Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN (E): 2320-3862
ISSN (P): 2394-0530
NAAS Rating 2017: 3.53
JMPS 2017; 5(3): 95-100

Received: 08-03-2017
Accepted: 10-04-2017

Antonia Kotsiou
Assistant Professor for Clinical Pharmacy-Pharmacology, National and Kapodistrian University of Athens, Medical School, Aretaieio Univ. Hospital, Vas Sophias, Athens Greece

Christine Tesseromatis Prof. of Pharmacology, National and Kapodistrian University of Athens, Medical School, Mikras Assias, Greece

Correspondence
Antonia Kotsiou
Assistant Professor for Clinical Pharmacy-Pharmacology, National and Kapodistrian University of Athens, Medical School, Aretaieio Univ. Hospital, Vas Sophias, Athens Greece

Oleocanthal an extra-virgin olive oil bioactive component

Antonia Kotsiou and Christine Tesseromatis

Abstract
Oleocanthal, a phenolic compound in virgin olive oil, is a potential nutraceutical therapeutic for many health conditions. The Greek physician Hippocrates (460 -370 BC) mentions approximately 60 of them.
Oleocanthal inhibits cyclooxygenase 1 and 2 (COX 1 & 2) enzymes in a dose-dependent manner, and mimics the anti-inflammatory action of the synthetic NSAID ibuprofen.
Oleocanthal modulates Alzheimer's disease, by altering the fibrillization of tau protein and by enhancement of β-amyloid clearance from the brain.
Oleocanthal induced cell death in all cancer cells by various mechanisms- inhibition of COX 2, rapamycin (mTOR), HGF-induced c-Met activation and its downstream mitogenic signaling pathways, heat-shock proteins HSP70 and HSP90.
Oleocanthal provides an exceptional antioxidative activity, removing harmful oxidants from the body and preventing many diseases.

Keywords: Oleocanthal, olive-oil, anti-inflammatory, anti-oxidant

1. Introduction
Throughout history virgin olive oil extracted from the fruit of the tree *Olea europaea* L., has been recognized as valuable pharmacological agent in the hands of ancient Greek doctors. n Hippocrates mentions approximately 60 health conditions where virgin olive oil use can be beneficial, for example many skin conditions, wounds and burns, amongst others [1].
Oleocanthal, initially as a phenolic compound was known as decarboxy methyl ligstroside aglycone, eliciting an unusual oral pungency sensed almost exclusively in the throat. It was the sole irritant phenolic responsible for the peppery stinging sensation experienced with virgin olive oil ingestion and it was named oleocanthal (*oleo* for olive, *canth* for sting, and *al* for aldehyde). The confirmatory finding that oleocanthal is the sole irritating compound in virgin olive oil was achieved by quantifying oleocanthal from various virgin olive oils and measuring the throat irritation accompanying ingestion. However, to exclude the possibility that other compounds may also contribute to the unique perceptual characteristic, oleocanthal was synthesised and dissolved in corn oil. The measure of the throat irritation from the addition of oleocanthal to non-irritating corn oil was found to be dose dependent on oleocanthal and mimicked the irritation of virgin olive oil confirming that indeed oleocanthal is the sole compound responsible for throat irritating sensation [2].
A valuable source of oleocanthal is also olive pomace waste. In a study the concentration of oleocanthal in olive pomace waste was determined and compared to its concentration in extra-virgin olive oil (EVOO). The concentration of oleocanthal in freshly pressed EVOO and its subsequent waste was analysed at early, mid and late season harvests. Oleocanthal concentrations were quantified using high-performance liquid chromatography-mass spectrometry. In oil, oleocanthal concentration was as follows: 123.24 ± 6.48 mg kg (-1) in early harvest, 114.20 ± 17.42 mg kg (-1) in mid harvest and 152.22 ±10.54 mg kg (-1) in late harvest. Its concentration in waste was determined to be: 128.25 ± 11.33 mg kg (-1) in early harvest, 112.15 ± 1.51 mg kg (-1) in mid harvest and 62.35 ± 8.00 mg kg (-1) in late harvest [3].
Pungency and irritation is a key characteristic of virgin olive oil quality. These attributes are recognized as the positive reinforcement of virgin olive oil quality by those who frequently consume the oil, such as Mediterranean populations. So much so, that prized virgin olive oil'sare rated as one cough or two cough oils, with the latter classed as superior. There is reported variation in the concentration of oleocanthal contained in virgin olive oil. A recent study has reported that the concentration of oleocanthal contained in virgin olive oils ranges

From 284 to 711 mg/kg in a variety of Greek oils [4, 5].

