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Oleocanthal: A Naturally Occurring Anti-Inflammatory Agent in Virgin Olive Oil

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1. Introduction

Research on the non-steroidal anti-inflammatory olive oil phenolic, (-)- decarboxymethyl ligstroside aglycone (more commonly known as oleocanthal) has supported speculation that this compound may confer some of the health benefits associated with the traditional Mediterranean diet. Oleocanthal elicits a peppery, stinging sensation at the back of the throat similar to that of the non-steroidal anti-inflammatory drug (NSAID), ibuprofen (Beauchamp et al., 2005) and this localized irritation is due to stimulation of the transient receptor potential cation channel A1 (TRPA1) (Peyrot des Gachons et al., 2011). The perceptual similarity between oleocanthal and ibuprofen spurred the hypothesis that these two compounds may possess similar pharmacological properties. Further investigation demonstrated that oleocanthal inhibits inflammation in the same way as ibuprofen, and moreover, is substantially more potent on a equimolar basis (Beauchamp et al., 2005). Subsequent studies have shown that oleocanthal exhibits various modes of action in reducing inflammatory-related disease, including neuro-degenerative disease (Pitt et al., 2009, Li et al., 2009), joint-degenerative disease (Iacono et al., 2010) and specific cancers (Elnagar et al., 2011). Therefore, long term consumption of extra virgin olive oil (EVOO) containing oleocanthal may contribute to the health benefits associated with the Mediterranean dietary pattern. This chapter summarizes the current knowledge on oleocanthal, in terms of its sensory and physiological properties, its extraction from the oil matrix and subsequent identification and quantification, and finally the factors that may influence the concentration of oleocanthal in EVOO.

2. Olive oil, a hallmark of the Mediterranean diet

The health benefits of following a Mediterranean eating pattern were first acknowledged in the Seven Countries Study (Keys, 1970). Thereafter over a period of 30 years, a number of investigators have reported that the Mediterranean diet is associated with low rates of degenerative diseases such as cardiovascular disease (CVD) (Estruch et al., 2006, Pitsavos et al., 2005), coronary heart disease (CHD) (Fung et al., 2009), stroke (Fung et al., 2009), certain types of cancers (La Vecchia, 2004, Dixon et al., 2007), diabetes (Martinez-Gonzalez et al., 2008), Alzheimer's disease (Scarmeas et al., 2009) and non-alcoholic fatty liver disease (Fraser et al., 2008). Research has also demonstrated that Mediterranean populations have

increased life expectancy (Hu, 2003, Visioli et al., 2005, Trichopoulou et al., 2005), reduced risk of developing disorders such as metabolic syndrome (Tortosa et al., 2007, Babio et al., 2008) and have decreased levels of systematic inflammation (Dai et al., 2009, Fragopoulou et al., 2010, Panagiotakos et al., 2009).

The traditional Mediterranean diet is defined as the pattern of eating observed in the olive growing areas of the Mediterranean region, namely Greece and Southern Italy in the 1960s. An integral component of this dietary pattern is the consumption of EVOO (Stark and Madar, 2002, Kok and Kromhout, 2004). EVOO, the pillar of Mediterranean recipes, is commonly incorporated into cooked dishes as well as in salads. Typically, the intake of EVOO ranges from 25 to 50 ml per day in the Mediterranean diet (Corona et al., 2009). Therefore, the apparent health benefits have been partially attributed to the dietary consumption of EVOO by Mediterranean populations. Figure 1 displays the Mediterranean diet pyramid featuring EVOO as a core component of this dietary pattern.

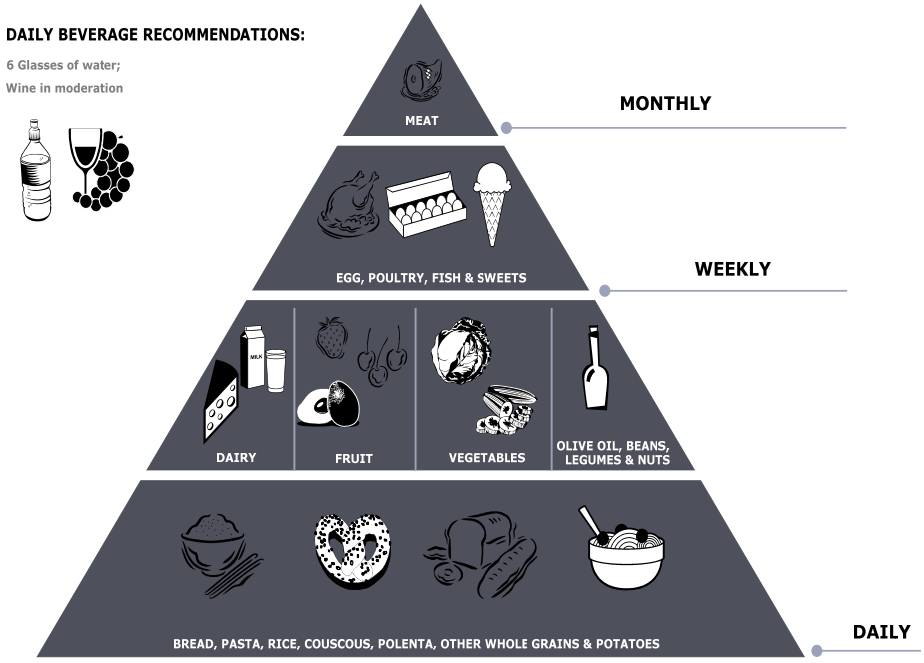

Fig. 1. Food pyramid reflecting the traditional Mediterranean diet. As depicted, EVOO is an integral food component of this diet residing in the consume 'daily' food group.

