Anticancer, Anti-inflammatory, and Neuroprotective Effect of Oleocanthal from Virgin Olive Oil – A Review

Subasini Uthirapathy [1*]

Abstract

Background: Oleocanthal (OC), a phenolic compound found in extra virgin olive oil (EVOO), is renowned for its bioactive properties, including anti-inflammatory, anticancer, and neuroprotective effects. OC has been shown to inhibit the growth of various cancer cells, such as colon, breast, liver, and melanoma. Additionally, its potential role in neuroprotection, particularly in Alzheimer's disease, has been extensively researched. Methods: A comprehensive literature review was conducted to evaluate the pharmacokinetics, dynamics, and therapeutic mechanisms of OC. Databases such as PubMed, SCOPUS, and Web of Science were used to identify studies on OC's therapeutic effects, particularly in cancer, Alzheimer's disease, inflammation, and microbial infections. Results: OC demonstrated potent anti-inflammatory effects by inhibiting cyclooxygenase (COX) enzymes and reducing pro-inflammatory signaling molecules. It also showed significant anticancer activity by modulating pathways like the apoptotic and HGF/c-Met pathways. In Alzheimer's disease, OC reduced astrocyte inflammation and promoted the clearance of amyloid beta proteins, supporting its neuroprotective role. Moreover, OC exhibited antimicrobial and antioxidant properties, further contributing to its therapeutic potential. Conclusion: Oleocanthal exhibits promising therapeutic effects across a range of diseases, including cancer and neurodegenerative disorders. However, while its in vitro pharmacological properties are well-established, further in vivo studies are needed to fully understand its potential as a medicinal agent. The findings of this review underscore OC's potential to serve as a therapeutic lead molecule for a variety of conditions.

Keywords: Oleocanthal, cancer therapy, inflammation, Alzheimer's disease, extra virgin olive oil.

Significance | This review highlights oleocanthal's unique pharmacological properties, emphasizing its therapeutic potential in cancer, inflammation, Alzheimer's, and microbial infections.

*Correspondence. Subasini Uthirapathy, Tishk International University, Erbil, Kurdistan Region, Iraq.
E-mail: subasini.uthirapathy@tiu.edu.iq

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Introduction

Oleocanthal (OC) is a phenolic compound derived from secoiridoids, which are also known as dialdehyde of p-hydroxy phenyl ethanol and elenolic acid (Smith, Sperry, & Han, 2007). It is a natural constituent of extra virgin olive oil (EVOO) and has been widely studied for its beneficial properties, including anti-inflammatory, anti-cancer, and antioxidant effects. Among these, its anticancer properties have received significant attention, as research has shown that OC can inhibit the growth of colon, breast, liver, and melanoma cancer cells (Guis, Wang, & Peng, 2016). OC's potential neuroprotective effects have also been explored, particularly in relation to Alzheimer's disease. Studies have demonstrated that OC can reduce astrocyte inflammation and promote the clearance of amyloid beta protein from neurons, which is a hallmark of Alzheimer's disease (Kelly et al., 2019; Chin & Pang, 2017).

OC is often associated with the characteristic peppery sensation experienced when tasting high-quality olive oil, though it accounts for only 10% of the polyphenols present in olive oil (Fogliano &

Author Affiliation.
[1] Pharmacy Department, Tishk International University, Erbil, Kurdistan Region, Iraq.

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Sacchi, 2006). Despite this relatively small proportion, its unique biological activities have drawn increasing scientific interest. The chemical structure of OC was first discovered in 1992, and its detailed characterization was published by Montedoro et al. in 1993. OC can exist in two chiral forms, with the natural compound possessing an S-configuration and the synthetic form an R-configuration (Beauchamp et al., 2005). The name "oleocanthal" was also coined by Beauchamp and colleagues (Smith et al., 2005).

Research into the stability of OC has revealed that it remains stable for up to four hours at 37°C in acidic conditions, with approximately half of the compound diffusing from the oil phase into an aqueous solution (Romero et al., 2007). However, the pharmacokinetics of OC in humans are not yet fully understood. A limited number of studies have detected OC and its secoiridoid metabolites in human urine 4-6 hours after consumption of EVOO. The primary metabolic pathways of OC involve phase I metabolism (hydrogenation, hydroxylation, and hydration), followed by phase II metabolism, which includes glucuronidation.