The oleocanthal pungency sensed almost exclusively in the throat and is specific to the oropharyngeal region contrasts with most other common oral irritant or pungent compounds, such as cinnamaldehyde, capsaicin, and alcohol, which irritate mucus membranes throughout the oral cavity. It is shown that this rare irritation pattern is a consequence of both the specificity of oleocanthal for a single sensory receptor and the anatomical restriction of this sensory receptor to the pharynx, within the oral cavity. It is demonstrated, *in vitro*, that oleocanthal selectively activates the Transient receptor potential cation channel, subfamily a, member 1, TRPA1 channel in HEK 293 cells and that its ability to excite the trigeminal nervous system in rodents requires a functional TRPA1. Similarly it is demonstrated that the over-the-counter analgesic, ibuprofen, which elicits the same restricted pharyngeal irritation as oleocanthal, also specifically excites rodent sensory neurons via TRPA1. These findings provide an anatomical and molecular explanation for a distinct oral sensation that is elicited by oleocanthal and ibuprofen and that is commonly experienced around the world when consuming many extra-virgin olive oils. The large inter-individual variation in sensitivity to oleocanthal may be due to variation in expression of TRPA1 receptors in the oropharyngeal region [6].

Oleocanthal, a phenolic compound in virgin olive oil, has emerged as a potential nutraceutical therapeutic for inflammation, cancers and neurodegenerative diseases [7].

Methods

Current literature on olive –oil phenols is reviewed**.**

Results

1. Oleocanthal and inflammation

It was observed that oleocanthal inhibits the cyclooxygenases (COX-1 and -2) responsible for prostaglandin production on immuno-inflammatory and oxidative stress responses in young and old people [8]

Oleocanthal inhibits cyclooxygenase 1 and 2 (COX 1 & 2) enzymes in a dose-dependent manner, and does in fact mimic the anti-inflammatory action of the synthetic NSAID ibuprofen and furthermore oleocanthal (25 μM) inhibits 41%–57% of COX activity in comparison to ibuprofen (25 μM) which inhibits 13%–18% of COX activity [2]

Oleocanthal is therefore acknowledged as a naturally occurring NSAID. This pharmacological similarity has provoked interest in oleocanthal and its anti-inflammatory and potential therapeutic actions since chronic inflammation is a critical factor in the pathogenesis of many inflammatory disease states including cardiovascular disease, cancer, diabetes, degenerative joint diseases and neurodegenerative diseases. Popular methods to deal with inflammation involve the use of non-steroidal anti-inflammatory drugs, however the use of these drugs are associated with severe side effects so natural methods of inflammatory control are highly desirable. Therefore, low, chronic doses of a naturally occurring NSAID such as oleocanthal may attenuate inflammation over time, and may then contribute to significant reductions in the development of chronic inflammatory disease [9, 10].

Levels of oxidative stress markers 8-hydroxy-deoxguanosine (8-HOdG) and malondialdehyde (MDA) are significantly higher in periodontitis and other chronic inflammatory conditions. There is a clear link between periodontitis and diseases associated with significant systemic inflammatory loading, such as metabolic syndrome. Micro- and macro-nutrients have proven to be effective in curbing molecular mechanisms that generate reactive oxygen and nitrogen species. Oleocanthal isolated in virgin olive oil has similar anti-inflammatory actions to that of ibuprofen. Epigenetics influenced by environmental factors and interactions between genes and nutrients as therapeutic adjuncts, could enhance the antioxidant capacity of an inherent glutathione system and overcome oxidative effects, thereby mitigating therapeutic side-effects [11].

