Olive Oil Polyphenols in Neurodegenerative Pathologies

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1 Introduction

The aftermath of neuronal death as well as the progressive loss of structure or function of neurons in the brain or the spinal cord is specified as neurodegenerative disorders. The specific central nervous system region involved in the loss and decay of nerve cells characterizes the clinical features of the neurological disorder (Yacoubian 2017). The group of neurodegenerative disorders includes conditions such as amyotrophic lateral sclerosis (ALS) and Huntington's disease, but the most frequent are Alzheimer's disease and Parkinson's disease. The previously mentioned disorders are a primary health issue, predominately in the aging population

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(Antoniou et al. 2018a). In the near future, neurodegenerative disorders are anticipated to escalate, as life expectancy increases, leading to a financial and societal affliction (Gitler et al. 2017). Such diseases are most commonly caused by inflammation and oxidative stress (Barnham et al. 2004), and by the time the symptoms are obvious enough for a diagnosis to be made, the disorder has been developing for about 20 to 30 years prior. Alzheimer's disease and Parkinson's disease are related with high morbidity and mortality, while they leave very few alternatives for therapy (Antoniou et al. 2018b; Ritchie and Lovestone 2002). In the developed countries, a noticeable percentage of people suffer from the most common form of dementia, namely, Alzheimer's disease, which is considered a protein misfolding disease.

Alzheimer's disease is characterized by intracellular neurofibrillary tangles of hyperphosphorylated tau, or extracellular amyloid deposits (Aβ), located in defuse and senile plaques around cerebral vessels of dystrophic and degenerating neuritis of the brain (Citron 2010). Almost 30 million people are affected, nowadays, by Alzheimer's disease, with occurrence of the disease increasing by 1% in the age of 60–70 and 6–8% in the age of 85 years (Ferri et al. 2005; Kukull et al. 2002). These numbers are expected to grow to a great extent by 2050 (Citron 2010).

Parkinson's disease is located in substantia nigra, distinguished by the selective degeneration of dopamine-containing pigmented neurons (Cheng et al. 2010). Parkinson's disease is the most known neurodegenerative disease, and it influences more than 1% of the population above the age of 65 years (Farrer 2006; Harhangi et al. 2000).

Among the fatal brain disorders, and a form of dementia, is Creutzfeldt-Jakob disease (Sikorska et al. 2012), which is caused by misfolded proteins in neurons of the central nervous system. This disorder affects the signaling process and damages the neurons. Recent computational studies have attempted to address the 3D conformational arrangement of these proteins using advanced statistics and deep learning (Amidi et al. 2018, 2016, 2017; Bencurova et al. 2015). Also, novel approaches have been proposed in structural bioinformatics (Kontopoulos et al. 2016a, b; Carvalho et al. 2013).

2 The Setting

For more than 2500 years, olive tree has been the most prominent plant of the Mediterranean region. It has been used for social and religious purposes. Almost all of the ancient civilizations have used its derivatives, from ancient Greeks to ancient Egyptians. It has been mentioned in the bible and in the Koran. Since decades ago it has been linked with healing and longevity properties. Nowadays its correlation with longevity, lower incidence of coronary heart disease, cancer, and neurodegenerative disorders has been mentioned in a large number of studies (Visioli et al.

2018). Various studies have also termed olive derivatives as "medical foods." Medical foods are specific products, needed when a disease requires particular dietary management, that are established by medical and scientific evaluation (Lichtenstein 2017; Thaipisuttikul and Galvin 2012). Mediterranean diet seems to include a wide group of medical foods, the most prominent being extra virgin olive oil. Mediterranean populations are estimated to consume 25 to 50 ml of olive oil per day. Besides the dietary use of olive oil and olives, olive in the Mediterranean area is an asset of great importance, economically and culturally, while 90% of the world's olive oil is produced in that region. There are many olive cultivars that produce olive oils with different organoleptic characteristics. The beneficial role of extra virgin olive oil and its components are being revealed, and future research will show more about its benefits on human health (Nocella et al. 2018; Rigacci 2015). Olive oil is the principal source of fat in the Mediterranean diet and contains a great number of chemical compounds, such as several carotenes and phenolic compounds that act as antioxidants (Pandey and Rizvi 2009; Rigacci 2015; Vissers et al. 2004). Polyphenols are secondary plant metabolites that belong to a chemical group characterized by the presence of one or more aromatic rings with one or more hydroxyl substituent's group (Kennedy 2014). The olive tree synthesizes different and specific polyphenols, that are a part of the phytoalexin family, and their main role is to defend against microbial or fungal invasions or insect attacks (Cowan 1999). Polyphenols are located in the lipid and water components of olive oil. Primary polyphenols of olive oil are oleuropein aglycone, tyrosol, oleocanthal, oleacein, and hydroxytyrosol. The content of polyphenols in the olive depends on various circumstances such as the environment, ripening stage, storage, extraction, cultivar, etc. Said content can vary substantially, and it is known to reach levels as high as 60mg/100gr.

