*, 1519–1529. [CrossRef] [PubMed]
5. Farshi, E. Comprehensive overview of 31 types of cancer: Incidence, categories, treatment options, and survival rates. *Int. J. Gastroenterol. Hepatol.* **2024**, *5*, 1.
6. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: The next generation. *Cell* **2011**, *144*, 646–674. [CrossRef] [PubMed]
7. Gebretsadik, A.; Dulla, D. The top ten cancer burdens at Hawassa University's comprehensive specialized hospital from 2013 to 2019. *Ethio. J. Med. Health Sci.* **2024**, *4*, 380–389.
8. Keum, N.; Giovannucci, E.; Giovannucci, E. Global burden of colorectal cancer: Emerging trends, risk factors and prevention strategies. *Nat Rev Gastroenterol Hepatol.* **2019**, *16*, 713–732. [CrossRef]
9. Estupiñán Fdez de Mesa, M.; Ferguson, M.; Green, S.; Marcu, A.; Ream, E.; Whitaker, K.L. Applying the intersectionality lens to understand minority ethnic women's experiences of the breast cancer care pathway in England: A qualitative interview study. *Psycho-Oncol.* **2025**, *34*, e70092. [CrossRef]
10. Damar, M.; Damar, H.T.; Özbiçakci, Ş.; Yasli, G.; Erenay, F.S.; Özdağoğlu, G.; Pinto, A.D. Mapping intellectual structure and research hotspots of cancer studies in primary health care: A machine-learning-based analysis. *Medicine* **2025**, *104*, e41749. [CrossRef]
11. Yousefi, M.; Reihani, H.; Heydari, M.; Azgomi, R.N.; Hashempur, M.H. Complementary and alternative medicine use among cancer patients in Iran: A systematic review. *Prev. Med. Rep.* **2024**, *39*, 102644. [CrossRef]
12. Banda, J.C. The prevalence and correlates of probable major depressive disorder among patients living with cancer at Kamuzu Central Hospital in Malawi: A cross-sectional study. *Medicon Med. Sci.* **2024**, *7*, 11–20.
13. Keinki, C.; Klein, M.A.; Käsmann, L.; Münstedt, K.; Hübner, J. Patients' information on side effects of cancer treatment and usage of complementary and alternative medicine—A cross-sectional study. *Adv. Integr. Med.* **2025**, *100*, 497. [CrossRef]
14. Baladi, A.; El Fadli, M.; Tafenzi, H.A.; El Bouaouidi, K.; Benhima, N.; Afani, L.; Essâdi, I.; Belbaraka, R. Prevalence and associated factors of herbal medicine use among breast cancer patients: A cross-sectional study in Morocco. *ecancermedicalscience* **2024**, *18*, 1786. [CrossRef] [PubMed]
15. Ben-Arye, E.; Samuels, N.; Goldstein, L.H.; Mutafoglu, K.; Omran, S.; Schiff, E.; Charalambous, H.; Dweikat, T.; Ghrayeb, I.; Bar-Sela, G.; et al. Potential risks associated with traditional herbal medicine use in cancer care: A study of Middle Eastern oncology health care professionals. *Cancer* **2016**, *122*, 598–610. [CrossRef] [PubMed]
16. Kiritsakis, A.; Keceli, T.M.; Anousakis, C.; Iorio, E.L.; Tsitsipas, C.; Shahidi, F.; Evangelou, E. Olive oil and Mediterranean diet: The importance of olive oil constituents, and mainly of its polyphenols, in human health—The redox system—Xenohormesis hypothesis. In *A Review on Diverse Neurological Disorders*; Academic Press: Cambridge, MA, USA, 2024; pp. 603–619.
17. Saad, B. Prevention and treatment of obesity-related inflammatory diseases by edible and medicinal plants and their active compounds. *Immuno* **2022**, *2*, 609–629. [CrossRef]
18. Saad, B. A review of the anti-obesity effects of wild edible plants in the Mediterranean diet and their active compounds: From traditional uses to action mechanisms and therapeutic targets. *Int. J. Mol. Sci.* **2023**, *24*, 12641. [CrossRef]
19. Saad, B. History, present and prospect of Greco-Arab and Islamic herbal medicine. In *History, Present and Prospect of World Traditional Medicine*; World Scientific: London, UK, 2024; pp. 235–300. [CrossRef]
20. Uthirapathy, S. Anticancer, anti-inflammatory, and neuroprotective effect of oleocanthal from virgin olive oil—A review. *J. Angiother.* **2024**, *8*, 1–9.