Oleocanthal shares also unique chemesthetic qualities with ibuprofen. Chemesthetic sensations elicited by ibuprofen, extra-virgin olive oil, and capsaicin were compared to quantify perceptual differences between known agonists of TRPA1 and TRPV1.Pilot work suggested participants had difficulty distinguishing between multiple chemesthetic subqualities (e.g.,burn, sting, itch, tickle, etc.) in a multiattribute rating task. Here, we assessed overall irritation via direct scaling, and a check all that apply task was used to collect information about chemesthetic subqualities over time. The correlation found between olive oil and capsaicin may suggest the presence of unknown TRPV1 agonists in olive oil. This view was also supported by the qualitative data: capsaicin was described most often as burning and warm/hot, whereas ibuprofen was numbing and tickling. Olive oil shared characteristics with both capsaicin (warm/hot) and ibuprofen (tickle) [12].

2. Oleocanthal and Joint Degenerative Disease

Oleocanthal may be of interest in the quest to find suitable natural NSAIDs for the treatment of joint degenerative disease. Pro-inflammatory cytokines stimulate nitric oxide (NO) production. NO is biosynthesized by nitric oxide synthase (NOS). Another form of NOS is inducible NOS (iNOS) which is primarily responsible for the inflammatory actions of NOS. Oleocanthal and synthesized derivatives, attenuate production of iNOS protein expression in an LPS challenged murine chondrocytes, in a dose dependent manner [10, 13].

Also, as oleocanthal inhibits COX enzymes, and prostaglandins are downstream of COX then it is possible that oleocanthal may also exert pharmacological actions in the treatment of both rheumatoid arthritis and osteoarthritis through COX inhibition. COX enzymes are a catalyst for the formation of prostaglandins and prostaglandins are highly expressed in the arthritic spine in an animal model. Therefore, oleocanthal may attenuate arthritic pain through inhibition of prostaglandins, specifically the synthesis of PGE_2 that accompanies COX inhibition [14].

Oleocanthal is considered as a potential therapeutic weapon for the treatment of inflammatory degenerative diseases since it proved to inhibit LPS-induced NO production in J774 macrophages, without affecting cell viability. Moreover, it inhibits MIP-1α and IL-6 mRNA expression, as well as protein synthesis, in both ATDC5 chondrocytes and J774 macrophages. Oleocanthal also inhibits IL-1β, TNF-α and GM-CSF protein synthesis from LPS-stimulated macrophages. These data confirm a clear potent role of oleocanthal as anti-inflammatory therapeutic agent for future treatment of arthritis or other inflammatory diseases [15].

3. Oleocanthal and Alzheimer's disease

A common molecular feature of amyloid neurodegenerative diseases is the unfolding/misfolding of specific proteins/peptides which consequently become prone to aggregate into toxic assemblies and deposits that are the key

histopathological trait of these pathologies. These neurodegenerative diseases are usually age-associated disorders the so-called 'nutraceutical approach' suggests life-long healthy diets. Natural phenols abundant in 'healthy' foods such as extra virgin olive oil, red wine, appear particularly promising. Virgin olive oil has been associated with a reduced incidence of neurodegenerative diseases and better cognitive performance. Oleocanthal has attracted considerable attention in the modulation of Alzheimer's disease [16, 17].

Oleocanthal is capable of altering the fibrillization of tau protein, which is one of the key factors at the basis of neurodegenerative diseases, and of covalently reacting with lysine ε-amino groups of the tau fragment K18 in an unspecific fashion. Oleocanthal has been found to interact with tau-441, inducing stable conformational modifications of the protein secondary structure and also interfering with tau aggregation. These findings provide experimental support for the potential reduced risk of neurodegenerative diseases associated with olive oil consumption and may offer a new chemical scaffold for the development of Alzheimer's disease -modulating agents [18].

An interpretation of the oleocanthal mechanism to abrogate fibrillization of tau protein has been attempted through a detailed mass spectrometric investigation of the oleocanthal reactive profile with both tau protein fibrillogenic fragment K18 and propylamine in biomimetic conditions. It was shown that K18 is prone to be covalently modified by oleocanthal through Schiff base formation between the ε-amino group of lysine residues and oleocanthal aldehyde carbonyls. Moreover, as expected from its de-structured conformation, K18 shows a non-selective modification profile, reacting with several lysine residues to give cyclic pyridinium-like stable adducts. These data give new insights on the mechanism of inhibition of tau fibrillization mediated by oleocanthal [19].