3 Is Olive Oil the Key?

At this moment, there are many limitations regarding the medication and treatment of neurodegenerative disorders since their main aim is to only address the symptoms. Therefore, there is no available therapy which can terminate the loss of neurons, especially for Alzheimer's and Parkinson's disease (Lanctot et al. 2009; Yacoubian 2017). Medications used for treatment of pathologies like Alzheimer's disease are restricted (Lanctot et al. 2009) and only delay the manifestation of the pathology or decrease the progression rate of symptoms, without blocking dopaminergic neuronal loss (Surmeier et al. 2010; Yacoubian 2017). Acetylcholinesterase inhibitors, (McGleenon et al. 1999) including donepezil, rivastigmine, galantamine, and glutamate receptor antagonist (Wang and Reddy 2017) such as memantamine, are currently the key therapeutic molecules used for treatment (Casey et al. 2010). Treatment of Alzheimer's disease has focused on the amyloid hypothesis, but this approach seems to have been unsuccessful so far

(Karran and Hardy 2014). Amyloid's product Aβ produces Aβ40 and Aβ42, and its accumulation seems to be connected to the pathological changes that Alzheimer's patients follow (Hardy 2009), but the most used acetylcholinesterase inhibitor, donepezil, has a moderate effect in decreasing Aβ pathology (Kim et al. 2014). Focusing on the detox mechanism is also very important (Axarli et al. 2016; Balatsos et al. 2012, 2009; Boulaki et al. 2018; Brancale et al. 2008; Chatzikonstantinou et al. 2017).

On the other hand, an extensive number of studies in the past few years have pointed out the beneficial effect of the Mediterranean diet against various pathologies, including neurodegenerative disorders (Alcalay et al. 2012). A decreased risk of dementia has been correlated with the consumption of olive oil, and by extension with its natural chemical products, "polyphenols" (Scarmeas et al. 2006). This results by enhancing cognitive function, reducing the risk of mild cognitive impairment and decreasing the progression rate of Alzheimer's disease (Scarmeas et al. 2009). The beneficial role of polyphenols, especially those found in extra virgin olive oil, is supported by a rising number of researchers. Extra virgin olive oil, as medical food, can benefit the majority of people, due to its wide availability and affordability (Table 1).

The cognitive behavior, of a group comprised of elderly people, presented a remarkable improvement when linked to a diet with extra virgin olive oil (Valls-Pedret et al. 2012), and similar results were obtained in a study with animal models after extra virgin olive oil consumption (Farr et al. 2012). The idea that the intake of polyphenols, as part of Mediterranean diet, contributes to a potent protection against neurodegenerative disorders has been reinforced by population studies and clinical trials (Rigacci 2015; Visioli et al. 2018). The existence of polyphenols has the ability to alleviate redox status and consequently reinstate optimal neuronal function, not only by their antioxidant ability but also by reinstitution of mitochondrial function, following activation of the nuclear factor pathway, which is involved in cell protection (Li et al. 2009). In addition, various beneficial effects have been revealed, including their potential to successfully impede protein aggregation, preventing self-assembly of misfolded proteins into toxic amyloid oligomers and fibrils (Daccache et al. 2011; Rigacci et al. 2011). When mice were fed with two different diets, one including extra virgin olive oil and one without, it was observed that the former showed a decrease in Alzheimer's disease (AD) symptomology (Lauretti et al. 2017). One of the most significant polyphenols which shows encouraging prospective in the determent of neurodegenerative diseases is hydroxytyrosol (Rodriguez-Morato et al. 2015). When tested to a mouse model related with Alzheimer's disease, it resulted in a remarkable development of the neurobehavioral dysfunction (Arunsundar et al. 2015). Moreover, plaque load in the hippocampus was significantly decreased when animals were administrated with Oleocanthal for 4 weeks, in a study performed on a human blood-brain barrier model and on the TgSwDI murine model of Alzheimer's disease. Furthermore, according to Batarseh et al., donepezil when combined with extra virgin olive oil nutrition significantly decreased Aβ load and its correspond-

