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Review Article

Oleocanthal and Human Health – An Overview

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Abstract

The chemistry of oleocanthal (OCL) and its presence in, and extraction from, extra virgin olive oil (EVOO) is briefly discussed. The health benefits of OCL are reviewed, notably its nonsteroidal anti-inflammatory drug activity shown by *in vitro* studies to modulate NO production in chondrocytes. Consequently, OCL is a promising agent for the treatment of inflammation in cartilage and also to prevent disease progression. Studies also indicate that OCL may have a beneficial effect on the progress of Alzheimer's disease, the neurodegenerative disease characterized by accumulation of β-amyloid and tau proteins in the brain. There are also in vitro studies indicating that OCL has antitumor activity against various tumor models. Clinical studies have shown that ingestion of EVOO with a high OCL content had clear beneficial effects on metabolic parameters, inflammatory cytokines and abdominal fat distribution in the test subjects.

Keywords: *Oleocanthal; Human Health*

Introduction

Olives and olive oil have long been regarded as nutraceutical therapeutics for many health conditions [1], with the Greek physician Hippocrates (460 - 370 BC) mentioning some 60 of them benefitting from their ingestion. These physiological benefits, notably protection of blood lipids from oxidative stress, have been attributed to the polyphenol content of olive oil by the European Food Safety Authority (EFSA) in 2012 [2]. In fact, the daily consumption of 20g of olive oil provides at least 250mg/kg of the phenolic compounds present in the oil.

Oleocanthal is one of the approximately 36 natural phenolics found only in Extra Virgin Olive Oil (EVOO)**.** The oleocanthal content, and that of other anti-oxidants such as hydroxytyrosol, of olive oil depends on the growth location and olive tree variety as well as on the harvesting and milling practices but it averages at about 135 mg/kg of oil [3,4].

Oleocanthal is the source of the familiar "throat burn" sensation with EVOO which was only ascribed to the compound decarboxy-methyl ligstroside aglycon in 1993 [5]. This compound, known chemically as a dialdehyde, derives from 2-(4-hydroxyphenyl)ethanol and is sometimes referred to as a secoiridoid since it is produced by secondary metabolism of plants and is present in all olive tissues. After researchers at the University of Pennsylvania determined the precise stereochemistry of the compound in 2005 [6], Figure 1, it was given the more convenient name of oleocanthal.

It is not clear whether the natural product is a mixture of E/Z isomers or a single isomer as the two isomers readily interconvert in solution and most pharmacological studies have been performed using a mixture of the isomers.

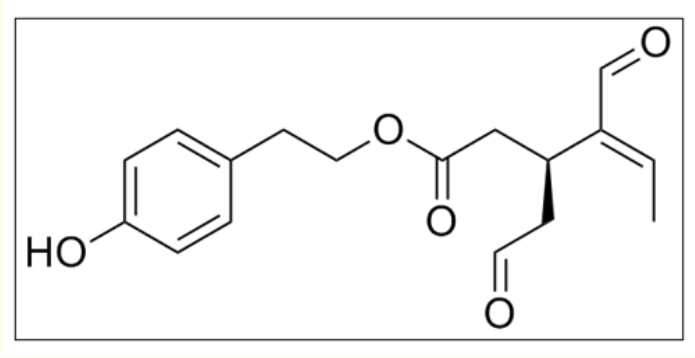

Figure 1: *Chemical structure of oleocanthal.*

Although oleocanthal (OCL) is a relatively minor component of extra virgin olive oil, it is considered to be one of the most important nutraceutical therapeutic ingredients [1,5,7-9]. OCL can be extracted from EOO by various techniques but commonly by adding water and a carrier such as starch to the oil and then spray drying the mixture. Subcritical extraction is then performed with a solvent such as propane and dimethyl ether followed by ethanol extraction and then spray drying to prepare the finished product.

Health-benefiting properties

A number of health claims are claimed for OCL, including being a nutraceutical, possessing antioxidant properties, functioning as a cyclooxygenase-1 and a cyclooxygenase-2 (COX-1 and COX-2) [1] inhibitor, exhibiting neuroprotective activity, functioning as an anti-neoplastic agent, an inducer of apoptosis, a Hsp90 [2] inhibitor, a non-steroidal anti-inflammatory drug and an anti-inflammatory agent.

Anti-inflammatory effects

Because bitterness is often associated with pharmacological activity, this characteristic of oleocanthal was predicted to have anti-inflammatory effects akin to but superior to those of ibuprofen, and there have been a number of studies investigating this property of OCL [1,5,8-14]. The importance of a novel anti-inflammatory agent such as OCL is because chronic inflammation is a critical factor in the pathogenesis of many inflammatory disease states. The latter include, but are not limited to, cardiovascular disease, cancer, degenerative joint diseases such as osteoarthritis, diabetes and neurodegenerative diseases such as Alzheimer's disease.

Although chronic inflammation is poorly understood, it is known that dietary habits can induce or attenuate inflammatory responses. Although the most common approach to dealing with inflammation and its sequelae is the use of non-steroidal anti-inflammatory drugs (NSAIDs), the use of these drugs often elicits severe side effects.