21. Nsairat, H.; Jaber, A.M.; Faddah, H.; Ahmad, S. Oleuropein impact on colorectal cancer. *Future Sci. OA* **2024**, *10*, FSO. [CrossRef]
22. Ahmed, Z.S.; Khan, E.; Elias, N.; Elshebiny, A.; Dou, Q. Updated review on natural polyphenols: Molecular mechanisms, biological effects, and clinical applications for cancer management. *Biomolecules* **2025**, *15*, 629. [CrossRef]
23. Elbaylek, H.; Ammor, S. Adherence to the Mediterranean diet and colorectal cancer risk among Moroccan population: Hospital-based case control study. *Asian Pac. J. Cancer Prev.* **2024**, *25*, 2853. [CrossRef]
24. Roşian, Ş.H.; Boarescu, I.; Boarescu, P.M. Antioxidant and anti-inflammatory effects of bioactive compounds in atherosclerosis. *Int. J. Mol. Sci.* **2025**, *26*, 1379. [CrossRef]
25. Sichetti, M.; Giuseffi, M.; Giglio, E.; Marino, G.; Mecca, M. Effect of natural polyphenols on breast cancer chemoprevention and treatment. *Mol. Nutr. Food Res.* **2025**, *69*, e70055. [CrossRef]
26. Kumar, A.; Singh, B.; Paul, K.; Bakshi, P.; Bajaj, P.; Kumar, M.; Dhiman, S.; Jasrotia, S.; Kumar, P.; Dutta, R. Hydroxytyrosol in cancer research: Recent and historical insights on discoveries and mechanisms of action. *Future J. Pharm. Sci.* **2024**, *10*, 129. [CrossRef]
27. Rishmawi, S.; Haddad, F.; Dokmak, G.; Karaman, R. A comprehensive review on the anti-cancer effects of oleuropein. *Life* **2022**, *12*, 1140. [CrossRef]
28. Ferreira, D.M.; Oliveira, M.B.; Alves, R.C. A comprehensive review of the antitumor activity of olive compounds: The case of olive oil, pomace, and leaf extracts, phenolic alcohols, secoiridoids, and triterpenes. *Antioxidants* **2025**, *14*, 237. [CrossRef]

29. Alkhalifa, A.E.; Al-Ghraiybah, N.F.; Kaddoumi, A. Extra-virgin olive oil in alzheimer's disease: A comprehensive review of cellular, animal, and clinical studies. *Int. J. Mol. Sci.* **2024**, *25*, 1914. [CrossRef] [PubMed]
30. Tessier, A.J.; Cortese, M.; Yuan, C.; Bjornevik, K.; Ascherio, A.; Wang, D.D.; Chavarro, J.E.; Stampfer, M.J.; Hu, F.B.; Willett, W.C.; et al. Consumption of olive oil and diet quality and risk of dementia-related death. *JAMA Netw. Open* **2024**, *7*, e2410021. [CrossRef]
31. Chiavarini, M.; Rosignoli, P.; Giacchetta, I.; Fabiani, R. Health outcomes associated with olive oil intake: An umbrella review of meta-analyses. *Foods* **2024**, *13*, 2619. [CrossRef]
32. Li, S.; Shao, H.; Sun, T.; Guo, X.; Zhang, X.; Zeng, Q.; Fang, S.; Liu, X.; Wang, F.; Liu, F.; et al. Anti-neuroinflammatory effect of hydroxytyrosol: A potential strategy for anti-depressant development. *Front. Pharmacol.* **2024**, *15*, 1366683. [CrossRef]
33. Gonçalves, M.; Vale, N.; Silva, P. Neuroprotective effects of olive oil: A comprehensive review of antioxidant properties. *Antioxidants* **2024**, *13*, 762. [CrossRef] [PubMed]
34. Bonvino, N.P.; Liang, J.; McCord, E.D.; Zafiris, E.; Benetti, N.; Ray, N.B.; Hung, A.; Boskou, D.; Karagiannis, T.C. OliveNet™: A Comprehensive Library of Compounds from *Olea europaea*. *Database* **2018**, *2018*, bay016. [CrossRef] [PubMed]
35. Jimenez-Lopez, C.; Carpena, M.; Lourenço-Lopes, C.; Gallardo-Gomez, M.; Lorenzo, J.M.; Barba, F.J.; Simal-Gandara, J. Bioactive compounds and quality of extra virgin olive oil. *Foods* **2020**, *9*, 1014. [CrossRef]
36. Basso, C.; Uliana, G.C.; Richards, N.S.P.S. Bioactive Compounds Present in Olive Oil and Its By-Products: Bibliographic Review. *Res. Soc. Dev.* **2022**, *11*, e196111032580. [CrossRef]
37. Gagour, J.; Hallouch, O.; Asbbane, A.; Bijla, L.; Laknifli, A.; Lee, L.H.; Gharby, S. A review of recent progresses on olive oil chemical profiling, extraction technology, shelf-life, and quality control. *Chem. Biodivers* **2024**, *21*, e202301697. [CrossRef]
38. Servili, M.; Esposto, S.; Fabiani, R.; Urbani, S.; Taticchi, A.; Mariucci, F.; Montedoro, G.F. Phenolic compounds in olive oil: Antioxidant, health and organoleptic activities according to their chemical structure. *Inflammopharmacology* **2009**, *17*, 76–84. [CrossRef]
39. Gorzynik-Debicka, M.; Przychodzen, P.; Cappello, F.; Kuban-Jankowska, A.; Marino Gammazza, A.; Knap, N.; Gorska-Ponikowska, M. Potential health benefits of olive oil and plant polyphenols. *Int. J. Mol. Sci.* **2018**, *19*, 686. [CrossRef]
40. Gallardo-Fernández, M.; Gonzalez-Ramirez, M.; Cerezo, A.B.; Troncoso, A.M.; Garcia-Parrilla, M.C. Hydroxytyrosol in foods: Analysis, food sources, EU dietary intake, and potential uses. *Foods* **2022**, *11*, 2355. [CrossRef]
41. Cicerale, S.; Lucas, L.J.; Keast, R.S.J. Oleocanthal: A naturally occurring anti-inflammatory agent in virgin olive oil. In *Olive Oil-Constituents, Quality, Health Properties and Bioconversions*; IntechOpen: Rijeka, Croatia, 2012; pp. 357–374.
42. Gatt, L.; Lia, F.; Zammit-Mangion, M.; Thorpe, S.J.; Schembri-Wismayer, P. First profile of phenolic compounds from Maltese extra virgin olive oils using liquid-liquid extraction and liquid chromatography-mass spectrometry. *J. Oleo Sci.* **2021**, *70*, 145–153. [CrossRef]
43. Ussia, S.; Ritorto, G.; Mollace, R.; Serra, M.; Tavernese, A.; Altomare, C.; Macrì, R. Exploring the benefits of extra virgin olive oil on cardiovascular health enhancement and disease prevention: A systematic review. *Nutrients* **2025**, *17*, 1843. [CrossRef]
44. Blasi, F.; Ianni, F.; Cossignani, L. Phenolic profiling for geographical and varietal authentication of extra virgin olive oil. *Trends Food Sci. Technol.* **2024**, *147*, 104444. [CrossRef]
45. López-Huertas, E.; Lozano-Sánchez, J.; Segura-Carretero, A. Olive oil varieties and ripening stages containing the antioxidants hydroxytyrosol and derivatives in compliance with EFSA health claim. *Food Chem.* **2021**, *342*, 128291. [CrossRef]
46. Safarzadeh Markhali, F. Effect of processing on phenolic composition of olive oil products and olive mill by-products and possibilities for enhancement of sustainable processes. *Processes* **2021**, *9*, 953. [CrossRef]
47. Rey-Giménez, R.; Vázquez Ayala, S.; Laya Reig, D.; Sánchez-Gimeno, A.C. Chemometric and Physico-Chemical Characterization of Fruit and Olive Oils from Autochthonous Cultivars Grown in Aragon (Spain). *Foods* **2023**, *12*, 803. [CrossRef]
