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Review Article

The Biophenols behind the Mediterranean Diet

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Abstract

The chemistry and bioactivity of the biophenols hydroxytyrosol, tyrosol and oleuropein, present in olive oil, are reviewed. In particular, the scientific literature regarding their antioxidant, antimicrobial, anticancer and neuroprotective activities is discussed in detail. The identified bioactivities of these compounds are astonishing and clearly demonstrate and validate the overwhelming health benefits arising from the consumption of olive oil in the Mediterranean diet.

Keywords: *Bioactive Components; Olive Oil; Mediterranean Diet*

Introduction

The health benefits of olives, olive leaves and olive oil have been recognized since the time of Ancient Greece and it is now commonplace for health-conscious individuals to preferentially consume the "Mediterranean diet". This diet comprises plant-based foods, fish and olive oil, and is associated with a reduced risk of most age-related diseases, cardio-vascular problems and neurodegenerative disorders.

The characteristics and principal components of olive oil have been discussed in a previous review [1]. However, the physiological benefits of olive oil were attributed to its content of bioactive polyphenols or *biophenols* by the European Food Safety Authority (EFSA) in 2012 [2]. It should be noted, however, that the biophenol content of olive oil will vary with a number of factors but, notably, with the olive variety, the growth location, local environmental and soil conditions, harvesting procedures and milling conditions [3].

Both virgin olive oil (VOO) and extra virgin olive oil (EVOO) contain approximately 36 biophenols. Of these biophenols, the most important in terms of health benefits appear to be tyrosol, hydroxytyrosol, oleuropein and oleocanthal although the latter is present only EVOO. The bioactivity of oleocanthal has recently been reviewed [4] whereas the properties of hydroxytyrosol, tyrosol and oleuropein are discussed here.

Biophenols in olive oil

Hydroxytyrosol

Hydroxytyrosol (HXT), figure 1, is an important contributor to many of olive oil's health benefits [5] and shares structural similarities with epicatechin and resveratrol, the biophenols present in green tea and red wine respectively. HXT is also endogenously synthesized in the body as a byproduct of dopamine metabolism.

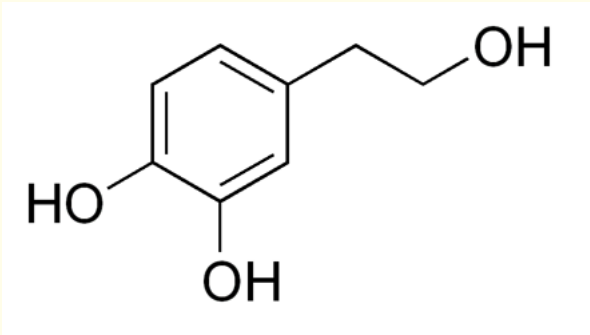

Figure 1: *Structure of 4-(2-Hydroxyethyl)benzene-1,2-diol (Hydroxytyrosol).*

European regulatory standards require olive oil products to have a minimum content of hydroxytyrosol (and its derivatives) of 5 mg/20g and 250 mg/kg of polyphenols to claim health benefits [3]. Its presence in olives and olive leaves enables the manufacture of hydroxytyrosol-rich olive leaf extract supplements [6].

Hydroxytyrosol is actually a precursor and a metabolite of oleuropein which is discussed later. During ripening of olives, some oleuropein is converted into hydroxytyrosol within the fruit although as olive oil is consumed and digested, much of the remaining oleuropein is converted into hydroxytyrosol by enzymatic hydrolysis in the body. In fact, hydroxytyrosol is a principal contributor to the high stability of olive oil.

Numerous health benefits are attributed to hydroxytyrosol, including anti-inflammatory, antioxidant, antimicrobial, anti-thrombotic, anticancer and even anti-fungal activity, many of these claims being supported by the scientific literature [5,7-9]. These bioactive properties of HXT are accomplished through nutrigenomic and immunomodulatory mechanisms [10].