3. Olive oil phenolic compounds

Historically, the health promoting properties of EVOO were attributed to the high concentration of monounsaturated fatty acids (MUFAs), in particular oleic acid, contained in EVOO. However other seed oils (i.e. sunflower, soybean, and rapeseed), which also contain high concentrations of oleic acid, do not exhibit the same health benefits as EVOO (López-

Miranda et al., 2010, Harper et al., 2006, Aguilera et al., 2004). In addition to oleic acid, EVOO contains a minor, yet significant phenolic fraction that other seed oils lack and this fraction has generated much interest regarding its health promoting properties.

Currently, 36 phenolic compounds have been identified in EVOO and studies (human, animal, *in vivo* and *in vitro*) have demonstrated that olive oil phenolics have positive effects on certain physiological parameters such as plasma lipoproteins, oxidative damage, inflammatory markers, platelet and cellular function, antimicrobial activity, and bone health (for review see (Cicerale et al., 2010)), possibly reducing the risk of chronic disease development.

4. Discovery of oleocanthal

The phenolic compound (-)- decarboxymethyl ligstroside aglycone was first reported in EVOO by Montedoro *et al.* (Montedoro and Servili, 1993) in 1993 (Figure 2). A decade after its discovery, Andrewes and colleagues (Andrewes et al., 2003) reported that decarboxymethyl ligstroside aglycone was responsible for the throat irritation and pungency elicited by some EVOOs. In 2005, Beauchamp *et al.* (Beauchamp et al., 2005) confirmed that the phenolic compound, decarboxymethyl ligstroside aglycone was indeed responsible for the throat irritation elicited by EVOOs post-ingestion. This confirmation was carried out by isolating the compound from various EVOOs and measuring the throat irritation elicited. However, at that stage, there was a possibility that co-elution of a minor component or a mixture of components along with decarboxymethyl ligstroside aglycone may collectively cause the localized throat irritation. Therefore, the authors chemically synthesized decarboxymethyl ligstroside aglycone and dissolved it in non-irritating corn oil. Throat irritation elicited by the synthesized decarboxymethyl ligstroside aglycone was found to be dose-dependent on the concentration of this phenolic in corn oil and mimicked that of EVOO containing this compound naturally. Decarboxymethyl ligstroside aglycone was thus deemed the sole throat irritant in EVOO and was named oleocanthal (*oleo* for olive, *canth* for sting, and *al* for aldehyde) (Beauchamp et al., 2005).

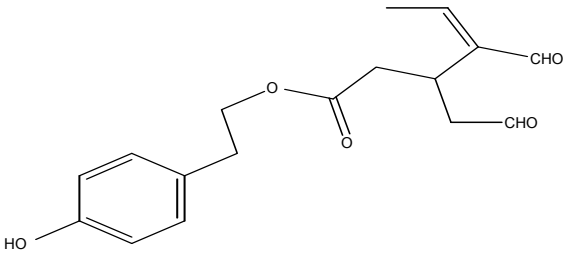

Fig. 2. Oleocanthal structure

5. Sensory properties of oleocanthal

The intake of EVOO is often associated with a peppery sting that is localized to the oropharyngeal region in the oral cavity (Figure 3). There is wide inter-individual variation in sensitivity to oleocanthal which can range from a slight irritation in the throat, to an irritation that is strong enough to produce a cough in those highly sensitive. Of particular

interest is the spatial location of irritation produced by oleocanthal. Irritating, pungent compounds often aggravate all regions in the oral cavity rather than acting on one localized area (Peyrot des Gachons et al., 2011), which implies a sensory receptor specific to oleocanthal exists in the oropharyngeal region of the oral cavity. Recent investigations have indeed verified that the TRPA1 is the receptor linked to oleocanthal and the anatomical location of this receptor has been found in the oropharyngeal region of the oral cavity (Peyrot des Gachons et al., 2011).

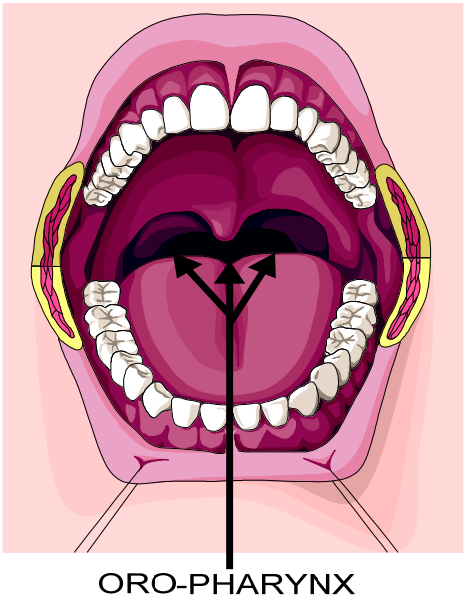

Fig. 3. Oleocanthal irritation occurs solely in the oropharyngeal region (area shaded in black) of the oral cavity.