48. Boronat, A.; Soldevila-Domenech, N.; Rodríguez-Morató, J.; Martínez-Huélamo, M.; Lamuela-Raventós, R.M.; De la Torre, R. Beer phenolic composition of simple phenols, prenylated flavonoids and alkylresorcinols. *Molecules* **2020**, *25*, 2582. [CrossRef]
49. Khalil, A.A.; Rahman, M.M.; Rauf, A.; Islam, M.R.; Manna, S.J.; Khan, A.A.; Ullah, S.; Akhtar, M.N.; Aljohani, A.S.; Abdulmonem, W.A.; et al. Oleuropein: Chemistry, extraction techniques and nutraceutical perspectives-An update. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 9933–9987. [CrossRef]
50. Charoenprasert, S.; Mitchell, A. Factors influencing phenolic compounds in table olives (*Olea europaea*). *J. Agric. Food Chem.* **2012**, *60*, 7081–7095. [CrossRef] [PubMed]
51. López-Yerena, A.; Ninot, A.; Jiménez-Ruiz, N.; Lozano-Castellón, J.; Pérez, M.; Escribano-Ferrer, E.; Vallverdú-Queralt, A. Influence of the ripening stage and extraction conditions on the phenolic fingerprint of 'Corbella' extra-virgin olive oil. *Antioxidants* **2021**, *10*, 877. [CrossRef]
52. Tsimidou, M.Z. A critical appraisal of the separation protocols proposed for the implementation of the health claim on "olive oil polyphenols" (EC regulation 432/2012). *Separations* **2022**, *9*, 351. [CrossRef]

53. De Medina, V.S.; Miho, H.; Melliou, E.; Magiatis, P.; Priego-Capote, F.; de Castro, M.D.L. Quantitative method for determination of oleocanthal and oleacein in virgin olive oils by liquid chromatography–tandem mass spectrometry. *Talanta* **2017**, *162*, 24–31. [CrossRef]
54. Apak, R.; Güçlü, K.; Demirata, B.; Özyürek, M.; Celik, S.E.; Bektaşoğlu, B.; Berker, K.I.; Özyurt, D. Comparative evaluation of various total antioxidant capacity assays applied to phenolic compounds with the CUPRAC assay. *Molecules* **2007**, *12*, 1496–1547. [CrossRef]
55. Prior, R.L.; Wu, X.; Schaich, K. Standardized methods for the determination of antioxidant capacity and phenolics in foods and dietary supplements. *J. Agric. Food Chem.* **2005**, *53*, 4290–4302. [CrossRef]
56. Rice-Evans, C.A.; Miller, N.J.; Paganga, G. Structure-antioxidant activity relationships of flavonoids and phenolic acids. *Free Radic. Biol. Med.* **1996**, *20*, 933–956. [CrossRef]
57. Bucciantini, M.; Leri, M.; Nardiello, P.; Casamenti, F.; Stefani, M. Olive Polyphenols: Antioxidant and Anti-Inflammatory Properties. *Antioxidants* **2021**, *10*, 1044. [CrossRef]
58. Santos-Buelga, C.; Scalbert, A. Proanthocyanidins and tannin-like compounds–nature, occurrence, dietary intake and effects on nutrition and health. *J. Sci. Food Agric.* **2000**, *80*, 1094–1117. [CrossRef]
59. Viuda-Martos, M.; Ruiz-Navajas, Y.; Fernández-López, J.; Pérez-Álvarez, J.A. Functional properties of honey, propolis, and royal jelly. *J. Food Sci.* **2008**, *73*, R117–R124. [CrossRef]
60. Rajendran, P.; Abdelsalam, S.A.; Renu, K.; Veeraraghavan, V.; Ben Ammar, R.; Ahmed, E.A. Polyphenols as potent epigenetics agents for cancer. *Int. J. Mol. Sci.* **2022**, *23*, 11712. [CrossRef]
61. Mamun, M.A.A.; Rakib, A.; Mandal, M.; Khandaker, M.U.; Reza, H.M.; AlAjmi, M.F.; Alruwaili, N.K.; Dhama, K. Polyphenols: Role in modulating immune function and obesity. *Biomolecules* **2024**, *14*, 221. [CrossRef]
62. Krawczyk, M.; Burzynska-Pedziwiatr, I.; Wozniak, Ł.A.; Bukowiecka-Matusiak, M. Impact of polyphenols on inflammatory and oxidative stress factors in diabetes mellitus. *Biomolecules* **2023**, *13*, 1402. [CrossRef]
63. Milenkovic, D.; Jude, B.; Morand, C. miRNA as molecular target of polyphenols underlying their biological effects. *Free Radic. Biol. Med.* **2013**, *64*, 40–51. [CrossRef]
64. Wang, J.; Yan, T.; Long, C.; Cai, W. Oncogenic function and prognostic significance of Abelson interactor 1 in hepatocellular carcinoma. *Int. J. Oncol.* **2017**, *50*, 1889–1898. [CrossRef] [PubMed]
65. Izquierdo-Torres, E.; Hernández-Oliveras, A.; Meneses-Morales, I.; Rodríguez, G.; Fuentes-García, G.; Zarain-Herzberg. Á Resveratrol up-regulates ATP2A3 gene expression in breast cancer cell lines through epigenetic mechanisms. *Int. J. Biochem. Cell Biol.* **2019**, *113*, 37–47. [CrossRef] [PubMed]
66. Ruiz-García, I.; Ortíz-Flores, R.; Badía, R.; Serrano-Moratalla, B.; Martínez-Hervás, S.; Ascaso, J.F.; Valls, R.M.; Caimari, A. Rich oleocanthal and oleacein extra virgin olive oil and inflammatory and antioxidant status in people with obesity and prediabetes. *Clin. Nutr.* **2023**, *42*, 1389–1398. [CrossRef] [PubMed]
67. Serreli, G.; Boronat, A.; De la Torre, R.; Pali-Casanova, R. Cardiovascular and metabolic benefits of extra virgin olive oil phenolic compounds: Mechanistic insights from in vivo studies. *Cells* **2024**, *13*, 1555. [CrossRef]
68. Lee, Y.H.; Kalailingam, P.; Delcour, J.A.; Fogliano, V.; Thanabalu, T. Olive-Derived Antioxidant Dietary Fiber Modulates Gut Microbiota Composition and Attenuates Atopic Dermatitis Like Inflammation in Mice. *Mol. Nutr. Food Res.* **2023**, *67*, 2200127. [CrossRef]
69. Tamburini, B.; Di Liberto, D.; Pratelli, G.; Rizzo, C.; Barbera, L.L.; Lauricella, M.; Carlisi, D.; Maggio, A.; Palumbo Piccionello, A.; D'Anneo, A.; et al. Extra Virgin Olive Oil Polyphenol-Enriched Extracts Exert Antioxidant and Anti-Inflammatory Effects on Peripheral Blood Mononuclear Cells from Rheumatoid Arthritis Patients. *Antioxidants* **2025**, *14*, 171. [CrossRef]
70. Rosillo, M.Á.; Villegas, I.; Vázquez-Román, V.; Fernández-Santos, J.M.; Ortega-Vidal, J.; Salido, S.; González-Rodríguez, M.L.; Alarcón-de-la-Lastra, C. Dietary oleacein, a secoiridoid from extra virgin olive oil, prevents collagen-induced arthritis in mice. *Food Funct.* **2024**, *15*, 838–852. [CrossRef]
71. Mantovani, A.; Marchesi, F.; Malesci, A.; Laghi, L.; Allavena, P. Tumour-associated macrophages as treatment targets in oncology. *Nat. Rev. Clin. Oncol.* **2017**, *14*, 399–416. [CrossRef]
72. Vitale, I.; Manic, G.; Coussens, L.M.; Kroemer, G.; Galluzzi, L. Macrophages and metabolism in the tumor microenvironment. *Cell Metab.* **2019**, *30*, 36–50. [CrossRef]
73. Zhang, X.; Cao, J.; Jiang, L.; Zhong, L. Suppression of inflammation and oxidative stress in macrophages by hydroxytyrosol via activation of AMPK/Nrf2 signaling pathway. *J. Agric. Food Chem.* **2019**, *67*, 3984–3993.