The primary objective of this review is to explore the mechanisms by which OC exerts its therapeutic effects in various diseases, including inflammation, cancer, type II diabetes, Alzheimer's disease, microbial infections, and oxidative stress. The review aims to further investigate OC's biological activities using contemporary scientific validation methods and to potentially discover new therapeutic lead molecules for the treatment of a variety of diseases. By providing a comprehensive overview of how oleocanthal and other related polyphenols in EVOO promote health, this review seeks to contribute to the understanding of their pharmacological mechanisms in the human body.

2. Methodology

2.1 Information Sources and Search Strategy

To identify relevant studies on the pharmacokinetics, dynamics, and mechanisms of action of oleocanthal (OC) and its therapeutic effects, we conducted a comprehensive literature search using both medical subject headings (MeSH) and keyword text phrases. These terms included "Oleocanthal," "drugs," "mechanism of action," and "anticancer medicines." The search aimed to ensure that the most relevant studies, particularly those related to the treatment of cancer, diabetes, inflammation, and antibiotic resistance, were captured.

The search strategy was developed to be thorough, using these terms both individually and in combination to increase the range of results. The primary databases searched were PubMed, Google Scholar, SCOPUS, Web of Science, and Embase. These databases were selected for their extensive collections of biomedical and pharmacological literature, allowing us to retrieve published abstracts containing pertinent data on OC. Following this search, articles were screened for relevance based on the primary focus of the review, and those that matched the inclusion criteria were selected for further analysis.

Data extraction was conducted manually, summarizing key findings from each relevant study. These findings were compiled and organized into the final review. Figure 1 highlights the primary pharmacological effects of oleocanthal identified through this process.

2.2 Oleocanthal: Discovery and Sensory Profile

Oleocanthal, derived from "oleo" (olive), "canth" (sting), and "al" (aldehyde), was first recognized as a phenolic component of virgin olive oil in the early 1990s (Andrewes et al., 2003). A decade later, it was identified as the sole phenolic compound responsible for the characteristic pungency and sore throat sensation associated with high-quality virgin olive oil. This was confirmed by Beauchamp et al. (2005), who described "decarboxy methyl ligstroside aglycone" as the only phenolic irritant contributing to olive oil's peppery stinging sensation, and named it oleocanthal.

Recent research has further clarified that this stinging sensation is mediated by TRPA1 (Transient Receptor Potential Cation Channel Subfamily A Member 1), a receptor known for its role in sensing irritants (Peyrot des Gachons et al., 2021). Inter-individual variations in oleocanthal sensitivity have been linked to differences in TRPA1 receptor expression in the oropharyngeal region, which may explain the varying perceptions of OC's sensory effects. Moreover, inflammatory cytokines have been shown to activate the TRPA1 receptor, potentially modulating sensitivity in certain conditions.

In terms of dosage, research suggests that consuming 25–50 mL of olive oil per day yields less than 0.9 mg of OC (Fogliano & Sacchi, 2006; De la Torre, 2008). This highlights a potential challenge in translating the beneficial effects observed in animal studies, where doses of 10–40 mg/kg of OC are typically used, into human dietary consumption. As a result, using pure OC as a dietary supplement may offer a more practical approach to achieving therapeutic effects in humans.

3. Pharmacological Actions

3.1 Anti-inflammatory Effects

Oleocanthal (OC) is known for its anti-inflammatory properties, which are believed to stem from its ability to inhibit cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2. These enzymes are essential in the inflammatory response as they are involved in the production of pro-inflammatory prostaglandins (Carrasco-Pancorbo et al., 2010). By inhibiting these enzymes, OC mirrors the action of non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, which also target COX enzymes to reduce inflammation (Cicerale et al., 2009).

Beauchamp et al. (2005) identified OC as "decarboxy methyl ligstroside aglycone," and noted that its anti-inflammatory effects are comparable to those of ibuprofen, earning OC the designation of a natural NSAID. Additionally, OC has been shown to inhibit lipopolysaccharide (LPS)-induced increases in pro-inflammatory signaling molecules such as GM-CSF, MIP-1α, IL-1β, and TNF-α (Scotece et al., 2012), further highlighting its role in reducing inflammation.