A large variability among subjects in the perceived irritation from oleocanthal has been noted (Cicerale et al., 2009a). Such individual variation in perception of oleocanthal may be related directly to the quantity of the TRPA1 receptor, as has been reported for other oral stimuli such as the bitter compounds: 6-n-propylthiouracil (PROP) and phenylthiocarbamide (PTC) (Hansen et al., 2006), which activate the TAS2R38 bitter receptor (Hayes et al., 2011). The important link between the perceptual aspects of oleocanthal and health benefits is the notion that variation in sensitivity to oleocanthal irritation may relate to potential differences in sensitivity to the anti-inflammatory action of this compound. However, further research is required to investigate this.

6. Physiological properties of oleocanthal and its putative health benefits

Research conducted by Beauchamp and colleagues (Beauchamp et al., 2005) demonstrated that oleocanthal inhibits cyclooxygenase (COX) enzymes in a dose-dependent manner, mimicking the anti-inflammatory action exerted by ibuprofen. Cyclooxygenase 1 and 2 (COX 1 and COX 2) enzymes are responsible for the conversion of arachidonic acid to

prostaglandins and thromboxane which are produced in response to inflammatory or toxic stimuli. COX 1 and COX 2 can be harmful to the body. In particular, COX 2 has been implicated in the pathogenesis of several cancers in both human and animal studies (Harris et al., 2003, Boland et al., 2004, Subbaramaiah et al., 2002, Ristimäki et al., 2002), and may also play a role in atherosclerosis (Chenevard et al., 2003). The novel findings presented by Beauchamp and colleagues (Beauchamp et al., 2005) demonstrate that oleocanthal not only mimics the mode of ibuprofen action, it exhibits increased potency (compared with ibuprofen) in inhibiting COX 1 and COX 2 enzymes at equimolar concentrations. For instance, oleocanthal (25 μM) inhibited 41-57% of COX activity in comparison to ibuprofen (25 μM) which inhibited only 13-18% of COX activity.

Moreover, Beauchamp and colleagues (Beauchamp et al., 2005) put forth the suggestion that chronic ingestion of small quantities of oleocanthal via EVOO consumption, may be responsible, in part, for the lowered prevalence of disease associated with the Mediterranean diet. Thus, if an olive oil consumer ingests around 50 g of EVOO a day containing approximately 200 μg/kg of oleocanthal, the person would ingest approximately 10 mg/day of oleocanthal. This would equate to a relatively low (10%) equivalent dose of ibuprofen (recommended for adult pain relief). Chronic low doses of ibuprofen and other COX inhibitors such as aspirin are known to have important health benefits in the prevention of cancer development (e.g. colon and breast) (Garcia-Rodriguez and Huerta-Alvarez, 2001, Harris et al., 2006) and CVD (Hennekens, 2002). Therefore, long term ingestion of oleocanthal via EVOO consumption may contribute to a reduction in chronic disease development and certainly emerging evidence supports this notion.

Finally, it is important to note oleocanthal's bioavailability within the body. Only one study has investigated this to date. A study by Garcia-Villalba et al. (Garcia-Villalba et al., 2010) noted that oleocanthal was readily metabolized however further studies are required to gain a more thorough understanding of the metabolism and bioavailability of this compound.

6.1 Oleocanthal and neuro-degenerative disease

Ibuprofen is known to exert beneficial effects on markers of neuro-degenerative disease (Van Dam et al., 2008) and based on the similar oral irritant properties and shared anti-inflammatory mode of action via COX inhibition, oleocanthal was investigated for potential neuro-protective properties. Li and collegues (Li et al., 2009) presented significant findings demonstrating that oleocanthal inhibits tau fibrillization *in vitro* by forming an adduct with PHF6 peptide, which is a VQIXXK motif that resides in the microtubule binding region, and is crucial in the formation of tau fibrils (Li and Virginia, 2006) Hyperphosphorylated tangles of tau are lesions that are observed in neuro-degenerative disease (i.e. Alzheimer's disease) and PHF6 enables the phosphorylation of tau, thus the convalent modification of PHF6 peptide disrupts tau-tau interaction and subsequent fibril formation (Li et al., 2009) (Figure 4). B-amyloid peptides (Aβ) are another type of lesion that are characteristic of Alzheimer's disease (Guela et al., 1998), as Aβ derived diffusible ligands (ADDLs) are neurotoxic factors proposed to instigate the onset of Alzheimer's disease (Pitt et al., 2009). Pitt and colleagues (2009) demonstrated that *in vitro*, oleocanthal alters the structure of ADDLs and augments antibody clearance of ADDLs, therefore protecting hippocampal neurons from ADDL toxicity. This data supports research showing a 40% decrease in Alzheimer's disease in populations consuming a Mediterranean style diet (Scarmeas et al., 2009).