Table 1 The major polyphenols of the extra virgin olive oil

A/A	Olive oil polyphenols	IUPAC name	Chemical formula
1	*Tyrosol*	4-(2-Hydroxyethyl)phenol p-Hydroxyphenethylalcohol 2-(4-Hydroxyphenyl)ethanol 4-Hydroxyphenylethanol	$C_RH_{10}O_2$
2	*Oleuropein aglycone*	4-[2-[2-(3,4-Dihydroxyphenyl) ethoxy]-2-oxoethyl]-5-ethylidene-6-[[(2S,3R,4S,5S,6R) 3,4,5-Trihydroxy-6-(hydroxymethyl)-2-tetrahydropyranyl]oxy]-4H-pyran-3-carboxylic acid, methyl ester	$C_{25}H_{32}O_{13}$
3	*Hydroxytyrosol*	4-(2-Hydroxyethyl)-1,2-benzenediol 3-Hydroxytyrosol 3,4-Dihydroxyphenylethanol (DOPET) Dihydroxyphenylethanol 2-(3,4-Di-hydroxyphenyl)-ethanol (DHPE) 3,4-Dihydroxyphenolethanol (3,4-DHPEA)	$C_8H_{10}O_3$
4	*Oleocanthal*	2-(4-Hydroxyphenyl)ethyl (3S,4E)-4-formyl 3-(2-Oxoethyl)hex-4-enoate	$C_{17}H_{20}O_5$
5	*Oleacein*	2-(3,4-Dihydroxyphenyl)ethyl (4Z)-4-formyl-3-(2-oxoethyl)hex-4-enoate; 2-(3,4-dihydroxyphenyl)ethyl 4-formyl-3-formylmethyl-4-hexenoate; (E)-3-(2-oxoethyl)-4-formyl-4-hexenoic acid 3,4-dihydroxyphenethyl ester; 3-(2-oxoethyl)-4-formyl-4-hexenoic acid	$C_{17}H_{20}O_6$
6	*Pinoresinol*	4-[(3S,3aR,6S,6aR)-6-(4-hydroxy-3-methoxyphenyl)-1,3,3a,4,6,6a-hexahydrofuro[3,4-c] furan-3-yl]-2-methoxyphenol	$C_{20}H_{22}O_6$
7	*Vanillic acid*	4-Hydroxy-3-methoxybenzoic acid	$C_8H_8O_4$
8	*P-coumaric acid*	(E)-3-(4-hydroxyphenyl)prop-2-enoic acid	$C_9H_8O_3$
9	*Caffeic acid*	(E)-3-(3,4-dihydroxyphenyl)prop-2-enoic acid	$C_9H_8O_4$
10	*Ferulic acid*	(E)-3-(4-hydroxy-3-methoxyphenyl)prop-2-enoic acid	$C_{10}H_{10}O_4$

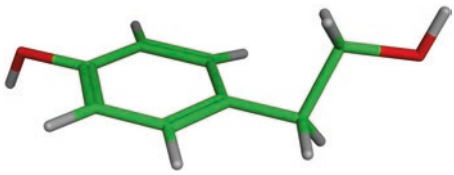

Fig. 1 Structural conformation of tyrosol phenolic compound in the 3D space

ing toxicity in a mouse model. The same researchers concluded that extra virgin olive oil integrated with donepezil upregulated synaptic proteins can elevate the blood-brain barrier tightness and minimize neuroinflammation (Batarseh and Kaddoumi 2018) (Fig. 1).

4 Polyphenol's Affiliation with Protein Related to Parkinson's Disease

One of the most important polyphenols present in the olive tree (*Olea europaea*), tyrosol, has been found to interact with a protein, which appears to be associated with neurodegenerative disorders (Table 2). In particular, the tyrosol polyphenol has been found to interact with the active site of tyrosinase, based on the crystal structure complex (PDB ID: 4P6T) (Goldfeder et al. 2014). Tyrosinase, a copper-containing protein, is a key molecule in the biosynthesis of melanin and other chemical compounds (Cass and Hill 1980). Hydroxylation of tyrosine to L-DOPA and oxidation of L-DOPA to dopaquine are both catalyzed by tyrosinase (Korner and Pawelek 1982; Sanchez-Ferrer et al. 1995). It is also possible that dopamine's oxidization to form melanin can be generated by tyrosinase (Miranda et al. 1984). Goldfeder et al. (Goldfeder et al. 2014), derived the following conclusions: (i)