3.2 Alzheimer's Disease

Recent studies have linked the phenolic component of virgin olive oil, oleocanthal, to a reduced risk of Alzheimer's disease (AD), a neurodegenerative disorder marked by the accumulation of β-amyloid (Aβ) and tau proteins in the brain (Abuznait et al., 2013). Research by Monti et al. (2011) demonstrated that OC can inhibit tau fibrillization and aggregation through covalent interactions with the fibrillogenic regions of tau proteins. Another proposed mechanism is OC's ability to prevent the formation of β-amyloid senile plaques, which are a hallmark of Alzheimer's disease (Pitt et al., 2009). By interacting with Aβ, OC alters its oligomerization state, protecting neurons from the synaptic damage associated with Aβ aggregation and plaque formation. These findings suggest that OC may have neuroprotective properties that could help mitigate the progression of Alzheimer's disease.

3.3 Anticancer Activity

Cancer remains one of the leading causes of death worldwide, and oleocanthal has shown promise as an anticancer agent. Research by Gu and Wang (2016b) found that OC inhibited the migration, invasion, proliferation, and tube formation of human umbilical vascular endothelial cells. This review highlights the most recent findings on OC's anticancer efficacy, with a particular focus on the molecular signaling pathways that OC affects in different tumor cell types. Key mechanisms of OC's anticancer activity include the modulation of the apoptotic pathway, the HGF/c-Met pathway, and the STAT3 signaling pathway (Lozano-Castellon et al., 2020). In vitro studies have demonstrated that OC can work synergistically with conventional anticancer drugs, enhancing their efficacy (Lozano-Castellon et al., 2020).

OC also inhibits COX-1 and COX-2 enzymes, which convert arachidonic acid into prostaglandins and thromboxane in response to inflammatory stimuli. This inhibition is significant because the COX-2 enzyme, in particular, has been implicated in the pathophysiology of various cancers in both human and animal studies (Masferrer et al., 2000; Boland et al., 2004). As a natural COX inhibitor, OC is gaining increasing attention in cancer research for its potential to inhibit cancer growth and metastasis.

3.3.1 Melanoma

Although OC has demonstrated potential anticancer activity, limited data are available regarding its efficacy in treating cutaneous malignant melanoma. A study by Fogli et al. (2016) suggested that OC could inhibit melanoma metastasis. In a lung metastasis model, OC was shown to reduce melanoma cell proliferation and angiogenesis, as measured by Ki-67 and CD31 immunohistochemical labeling (Siddique et al., 2020). Furthermore, OC decreased the nuclear localization of signal transducer and activator of transcription 3 (STAT3), significantly reducing STAT3 phosphorylation and impairing its transcriptional activity (Momtaz et al., 2016). These findings point to OC's potential as a therapeutic agent in melanoma treatment.

3.3.2 Breast Cancer

Oleocanthal (OC) exhibits promising anticancer activity against breast cancer by inhibiting the c-Met receptor signaling pathway. This action prevents the proliferation of various breast cancer cell lines, including the triple-negative MDA-MB-231 cell line and the estrogen receptor-positive (ER+) MCF7 and BT474 cell lines (Diez-Bello et al., 2019). Additionally, oleocanthal treatment has been shown to suppress hepatocyte growth factor (HGF)-induced cell migration, invasion, and G1/S cell cycle progression in these breast cancer cell lines in a dose-dependent manner. This growth inhibition is also linked to reduced cellular motility and blockade of epithelial-mesenchymal transition (EMT) (Akl et al., 2014). Furthermore, a significant reduction in mTOR phosphorylation was observed in MDA-MB-231 cells treated with oleocanthal, suggesting that mTOR inhibition contributes to its anticancer effects (LeGendre, Breslin, & Foster, 2015). This inhibition of the mTOR pathway is believed to be a key factor in oleocanthal's anticancer and neuroprotective properties (Khanfar et al., 2015).