The effect of oleocanthal on pathological hallmarks of Alzheimer's disease in TgSwDI, an animal model of Alzheimer's disease, was investigated. Mice treatment for 4 weeks with oleocanthal significantly decreased amyloid load in the hippocampal parenchyma and microvessels. This reduction was associated with enhanced cerebral clearance of Aβ across the blood-brain barrier. Further mechanistic studies demonstrated oleocanthal to increase the expression of important amyloid clearance proteins at the blood-brain barrier including P-glycoprotein and LRP1, and to activate the ApoE-dependent amyloid clearance pathway in the mice brains. The anti-inflammatory effect of oleocanthal in the brains of these mice was also obvious where it was able to reduce astrocytes activation and IL-1β levels. Finally, we could recapitulate the observed protective effect of oleocanthal in an in vitro human-based model, which could argue against species difference in response to oleocanthal. In conclusion, findings from in vivo and in vitro studies provide further support for the protective effect of oleocanthal against the progression of AD [20].

The mechanism by which oleocanthal exerts its neuroprotective effect in Alzheimer's disease characterized by accumulation of β-amyloid (Aβ) and tau proteins in the brain was studied in vitro and in vivo. Results demonstrated similar and consistent pattern of oleocanthal in controlling Aβ levels. In cultured mice brain endothelial cells, oleocanthal treatment increased P-glycoprotein and lipoprotein receptor related protein-1 expression and activity, an evidence for the potential of oleocanthal to enhance Aβ clearance from the brain via up-regulation of P-glycoprotein and LDL, major Aβ transport proteins, at the blood-brain barrier. Furthermore there was a significant increase in (125)I-Aβ40 degradation as a result of the up-regulation of Aβ degrading enzymes following oleocanthal treatment. These findings provide experimental support that potential reduced risk of Alzheimer's disease, associated with extra-virgin olive oil could be mediated by enhancement of Aβ clearance from the brain [21].

It appears likely that soluble oligomers of amyloid-beta1-42 peptide, rather than insoluble fibrils, act as the primary neurotoxin in Alzheimer's disease (AD). Consequently, compounds capable of altering the assembly state of these oligomers (referred to as ADDLs) may have potential for AD therapeutics. oleocanthal disrupted Abeta oligomerization and reduced pathogenicity, increased the immunoreactivity of soluble Abeta species, when assayed with both sequence- and conformation-specific Abeta antibodies, indicating changes in oligomer structure. In comparison with control ADDLs, oligomers formed in the presence of oleocanthal (Abeta-OC) showed equivalent colocalization at synapses but exhibited greater immunofluorescence as a result of increased antibody recognition. Decreased binding to synapses was accompanied by significantly less synaptic deterioration assayed by drebrin loss. Additionally, treatment with oleocanthal improved antibody clearance of ADDLs. These results indicate oleocanthal is capable of altering the oligomerization state of ADDLs while protecting neurons from the synaptopathological effects of ADDLs and suggest oleocanthal as a lead compound for development in AD therapeutics [22].

A recent cross sectional Australian study concluded that those suffering neurodegenerative disease showed a significantly lower adherence to a Mediterranean style dietary pattern, and there is a plethora of evidence research showing up to a 40% decrease in Alzheimer's disease in populations consuming a Mediterranean style diet. Perhaps oleocanthal, in conjunction with other phenolics, exerts a neuro-therapeutic potential that is reflected in the low incidence of neurodegenerative disease in populations that regularly consume olive oil [23, 24].

4. Oleocanthal and Cancer

Numerous *in vitro* studies have reported that the phenolic compounds in virgin olive oil can inhibit the initiation and metastasis of several types of cancer. This in turn supports the abundance of associative evidence highlighting the lower incidence of many types of cancer, including breast, prostate, lung and gastrointestinal cancer that are observed in Mediterranean populations when compared to Western populations [25].

Oleocanthal induced cell death in all cancer cells examined as rapidly as 30 minutes after treatment in the absence of serum. Oleocanthal treatment of non-transformed cells suppressed their proliferation but did not cause cell death. Oleocanthal induced both primary necrotic and apoptotic cell death via induction of lysosomal membrane permeabilization [26].