Table 2 Tyrosol's related studies and function pathways in the PubChem database (Kim et al. 2016)

A/A	Used in drugs for human necessities under patent classification for	Biological test results were tested substance is active
1	Colorectal cancer	Inhibition of *Mycobacterium tuberculosis* recombinant Rv1284 beta-carbonic anhydrase
2	Prostate, kidneys, bladder	Inhibition of *Cryptococcus neoformans* recombinant Can2 beta-carbonic anhydrase
3	Genital or sexual disorders	Inhibition of *Candida albicans* recombinant Nce103 beta-carbonic anhydrase
4	Disorders of the urinary system	Inhibition of NADPH oxidase in human HUVEC cells
5	Antioxidant	Inhibition of human recombinant alpha-carbonic anhydrase 2
6	Disorders of the nervous system/ neurodegenerative disorders	Inhibition of *Mycobacterium tuberculosis* recombinant Rv3273 beta-carbonic anhydrase
7	Anti-Parkinson drugs	Toxicity against *Choristoneura fumiferana*
8	Mania or schizophrenia	Toxicity against *Saccharomyces cerevisiae*
9	Alcohol/opioid abuse	Inhibition of human recombinant carbonic anhydrase 2, 5A, 5B
10	Antibacterials/antivirals	Antioxidant activity assessed as oxygen radical scavenging activity
11	Leukemia	Activity at mushroom tyrosinase assessed as decrease in absorbance
12	HIV	
13	Anti-aging preparations	
14	Hypnotics	
15	Dermatological disorders	

albinism in human species is primarily generated by a mutated tyrosinase, (ii) tyrosinase is noticeably targeted by the pharmaceutical industry, and (iii) many organisms owe the production of melanin to tyrosinase. Moreover, as stated by Fairhead and Thony-Meyer (Fairhead and Thony-Meyer 2012), UV protection, detoxification of phenols, and wound healing are related to the action of tyrosinase. Olivares and Solano (Olivares and Solano 2009) supported the fact that melanoma can be affiliated with tyrosinase's mutations. There has been extensive research on the effects of such mutations (Dalkas et al. 2013; Filntisi et al. 2014; Inturi et al. 2014; Kandil et al. 2009; Kapasa et al. 2012; Maltezos et al. 2014; Marinou et al. 2018; Nicolaides et al. 2015, 2016). Dopamine levels in the brain are maintained through excessive oxidation of cytosolic dopamine and L-DOPA by tyrosinase, which is also preventing cell decay by dopamine auto-oxidation (Asanuma et al. 2003). Following the same study, in the absence of tyrosine hydroxylase, tyrosinase's ability for double-edge synthesizing and oxidizing in the dopaminergic system is indicated for the composition of dopamine in long-standing Parkinson's patients. Equally, tyrosinase's overexpression enlarged the amount of dopamine which accompanied by the development of melanin pigments that ultimately triggered apoptotic cell death (Hasegawa 2010). In closing, tyrosinase promoter is energetic during murine brain growth, and in accordance to Tief et al., it may be connected to neuromelanin's evolution in neurodegenerative diseases, like Parkinson's disease (Tief et al. 1996) (Fig. 2).

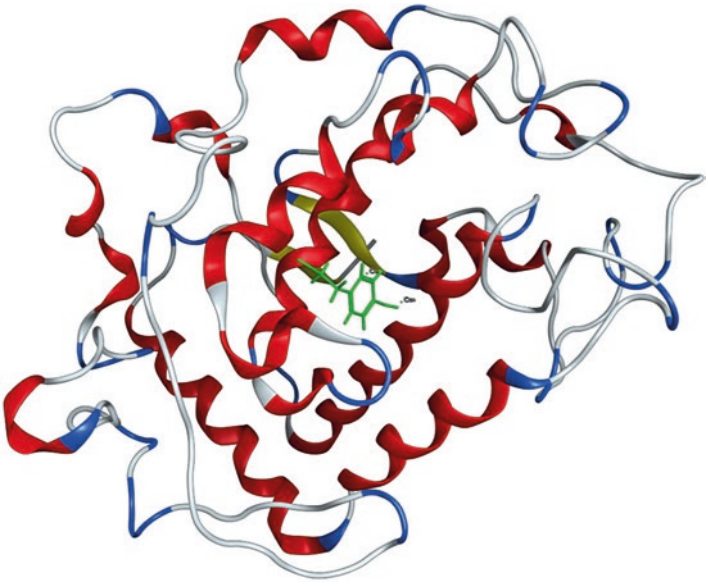

Fig. 2 Ribbon representation of the crystal structure (PDB ID: 4P6T) of tyrosinase protein bound with tyrosol (colored green) in its active site