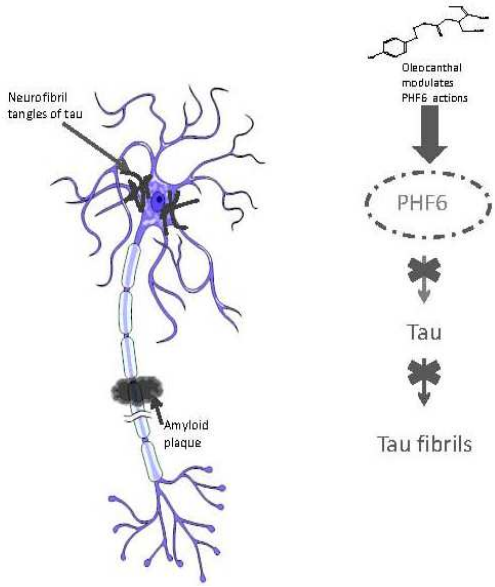

Fig. 4. Oleocanthal inhibits tau fibrilisation by covalently modifying the PHF-6 peptide which is crucial for the formation of tau fibrils. The fibrilisation of tau leads to neurofibrillary tangles which are inherently associated with neurodegenerative diseases such as Alzheimer's disease.

6.2 Oleocanthal and joint-degenerative disease

In vitro research draws attention to oleocanthal, as a potential therapeutic compound that may be of interest in the quest to find suitable natural NSAIDs for the treatment of joint degenerative disease. Pro-inflammatory cytokines up-regulate the synthesis of cartilage to degrading enzymes, and stimulate nitric oxide (NO) production (Scher et al., 2007), as well as increase prostaglandin PGE_2 production, which have all been implicated in the development of arthritic pain and thus joint-degenerative disease. COX enzymes are a catalyst for the formation of prostaglandins and have also been reported to be highly expressed in arthritic spine in an animal model (Procházková et al., 2009). Therefore, oleocanthal may influence arthritic pain through inhibition of PGE_2 synthesis accompanying COX inhibition.

NO plays an integral role in joint-degenerative disease and the stable end product of NO, nitrite (NO_2), is significantly expressed in arthritic synovial fluid (Iacono et al., 2010). In osteoarthritis arthritis (OA) pathogenesis, diseased cartilage synthesizes NO spontaneously from diseased chrondocytes (Tung et al., 2002). NO is biosynthesized by nitric oxide synthase (NOS). Another form of NOS is inducible NOS (iNOS) which is largely responsible for the inflammatory actions of NOS (Espey et al., 2000) (Figure 5). Iacano and collegues (2010) have shown that oleocanthal and synthesized derivatives, decrease production of iNOS protein expression in LPS challenged murine chondrocytes, dose dependently, further highlighting the anti-inflammatory actions of oleocanthal and the pharmacological potential. Also, as oleocanthal mediates prostaglandin synthesis via inhibitory actions on COX enzymes, it is possible that oleocanthal may exert pharmacological actions in the treatment of both rheumatoid arthritis and osteoarthritis through COX inhibition.

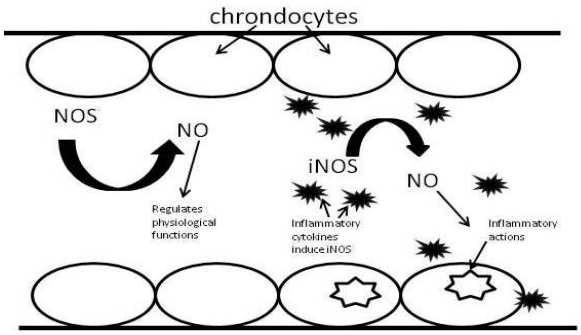

Fig. 5. Nitric oxide (NO) derived from nitric oxide synthase (NOS), functions as a neurotransmitter and vasodilator, and is important in normal physiological responses. Inducible nitric oxide synthase (iNOS) is a third form of NOS and is not present in resting cells, but rather is induced by inflammatory cytokines. NO produced from iNOS promotes inflammation in chrondocytes and is associated with cartilage degenerative diseases such as osteoarthritis.

6.3 Oleocanthal and cancer

Recent evidence demonstrates that oleocanthal may exert therapeutic properties against the pathogenesis of c-Met kinase induced malignancies. Elnagar and colleagues (Elnagar et al., 2011) have reported that oleocanthal possesses anti-proliferative effects in human breast and prostate cancer lines (Elnagar et al., 2011). Also Khanal and collegues (Khanal et al., 2011) recently showed that oleocanthal has an anti-proliferative effect and prevents tumour induced cell transformation in mouse epidermal JB6 Cl41cells. The mechanism of action in which oleocanthal achieved this was via the inhibition of extracellaullar signal-regulated kinases 1/2 and p90RSK phosphorylation. Furthermore, oleocanthal has also been shown to promote cell apoptosis by activating caspase-3 and poly-adenosine diphosphate-ribose polymerase, the phosphorylation of p53 (Ser15), and also induced fragmentation of DNA in HT-29 cells derived from human colon adenocarcinoma (Khanal et al., 2011). These findings suggest that oleocanthal may have potential as a therapeutic agent in the inhibition of carcinoma progression and supports substantial evidence that populations residing in the Mediterranean region have a reduced incidence of prostate, breast, lung and gastrointestinal cancer (Trichopoulou et al., 2000, La Vecchia, 2004, Fortes et al., 2003, Dixon et al., 2007). It is important to note that while there is strong evidence that oleocanthal is an effective anti-inflammatory agent and demonstrates pharmacological characteristics *in vitro,* future *in vivo* studies are required to fully elucidate the efficacy of this natural NSAID. Caution is required when extrapolating results from a single compound out of the matrix in which it normally exists. Oleocanthal is one of many phenolic compounds contained in EVOO, and it is probable that the synergistic and interactive actions of these phenolics combined are responsible for the low incidence of chronic inflammation associated with EVOO intake. Furthermore, the bioavailability of oleocanthal needs to be firmly established in future research to consolidate the pharmacological potential of this compound.