3.3.3 Liver and Colon Cancer

Oleocanthal has also demonstrated significant anticancer activity in liver (hepatocellular carcinoma, HCC) and colon (colorectal carcinoma, CRC) cancer cells. Studies have shown that OC is more effective in inhibiting cell growth in these cancer types (Zhang & Zheng, 2012). The mechanisms involved include PARP cleavage, activation of caspases 3 and 7, and chromatin condensation, all of which contribute to reduced colony formation and the induction of apoptosis (Khanal et al., 2011). Additionally, OC treatment induces the production of intracellular reactive oxygen species (ROS) and leads to mitochondrial depolarization. This mitochondrial disruption is accompanied by an increase in the expression of γH2AX, a marker of DNA damage, in a dose-dependent manner. Importantly, the ROS scavenger N-acetyl-L-cysteine was shown to mitigate the effects of OC, suggesting that ROS generation is a key factor in its anticancer activity (Pei et al., 2016).

3.4 Antimicrobial Activity

Oleocanthal also possesses notable antimicrobial properties. Antimicrobials either kill or inhibit the growth of microorganisms, and polyphenols, such as those found in olive oil, are bioactive compounds with well-established antibacterial and antioxidant effects (Zbakh & Abbassi, 2012). The high phenolic content of olive oil, including hydroxytyrosol, has been shown to inhibit bacterial

Table 1. Extra Virgin Olive Oil – Oleocanthal Pharmacological Activity

Phenolic compounds	Properties	Pharmacological action	References
Simple phenolic compounds	based on the derivatives of cinnamic acids' C6-C3 structure and benzoic acids' C6-C1 structure	Antidiabetic agent, Antimicrobial agent, anticancer	Pang and Chin, 2018; Clin invest et al., 2004
Phenolic alcohol carotenoids	based on the derivatives of cinnamic acids' C6-C3 structure and benzoic acids' C6-C1 structure	Antibacterial agent and immunomodulatory effect	Cicerale et al., 2012; Dick, 2018
Secorinoids (93 %) Oleacein (21 %) Oleocanthal (70 %) Oleuropein	defined by the existence of derivatives of elenolic acid or elenolic acid.	Antioxidant, anti-inflammatory and antiproliferative effects.	Marilena Celano et al., 2019
Hyroxycinnamic acids (HCAs)	(HCAs) are a class of phenolic compounds that have a radical with a carboxyl group and a phenolic ring as two of their structural characteristics.	Antioxidant, anti-inflammatory, antimicrobial and anti-tyrosinase activities, Ultraviolt (UV) protective effects, anti-aging	Taofiq et al., 2016
Hydroxytyrosol, tyrosol and oleuropein	Hydroxytyrosol by a linear three-carbon chain connecting two benzene rings. Occasionally hydroxytyrosol acetate They can be separated into flavones and flavanols further.	Antiviral, anticancer, anti-inflammatory, anticancer, antioxidant.	Lubna Ghani et al., 2020
Lignans tyrosol, oleuropein, and Htyr	The structure is founded on the condensation of aromatic aldehydes.	Anti-inflammatory, Antioxidant and Renoprotective	Asad Ullah et al., 2020
Oleic acid and polyphenols	based on the derivatives of the C6-C3 structure of cinnamic acids and the C6-C1 structure of benzoic acids	Hepatic disorders such as hepatic fibrinogenesis, hepatocyte ballooning and liver steatosis	Han et al., 2016; Pirozzi et al., 2016.
Oleocanthal	PHF6 peptide, disrupting tau-tau interaction and fibril formation. Phenolic derivatives of Toll-like receptor 4 signal pathway.	Anti-neurodegenerative effects, anti-obesity and antihyperglycemic effects, and Human pancreatic adenocarcinoma	De Paola et al., 2016; Cusimano et al., 2017; LeGendre et al., 2015
Flavonoids Luteolin Apigenin	Cytotoxicity and apoptosis induction and Reduced tumour area	Anticaner- Human acute promyelocytic leukemia HL-60 cell	Khanal et al., 2011;
Other type of phenols	Increased P-gp expression and activity and non-cytotoxic up to 60 μM (72 h)	Human colon adenocarcinoma - Human breast cancer Tumor growth, proliferation, and angiogenesis were all inhibited.	Mohyeldin et al., 2016; Abuznait et al., 2011
1-Acetoxypinoresinol Pinoresinol	Apoptosis induction Activated ERK 1/2 signalling	Hepatocellular carcinoma - Tumor development and proliferation were inhibited.	Pei et al., 2016; Cassiano et al., 2015