Anti-inflammatory and anti-cancer activity

Preclinical (rodent) and *in vitro* studies [6,7,11-13] have shown that HXT relieves acute inflammation and nociception[1]. The research findings indicate that HXT has the ability to reduce many inflammatory markers, including tumor necrosis factor-α (TNF-α)[2], cyclooxygenase-2 (COX 2) enzyme[3], cytokines[4] and chemokines[5]. In fact, it appears that the anti-inflammatory activity of hydroxytyrosol operates through a variety of mechanisms, even stimulating cytokine immune cells to secrete the anti-inflammatory compound interleukin-10 (IL-10). There is also evidence that hydroxytyrosol exhibits antiproliferative, antioxidant and anti-inflammatory effects on human hepatoma HepG2 and Hep3B cell lines.

[1]Nociception is the term for the perception or sensation of pain.

[2]Tumor necrosis factor alpha (TNF-α) causes the necrosis of tumors, but is also important as a pathological component of autoimmune-diseases, immune responses and inflammation.

[3]Cyclooxygenase-2 (COX-2) is a key enzyme mediating prostaglandin synthesis and is involved in tumor invasiveness and angiogenesis (growth of new blood vessels). It is a major target of non-steroidal anti-inflammatory drugs (NSAIDs).

[4]Cytokines are signaling proteins such as interferon, interleukin, and growth factors secreted by cells of the immune system and have an effect on other cells. Most are produced in the presence of disease or immunization and contribute to immune responses and inflammation.

[5]Chemokines are small cytokines secreted by cells that induce directional movement of leukocytes (white blood cells). They are important in activating immune responses, morphogenesis and wound healing as well as in the pathogenesis of diseases like cancers.

These findings suggest that the anti-inflammatory activity of hydroxytyrosol may impact the neuroinflammation found in Parkinson's and other neurodegenerative diseases. There are also indications that hydroxytyrosol may induce apoptosis (programmed cancer cell death) and interfere with the ability of cancer cells to grow new blood vessels and metastasize.

Antioxidant activity

Hydroxytyrosol (HXT) is considered one of the most powerful antioxidant phenolic compounds after gallic acid[6] and the most potent antioxidant found in olive oil [3,8-10]. These antioxidant properties arise from scavenging of free radicals and the stimulation of synthesis and activity of antioxidant enzymes, e.g. COX-2. These actions will also limit the lipid peroxidation of low-density lipoprotein (LDL) cholesterol, a hallmark of atherosclerosis [14]. In the latter case, HXT apparently prevents the oxidation of LDL cholesterol (low-density lipoprotein) into an even more harmful form of cholesterol by restoring levels of glutathione[7]. Lowered inflammation and oxidative stress together with an improved lipid profile were demonstrated in healthy subjects as well as in metabolic syndrome patients after hydroxytyrosol (HXT) supplementation.

The beneficial effect of HXT with regard to cardiovascular disease, metabolic syndrome and possibly AIDS have been discussed by several researchers [5,15,16]. The research findings indicate that a daily intake of 5 mg of HXT should reduce cardiovascular risk [14]. Further, daily HXT intake may also provide neuroprotective action.

This antioxidant activity may be a contributing factor for dietary olive oil being linked to improved cardiac health, a reduced risk of cancer and improvements in levels of blood lipids like cholesterol. There are also indications that hydroxytyrosol is anti-thrombotic[8] through its ability to significantly reduce platelet aggregation [17].

It should be mentioned, however, that at least one study has suggested that the antioxidant activities of the main metabolites of hydroxytyrosol do not contribute to beneficial health effects after olive oil ingestion [18]. It was stated that their bioavailability in humans is poor, and they are mainly found as conjugated metabolites in biological fluid. In a limited but interesting intervention study of 11 healthy volunteers whose diet was supplemented with 50 ml of virgin olive oil, the measured low concentrations of free phenols were thought to be unlikely to explain the biological activities seen in humans after olive oil intake. In particular, the antioxidant activities of the conjugated metabolites, notably glucuronides and core compounds, tested at a range of concentrations compatible with their dietary consumption did not display significant antioxidant activities. These findings indicate that the health benefits of olive oil may not be attributable to a single component.