74. Bulotta, S.; Celano, M.; Lepore, S.M.; Montalcini, T.; Pujia, A.; Russo, D. Beneficial effects of the olive oil phenolic components oleuropein and hydroxytyrosol: Focus on protection against cardiovascular and metabolic diseases. *J. Transl. Med.* **2014**, *12*, 219. [CrossRef]
75. Elnagar, A.Y.; Sylvester, P.W.; El Sayed, K.A. (-)-Oleocanthal as a c-Met inhibitor for the control of metastatic breast and prostate cancers. *Planta Med.* **2011**, *77*, 1013–1019. [CrossRef]

76. Wang, R.; Ganbold, M.; Ferdousi, F.; Tominaga, K.; Isoda, H. A rare olive compound oleacein improves lipid and glucose metabolism, and inflammatory functions: A comprehensive whole-genome transcriptomics analysis in adipocytes differentiated from healthy and diabetic adipose stem cells. *Int. J. Mol. Sci.* **2023**, *24*, 10419. [CrossRef]
77. Marrero, A.D.; Ortega-Vidal, J.; Salido, S.; Castilla, L.; Vidal, I.; Quesada, A.R.; Altarejos, J.; Martínez-Poveda, B.; Medina, M.Á. Anti-angiogenic effects of oleacein and oleocanthal: New bioactivities of compounds from extra virgin olive oil. *Biomed. Pharmacother.* **2023**, *165*, 115234. [CrossRef]
78. González-Rodríguez, M.; Ait Edjoudi, D.; Cordero-Barreal, A.; Farrag, M.; Varela-García, M.; Torrijos-Pulpón, C.; Ruiz-Fernández, C.; Capuozzo, M.; Ottaiano, A.; Lago, F.; et al. Oleocanthal, an antioxidant phenolic compound in extra virgin olive oil (EVOO): A comprehensive systematic review of its potential in inflammation and cancer. *Antioxidants* **2023**, *12*, 2112. [CrossRef]
79. Balkwill, F.; Mantovani, A. Inflammation and cancer: Back to Virchow? *Lancet* **2001**, *357*, 539–545. [CrossRef] [PubMed]
80. Abbattista, R.; Losito, I.; Calvano, C.D.; Cataldi, T.R.I. Exploring the isomeric precursors of olive oil major secoiridoids: An insight into olive leaves and drupes by liquid-chromatography and Fourier-transform tandem mass spectrometry. *Foods* **2021**, *10*, 2050. [CrossRef] [PubMed]
81. Hibino, S.; Kawazoe, T.; Kasahara, H.; Itoh, S.; Ishimoto, T.; Sakata-Yanagimoto, M.; Taniguchi, K. Inflammation-Induced Tumorigenesis and Metastasis. *Int. J. Mol. Sci.* **2021**, *22*, 5421. [CrossRef]
82. De Stefanis, D.; Schembari, A.; Muscat, A.; Melaiu, O.; Dominici, C.; Gallì, R.; Ferretti, E. Antiproliferative effects of EVOO phenolics in liver cancer cells. *Cancers* **2019**, *11*, 1640. [CrossRef]
83. Qusa, M.H.; Kumar, D.; Ghosh, S.; Alazzam, M.; Alshammari, F. Oleocanthal xylitol-based solid dispersion for breast cancer. *Int. J. Pharm.* **2019**, *569*, 118596. [CrossRef]
84. Muñoz-García, R.; Marín-Aguilar, F.; García-Fuentes, E.; Varela-López, A.; Giampieri, F.; Alvarez-Suarez, J.M.; Cordero, M.D.; Battino, M. Oleocanthal diet ameliorates lupus in mice. *Antioxidants* **2023**, *12*, 1303. [CrossRef]
85. Montoya, T.; Vicente, J.; Domínguez, C.; Bautista-Lorite, J.; Reyes-Zurita, F.J.; Sánchez-Quesada, C.; Sánchez-Fidalgo, S. Oleocanthal reduces inflammation in arthritis mice. *Antioxidants* **2021**, *10*, 650. [CrossRef]
86. Patnaik, R.; Varghese, R.; Jannati, S.; Naidoo, N.; Banerjee, Y. Targeting PAR2-mediated inflammation in osteoarthritis: A comprehensive in vitro evaluation of oleocanthal's potential as a functional food intervention for chondrocyte protection and anti-inflammatory effects. *BMC Musculoskelet. Disord.* **2024**, *25*, 769. [CrossRef]
87. Montoya, T.; Sánchez-Hidalgo, M.; Castejón, M.L.; Vazquéz-Román, M.V.; de Sotomayor, M.A.; Ortega-Vidal, J.; González, M.L.; Alarcón-de-la-Lastra, C. Oleocanthal supplemented diet improves renal damage and endothelial dysfunction in pristane-induced systemic lupus erythematosus in mice. *Food Res. Int.* **2023**, *163*, 112140. [CrossRef]