Table 2. Extraordinary Health Benefits of Oleocanthal

Oleocanthal's Health Benefits	Mechanism of action	References
Anti-inflammatory effects	Oleocanthal has anti-inflammatory properties similar to NSAIDs but without side effects.	Rosignoli et al., 2013; Yang et al., 2018
Antioxidant effects	Oleocanthal is a powerful antioxidant that fights free radicals. It removes oxidative stress-causing substances and damaged cells as a powerful antioxidant.	Mete et al., 2017; Castejón et al., 2020
Cardiovascular effects	The heart-protective qualities of oleocanthal fascinate researchers worldwide. Its antioxidant and anti-inflammatory properties improve cardiovascular health, according to research. Regular usage of oleocanthal-rich olive oil reduces cardiovascular disease risk.	Castejón et al., 2020; Francisco et al., 2019
Hyperlipidemia effects	Regular usage of oleocanthal-rich olive oil reduces cardiovascular disease risk. These risk factors include decreased cholesterol and blood pressure.	Salas-Salvado et al., 2008
Neuroprotective effects	Oleocanthal may protect the brain against cognitive decline, according to recent studies.	Mete et al., 2017
Alzheimer's disease	Researchers believe it affects the synthesis of damaging proteins that contribute to Alzheimer's disease.	Lozano-Castellón et al., 2020
Anticancer effects	This chemical may induce apoptosis, which kills cancer cells but leaves healthy ones intact.	Scotece et al., 2013; Lozano-Castellón et al., 2020; Polini et al., 2018
Antimicrobial effects	To inhibit the development and spread of various microorganisms.	Pang and Chin, 2018