7. Extraction, identification and quantification of oleocanthal

The method used for the extraction, identification and quantification of oleocanthal described herein, is selective for oleocanthal and was developed by Beauchamp and co-workers (Beauchamp et al., 2005). More recently, this method was adapted and involves the quantification of oleocanthal using an internal standard (ISTD), 3,5 dimethoxyphenol (Beauchamp et al., 2005, Cicerale et al., 2009b).

The extraction of oleocanthal from the oil matrix involves liquid-liquid partitioning using both hexane and acetonitrile, whereby the phenolic fraction partitions into the acetonitrile phase. Acetonitrile is then removed and the dried down extract is dissolved in methanol:water and analyzed by HPLC. Separation of the oleocanthal phenolic compound is carried out using a HPLC system with a diode array detector set to 278 nm. A reverse phase-C18 column (250 mm × 4.6 mm ID, 5 µm) is used for the separation at a constant temperature of 25°C using the gradients listed in Table 1. A flow rate of 1 ml/min is used, and the injection volume is 20 µl. See Figure 6 for HPLC chromatogram.

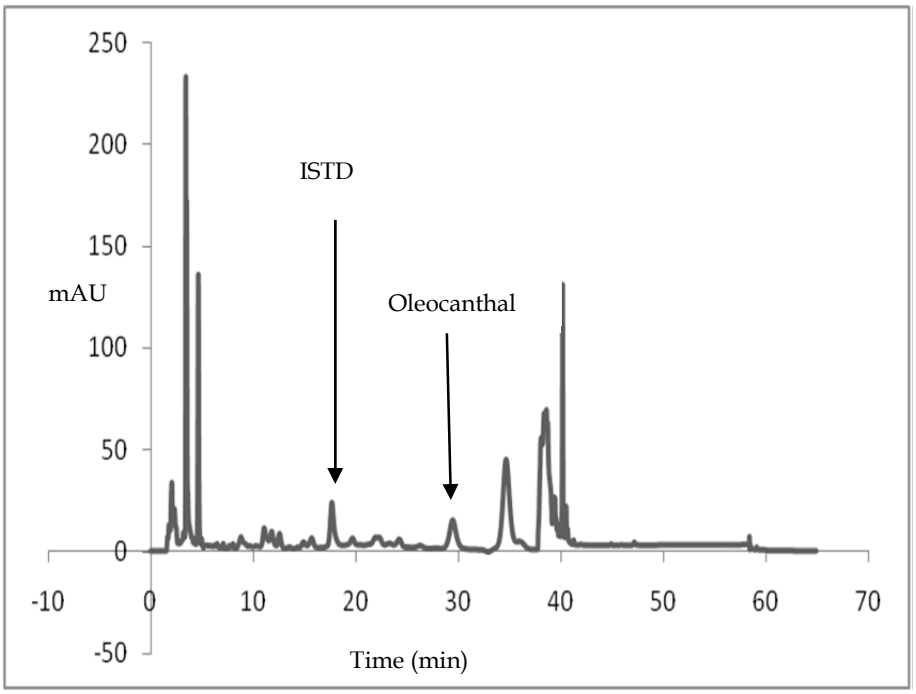

Fig. 6. HPLC chromatogram of olive oil phenolic extract containing oleocanthal and 3,5 dimethoxyphenol (ISTD) (Cicerale et al., 2009b).

Via mass spectrometry (6210 MSDTOF), oleocanthal is further identified under the following conditions: drying gas, nitrogen (N_2) (7 mL^{-1}, 350°C); nebulizer gas, N_2 (15 psi); capillary voltage 4.0 kV; vaporizer temperature, 350°C; and cone voltage, 60 V. Figure 7 displays the negative ion mass spectrum of oleocanthal with the characteristic $[M-H]^-$ ion at *m/z* 303.12 highlighted.

Time	Gradient
0-35 min	75% water, 25% acetonitrile
36-55 min	90% acetonitrile, 10% methanol
56-65 min	75% water, 25% acetonitrile

Table 1. Mobile phase gradient for oleocanthal separation.