5 Time to Change Viewpoint?

The discovery of exploitable molecules related to dietary regimens in order to decrease the risk of neurodegenerative disorders provides a great potential for effective treatment against such diseases (Scarmeas et al. 2009). The effects of Mediterranean diet, that contains polyphenols, in intercepting various age-related flaws, neurodegenerative disorders, as well as cancer have been well demonstrated by many researchers (Casamenti and Stefani 2017). More effective therapeutic approaches for neurodegenerative diseases, including treatments with the safe substitute of medical food therapies, need to be addressed. The level of contribution of olive polyphenols to neuroprotective effects and management of neurodegenerative disorders requires additional research (Rodriguez-Morato et al. 2015). A medical need in the coming years will be the discovery of molecules that are capable to differentiate protein and peptide aggregation by blocking the formation of the plaque accumulation (Vlachakis and Kossida 2013a, b; Vlachakis et al. 2013c, d). Moreover, functional portions of olive polyphenols, necessary to establish health tranquillity, will need to be examined. Future research and clinical trials on the role of Mediterranean diet and olive oil will provide further scientific knowledge, besides the beneficial effects on multiple neurodegenerative disorders as a general effect on the brain, and lead to a better understanding of the mechanisms interfering this association.

For better understanding of the olive oil benefits on health, many computational methods have been developed in the molecular and structural level (Palaiomylitou et al. 2008, 2016a, b, 2014, 2017). Comprehensive structural studies have helped in elucidating the role of key metabolizing enzymes (Pavlopoulou et al. 2013; Vlachakis et al. 2014a, b, 2017). All the information is handled by large computational systems (Theoharaki et al. 2018; Tsiliki et al. 2014; Vangelatos et al. 2009; Vlachakis et al. 2018, 2015; Vlachakis 2009; Polychronidou et al. 2015). Molecular modelling and structural bioinformatics are paving the way to a greater understanding of the role of olive oil ingredients in our health (Schnerch et al. 2016; Sellis et al. 2012; Sertedaki et al. 2016; Steinhauf et al. 2014; Tagkalakis et al. 2017; Vlachakis et al. 2013a, b). The metabolism of glucose, the level of steroids, and the nutrients that we intake from our diet are key to maintaining homeostasis (Vlachakis et al. 2014c, 2012, 2013e, f, g). In the long run, the maintenance of stable homeostatic parameters, like HPA axis, circadian rhythms, and hormone levels, will have a protective role against illness and disease.

6 Conclusions

Despite the great efforts that have been made so far in the fight against neurodegenerative disorders, there is no available treatment. Medications used for such pathologies only delay the progression of symptoms and have proven to be unsuc-

cessful thus far. Contrary, the consumption of extra virgin olive oil as a medical food and the olive polyphenols such as tyrosol, oleuropein aglycone, oleocanthal, and hydroxytyrosol appears to be potentially beneficial in the confrontation of neurodegenerative disorders, as stated by many researchers. Additionally, tyrosol interacts with the active site of tyrosinase, a protein responsible for albinism in mammals, which is a target excessively employed in the pharmaceutical industry, and it is also strongly associated with Parkinson's disease. In conclusion, there is a growing need to discover the potential beneficial effects of medical foods, like the extra virgin olive oil, against neurodegenerative disorders and unlock the connections of these pathologies in a molecular level. Current research has set the foundation for future studies and clinical trials for identifying the possible role of olive polyphenols on the human brain.FundingResearch was supported by a Microsoft Azure for Genomics research Grant (CRM:0740983) and by the FrailSafe Project (H2020-PHC-21-2015 – 690140) "Sensing and predictive treatment of frailty and associated comorbidities using advanced personalized models and advanced interventions," co-funded by the European Commission under the Horizon 2020 research and innovation program. EP was supported by the State Scholarships Foundation (IKY) – European Union (European Social Fund, ESF) and Greek national funds through the action entitled "Strengthening Human Resources Research Potential via Doctorate Research" in the framework of the operational program "Human Resources Development Program, Education, and Lifelong Learning" of the National Strategic Reference Framework (NSRF) 2014–2020.

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