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Olive oil and wine as source of multi-target agents in the prevention of Alzheimer disease.

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Abstract

Olive oil and wine are consumed daily worldwide and they constitute the fundamental pillars of the healthy Mediterranean diet. Polyphenolic compounds, naturally present in both olive oil and wine, are responsible for their beneficial properties. Current studies have shown the neuroprotective effects of polyphenols independently of their well-known antioxidant action. In this work, we have focused on reviewing the protective effect of polyphenols from extra virgin olive oil and wine in Alzheimer´s disease (AD), to emphasize that both food could be a possible therapeutic tool. Beneficial effects have been described in β-aggregation, neurofibrillary tangles, autophagy and mitochondrial function, as well as in cerebral insulin resistance. Furthermore, to date a harmful dose has not been described. Both preclinical and clinical works demonstrate that polyphenols act on neuropathological and cognitive disorders of AD, preventing or stopping the onset of this devastating disease. However, there are certain limitations in these studies, since it is very difficult to research diseases that lead to cognitive impairment. Although all the findings obtained are very encouraging, more studies should be carried out to use the polyphenols from olive oil and wine as therapeutic agents in the progression of AD. Therefore, more longitudinal studies in humans with a homogeneous cohort of patients are necessary to corroborate the efficacy of these nutraceuticals, as well as analyze which is the most appropriate dose for this purpose.

Keywords: Polyphenols; Mediterranean Diet; Alzheimer's disease; Oleuropein; Hydroxytyrosol; Olive Oil; Wine; Resveratrol

1. Introduction

Olive oil is defined as a common vegetable oil of culinary use, extracted from olives, fruits of Olea Europaea tree. The origin of this tree dates from Upper Miocen, 20 million years ago. Since then, olive oil or the recent named “liquid gold” is a Mediterranean´s treasure, and major according to Georges Duhamel, French doctor, writer, and poet, “the Mediterranean finishes where no grow the olives”. In the Ancient Egypt, beneficial and healing properties have been attributed to olive oil as well as a divine character, being the olive tree a signal of peace and prosperity. Nowadays, olive oil is consumed daily worldwide, being one of the fundamental pillars of the healthy Mediterranean diet, together with other foods as, fresh fruits, vegetables, legumes, seeds, moderate amounts of red wine, fish, and meat rich in unsaturated fats. Scientific literature has showed all the health benefits associated with olive oil consumption as well as its relationship with a lower prevalence of vascular disease, obesity, arthritis, cancer, and age-associated cognitive decline even the onset Alzheimer´s disease (AD) (Román, Jackson, Reis, Román, Toledo, & Toledo, 2019). However, in the last decade, the scientific community has wondered what bioactive components possess olive oil to be so healthy. Leaving aside unsaturated fatty acids and minor compounds, numerous studies have reported that olive polyphenols, predominantly presents in extra virgin olive oil (EVOO), are responsible for most of the properties described so far. In fact, the European Food Safety Authority (EFSA) authorized the following health claim for EVOO “contribute to the protection of blood lipids from oxidative stress”, providing that its content is, at least, 250 mg/kg of these phenolic compounds (EFSA J., 2012). The olive polyphenols content depends on multiple factors (climate on place cultivation, variety of the olive, level of ripening at the time of harvest and extraction method). Currently, the beneficial antioxidant properties for the health of some olive polyphenols have been recognized by EFSA at the minimum dose of 5 mg in 20 g of EVOO (López-Huertas et al., 2021). However, another study has reported that antioxidant role of polyphenols EVOO on rat redox status depending on the tissue. Specifically, this dose was beneficial for brain, blood, muscle and small intestine, and damaging for other tissues (Kouka et al., 2020). To date, no studies have attributed to olive polyphenols a harmful effect on health, since both "*in vitro*" and "*in vivo*" toxicological studies have corroborated (Añon-Calles et al., 2013a, 2013b).