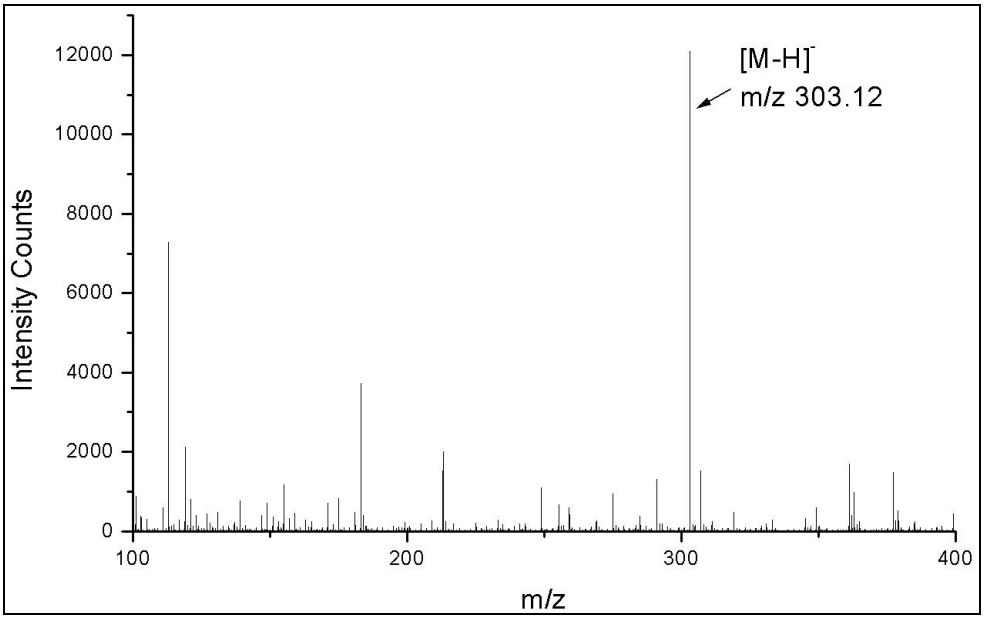

Fig. 7. Negative ion mass spectrum of oleocanthal with the characteristic $[M-H]^-$ ion at *m/z* 303.12 (Cicerale et al., 2009b).

8. Oleocanthal concentration in olive oil and factors which may affect its concentration

Oleocanthal concentration in EVOO is highly variable, ranging from as little as 0.2 mg/kg to as high as 498 mg/kg (Gomez-Rico et al., 2006). Such variation in oleocanthal concentration amongst differing EVOOs may be due to multiple factors that have the capacity to modify the concentration of this compound (Carrasco-Pancorbo et al., 2005). These factors include: method of phenolic extraction and quantification, geographic region of olive growth, olive tree cultivar, agricultural techniques applied to cultivate olives, olive maturity, processing of the olives to oil, storage of oil, and domestic heat application to oil.

8.1 Extraction and quantification

The analytical method used to quantify phenolics present in EVOO has an influence on the reported concentration and therefore is an important consideration when interpreting and comparing the data of such investigations (Carrasco-Pancorbo et al., 2005). Regarding the

analysis of oleocanthal, Beauchamp and colleagues (Beauchamp et al., 2005) in collaboration with Impellizzeri et al. (Impellizzeri and Lin, 2006), developed an extraction and quantification method specific for this compound. Utilizing this method, Impellizeri et al. (Impellizzeri and Lin, 2006) and Franconi et al. (Franconi et al., 2006) found the concentration of oleocanthal ranged between 8.3 ± 4.0 and 189.9 ± 2.7 mg/kg. An adaption of the Beauchamp and co-workers' (Beauchamp et al., 2005) methodology, was also utilized in studies by Cicerale and colleagues (Cicerale et al., 2009a, Cicerale et al., 2009b, Cicerale et al., 2011b, Cicerale et al., 2011a). The resultant oleocanthal concentrations in these investigations were similar to those found by Franconi et al. (Franconi et al., 2006) and Impellizzeri et al. (Impellizzeri and Lin, 2006) (53.9 ± 7.7 to 152.2 ± 10.5 mg/kg). However, a number of methods not specific for oleocanthal have also been used to quantify this compound and may account partially for the large variation in oleocanthal concentration observed (5.0 ± 0.3 – 498.0 ± 47.0 mg/kg) (Vierhuis et al., 2001, Servili et al., 2007b, Servili et al., 2007a, Romero et al., 2002, Morello et al., 2004, Tovar et al., 2001, De Stefano et al., 1999, Montedoro et al., 1992, Gomez-Alonso et al., 2003, Gomez-Rico et al., 2006, Allouche et al., 2007)

8.2 Geographic region

Geographic region in which olives are grown has been shown to be an important factor in regards to phenolic composition and concentration in general (Vinha et al., 2005, Cerretani et al., 2005). Beauchamp et al. (Beauchamp et al., 2005) demonstrated that EVOOs produced in differing countries had variable oleocanthal concentrations. For instance, EVOO produced in the U.S.A., contained a low concentration of oleocanthal (22.6 ± 0.6 mg/kg), however EVOOs produced in Italy contained some of the highest quantities of this compound (up to 191.8 ± 2.7 mg/kg).

8.3 Cultivar

Several studies have demonstrated differences between olive cultivar and oleocanthal concentration in the oil produced. In one study, the Coratina cultivar EVOO contained 78.2 ± 0.5 mg/kg oleocanthal, whereas the Oliarola cultivar EVOO contained 21.0 ± 0.8 mg/kg oleocanthal, a 3-fold difference (De Stefano et al., 1999). In another study, EVOO produced from the Frantoio cultivar had an oleocanthal concentration of 43.8 ± 3.1 mg/kg, whilst EVOO obtained from the Coratina cultivar, contained a 2-fold higher oleocanthal content at 92.8 ± 7.8 mg/kg (Servili et al., 2007b). A study by Franconi and colleagues (Franconi et al., 2006) also showed significant differences in oleocanthal concentration amongst differing olive cultivars. For instance, an oleocanthal concentration of 8.3 ± 4.0 mg/kg and 53.0 ± 12.0 mg/kg in EVOOs produced from the Taggiasca and Seggianese cultivars respectively, was noted.