88. Siddique, A.B.; Ayoub, N.M.; Tajmim, A.; Ebrahim, H.Y.; Mohyeldin, M.M.; El Sayed, K.A. (-)-Oleocanthal prevents breast cancer locoregional recurrence in orthotopic mouse models. *Cancers* **2019**, *11*, 637. [CrossRef]
89. Xiang, C.; Chen, J.; Fu, P. HGF/Met signaling in cancer invasion: Impact on cytoskeleton remodeling. *Cancers* **2017**, *9*, 44. [CrossRef]
90. Akl, M.R.; Ayoub, N.M.; Mohyeldin, M.M.; Busnena, B.A.; Foudah, A.I.; Liu, Y.-Y.; El Sayed, K.A. Olive phenolics as c-Met inhibitors: (-)-Oleocanthal attenuates tumor growth in breast cancer models. *PLoS ONE* **2014**, *9*, e95954. [CrossRef]
91. Siddique, A.B.; Kilgore, P.C.S.R.; Tajmim, A.; Singh, S.S.; Meyer, S.A.; El Sayed, K.A.; Rao, P.P.N. (-)-Oleocanthal as a dual c-MET/COX-2 inhibitor for lung cancer control. *Nutrients* **2020**, *12*, 1749. [CrossRef]
92. Mohyeldin, M.M.; Busnena, B.A.; Akl, M.R.; El Sayed, K.A. Semisynthetic analogs enhance oleocanthal's c-Met inhibition in breast cancer. *Eur. J. Med. Chem.* **2016**, *118*, 299–315. [CrossRef]
93. Siddique, A.B.; Ayoub, N.M.; Ebrahim, H.Y.; Mohyeldin, M.M.; El Sayed, K.A. Oleocanthal attenuates castration-resistant prostate cancer by targeting SMYD2. *Cancers* **2022**, *14*, 3542. [CrossRef]
94. Khanfar, M.A.; Bardaweel, S.K.; Akl, M.R.; El Sayed, K.A. Oleocanthal as a potent mTOR inhibitor: Biological and modeling studies. *Phytother. Res.* **2015**, *29*, 1776–1782. [CrossRef]
95. Gu, Y.; Wang, J.; Peng, L. (-)-Oleocanthal inhibits STAT3 signaling in melanoma cells. *Oncol. Rep.* **2017**, *37*, 483–491. [CrossRef]
96. Pei, T.; Meng, Q.; Han, J.; Sun, H.; Li, L.; Song, R.; Sun, B.; Pan, S.; Liang, D.; Liu, L. (-)-Oleocanthal blocks STAT3 activation in hepatocellular carcinoma. *Oncotarget* **2016**, *7*, 43475–43491. [CrossRef]
97. Kugić, A.; Dabelić, S.; Brala, C.J.; Barbarić, M.; Urlić, I.; Roje, M.; Smolko, A.; Samaržija, I. Secoiridoids modulate metabolic activity in melanoma cells. *Molecules* **2022**, *27*, 3310. [CrossRef] [PubMed]
98. Polini, B.; Digiacomo, M.; Carpi, S.; Bertini, S.; Gado, F.; Saccomanni, G.; Macchia, M.; Nieri, P.; Manera, C.; Fogli, S. Oleocanthal and oleacein inhibit Erk/Akt and B-Raf in non-melanoma skin cancer cells. *Toxicol. Vitr.* **2018**, *52*, 243–250. [CrossRef] [PubMed]
99. Tarun, M.T.I.; Elsayed, H.E.; Ebrahim, H.Y.; El Sayed, K.A. The olive oil phenolic (-)-oleocanthal suppresses colorectal cancer progression and recurrence by modulating SMYD2–EZH2 and c-Met activation. *Nutrients* **2025**, *17*, 397. [CrossRef]
100. Alhajri, H.; Alterary, S.; Alrfaei, B.M.; Al-Qahtani, W.S. Therapeutic potential evaluation of green synthesized silver nanoparticles derived from olive (*Olea europaea* L.) leaf extracts against breast cancer cells. *J. Nanophotonics* **2021**, *15*, 036003. [CrossRef]

101. Ci, Y.; Qiao, J.; Han, M. Oleuropein suppresses the metastasis of MCF-7 human breast cancer cells via inhibition of the PI3K/AKT/NF-κB pathway. *Molecules* **2016**, *21*, 1634. [CrossRef]
102. Liu, L.; Ahn, K.S.; Shanmugam, M.K.; Wang, H.; Shen, H.; Arfuso, F.; Chinnathambi, A.; Zayed, M.E.; Alharbi, S.A.; Sethi, G. Oleuropein induces apoptosis in breast cancer cells via the p53 pathway. *J. Cell Biochem.* **2019**, *120*, 4504–4513. [CrossRef]
103. Bossio, S.; Perri, A.; Malivindi, R.; Giordano, F.; Rago, V.; Mirabelli, M.; Salatino, A.; Brunetti, A.; Greco, E.A.; Aversa, A. Oleuropein counteracts both the proliferation and migration of intra- and extragonadal seminoma cells. *Nutrients* **2022**, *14*, 2323. [CrossRef]
104. Aggarwal, V.; Kumar, G.; Aggarwal, D.; Yerer, M.B.; Cumaoğlu, A.; Kumar, M.; Sak, K.; Mittal, S.; Tuli, H.S.; Sethi, G. Cancer preventive role of olives and olive oil via modulation of apoptosis and nuclear factor-kappa B activation. In *Olives and Olive Oil in Health and Disease Prevention*; Academic Press: Cambridge, MA, USA, 2021; pp. 377–388.