The established anticancer and neuroprotective properties of oleocanthal combined with the reported role of mammalian target of rapamycin (mTOR) in cancer and Alzheimer's disease development encouraged us to examine the possibility that oleocanthal inhibits m TOR. To validate this hypothesis, we docked oleocanthal into the adenosine triphosphate binding pocket of a close m TOR protein homologue, namely, PI3K-γ. Apparently, oleocanthal shared nine out of ten critical binding interactions with a potent dual PIK3-γ/mTOR natural inhibitor. Subsequent experimental validation indicated that oleocanthal indeed inhibited the enzymatic activity of mTOR

with an IC50 value of 708 nM. Oleocanthal inhibits the growth of several breast cancer cell lines at low micromolar concentration in a dose-dependent manner. Oleocanthal treatment caused a marked down regulation of phosphorylated mTOR in metastatic breast cancer cell line (MDA-MB-231). These results strongly indicate that mTOR inhibition is at least one of the factors of the reported anticancer and neuroprotective properties of oleocanthal [27].

The inflammatory enzymes attenuated by oleocanthal, COX 1 and COX 2, are responsible for the conversion of arachidonic acid to prostaglandins and thromboxane, which are produced in response to inflammatory or toxic stimuli. One cyclooxygenase enzyme, COX 2 is implicated in the pathogenesis of several cancers, in both human and animal studies. Because oleocanthal is a naturally occurring COX inhibitor, it is becoming a compound of interest in cancer research. [28, 29, 30].

Oleocanthal can have potential therapeutic use for the control of c-Met-dependent malignancies. The proto-oncogene receptor tyrosine kinase c-Met encodes the high-affinity receptor for hepatocyte growth factor (HGF). Dysregulation of the HGF-c-Met pathway plays a significant oncogenic role in many tumors. Overexpression of c-Met is a prognostic indicator for some transitional cell carcinomas. Computer-Assisted Molecular Design (CAMD) identified oleocanthal as a potential virtual c-Met inhibitor hit. Oleocanthal inhibited the proliferation, migration, and invasion of the epithelial human breast and prostate cancer cell lines MCF7, MDA-MB-231, and PC-3, respectively, with an IC (50) range of 10-20 μM, and demonstrated anti-angiogenic activity via downregulating the expression of the microvessel density marker CD31 in endothelial colony forming cells with an IC (50) of 4.4 μM. It inhibited the phosphorylation of c-Met kinase IN VITRO in the Z'-LYTE™ assay, with an IC (50) value of 4.8 μM. (-) [31].

The effects of oleocanthal on the expression and activity of in human adenocarcinoma cells (LS-180) was investigated. Accumulation studies demonstrated 31-38% decrease in rhodamine 123 intracellular levels as a result of P-glycoprotein induction [32].

Dysregulation of the Hepatocyte growth factor (HGF)/c-Met signaling axis upregulates diverse tumor cell functions, including cell proliferation, survival, scattering and motility, epithelial-to-mesenchymal transition, angio genesis, invasion, and metastasis. (-)-Oleocanthal showed antiproliferative and antimigratory activity against different cancer cell lines that7 (-)-oleocanthal inhibits the growth of human breast cancer cell lines MDA-MB-231, MCF-7 and BT-474. It also caused a dose-dependent inhibition of HGF-induced cell migration, invasion and G1/S cell cycle progression in breast cancer cell lines. Moreover, (-)-oleocanthal treatment effects were found to be mediated via inhibition of HGF-induced c-Met activation and its downstream mitogenic signaling pathways. Further results from in vivo studies showed that (-)-oleocanthal treatment suppressed tumor cell growth in an orthotopic model of breast cancer in athymic nude mice. Oleocanthal is a promising dietary supplement lead with potential for therapeutic use to control malignancies with aberrant c-Met activity [33].