Antimicrobial properties

In vitro studies have shown that hydroxytyrosol is antimicrobial and has bactericidal or bacteriostatic effects on a variety of pathological intestinal and respiratory bacteria, including *H. pylori, Staph. aureus* and *Staph. epidermis* [19-21]. This antimicrobial activity combined with the antioxidative and anti-inflammatory properties of HXT clearly contribute to benefits of olive oil with regard to gut health. These properties may also explain the reported protective action for the skin against UVA damage and promotion of wound healing.

[6]Gallic acid is a trihydroxy benzoic acid and is classified as a phenolic acid that has strong antioxidant properties. It is found in sumac, witch hazel, tea leaves, oak bark and gallnuts.

[7]Glutathione is a tripeptide antioxidant found in plants, animals, fungi and some bacteria. It prevents damage to important cellular components by reactive oxygen species such as free radicals and peroxides as well as heavy metals.

[8]Anti-thrombotic indicates the ability to reduce the formation of blood clots.

Tyrosol

Tyrosol (Tyr), 4-hydroxyphenethyl alcohol or 4-OH[9], is one of the major biophenols found in EVOO but it is also endogenously synthesized in the body as a byproduct of tyramine[10] metabolization. Tyrosol (Tyr), like hydroxytyrosol, oleuropein, oleocanthal and oleacein in EVOO, is widely recognized for its reported health benefits. These claimed benefits include antioxidant, antimicrobial, antiatherogenic, cardioprotective, anticancer, neuroprotective and endocrine effects [21-25].

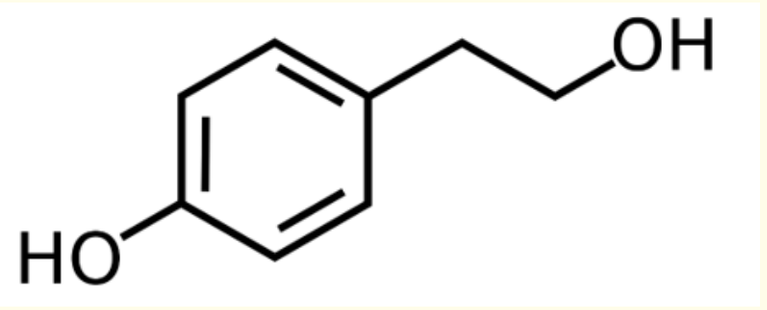

Figure 2: *Chemical structure of tyrosol (4-hydroxyphenethyl alcohol).*

Dietary tyrosol has been shown in preclinical studies to be hydroxylated into HXT by isomers of cytochrome P450[11], which contributes to its cardiovascular effects [24]. Further, a limited clinical trial in which participants received white wine and 25 mg of Tyr showed a high recovery of HXT and improved endothelial function[12] compared to controls [24], i.e. there was an improvement in cardiovascular conditions. Interestingly, a clinical study by other researchers found that the biotransformation of Tyr to HXT was increased by beer and red wine, with the latter having the greatest effect [26]. The findings supported an indirect beneficial effect of wine (and beer) combined with tyrosol on cardiovascular health.

There are various reports of the antioxidant properties of tyrosol in the literature [25,27] and the restoration of intracellular antioxidant levels despite Tyr actually being an antioxidant. This effect may be due to intracellular accumulation of Tyr over time and provides further support for the contention that EVOO and Tyr consumption helps counteract cardiovascular disease [27]. There is also some evidence that Tyr may function as a neuroprotectant, in part because of its antioxidative properties [25]. Although it is known that tyrosol has a significantly lower antioxidant activity than hydroxytyrosol, but it nevertheless exerts a powerful protective effect against oxidative injuries in cell systems and, therefore, can improve the intracellular antioxidant defenses. This hypothesis has been validated by an *in vitro* study that showed Tyr reduced apoptotic[13] markers and protected HaCaT[14] cells from damage [28]. These findings suggest that because Tyrosol has a potential role in protecting cells from apoptotic cell death, it could be used as an ingredient in topical preparations to prevent skin damage [28].