105. Giner, E.; Recio, M.C.; Ríos, J.L.; Cerdá, B.; Gálvez, J.; De la Fuente, J.; Nieto, M.L. Olive oil polyphenols modulate cannabinoid CB1 receptor gene expression in colon cancer. *Mol. Nutr. Food Res.* **2016**, *60*, 242–255. [CrossRef]
106. Bhattacherjee, D.; Raina, K.; Mandal, T.K.; Thummer, R.P.; Bhabak, K.P. Targeting Wnt/β-catenin signaling pathway in triple-negative breast cancer by benzylic organotrisulfides: Contribution of the released hydrogen sulfide towards potent anti-cancer activity. *Free Radic. Biol. Med.* **2022**, *191*, 82–96. [CrossRef]
107. Wang, K.; Qiu, X.; Zhao, Y.; Wang, H.; Chen, L. The Wnt/β-catenin signaling pathway in the tumor microenvironment of hepatocellular carcinoma. *Cancer Biol. Med.* **2022**, *19*, 305–318. [CrossRef]
108. Oliveira, L.F.; Predes, D.; Borges, H.L.; Abreu, J.G. Therapeutic potential of naturally occurring small molecules to target the Wnt/β-catenin signaling pathway in colorectal cancer. *Cancers* **2022**, *14*, 403. [CrossRef] [PubMed]
109. Tewari, D.; Bawari, S.; Sharma, S.; DeLiberto, L.K.; Bishayee, A. Targeting the crosstalk between canonical Wnt/β-catenin and inflammatory signaling cascades: A novel strategy for cancer prevention and therapy. *Pharmacol. Ther.* **2021**, *227*, 107876. [CrossRef] [PubMed]
110. Wang, C.; Lv, T.; Jin, B.; Li, Y.; Fan, Z. Regulatory role of PPAR in colorectal cancer. *Cell Death Discov.* **2025**, *11*, 28. [CrossRef] [PubMed]
111. De Cicco, P.; Ercolano, G.; Tenore, G.C.; Ianaro, A. Olive leaf extract inhibits metastatic melanoma spread through suppression of epithelial to mesenchymal transition. *Phytother. Res.* **2022**, *36*, 4002–4013. [CrossRef]
112. Huang, Q.; Liang, X.; Ren, T.; Huang, Y.; Zhang, H.; Yu, Y.; Chen, C.; Wang, W.; Niu, J.; Lou, J.; et al. The role of tumor-associated macrophages in osteosarcoma progression—Therapeutic implications. *Cell. Oncol.* **2021**, *44*, 525–539. [CrossRef]
113. Korbecki, J.; Simińska, D.; Gąssowska-Dobrowolska, M.; Listos, J.; Gutowska, I.; Chlubek, D.; Baranowska-Bosiacka, I. Chronic and cycling hypoxia: Drivers of cancer chronic inflammation through HIF-1 and NF-κB activation—A review of the molecular mechanisms. *Int. J. Mol. Sci.* **2021**, *22*, 10701. [CrossRef]
114. Zheng, Y.; Liu, Z.; Yang, X.; Liu, L.; Ahn, K.S. An updated review on the potential antineoplastic actions of oleuropein. *Phytother. Res.* **2022**, *36*, 365–379. [CrossRef]
115. Öner, Ç.; Çolak, E. Novel natural compounds for hepatocellular carcinoma treatment. *Front. Nat. Prod. Chem.* **2023**, *11*, 32–72.
116. Kwon, M.J. Matrix metalloproteinases as therapeutic targets in breast cancer. *Front. Oncol.* **2023**, *12*, 1108695. [CrossRef] [PubMed]
117. Ansari, B.; Küpeli Akkol, E.; Khan, H.; Shah, M.A. Olive leaf (*Oleuropein*) and its role in cancer: Therapeutic updates. In *Nutraceuticals and Cancer Signaling: Clinical Aspects and Mode of Action*; Springer: Berlin/Heidelberg, Germany, 2021; pp. 367–400.
118. Albogami, S.; Hassan, A.M. Assessment of the efficacy of olive leaf (*Olea europaea* L.) extracts in the treatment of colorectal cancer and prostate cancer using in vitro cell models. *Molecules* **2021**, *26*, 4069. [CrossRef] [PubMed]
119. Mahmood, T.H.; Al-Samydai, A.; Sulaibi, M.A.; Alqaraleh, M.; Abed, A.I.; Shalan, N.; Alsanabrah, A.; Alsotari, S.T.; Nsairat, H.; Alshaer, W. Development of pegylated nano-phytosome formulation with oleuropein and rutin to compare anti-colonic cancer activity with *Olea europaea* leaves extract. *Chem. Biodivers.* **2023**, *20*, e202300534. [CrossRef] [PubMed]
120. Yılmaz, G.; Özdemir, F. Novel anti-tumor strategy for breast cancer: Synergistic role of oleuropein with paclitaxel therapeutic in MCF-7 cells. *Anti-Cancer Agents Med. Chem.* **2024**, *24*, 224–234. [CrossRef]
121. Flore, G.; Deledda, A.; Lombardo, M.; Armani, A.; Velluzzi, F. Effects of functional and nutraceutical foods in the context of the Mediterranean diet in patients diagnosed with breast cancer. *Antioxidants* **2023**, *12*, 1845. [CrossRef]
122. Karousi, P.; Kontos, C.K.; Papakotsi, P.; Kostakis, I.K.; Skaltsounis, A.L.; Scorilas, A. Next-generation sequencing reveals altered gene expression and enriched pathways in triple-negative breast cancer cells treated with oleuropein and oleocanthal. *Funct. Integr. Genom.* **2023**, *23*, 299. [CrossRef]
123. Ahmed, N.A.; Mohyeldin, M.M.; Ebrahim, H.Y.; McGehee, O.C.; Tarun, M.T.; El Sayed, K.A. (-)-Oleuropein as a novel metastatic castration-resistant prostate cancer progression and recurrence suppressor via targeting PCSK9-LDLR axis. *Nutrients* **2025**, *17*, 1445. [CrossRef]
124. Gervasi, F.; Pojero, F. Use of oleuropein and hydroxytyrosol for cancer prevention and treatment: Considerations about how bioavailability and metabolism impact their adoption in clinical routine. *Biomedicines* **2025**, *12*, 502. [CrossRef]
125. Pruthi, S.; Heisey, R.E.; Bevers, T.B. Chemoprevention for breast cancer. *Ann. Surg. Oncol.* **2015**, *22*, 3230–3235. [CrossRef]