Oleocanthal ia an excellent scaffold for the design of novel c-MET inhibitors. Chemically, (-)-oleocanthal is the elenolic acid ester of the common olive phenolic alcohol tyrosol. Therefore, several analogues were synthesized by esterification and carbamoylation of tyrosol using diverse phenolic naturally occurring in olive and heterocyclic acids as elenolic acid bioisosteres to assess the effect of replacing the acid moiety of (-)-oleocanthal. Their c-MET inhibitory activity as well as their antiproliferative, antimigratory, and anti-invasive activities against the highly metastatic human breast cancer cell line MDA-MB231 has been assessed. Generally, tyrosol esters showed better activities versus carbamate analogues. Tyrosol sinapate showed the best c-MET phosphorylation inhibitory activity in Z'-LYTE kinase assay. Tyrosol esters with a phenolic acid containing hydrogen bond donor and/or acceptor groups at the para-position have better anticancer and c-MET inhibitory activities. [34]

A copper-(I)-catalyzed variation of the Huisgen 1, 3-dipolar cycloaddition has been applied to lead the in living-cell mass-spectrometry based identification of protein targets of oleocanthal, a natural metabolite daily ingested by millions of people. Chemical proteomics revealed heat-shock proteins, HSP70 and HSP90, as main oleocanthal interactors in living systems. These two proteins are involved in cancer development and, thus, our findings could have important outcomes for a deep evaluation of the bio-pharmacological significance of oleocanthal [35, 36].

Multiple myeloma (MM) is a plasma cell malignancy that causes devastating bone destruction by activating osteoclasts in the bone marrow milieu. It has been demonstrated that macrophage inflammatory protein 1- alpha (MIP-1 α) is crucially involved in the development of osteolytic bone lesions in MM. Oleocanthal, on the human multiple myeloma cell line ARH-77 in vitro, inhibited MIP-1 α expression and secretion in MM cells. In addition, oleocanthal inhibits MM cells proliferation by inducing the activation of apoptosis mechanisms and by down-regulating ERK1/2 and AKT signal transduction pathways. This in vitro study suggests a therapeutic potential of oleocanthal in treating multiple myeloma [37].

In vitro, oleocanthal inhibited all the three closely related cancer processes: tumor angiogenesis, growth and metastasis. It inhibited proliferation, migration, invasion, in melanoma cells and angiogenesis in human umbilical vascular endothelial cells as measured by immunohistochemical staining of Ki-67 and CD31. Oleocanthal suppressed signal transducer and activator of transcription 3 phosphorylation (STAT3) down regulated its target genes, including Mcl-1, Bcl-xL, MMP-2, MMP-9, VEGF, which are involved in apoptosis, invasion and angiogenesis of melanoma [38].

Conclusion

Certainly there is strong evidence that oleocanthal is an effective anti-inflammatory agent and demonstrates pharmacological actions *in vitro*. In spite of this we should bear in mind that oleocanthal is normally contained in olive oil with other compounds and may function with them to exert the anti-inflammatory, anti-oxidant and other beneficial effects mentioned in this review. Further studies *in vitro* and *in vivo* are also necessary to establish oleocanthal as a pharmacological agent. Meanwhile there is no doubt that Virgin olive oil intake is associated with a lot of health benefits.

References

1. Caramia G, Gori A, Valli E, Cerretani L. Virgin olive oil in preventive medicine: From legend to epigenetics. Eur. J. Lipid Sci. Technol. 2012; 114:375-388.
2. Beauchamp GK, Keast RS, Morel D, Lin J, Pika J, Han Q, *et al*. Phytochemistry: Ibuprofen-like activity in extra-