Nevertheless, we must consider that these polyphenols are also found in many other foods of vegetable origin, typical from the Mediterranean diet (Leri et al., 2020). Hence, the daily intake of a substantial number of polyphenols from Mediterranean diet, reduces the incidence of many aging-associated diseases, among them, the AD (Abbatecola, Russo, &Barbieri, 2018) The Prevention with the Mediterranean Diet (PREDIMED) trial reported that a Mediterranean diet supplemented with EVOO and/or nuts, both foods rich in numerous bioactive polyphenols (Manach C., et al., 2004), provided beneficial effects on the prevention of chronic diseases (Estruch et al. 2013; Martinez-Gonzalez et al.,2015). Specifically, Scarmeas and collaborators, appointed that there was a close link between intake of Mediterranean diet and a reduction (Scarmeas et al., 2006). Furthermore, an interventional pilot study targeted to adults at risk of AD has suggested that a Mediterranean-ketogenic diet supplemented with olive oil may prevent cognitive decline (Neth et al., 2020). Moreover, Mediterranean diet – induced structural benefits were observed on brain of older adults (Gu et al., 2015). Wine health effects are debated when prevention or therapeutic approaches to different diseases are addressed including AD. Polyphenols have antioxidant proprieties, which can contribute to stop oxidative damage in cells and tissues (Peters et al., 2008). However, the antioxidant effect is in the centre of wine health benefits controversy. Some scientists argue that the beneficial effects of wine were obtained in studies with methodological limitations, which may have led to misinterpretations or biased conclusions (Naimi et al, 2019). In fact, most polyphenols have very low bioavailability and are largely transformed in the body. Maximum plasma levels of conjugated phenolic metabolites are reached between 1 to 2 h or 6 to 24 h after intake for the ones derived from small intestine absorption or the ones produced by the gut microbiota, respectively (Teng & Chen, 2019). Additionally, the antioxidant effect of conjugated metabolites is lower than the parent polyphenols due to the glycosylation, sulphation, or methylation reactions (Sobhani, Farzaei, Kiani, & Khodarahmi, 2020). Counteracting these facts, other researchers argue that antioxidant effects of the metabolite´s mixture occurring *in vivo* is higher than the one of the individual compounds *in vitro* (Wiczkowski, Szawara-Nowak, Topolska, Olejarz, Zielinski, & Piskula, 2014). Moreover, literature suggests that flavonoid aglycones and/or their methylated derivatives may be active in the body since cells comprise enzymes able to deconjugate the sulphated and glucuronidated polyphenols forms. Researchers who claim the beneficial health effects of wine also argue that polyphenols activity goes beyond their

antioxidant effects, since they may act as potential modulators of intracellular signalling cascades vital to cells (Cueva et al., 2017).

Among, people aged 60 years and over, AD is the most common form of dementia related neurodegenerative disease, characterized by cognitive function and memory impairments. Sporadic AD is an irreversible neurodegenerative disorder triggered by multiple factors. Neuropathologically, it is characterized by the presence of extracellular amyloid beta peptide (Aβ) plaques and intracellular neurofibrillary tangles (NFTs) of hyperphosphorylated tau protein in hippocampus and cerebral cortex (Long & Holtzman, 2019). These cerebral aggregations, favoured by a decreased autophagy, induced oxidative stress which is accompanied by an exacerbated mitochondrial dysfunction and neuroinflammation. Furthermore, the impairment of acetylcholinesterase activity and glutamate activation of N-methyl-D-aspartate receptors contribute to the neurological dysfunction and symptoms. Currently, many publications have observed that the insulin resistance present in brain of AD patients is tightly related to these cerebral formations (Neth & Craft, 2017). In summary, AD is a multifactorial disorder where these cerebral alterations, impair synapsis process, inducing a progressive neuronal loss. Therefore, to demonstrate the neuroprotective role of polyphenols, their effects have been evaluated on each one of these pathophysiological changes. In summary, polyphenols are natural substances, synthesized by plants, with chemical characteristics like phenolic compounds. Its structure is based on, at least, two phenyl rings and one or more hydroxyl substituents, originating a large number of molecules (Sigla et al, 2019). Regarding its main functions, polyphenols are antioxidant, and they have protective effects against acute and chronic neurodegeneration, since they prevent A□ polymerization, modulate autophagy, induce mitochondrial biogenesis, and protect against peripheral insulin resistance, among other effects (Angeloni et al, 2017).

This review focuses on the evidence, regarding the new neuroprotective role granted to polyphenols, from EVOO and wine, in AD.

2. Bioactive components from olive oil and wine

2.1. Olive Oil

Olive oil, and its production variant EVOO obtained directly from mechanical extraction of olives, are universally known for their healthy and nutritional value due to the presence of several bioactive components such as monounsaturated and polyunsaturated fatty acids (MUFAs and PUFAs), polyphenols, squalene, triterpenes, phytosterols, tocopherols and different pigments. These bioactive compounds give EVOO certain properties (anti-inflammatory, antimicrobial, antitumoral, protective against neurodegenerative diseases) which have given the nickname of "liquid gold", being considered a superfood over the world, symbol of the Mediterranean diet (Piroddi et al., 2016).