126. Flora, S.; Ferguson, L. Overview of mechanisms of cancer chemopreventive agents. *Mutat. Res.* **2005**, *591*, 8–15. [CrossRef] [PubMed]
127. Carpi, S.; Polini, B.; Manera, C.; Digiacomo, M.; Salsano, J.E.; Macchia, M.; Scoditti, E.; Nieri, P. miRNA modulation and antitumor activity by the extra-virgin olive oil polyphenol oleacein in human melanoma cells. *Front. Pharmacol.* **2020**, *11*, 574317. [CrossRef] [PubMed]
128. Cirmi, S.; Celano, M.; Lombardo, G.E.; Maggisano, V.; Procopio, A.; Russo, D.; Navarra, M. Oleacein inhibits STAT3, activates the apoptotic machinery, and exerts anti-metastatic effects in the SH-SY5Y human neuroblastoma cells. *Food Funct.* **2020**, *11*, 3271–3279. [CrossRef] [PubMed]
129. Uli, G.; Oliverio, M.; Bellizzi, D.; Gallo Cantafio, M.E.; Grillone, K.; Passarino, G.; Colica, C.; Nardi, M.; Rossi, M.; Procopio, A.; et al. Anti-tumor activity and epigenetic impact of the polyphenol oleacein in multiple myeloma. *Cancers* **2019**, *11*, 990. [CrossRef]
130. Kusuma, I.Y.; Habibie, H.; Bahar, M.A.; Budán, F.; Csupor, D. Anticancer Effects of Secoiridoids—A Scoping Review of the Molecular Mechanisms behind the Chemopreventive Effects of the Olive Tree Components Oleocanthal, Oleacein, and Oleuropein. *Nutrients* **2024**, *16*, 2755. [CrossRef]
131. Rojas Gil, A.P.; Kodonis, I.; Ioannidis, A.; Nomikos, T.; Dimopoulos, I.; Kosmidis, G.; Katsa, M.E.; Melliou, E.; Magiatis, P. The effect of dietary intervention with high-oleocanthal and oleacein olive oil in patients with early-stage chronic lymphocytic leukemia: A pilot randomized trial. *Front. Oncol.* **2022**, *11*, 810249. [CrossRef]
132. Wang, W.; Du, L.; Wei, Q.; Lu, M.; Xu, D.; Li, Y. Synthesis and health effects of phenolic compounds: A focus on tyrosol, hydroxytyrosol, and 3,4-dihydroxyacetophenone. *Antioxidants* **2025**, *14*, 476. [CrossRef]
133. Riolo, R.; De Rosa, R.; Simonetta, I.; Tuttolomondo, A. Olive oil in the Mediterranean diet and its biochemical and molecular effects on cardiovascular health through an analysis of genetics and epigenetics. *Int. J. Mol. Sci.* **2022**, *23*, 16002. [CrossRef]
134. Katsa, M.E.; Nomikos, T. Olive oil phenolics and platelets—From molecular mechanisms to human studies. *Rev. Cardiovasc. Med.* **2022**, *23*, 255. [CrossRef]
135. Calahorra, J.; Araujo-Abad, S.; Granadino-Roldán, J.M.; Naranjo, Á.; Martínez-Lara, E.; Siles, E. Tyrosol: Repercussion of the lack of a hydroxyl group in the response of MCF-7 cells to hypoxia. *J. Med. Food* **2023**, *26*, 511–520. [CrossRef]
136. Goldsmith, C.D.; Bond, D.R.; Jankowski, H.; Weidenhofer, J.; Stathopoulos, C.E.; Roach, P.D.; Scarlett, C.J. The olive biophenols oleuropein and hydroxytyrosol selectively reduce proliferation, influence the cell cycle, and induce apoptosis in pancreatic cancer cells. *Int. J. Mol. Sci.* **2018**, *19*, 1937. [CrossRef] [PubMed]
137. Luo, C.; Li, Y.; Wang, H.; Cui, Y.; Feng, Z.; Li, H.; Li, Y.; Wang, Y.; Wurtz, K.; Weber, P.; et al. Hydroxytyrosol promotes superoxide production and defects in autophagy leading to anti-proliferation and apoptosis on human prostate cancer cells. *Curr. Cancer Drug Targets* **2013**, *13*, 625–639. [CrossRef]
138. Bouallagui, Z.; Han, J.; Isoda, H.; Sayadi, S. Hydroxytyrosol-rich extract from olive leaves modulates cell cycle progression in MCF-7 human breast cancer cells. *Food Chem. Toxicol.* **2011**, *49*, 179–184. [CrossRef] [PubMed]
139. Xue, L.; Jin, Z. Tyrosol induces increased expression of NQO1 enzyme gene and inhibits cell proliferation in hepatocellular carcinoma cells. *Chin. J. Pathophysiol.* **2002**, *8*, 5–9.
140. El-Azem, N.; Pulido-Moran, M.; Ramirez-Tortosa, C.L.; Quiles, J.L.; Cara, F.E.; Sanchez-Rovira, P.; Granados-Principal, S.; Ramirez-Tortosa, M. Modulation by hydroxytyrosol of oxidative stress and antitumor activities of paclitaxel in breast cancer. *Eur. J. Nutr.* **2019**, *58*, 1203–1211. [CrossRef]
141. López de Las Hazas, M.C.; Piñol, C.; Macià, A.; Motilva, M.J. Hydroxytyrosol and the colonic metabolites derived from virgin olive oil intake induce cell cycle arrest and apoptosis in colon cancer cells. *J. Agric. Food Chem.* **2017**, *65*, 6467–6476. [CrossRef]
142. Zhao, B.; Ma, Y.; Xu, Z.; Wang, J.; Wang, F.; Wang, D.; Pan, S.; Wu, Y.; Pan, H.; Xu, D.; et al. Hydroxytyrosol, a natural molecule from olive oil, suppresses the growth of human hepatocellular carcinoma cells via inactivating AKT and nuclear factor-kappa B pathways. *Cancer Lett.* **2014**, *347*, 79–87. [CrossRef]
143. Toteda, G.; Lupinacci, S.; Vizza, D.; Bonofiglio, R.; Perri, E.; Bonofiglio, M.; Lofaro, D.; La Russa, A.; Leone, F.; Gigliotti, P.; et al. High doses of hydroxytyrosol induce apoptosis in papillary and follicular thyroid cancer cells. *J. Endocrinol. Investig.* **2017**, *40*, 153–162. [CrossRef]
144. Sarsour, E.H.; Goswami, M.; Kalen, A.L.; Lafin, J.T.; Goswami, P.C. Hydroxytyrosol inhibits chemokine C-C motif ligand 5 mediated aged quiescent fibroblast-induced stimulation of breast cancer cell proliferation. *Age* **2014**, *36*, 9645. [CrossRef]