virgin olive oil. Nature. 2005; 437:45-46.
3. Cicerale S, Conlan XA, Barnett NW, Keast RS. The concentration of oleocanthal in olive oil waste. Nat Prod Res. 2011; 25(5):542-8.
4. Karkoula E, Skantzari A, Melliou E, Magiatis P. Quantitative measurement of major secoiridoid derivatives in olive oil using qNMR. Proof of the artificial formation of aldehydic oleuropein and ligstroside aglycon isomers. J. Agric. Food Chem. 2014; 62:600-607
5. Karkoula E, Skantzari A, Melliou E, Magiatis P. Direct measurement of oleocanthal and oleacein levels in olive oil by quantitative ^{1}H-NMR. Establishment of a new index for the characterization of extra virgin olive oils. J. Agric. Food Chem. 2012; 60:11696-11703.
6. Peyrot des Gachons C, Uchida K, Bryant B, Shima A, Sperry JB, Dankulich-Nagrudny L *et al.* Unusual pungency from extra-virgin olive oil is attributable to restricted spatial expression of the receptor of oleocanthal. J Neurosci. 2011-19; 31(3):999-1009.
7. Scotece M, Conde J, Abella V, Lopez V, Pino J, Lago F, *et al.* New drugs from ancient natural foods. Oleocanthal, the natural occurring spicy compound of olive oil: a brief history. Drug Discov Today. 2015; 20(4):406-10.
8. Virruso C, Accardi G, Colonna-Romano G, Candore G, Vasto S, Caruso C. Nutraceutical properties of extra-virgin olive oil: a natural remedy for age-related disease? Rejuvenation Res. 2014; 17(2):217-20.
9. Lucas L, Russell A, Keast R. Molecular mechanisms of inflammation. Anti-inflammatory benefits of virgin olive oil and the phenolic compound oleocanthal. Curr Pharm Des. 2011; 17(8):754-68.
10. Iacono A, Gómez R, Sperry J, Conde J, Bianco G, Meli R, *et al.* Effect of oleocanthal and its derivatives on inflammatory response induced by LPS in chondrocyte cell line. Arthritis Rheum. 2010; 62:1675-1682.
11. El-Shinnawi U, Soory M. Actions of Adjunctive Nutritional Antioxidants in Periodontitis and Prevalent Systemic Inflammatory Diseases. Endocr Metab Immune Disord Drug Targets. 2015; 15(4):261-76.
12. Bennett SM, Hayes JE. Differences in the chemesthetic subqualities of capsaicin, ibuprofen, and olive oil. Chem Senses. 2012; 37(5):471-8.
13. Espey MG, Miranda KM, Feelisch M, Fukuto J, Grisham MB, Vitek MP, Wink DA. Mechanisms of cell death governed by the balance between nitrosative and oxidative stress. Ann. N. Y. Acad. Sci. 2000; 899:209-22.
14. Procházková M, Zanvit P, Doležal T, Prokešová L, Kršiak M. Increased gene expression and production of spinal cyclooxygenase 1 and 2 during experimental osteoarthritis pain. Physiol. Res. 2009; 58:419-425.
15. Scotece M, Gómez R, Conde J, Lopez V, Gómez-Reino JJ, Lago F, *et al*. Further evidence for the anti-inflammatory activity of oleocanthal: inhibition of MIP-1α and IL-6 in J774 macrophages and in ATDC5 chondrocytes. Life Sci. 2012-10; 91(23-24):1229-35.
16. Rigacci S, Stefani M. Nutraceuticals and amyloid neurodegenerative diseases: a focus on natural phenols. Expert Rev Neurother. 2015; 15(1):41-52. doi: 10.1586/14737175.2015.986101.
17. Rodríguez-Morató J, Xicota L, Fitó M, Farré M, Dierssen M, de la Torre R. Potential role of olive oil phenolic compounds in the prevention of neurodegenerative diseases. Molecules. 2015-13; 20(3):4655-80.
18. Monti MC, Margarucci L, Riccio R, Casapullo A. Modulation of tau protein fibrillization by oleocanthal. J Nat Prod. 2012-28; 75(9):1584-8.
19. Monti MC, Margarucci L, Tosco A, Riccio R, Casapullo A. New insights on the interaction mechanism between tau protein and oleocanthal, an extra-virgin olive-oil bioactive component. Food Funct. 2011; 2(7):423-8.
20. Qosa H, Batarseh YS, Mohyeldin MM, El Sayed KA, Keller JN, Kaddoumi A. Oleocanthal enhances amyloid-β clearance from the brains of TgSwDI mice and in vitro across a human blood-brain barrier model. ACS Chem Neurosci. 2015-18; 6(11):1849-59.
21. AH, Qosa H, Busnena BA, El Sayed KA, Kaddoumi A. Olive-oil-derived oleocanthal enhances β-amyloid clearance as a potential neuroprotective mechanism against Alzheimer's disease: in vitro and in vivo studies. ACS Chem Neurosci. 2013-19; 4(6):973-82.
22. Pitt J, Roth W, Lacor P, Smith AB 3r, Blankenship M, Velasco P, De Felice F, *et al* Alzheimer's-associated Abeta oligomers show altered structure, immunoreactivity and synaptotoxicity with low doses of oleocanthal. Toxicol Appl Pharmacol. 200915; 240(2):189-97.
23. Gardener S, Gu Y, Rainey-Smith SR, Keogh JB, Clifton PM, Mathieson SL, *et al*. Adherence to a Mediterranean diet and Alzheimer's disease risk in an Australian population. Transl. Psychiatry. 2012; 2:e164.
24. Scarmeas N, Luchsinger JA, Schupf N, Brickman AM, Cosentino S, Tang MX, Stern Y. Physical activity, diet, and risk of Alzheimer disease. J. Am. Med. Assoc. 2009; 302:627-637.
25. De Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Mediterranean dietary pattern in a randomized trial: Prolonged survival and possible reduced cancer rate. Arch. Intern. Med. 1998; 158:1181-1187
26. LeGendre O, Breslin PA, Foster DA. (-)-Oleocanthal rapidly and selectively induces cancer cell death via lysosomal membrane permeabilization. Mol Cell Oncol. 2015; 2(4):e1006077.
27. Khanfar MA, Bardaweel SK, Akl MR, El Sayed KA. Olive Oil-derived Oleocanthal as Potent Inhibitor of Mammalian Target of Rapamycin: Biological Evaluation and Molecular Modeling Studies. Phytother Res. 2015; 29(11):1776-82.
28. Boland G, Butt I, Prasad R, Knox W, Bundred N. COX-2 expression is associated with an aggressive phenotype in ductal carcinoma in situ. Br. J. Cancer. 2004; 90:423-429.
29. Subbaramaiah K, Norton L, Gerald W, Dannenberg A. Cyclooxygenase-2 is overexpressed in HER-2/neu-positive breast cancer. J. Biol. Chem. 2002; 277:18649-18657.
30. Masferrer J, Leahy K, Koki A, Zweifel B, Settle S, Woerner B, Edwards D, Flickinger A, Moore R, Seibert K. Antiangiogenic and antitumor activities of cyclooxygenase-2 inhibitors. Cancer Res. 2000; 60:1306-1311.
31. Elnagar AY, Sylvester PW, El Sayed KA. Oleocanthal as a c-Met inhibitor for the control of metastatic breast and prostate cancers. Planta Med. 2011; 77(10):1013-9.
32. Abuznait AH, Qosa H, O'Connell ND, Akbarian-Tefaghi J, Sylvester PW, El Sayed KA, Kaddoumi A. Induction of expression and functional activity of P-glycoprotein efflux transporter by bioactive plant natural products. Food Chem Toxicol. 2011; 49(11):2765-72.
33. Akl MR, Ayoub NM, Mohyeldin MM, Busnena BA,