[9]Two tyrosol-derived isomers, 2-hydroxyphenethyl alcohol or 2-OH and 3-hydroxyphenethyl alcohol or 3-OH, are also known.

[10]Tyramine is a natural compound found in plants and animals. It is a byproduct of the metabolization of tyrosine, one of the 20 amino acids used by cells in protein synthesis.

[11]Cytochrome P450, a large family of enzymes e involved in the metabolism of both exogenous and endogenous compounds, play a key role in the metabolization of drugs and other xenobiotics.

[12]The endothelium protects the tissues from toxins, regulates the blood clotting mechanism; controls the fluid, electrolytes and other substances passing between the blood and the tissues.

[13]Apoptosis or "programmed cell death" is the death of cells which occurs as a normal and controlled part of an organism's growth or development.

[14]HaCaT cells are human epidermal keratinocytes used to study multistep carcinogenesis in human cells, keratinocytes being the primary cells found in the epidermis.

There are indications that Tyr has antimicrobial activity [22] and that its antioxidative and antimicrobial effects are enhanced by synergistic interactions with commercial antioxidants and vitamin B2. These findings suggest that Tyr and its isomers may provide protection against food spoilage by reactive oxygen species and bacteria such as *Staph aureus* and *E. coli*.

Finally, there has been a recent *in vitro* study that evaluated the role of Tyr in adipogenesis [29]. It was found that tyrosol induced lipolysis, the breakdown of fats and other lipids by hydrolysis through activation of the AMPK-ATGL-HSL pathway[15]. It appears that Tyr downregulates adipogenic proteins, inflammation and oxidative stress as well as possibly inducing adipose tissue browning throughout the induction of the AMPK-ATGL-UCP1pathway [29]. In other words, Tyr may be a potential therapeutic agent for the prevention and treatment of obesity.

It follows from the above, that despite tyrosol being a less effective antioxidant than its hydroxylated counterpart HXT, it appears that Tyr possesses some unique bioactivity characteristics that benefit human health.

Oleuropein

Oleuropein (OLE) is an ester of 2-ethanol (3,4-dihydroxyphenyl). It is known as a secoiridoid, and is sourced from olive leaves, roots, extra virgin olive oil and olive mill waste (vegetation and wastewater). Oleuropein and its metabolite hydroxytyrosol are one source of the slightly sharp/bitter taste of olives. The bulk of olives produced globally are used in oil production (approximately 85 - 90%) with the rest being used in the production of table olives [30]. Although the content of biophenols in table olives is initially high, but the oleuropein concentration decreases through maturation and disappears at full ripeness [30,31]. The oleuropein concentration also decreases sharply after salt treatment.

Oleuropein is considered to be the most important phenolic compound in olive cultivars and its concentrations can be as high as 140 m/g in some olive species, with the average content ranging between 60 - 90 mg/g [30,32]. It should be noted that the literature does not always distinguish between oleuropein and its hydrolysis product oleuropein aglycon (Figure 3a and 3b) with most studies apparently be performed with the glycoside unless otherwise specified.