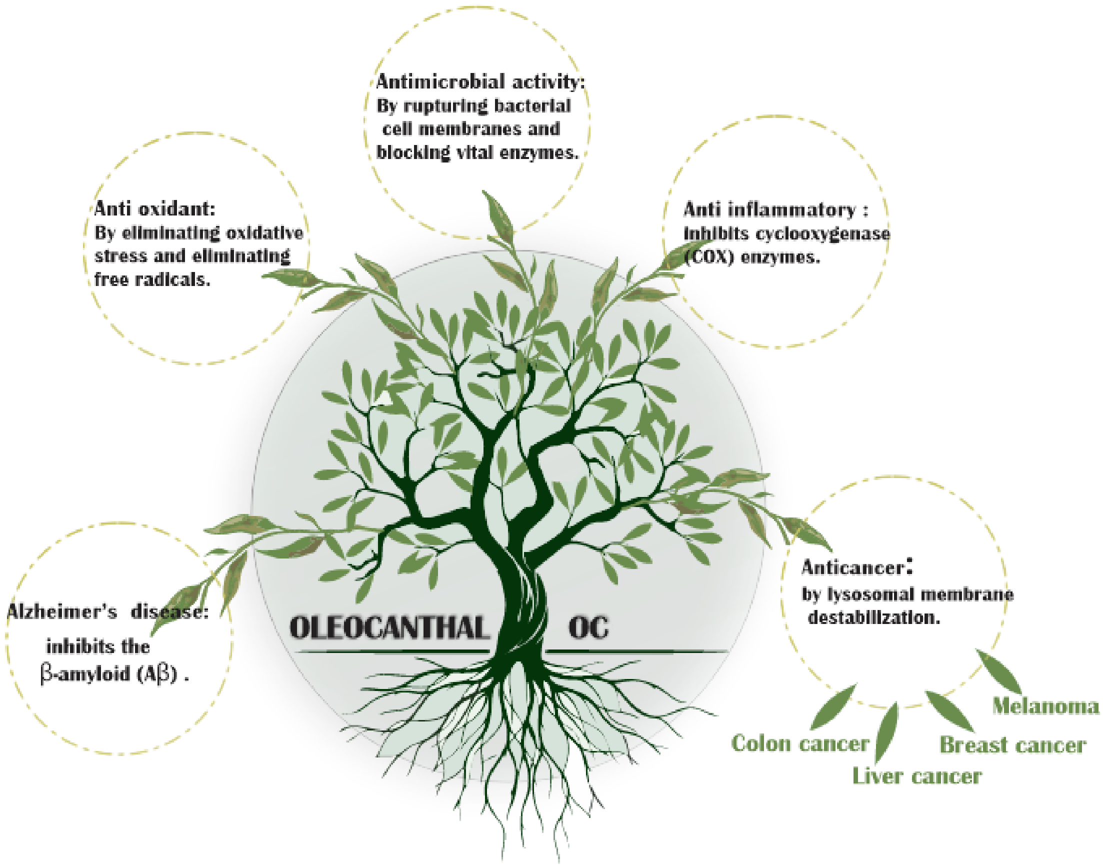

Figure 1. Pharmacological Action of Oleocanthal (OC)

growth in vitro. Specifically, olive oil's phenolic compounds exhibit antiatherogenic, hypocholesterolemic, anticancer, antihypertensive, cardioprotective, anti-inflammatory, antiviral, antibacterial, antioxidant, and hypoglycemic properties (Cayan & Erener, 2015). OC has been shown to possess antibacterial activity against foodborne pathogens such as Escherichia coli, Listeria monocytogenes, Salmonella, and Staphylococcus aureus (Medina et al., 2006). This antibacterial action is believed to occur through the disruption of bacterial cell membranes and the inhibition of key bacterial enzymes, which compromises the integrity and functionality of these microorganisms (Techathuvanan et al., 2014).

3.5 Antioxidant Activity

Oleocanthal functions as an antioxidant by eliminating oxidative stress and neutralizing free radicals. Its phenolic structure allows it to neutralize reactive oxygen species (ROS), which can have a protective effect against inflammation and cellular damage (Maalej et al., 2017). Additionally, OC may influence the activity of NADPH oxidase, reducing ROS production in cells. This modulation of ROS production is believed to be a contributing factor to the overall protective effects of oleocanthal against oxidative stress-related disorders (Medina et al., 2009).

3.6 Hepatoprotective Activity

The liver plays a critical role in maintaining the body's chemical environment by filtering and eliminating drugs and xenobiotics, regulating absorption, metabolism, and protecting the body from external toxins (Thirumalai et al., 2011; Saleem et al., 2010). Oleocanthal has shown hepatoprotective potential, especially in preventing mitochondrial dysfunction and hepatic steatosis induced by a high-fat diet, as demonstrated by Ortiz et al. (2020). Since free radicals can damage the liver and increase the risk of serious conditions such as cirrhosis, hepatitis, and liver cancer, there is an urgent need to explore hepatoprotective agents derived from plants (Ilavenil et al., 2015; Saeed et al., 2021). The antioxidant properties of oleocanthal and its ability to combat free radical damage suggest that it may serve as a promising candidate for preventing liver damage and other related disorders.

3.7 Anti-Neurodegenerative Activity

Neurodegenerative diseases, including stroke, Parkinson's disease, and Alzheimer's disease, represent significant global health concerns. These conditions often lead to inflammation, abnormal protein aggregation, cell death, oxidative stress, excitotoxicity, and calcium (Ca^{2+}) imbalance. A growing body of evidence supports the protective effects of the Mediterranean diet against neurodegeneration, largely due to the polyphenolic content of virgin olive oil (Angeloni et al., 2017). Specifically, oleocanthal, a phenolic compound in virgin olive oil, plays a crucial role in these protective effects. Studies suggest that oleocanthal may help combat Parkinson's disease by modulating cellular processes involved in its development (Sarrafchi et al., 2016; Maher, 2017). Additionally, oleocanthal has demonstrated numerous health benefits, including anti-inflammatory, anticancer, antibacterial, hepatoprotective, antioxidant, and neuroprotective properties. These findings underscore the potential of oleocanthal as a therapeutic agent for various neurodegenerative diseases. Table 1 summarizes the pharmacological effects and health benefits of oleocanthal.