First of all, EVOO is composed mainly of triglycerides, showing a high number of fatty acids and specifically, a huge content of MUFAs (65-83%). On the one hand, unsaturated acids represent up to 85% of its composition, since it has a high content in oleic acid (C18:1), which may range between 70–85%, and other as palmitoleic acid (16:1) or linoleic (C18:2). On the other hand, palmitic and stearic acids are the principal saturated acid of EVOO, representing the 14% of oil composition (Jimenez-Lopez et al., 2020). The oleic acid has effects on cardiovascular risk factors as well as on metabolic and gastrointestinal functions. Some of the biological effects of this MUFA are attenuation of inflammation and oxidative states in fasting conditions, modifications to lipoproteins and plasma lipid patterns, inhibition of coagulation, improvements in blood pressure and glucose homeostasis and effects on membrane fluidity and composition of blood cells, among others (Piroddi et al., 2016). Having said that, it is important to highlight that there are some crucial PUFA, like linolenic acid (C18:3) and linoleic acid. These two PUFAs are fundamental for the development of the brain and retina and are basic components of the cell structure (Piroddi et al., 2016).

The main antioxidants compounds found in EVOO are the polyphenols. The principal phenolic subclasses present in EVOO are phenolic alcohols, like oleocanthal, oleuropein, oleuroside or oleacein, flavonoids, lignans, phenolic acids and secoiridoids, being these the most abundant in EVOO. Due to the EVOO ageing and production, secoiridoids are hydrolyzed and transformed into free hydroxytyrosol (HT) and tyrosol (Angeloni, Malaguti, Barbalace, & Hrelia, 2017). HT, which is present in a mean concentration of 137 mg/kg of olive oil, has many beneficial effects in human health,

since that molecule can stimulate several antioxidant mechanisms in our organism, and it can also reduce reactive oxygen/nitrogen species as well as free radicals. In addition, it has been proposed that HT could play an important role in neuroprotection against several degenerative diseases like AD, since that molecule reduces insulin resistance, the mammalian target of rapamycin (mTOR) activation, nuclear factor-kappa beta (NF-B) translocation and protein oxidation, among other effects (Gorzynik-Debicka et al., 2018).

Among the minority bioactive components of EVOO, the squalene represents up to 0.7% (7 mg/g), is a crucial intermediate in the biosynthetic pathway of sterols in animals playing a key role as intermediate metabolite in cholesterol metabolism too, since it participates in the regulation of its absorption, synthesis, esterification, and elimination. Furthermore, its antioxidant and anticancer properties have been demonstrated (Fig. 1) (Sánchez-Fidalgo, Villegas, Rosillo, Aparicio-Soto, & De La Lastra, 2015).

Other bioactive molecules, that appear in low concentration in EVOO, are triterpenes. Specifically, the oleanolic acid presents concentrations between 17 and 344 mg/kg, the maslinic acid between 19 and 250 mg/kg and for ursolic acid, just traces are detected (Piroddi et al., 2016). The main biological activities related to these triterpenes are their role as anti-inflammatory, anticancer, antiviral, and several important neuroprotective effects, since oleanilic acid has a protective role in the brain of rats during hypoxic injury (Rodríguez-Morató, Xicota, Fitó, Farré, Dierssen, & De La Torre, 2015). Furthermore, maslinic acid protects cortical neurons against oxygen-glucose deprivation-induced injury and glutamate toxicity and the ursolic acid has been described as a protector of the brain of mice against ischemic injury (Rodríguez-Morató, Xicota, Fitó, Farré, Dierssen, & De La Torre, 2015).

Respecting phytosterols, more than 250 have been identified, being the □-sitosterol the main representant of them. They are the principal unsaponifiable molecules in EVOO with a range from 70 to 260 mg/100g. In addition, they have a similar structure and function to cholesterol, being crucial structural components of the cellular membrane having fundamental functions like regulating membrane fluidity and permeability. Specifically, it has been described that phytosterols may play a role in signal transmission through membranes, improving neuronal plasticity. Furthermore, they can interact with proteins and other lipids in the cell membrane (Vezza, Canet, De Marañón, Bañuls, Rocha, & Víctor, 2020; Moreau et al, 2018).

Regarding tocopherols, three isoforms of tocopherols are present in EVOO: α-, β- and □- tocopherol, being α-tocopherol the most abundant with a range of variability between 191.5 to 292.7 mg/kg of oil, depending on several variables like the year of harvest (Jimenez-Lopez et al., 2020). Their main function is to act as antioxidants and preventing lipid peroxidation of cellular membranes and lipoproteins (Jimenez-Lopez et al., 2020).