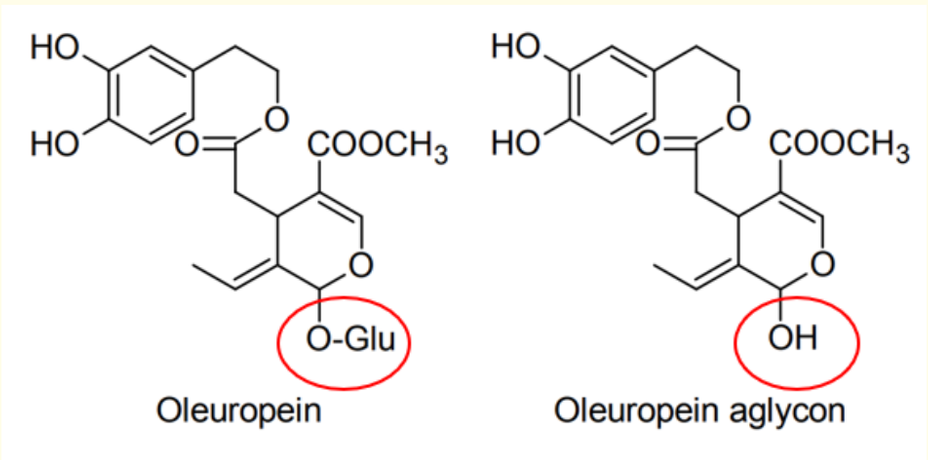

Figure 3a and 3b: *Chemical structures of oleuropein and oleuropein aglycon.*
(Note the presence of the glutamate group in oleuropein but absence in the aglycon, as circled in figure 3a and 3b).

[15]AMP-activated protein kinase (AMPK) is a metabolic "master switch" that functions as a rate-limiting enzyme regulating lipolysis in adipocytes, the cells that primarily compose adipose tissue that store energy as fat.

Numerous research studies comprising experimental, clinical and epidemiological investigations indicate that oleuropein exhibits many beneficial effects on health. These effects include antioxidant, antihypertensive, antimicrobial, anticancer, anti-inflammatory, anti-neuropathic and other activity [30-36]. In fact, oleuropein may be best known for its blood pressure lowering effect although this property may exacerbate hypotension in people that already have low blood pressure [32].

The bioactivity of oleuropein is the result of its rapid absorption, achieving maximum plasma concentration 2 hours after administration, and its high bioavailability through its metabolization into hydroxytyrosol and tyrosol [33].

Antioxidant activity

Oleuropein is well-known for its ability to inhibit oxidation of low-density lipoproteins [30,32,33,34]. This antioxidant activity of oleuropein is thought to be related to its ability to enhance or improve free radical stability by forming hydrogen bonds between the free hydrogen atoms of the hydroxyl groups and its phenoxy radicals. In fact, the antioxidant potential of oleuropein is similar to that of ascorbic acid (vitamin C) and α-tocopherol (vitamin E).

It has also been shown in animal studies that oleuropein not only reduced plasma levels of total, free and ester forms of cholesterol but also has the ability to scavenge nitric oxide (NO) and the potent oxidant hypochlorous acid. The latter is produced *in vivo* by the enzyme myeloperoxidase expressed in neutrophils (white blood cells) at the site of inflammation [30,33,34].

Other animal (notably rodent) studies suggest that these antioxidant properties of OLE may be effective in preventing cardiovascular and metabolic diseases [37,38]. Further, as discussed below, the antineoplastic function of EVOO has been ascribed to its antioxidative properties and provision of protection against oxidative stress due to its high content of oleuropein (and hydroxytyrosol).

Anti-cancer activity

Epidemiological studies clearly indicate that the incidence of some types of cancer in the Mediterranean basin is lower compared to other areas, primarily because of the Mediterranean diet which decreases the cancer risk by 61% [34]. In fact, there appears to be an inverse correlation between EVOO consumption and the incidence of certain cancers, notably colon, breast, lung and skin cancer [30,39]. Various mechanisms have been proposed to account for these effects including EVOO reducing the bioavailability of environmental and food carcinogens but, more likely, by the components of EVOO protecting cells from oxidative stress, as discussed below.

The literature contains reports of *in vitro* and preclinical (animal) research studies of the antineoplastic activity of oleuropein [40,41] as well as several reviews that summarize the findings of those studies [30,32,33,34,39]. The research data indicate that oleuropein is a potent inhibitor of human epidermal growth factor receptor-2 (HER 2), a protein frequently overexpressed in breast cancer cells, as well as exerting a chemo-preventative effect on colitis-associated colorectal cancer in mice [32]. It is believed that these anticancer effects are associated with oleuropein's ability to modulate gene expression and the activity of various signaling proteins that are involved in cell proliferation and apoptosis [42,43].