4. Nutritional Benefits of Oleocanthal

Supplementing with oleocanthal has been shown to reduce the proliferation of harmful cells, particularly by targeting their lysosomes. Researchers have also observed that oleocanthal helps regulate blood sugar levels and supports optimal glucose homeostasis, contributing to healthy metabolism (Allouche et al., 2011). Furthermore, oleocanthal enhances cognitive function, with studies demonstrating its role in promoting brain health and improving cognitive performance. It helps maintain proper blood flow, which is essential for supporting healthy brain activity and mental clarity (Salas-Salvado et al., 2008).

A distinctive feature of oleocanthal is the peppery or "bite" sensation it produces at the back of the throat, commonly experienced with the consumption of extra virgin olive oils, indicating its presence. This compound is also renowned for its powerful anti-inflammatory properties, comparable to nonsteroidal anti-inflammatory drugs (NSAIDs) but without the associated side effects (Rosignoli et al., 2013; Yang et al., 2018). Long-term inflammation can be effectively managed with oleocanthal, making it a valuable tool in reducing chronic inflammation.

Oleocanthal also plays a prominent role in combating oxidative stress by acting as a potent antioxidant. It neutralizes harmful free radicals, which are responsible for cellular damage and contribute to the aging process (Mete et al., 2017; Castejón et al., 2020). By promoting the health of cells, oleocanthal aids in delaying the onset of age-related conditions and supports overall cellular wellbeing.

4.1 Cardiovascular Protection

Researchers have increasingly focused on the potential cardiovascular benefits of oleocanthal. Its anti-inflammatory and antioxidant properties have been associated with improved cardiovascular health. Studies indicate that regular consumption of oleocanthal-rich olive oil is linked to reduced risk factors for cardiovascular disease, such as improved cholesterol levels and lowered blood pressure (Castejón et al., 2020; Francisco et al., 2019; Salas-Salvado et al., 2008).

4.2 Neuroprotective Potential

Recent research highlights the neuroprotective potential of oleocanthal, suggesting that it may help preserve brain function and reduce the risk of cognitive decline (Mete et al., 2017). Oleocanthal is thought to disrupt the formation of harmful proteins implicated in the development of neurodegenerative diseases such as Alzheimer's (Lozano-Castellón et al., 2020).

4.3 Anticancer Properties

Preliminary studies suggest that oleocanthal may possess anticancer properties. It has been shown to induce apoptosis, a process of programmed cell death, in cancer cells while sparing healthy cells. This selective mechanism highlights oleocanthal's potential as an anticancer agent. However, further research is necessary to fully understand its role in cancer prevention and treatment (Scotece et al., 2013; Polini et al., 2018).

As both an anti-inflammatory and antioxidant, oleocanthal is a potent bioactive compound that promotes overall health and wellbeing. Table 2 presents the outstanding health benefits of oleocanthal.

5. Conclusion

In conclusion, this review highlights the wide-ranging therapeutic potential of oleocanthal, a bioactive compound found in virgin olive oil, across various health conditions. Its potent anti-inflammatory, anticancer, antibacterial, hepatoprotective, anti-neurodegenerative, antimicrobial, and antioxidant properties demonstrate significant promise for both the prevention and treatment of nutritional and health-related disorders. Oleocanthal's ability to reduce inflammation, disrupt Alzheimer's-related processes, and protect brain function underscores its potential as a key therapeutic agent. Studies have also shown its effectiveness in reducing cancer cell proliferation, inhibiting cell migration, and inducing apoptosis, further supporting its role in cancer therapy.

Despite its promising in vitro pharmacological effects, further in vivo studies are essential to fully understand its therapeutic potential and establish it as a viable medicinal compound. Continued research could pave the way for oleocanthal to become a valuable tool in combating chronic inflammatory diseases, neurodegenerative disorders, and cancer, reinforcing its place in both preventive health and clinical medicine.

Author contributions

All authors made equal contributions to the study design, statistical analysis, and drafting of the manuscript. The corresponding author, along with the co-authors, reviewed and approved the final version of the article prior to submission to this journal.

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The authors have no conflict of interest.

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