In joint diseases such as osteoarthritis (OA), cartilage homeostasis is disrupted by combinations of biologic factors that vary according to the disease process although biomechanical stimuli predominate. It appears that the progression of OA is characterized by increased nitric oxide production in chondrocytes [1] the latter effect leading to cartilage degradation. The nonsteroidal anti-inflammatory drug activity of oleocanthal, similar to that of ibuprofen, has been shown by *in vitro* studies to modulate NO production in chondrocytes and to be a promising agent for the treatment of inflammation in cartilage and also to prevent disease progression [13,15]. Whether these effects can only be found by ingestion of OCL or through topical effects remains to be investigated.

Alzheimer's disease

Studies indicate that OCL may have a beneficial effect on the progress of Alzheimer's disease, a neurodegenerative disease characterized by accumulation of β-amyloid (Aβ) and tau proteins in the brain [7,8,16]. Although the effects are incompletely understood, *in vitro* and *in vitro* research indicates that oleocanthal modulates Alzheimer's disease by altering the fibrillization of tau protein, controls β-amyloid (Aβ) levels and enhances β-amyloid (Aβ) clearance from the brain [16,17]. Interestingly, OCL appears to operate across the blood-brain barrier and does not elicit any cytotoxic effects. Clearly, further studies need to be undertaken in this area, but the initial findings of studies performed in the early 2010s are a very exciting approach to tackling the increasingly prevalent and severely debilitating Alzheimer's disease.

Antineoplastic effects

Antineoplastic or anticancer drugs are used to treat malignancies**,** commonly referred to as cancerous growths, by controlling the growth of cancerous cells. Drug therapy may be used alone or in combination with other treatments such as radiation therapy or surgery. Although chemotherapy can be highly effective, it is notorious for its side-effects and the potential of OCL having antineoplastic effects and with no toxicity issues might be welcomed by oncologists and patients. The literature contains a few reports of *in vitro* studies indicating that OCL has antitumor activity against various tumor models [12,18-21].

The underlying mechanisms and intracellular targets involved in the antitumor activity of oleocanthal have not been completely elucidated. However, the principal mechanisms appear to include modulation of the apoptotic pathway, the HGF/c-Met pathway [4], and the signal transducer and activator of the transcription 3 signaling pathway. Further, *in vitro* studies indicate that OLC has synergistic effects with anticancer drugs [18].

Multiple myeloma (MM) is a plasma cell malignancy that causes severe bone destruction by activating osteoclasts in bone marrow and it is the second most common hematological malignancy. The macrophage inflammatory protein 1-alpha (MIP-1α) is heavily involved in the development of osteolytic bone lesions in MM and *in vitro* studies indicate that OCL inhibits the expression and secretion of MIP-1α in MM cells. Apparently oleocanthal inhibits proliferation of MM cells by activating apoptosis mechanisms and down-regulating certain signal transduction pathways. This study suggests a therapeutic potential of oleocanthal in treating multiple myeloma [19].

Research work has shown that OCL selectively induces cancer cell death via lysosomal membrane permeabilization by inhibiting the activity of the enzyme acid sphingomyelinase, which in turn destabilizes the interaction between proteins required for lysosomal membrane stability [20]. The study shows that cancer cells, which have more fragile lysosomal membranes than non-cancerous cells, are susceptible to cell death induced by OCL functioning as a lysosomotropic agents and this may be a novel approach to inducing cancer-specific cell death [19].

There also are indications from *in vitro* studies that oleocanthal exhibits a remarkable and selective activity for human melanoma cells versus normal dermal fibroblasts [21]. In other words, OCL may be an effective treatment against skin cancer.

Metabolic effects

The overall health conferring benefits of the Mediterranean diet and olive oil in particular are widely recognized and have been for thousands of years. As previously stated, dietary extra virgin olive oil (EVOO) intake is associated with reduced cardiovascular risk and oleocanthal has anti-oxidant and anti-inflammatory properties. A recent clinical study on 23 subjects (15 M and 8 W, age: 60 ± 11 yrs) with metabolic syndrome (MetS) [5] and hepatic steatosis (fatty liver disease) investigated the effect of daily consumption of EVOO with a

high OCL concentration for 2 months [22] It was found that ingestion of EVOO with a high OCL content had beneficial effects on metabolic parameters, inflammatory cytokines and abdominal fat distribution in the test subjects. In particular, the subjects were noted to have experienced a reduction in body weight, waist circumference, body mass index (BMI) and various metabolic parameters. This was an important finding for patients with MetS and hepatic steatosis, a patient category with a high cardiometabolic risk. Thus, daily ingestion of extra virgin olive oil really is beneficial to health.

Conclusions

This brief overview clearly demonstrates that oleocanthal may have a remarkably beneficent effect on human health and indicates that OCL may possess therapeutic potential for addressing several severely debilitating and potentially fatal diseases. The question remains, however, if oleocanthal is therapeutic in its own right or whether its efficacy improved by the presence of the other conjoint polyphenols present in extra virgin olive oil, fruit and leaves.

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