Overall, it appears that oleuropein aglycone is a very effective biophenol for decreasing the viability of cancer cells in breast, colon and kidney cancers i.e. it is more effective with regard to anticancer properties than oleuropein [30,32,41]. At least one study has shown that an application of a 400 μM dose of oleuropein and hydroxytyrosol caused a significant decrease in the cell proliferation of colon cancer (HT-29) 24-hours after treatment [41]. It has also been reported that oleuropein extracted from olive leaves, depending on the dosage, has marked antitumor effects on prostate, breast and hepatoma cancer cells [30,44]. Mechanistic studies suggest autophagy[16] through lysosomal digestion[17] together with inhibition of the target of rapamycin (mTOR[18]) operate in the protective effects of oleuropein

[16]Autophagy is the natural physiological degradation of the cell to remove unnecessary or dysfunctional/damaged components and aggregated proteins by lysosomal digestion. Autophagy defects are linked to various human diseases, including neurodegeneration and cancer.

[17]Lysosomes are membrane-bound cell organelles containing digestive enzymes involved in degrading excess or worn-out cell parts, and may also destroy invading viruses and bacteria.

[18]Mammalian target of rapamycin (mTOR) is a protein kinase (enzyme) which regulates protein synthesis and cell growth in response to growth factors, nutrients, energy levels and stress.

[33]. Oxidative stress and deregulation of the mTOR pathway is common with neurodegeneration, cancer, diabetes and physiological aging. This, in turn, suggests that the protective effects of oleuropein towards various disorders may occur through a shared molecular mechanism, notably by its effect on cholesterol and Aβ and preventing their accumulation in the arteries and brain.

On the other hand, the antineoplastic effect of oleuropein may be related to its anti-angiogenic properties [30]. Many types of tumors are connected with other cells through complex interactions in a permeable microstructure such that the forming tumor mass develops by initially forming a deoxygenated environment. However, angiogenesis occurs through stimulation of the multiplication and activity of endothelial cells, such that the tumor mass continues to grow through nutrition by the newly forming blood vessels [34]. If the anti-angiogenic properties of OLE inhibit endothelial cell multiplication, then continued development of the tumor mass should be obviated.

Antimicrobial properties

Antimicrobials control microbial growth by bacteriostatic or bactericidal activity, the former being to stop the replication and proliferation of the microorganism whereas the latter action kills the bacteria. The precise antibacterial action depends upon the antimicrobial agent and the target organism, i.e., whether it is Gram-positive or Gram-negative, aerobic or anaerobic, etc. Modern antimicrobials, which are commonly synthetic compounds, can perform both actions but now there is increasing use of natural antimicrobials because of the side effects of synthetic antimicrobials.

Because oleuropein is both an antioxidant and a phenolic, it is considered to be a natural antimicrobial agent that can reduce the growth rate of microorganisms [30,33,34]. Although antioxidant properties may play a role in antimicrobial action, this activity is more likely to be due to OLE (and HXT) damaging and penetrating the bacterial membrane and/or disrupting bacterial peptidoglycans[19]. It appears that the bactericidal efficacy of oleuropein is greater for Gram (+) bacteria than for Gram (-) bacteria, especially for *S. aureus* and *E. coli* species [30].

Early studies demonstrated antimicrobial activity for oleuropein (and hydroxytyrosol) against a variety of bacteria and both Gram-positive and Gram-negative bacteria, a finding confirmed in later studies [45]. In particular, the antimicrobial activity of oleuropein extracted from olive leaves was demonstrated towards *Campylobacter jejuni*[20], *Helicobacter pylori, Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA). Oleuropein also exhibits anti-mycoplasmal properties, having antimicrobial effects against mycoplasma bacteria strains, the latter commonly infect poultry but can also affect humans and are resistant to many antibiotics. Various antimicrobial effects of oleuropein have been reviewed by other workers [33,34].