Foudah AI, Liu YY, Sayed KA. Olive phenolics as c-Met inhibitors: (-)-Oleocanthal attenuates cell proliferation, invasiveness, and tumor growth in breast cancer models. PLoS One. 2014-21; 9(5):e97622.
34. Busnena BA, Foudah AI, Melancon T, El Sayed KA.Olive secoiridoids and semisynthetic bioisostere analogues for the control of metastatic breast cancer. Bioorg Med Chem. 2013-1; 21(7):2117-27.
35. Cassiano C, Casapullo A, Tosco A, Monti MC, Riccio R. In Cell Interactome of Oleocanthal, an Extra Virgin Olive Oil Bioactive Component. Nat Prod Commun. 2015; 10(6):1013.
36. Margarucci L, Monti MC, Cassiano C, Mozzicafreddo M, Angeletti M, Riccio R, *et al.* Chemical proteomics-driven discovery of oleocanthal as an Hsp90 inhibitor. Chem Commun (Camb). 2013-4; 49(52):5844-6.
37. Scotece M, Gómez R, Conde J, Lopez V, Gómez-Reino JJ, Lago F, *et al*. Oleocanthal inhibits proliferation and MIP-1α expression in human multiple myeloma cells. Curr Med Chem. 2013; 20(19):2467-75.
38. Gu Y, Wang J, Peng L. Oleocanthal exerts anti-melanoma activities and inhibits STAT3 signaling pathway. Oncol Rep. 2017; 37(1):483-491.