8.4 Agricultural methods

The concentration of phenolic compounds in EVOO is greatly affected by agricultural techniques used in the cultivation of olive fruit (Gomez-Rico et al., 2006, Ayton et al., 2007). Tovar and co-workers (Tovar et al., 2001) demonstrated that with increased irrigation applied to the olive tree, oleocanthal concentration decreased. For instance, in the EVOO obtained from the least irrigated olive trees (46 mm water per year) oleocanthal concentration was determined to be 50.9 ± 6.5 mg/kg. For the EVOO produced from highly irrigated olive trees (259 mm water per year), oleocanthal concentration was 23.1 ± 1.3 mg/kg. Gomez-Rico et al.

(Gomez-Rico et al., 2006) also demonstrated the negative effect of irrigation on oleocanthal concentration. Rain-fed olive trees produced EVOO containing higher concentrations of oleocanthal (229.0 ± 48.0 to 498 ± 47.0 mg/kg) compared to those that underwent the highest amount of irrigation (206 mm water per year), (119.0 ± 36.0 to 336.0 ± 81.0 mg/kg). Two additional studies (Romero et al., 2002, Servili et al., 2007a) are also in agreement with this data in that, they both observed a 37-38% decrease in oleocanthal concentration amongst the EVOOs from the highly irrigated olive trees compared to those least irrigated.

8.5 Olive maturation

Maturation of the olive fruit at harvest is an important predictor of the phenolic composition and concentration in EVOO. In regards to oleocanthal, one study found that with extended picking date and increased olive fruit ripeness, the concentration of oleocanthal in EVOO decreased by 43% (148.0 mg/kg to 84.0 mg/kg) over a short two month period (Morello et al., 2004). The researchers, Gomez-Rico et al. (Gomez-Rico et al., 2006) also observed a similar decrease of 20% and 54% in oleocanthal with increasing maturity index using two olive cohorts.

8.6 Processing

In general, the processing of olive fruit to oil has a substantial effect on the concentrations of phenolic compounds in EVOO (Kalua et al., 2006b, Cerretani et al., 2005, Vierhuis et al., 2001, Romero et al., 2004, Gimeno et al., 2002). EVOO produced by the traditional processing method (whereby the entire olive fruit is crushed, including the stone), was found to contain lower quantities of oleocanthal (43.8 ± 3.1 mg/kg) compared to EVOO produced by the stoning method in which the olive stone is removed before crushing (54.8 ± 3.1 mg/kg). The researchers from this study hypothesized that the differences may be due to the increased peroxidase (POD) activity that tends to accompany the crushed olive stone, which has an oxidizing effect on oleocanthal concentration (Servili et al., 2007b).

EVOO produced under nitrogen (N_2) flushing and with use of enzymatic treatment (which aids cell wall degradation and thus improves phenolic extraction) (Vierhuis et al., 2001), was found to contain oleocanthal concentrations of 31.4 ± 1.0 mg/kg. EVOO produced with no added enzymes and without nitrogen (N_2) flushing (therefore allowing oxygen (O_2) to be present) was found to contain a lower amount of oleocanthal (24.8 ± 1.9 mg/kg). EVOOs produced with use of N_2 flushing alone and enzymatic treatment alone, contained 28.4 ± 1.4 mg/kg and 29.4 ± 0.8 mg/kg oleocanthal respectively (Vierhuis et al., 2001).

EVOOs produced using two-phase centrifugation which uses no added water in the processing method, was found to contain a higher phenolic concentration compared to EVOOs obtained from three-phase centrifugation which utilizes a considerable amount of water (approximately 400 L/h) (De Stefano et al., 1999). De Stefano and et al. (De Stefano et al., 1999) found oleocanthal concentration in EVOO obtained from the two-phase centrifuge to be higher (78.2 ± 0.5 mg/kg) than that produced from the three-phase method (67.3 ± 2.6 mg/kg). The addition of water in the three-phase centrifugation method, may have a reducing effect on the more water-soluble phenolics from the oil phase during processing, thus reducing the concentration of oleocanthal in the resultant EVOO (Cicerale et al., 2009c).

8.7 Storage of EVOO

Immediately following oil extraction from the olive fruit, there is potential for the phenolic quality of the oil to decline, via oxidation catalysed by oxygen (O_2) and light (Kalua et al., 2006a, Morello, 2004). One study to date, has investigated the effect O_2, light, and storage time have on oleocanthal concentration. In this study, oleocanthal concentration decreased somewhat (15 - 37%) over a 10-month storage period, depending on the storage conditions. The largest decrease was seen in EVOO stored under exposure to O_2 and light (37%) and the smallest loss was found in the EVOO stored under O_2 and light limiting conditions (15%). Oils stored under sole exposure to O_2 or light were found to have a similar rate of oleocanthal degradation over the 10-month period (28% and 25% respectively) (Cicerale et al., 2011b).