Neurological effects

Worldwide, neurological disorders are increasing at a faster pace due to oxidative stress, protein aggregation, excitotoxicity[21] and neuroinflammation. It is now recognized that Alzheimer's disease (AD), the neurodegenerative amyloid disease that is the most common cause of dementia, has become a major social and clinical problem in recent decades, particularly in the Western countries.

The precise etiology of AD (and that of other degenerative diseases such as Parkinson's disease) is unclear but this proteinopathy is characterized by the toxic aggregation of Tau and *β*-amyloid (Aβ) proteins [34,46-48]. It has also been noted that oxidative stress and deregulation of the mTOR pathway is common with neurodegeneration and physiological aging as well as for cancer and diabetes [32].

[19]Peptidoglycan, also known as murein, is a polymer comprising the cell wall of most bacteria and forms a rigid envelope surrounding the cytoplasmic membrane of most bacterial species.

[20]*Campylobacter jejuni* is a common cause of food poisoning in the United States and Europe.

[21]Excitotoxicity is the damage or death of nerve cells due to levels of neurotransmitters, e.g. glutamate, becoming pathologically high and excessively stimulating receptors.

The scientific literature has increasing numbers of reports regarding the components of EVOO and neuroprotection [49,50]. This literature might be based on the early associations between the Mediterranean diet, olive oil and their beneficial effects with respect to AD, including reduced mortality in AD populations [48-50]. The consensus of scientific opinion appears to be that oleuropein is the main, if not principal, contributor to the observed neuroprotective effects [32,33,34,51]. Although the mechanism(s) involved in such neuroprotection has not been completely elucidated, one theory is that oleuropein prevents the aggregation of both amyloid beta (Aβ) and Tau, two proteins involved in Alzheimer's disease [34,51].

In addition to the accumulation of Tau and Aβ proteins, Alzheimer's disease is characterized by autophagy deficiency such that effective elimination of aggregates and damaged mitochondria is impaired. This facilitates accumulation of Tau and Aβ and increases their toxicity and oxidative stress. However, research studies [47] indicate that oleuropein aglycone is able to induce autophagy, decreasing aggregated proteins and reducing cognitive impairment *in vivo*. This effect is achieved by modulation of several pathways including the AMPK/mTOR axis which participates in the induction of apoptosis and autophagy. In other words, the data suggest that dietary supplementation with EVOO and oleuropein aglycone might have potential benefits for Alzheimer's patients by inducing autophagy.

Another theory regarding AD, dementia and aging is that free radicals cause oxidative injury to mitochondria[22] over the lifetime of an individual. This oxidative damage cannot be entirely counteracted and this in turn eventually leads to cellular dysfunction. Because mitochondrial membranes are very sensitive to free radical attack, this cellular dysfunction will lead to cognitive and neurodegenerative disease. The antioxidative properties of oleuropein may reduce or perhaps minimize such oxidative injury to mitochondria and have a positive impact on the incidence of age-related disorders such as dementia [51]. Regardless of the actual mechanism involved, the literature clearly indicates that oleuropein may have a positive and possibly a prophylactic effect with regard to Alzheimer's disease.

Conclusion

This overview of the scientific literature clearly demonstrates that hydroxytyrosol, tyrosol and oleuropein may have a remarkably beneficial effect on human health. In particular, together with the Mediterranean diet, they may possess therapeutic potential for addressing several severely debilitating and potentially fatal diseases. This appears to be highly relevant with the escalating prevalence of neurodegenerative diseases like Alzheimer's and Parkinson's diseases.

The question remains, however, if the individual biophenols are therapeutic in their own right or whether the bioefficacy is improved by or perhaps is reliant upon the presence of the other conjoint polyphenols in olives, olive oil and olive leaves.

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[22]Mitochondria are organelles present in large numbers in most cells and within which occur the biochemical processes of respiration and energy production.

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