145. Terzuoli, E.; Nannelli, G.; Frosini, M.; Giachetti, A.; Ziche, M.; Donnini, S. Inhibition of cell cycle progression by the hydroxytyrosol-cetuximab combination yields enhanced chemotherapeutic efficacy in colon cancer cells. *Oncotarget* **2017**, *8*, 83207–83224. [CrossRef]
146. Parra-Perez, A.M.; Pérez-Jiménez, A.; Gris-Cárdenas, I.; Bonel-Pérez, G.C.; Carrasco-Díaz, L.M.; Mokhtari, K.; García-Salguero, L.; Lupiáñez, J.A.; Rufino-Palomares, E.E.; Reyes-Zurita, F.J. Involvement of the PI3K/AKT intracellular signaling pathway in the anti-cancer activity of hydroxytyrosol, a polyphenol from *Olea europaea*, in hematological cells and implication of HSP60 levels in its anti-inflammatory activity. *Int. J. Mol. Sci.* **2022**, *23*, 7053. [CrossRef] [PubMed]

147. Granados-Principal, S.; Quiles, J.L.; Ramirez-Tortosa, C.; Camacho-Corencia, P.; Sanchez-Rovira, P.; Vera-Ramirez, L.; Ramirez-Tortosa, M.C. Hydroxytyrosol inhibits growth and cell proliferation and promotes high expression of sfrp4 in rat mammary tumors. *Mol. Nutr. Food Res.* **2011**, *55* (Suppl. S1), S117–S126. [CrossRef] [PubMed]
148. Sun, W.; Luo, M.; Liu, T. Hydroxytyrosol promotes mitochondrial apoptosis and inhibits the proliferation of human colon cancer cells via reactive oxygen species generation. *Food Funct.* **2014**, *5*, 1131–1139. [CrossRef] [PubMed]
149. Fernández-Arroyo, S.; Salvadó, M.J.; Mena, P.; García-Villalba, R.; Espín, J.C.; Perona, J.S. Modulatory effects of hydroxytyrosol and oleuropein on autophagy in breast cancer cells. *Antioxidants* **2020**, *9*, 376.
150. Han, J.; Talorete, T.P.N.; Yamada, P.; Isoda, H. Anti-proliferative and apoptotic effects of oleuropein and hydroxytyrosol on human breast cancer MCF-7 cells. *J. Breast Cancer* **2009**, *12*, 85–90. [CrossRef]
151. Bernini, R.; Gilardini Montani, M.S.; Romani, A.; D'Urso, G.; Agamennone, M.; Cossignani, L.; Amatori, S.; Ciriolo, M.R. Oleocanthal and oleacein inhibit angiogenesis by targeting endothelial cells: A comparative study. *Biomed. Pharmacother.* **2023**, *164*, 115115. [CrossRef]
152. Bender, C.; Candi, I.; Rogel, E.; Salvi, A.; Rossi, F.; Moretti, D.; Biasi, F.; Arciello, M.; Cattaruzza, M.S.; Toti, E.; et al. Efficacy of hydroxytyrosol-rich food supplements on reducing lipid oxidation in humans. *Int. J. Mol. Sci.* **2023**, *24*, 5521. [CrossRef]
153. Nikou, T.; Sakavitsi, M.E.; Kalampokis, E.; Perivolioti, E.; Halabalaki, M. Metabolism and bioavailability of olive bioactive constituents based on in vitro, in vivo and human studies. *Nutrients* **2022**, *14*, 3773. [CrossRef]
154. Nikou, T.; Karampetsou, K.V.; Koutsoni, O.S.; Skaltsounis, A.L.; Dotsika, E.; Halabalaki, M. Pharmacokinetics and metabolism investigation of oleocanthal. *J. Nat. Prod.* **2024**, *87*, 530–543. [CrossRef]
155. Costa, V.; Costa, M.; Videira, R.A.; Rocha, S.; Serra, A.T.; Paiva-Martins, F. Anti-inflammatory activity of olive oil polyphenols—The role of oleacein and its metabolites. *Biomedicines* **2022**, *10*, 2990. [CrossRef]
156. Marrero, A.D.; López, A.; Ortega, M.; Suárez, M.; Rodríguez, Y.; García, C.; Fernández-Cabezudo, M.J. Nanoformulation approaches for enhancing the stability and bioactivity of olive polyphenols. *Nutrients* **2024**, *16*, 1283. [CrossRef] [PubMed]
157. Martini, D.; Toti, E.; De Amicis, R.; Dellavia, C.; Marino, M.; Menna, R.; Cresci, A. Olive polyphenols and health outcomes: An umbrella review of systematic reviews and meta-analyses. *Nutrients* **2023**, *15*, 1471.
158. Saumet, A.; Fernandez-Cabezudo, M.J.; El-Serafi, A.T.; Bashir, G.; Bashir, M.A.; Suhail, M.; Bashir, H. Early-phase pilot clinical trial evaluating EVOO enriched with oleocanthal and oleacein in chronic lymphocytic leukemia. *J. Nutr. Biochem.* **2024**, *115*, 109408.
159. Saad, B. Management of Obesity-Related Inflammatory and Cardiovascular Diseases by Medicinal Plants: From Traditional Uses to Therapeutic Targets. *Biomedicines* **2023**, *11*, 2204. [CrossRef]
160. Lozano-Castellón, J.; Vallverdú-Queralt, A.; Rinaldi de Alvarenga, J.F.; Denoya, G.I.; Lamuela-Raventós, R.M. Health-promoting properties of oleocanthal and oleacein: Two secoiridoids from extra-virgin olive oil. *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 2532–2548. [CrossRef]
161. Kalua, C.M.; Bedgood, D.R., Jr.; Bishop, A.G.; Prenzler, P.D. Changes in virgin olive oil composition with malaxation temperature and time. *Food Chem.* **2006**, *99*, 385–391.
162. Blasi, F.; Ceccarini, M.R.; Bistarelli, S.; Galli, F.; Cossignani, L.; Bartolini, D.; Ianni, F. Impact of Extra-Virgin Olive Oil Storage Conditions on Phenolic Content and Wound-Healing Properties. *Foods* **2025**, *14*, 2104. [CrossRef]
163. Francioso, A.; Federico, R.; Maggiore, A.; Fontana, M.; Boffi, A.; D'Erme, M.; Mosca, L. Green Route for the Isolation and Purification of Hydroxytyrosol, Tyrosol, Oleacein and Oleocanthal from Extra Virgin Olive Oil. *Molecules.* **2020**, *25*, 3654. [CrossRef]

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