8.8 Domestic heat application

In general, research has shown that olive oil phenolic compounds are subject to degradation upon the application of heat during cooking (Brenes et al., 2002, Gomez-Alonso et al., 2003). However, oleocanthal has demonstrated to be relatively stable upon heating when the EVOO contains a considerable quantity of this compound initially.

One study found a 20% decrease in oleocanthal (96.7 ± 8.5 to 77.5 ± 2.4 mg/kg) upon 12 frying operations (each frying operation 10 min in length, at a temperature of 180°C) (Gomez-Alonso et al., 2003). Similarly, another study observed a 24% decrease (41.5 ± 0.3 to 31.4 ± 0.1 mg/kg) in oleocanthal after heating at 180°C for 36 hr (Allouche et al., 2007). However, for EVOO which naturally contained a lower quantity of oleocanthal to begin with (7.9 ± 0.5 mg/kg), oleocanthal degradation was substantially higher at 71%. It appears that oleocanthal possesses an antioxidative effect, in that oleocanthal is able to withstand heating and therefore protect itself to a greater degree when there is a higher concentration of it in EVOO.

Cicerale and co-workers (Cicerale et al., 2009b) also demonstrated oleocanthal to be stable upon heating at high temperatures (240°C) for extended periods of time (up to 90 min). The authors postulated that the minimal degradation of oleocanthal may be partially due to the chemical structure of this compound and subsequent antioxidant activity. The antioxidant capacity of phenolic compounds is dependent upon the number of hydroxyl groups bonded to the aromatic ring (Sroka and Cisowski, 2003). When free radicals are produced through oxidation, phenolic compounds with a higher number of hydroxyls and therefore increased antioxidant capacity, quickly diminish because they react rapidly with lipid radicals and are therefore consumed (Gomez-Alonso et al., 2003). Oleocanthal possesses one hydroxyl group. Moreover, the site of bonding and mutual position of hydroxyls in the aromatic ring was also postulated to play a role in the antioxidant potential of phenolic compounds (Sroka and Cisowski, 2003, Rice-Evans et al., 1996). Rice-Evans and co-workers (Rice-Evans et al., 1996) reported that a hydroxyl group in the *ortho* position in the aromatic ring results in increased antioxidant capacity compared to compounds with hydroxyl groups in the *meta* and *para* positions. Oleocanthal contains its one hydroxyl group in the *para* position. These structural features may help in explaining why a minimal degradation of oleocanthal was observed (Cicerale et al., 2009c).

9. Perspectives and future directions

In summary, EVOO a key component of the Mediterranean diet contains a number of phenolics, one being oleocanthal. The unique sensory qualities and anti-inflammatory actions

of oleocanthal, have prompted research to further verify its therapeutic potential. Oleocanthal has been shown, *in vitro*, to exert beneficial physiological effects in terms of neuro-degenerative disease, joint-degenerative disease and cancer. Therefore, it has been postulated that the long term ingestion of this compound via EVOO consumption may have significant health promoting action over time, thereby reducing the development of chronic disease.

However, the studies conducted on the health promoting potential of oleocanthal have involved *in vitro* investigations and it is difficult to extrapolate data from *in vitro* studies to actual physiological benefits. *In vivo* research is therefore required to substantiate the *in vitro* findings. Furthermore, the bioavailability of oleocanthal has not been adequately investigated. To date, only one study has reported on the post-ingestive fate of oleocanthal, noting that it was readily metabolized however the mechanism was not investigated. The degree to which oleocanthal is metabolized is an important consideration when reviewing the health benefits associated with ingestion, and further research on this is warranted. The link between the perceptual aspects of oleocanthal and health benefits is the notion that variation in sensitivity to oleocanthal oro-pharyngeal irritation may relate to potential differences in sensitivity to the anti-inflammatory action of this compound and this is also worthy of future investigations.

Finally, it was not the purpose of this overview to attribute the health benefits of the Mediterranean diet solely to one component and we did not aim to credit oleocanthal as being the lone therapeutic agent contained in EVOO. Other constituents of the Mediterranean diet and EVOO will contribute, either with independent actions, or in a synergistic and complementary manner to impart beneficial health effects (Lucas et al., 2011, Fogliano and Sacchi, 2006). However, the studies conducted to date investigating the pharmacological actions of oleocanthal are encouraging and show that this compound possesses substantial health benefiting properties. Further research will no doubt provide new insight into the pharmacological potential of oleocanthal and assess the role that oleocanthal has in the clinical treatment of chronic disease.

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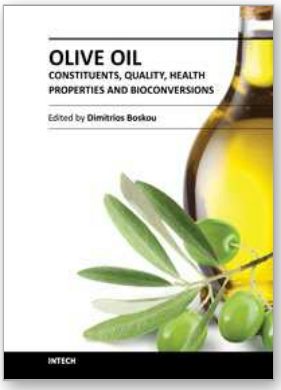

Olive Oil - Constituents, Quality, Health Properties and Bioconversions

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The health-promoting effects attributed to olive oil, and the development of the olive oil industry have intensified the quest for new information, stimulating wide areas of research. This book is a source of recently accumulated information. It covers a broad range of topics from chemistry, technology, and quality assessment, to bioavailability and function of important molecules, recovery of bioactive compounds, preparation of olive oil-based functional products, and identification of novel pharmacological targets for the prevention and treatment of certain diseases.

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