Finally, Jimenez-Lopez et al (2020) have been described that EVOO contains a large variety of pigments, like carotenoids and chlorophylls. These pigments can be detected in amounts up to 100 ppm of total carotenoids, being the concentration of β-carotene up to 15 ppm. However, these values, can vary depending on several factors like the geographic origin of the EVOO. The main beneficial effects of these pigments are its antioxidant capacity and the protective effect against the formation of age-related cataracts, being specific subtypes of age-related cataracts related etiologically with AD since genetic variation in delta catenin may cause cortical lens opacities and cognitive changes that could vaticinate the development of AD (Jimenez-Lopez et al., 2020; Jun et al., 2012).

2.2. Wine

Wine is composed by water and ethanol, which account for about 97% on a weight-for-weight (w/w) basis. Wine ethanol results from grape sugars transformation during alcoholic fermentation. In this hydroalcoholic solution exists a small percentage of several hundred of compounds, some have its origin in grapes and others in yeast activity during fermentation. Among those compounds are polyphenols, which give red wine flavour and colour. Polyphenols comprise a diverse range of molecules with one or more aromatic rings comprising at least one hydroxyl group. Wine polyphenols divide into two major groups: flavonoid and non-flavonoid. Flavonoids include flavonols, flavononols (also known as dihydroflavonols), anthocyanins, flavan-3-ols, flavanones and flavones. Non-flavonoid compounds comprise hydroxycinnamic and hydroxybenzoic acids, and stilbenes (Fig. 2) (Visioli, Panaite, & Tome-Carneiro, 2020). Wine polyphenol profile and concentration depends on *terroir*, i.e., varies with grape variety, climate, soil, as well as the oenological practices applied for winemaking and aging and storage (Prata-Sena, Castro-Carvalho, Nunes, Amaral, & Silva, 2018). For example, flavonoids are the predominant phenolic components in both young and aged red wines, however, in the former flavonoid top three is: flavan-3-ols oligomers and

polymers (750 mg/L), anthocyanidins (400 mg/L) and flavonols (100 mg/L), while in the aged wine is: flavan-3-ols oligomers and polymers (1000 mg/L), flavonols (200 mg/L) and anthocyanidins (90 mg/L). Regarding non-flavonoid compounds, in young red wine the most representative ones are the hydroxycinnamic acids (165 mg/L) while in aged red wine are the hydrolysable tannins (250 mg/L). Stilbenes is a non-flavonoid subclass which concentration do not change with age (7 mg/L) (Caruana, Cauchi, & Vassallo, 2016).

As previously mentioned, Aβ aggregation and the appearance of NFTs are the major hallmarks of AD (Long et al., 2019). Regarding wine, the major focus of the research has been the evaluation of the polyphenols potential in blocking Aβ aggregation in the brain. Several studies have been also carried out aiming to disclose the potential of wine polyphenols to avoid the appearance of hyperphosphorylated tau protein aggregates. The metabolism of Aβ and tau is critically affected by the autophagy (Q. Li, Liu, & Sun, 2017). Therefore, some trials evaluated the potential of wine polyphenols as regulators of autophagy. Central nervous system diseases, including AD, are characterized by impaired mitochondrial bioenergetics, and often disturbed mitochondrial dynamics, which leads to neuronal death due to inadequate respiratory chain function and reduced ATP production (Tillement et al., 2011; Quintanilla et al., 2009). Therefore, some authors explored the role of wine polyphenols in mitochondrial function, as a possible preventive mechanism of AD. Obesity, type 2 diabetes, and insulin resistance are risk factors for the development of AD (Neth et al., 2017) and the role of wine polyphenols in this relationship have been also studied.

Next, we will review the main studies focused on the role of the majority polyphenols from EVOO and wine in the prevention/treatment of AD.

3. Neuroprotective effects of olive oil and wine polyphenols in Alzheimer disease.

3.1. Aβ aggregation and toxicity

3.1.1. Olive oil

According to the "Amyloid Cascade Hypothesis" one of the main causes of AD is overexpression and aggregation of Aβ in the cellular membrane, mainly around the synapse of neuronal tissue. There is a transmembrane glycoprotein called amyloid protein precursor (APP), which can be processed through two different pathways. In the

non-amyloidogenic pathway, APP is cleaved by α-secretase and □-secretase producing a soluble extracellular APP fragment (sAPPα), a short extracellular p3 peptide and a cytosolic APP intracellular domain (AICD). However, APP can be processed by β (β-site amyloid precursor protein cleaving enzyme-1; BACE-1) and □-secretase. This pathway is the amyloidogenic and produces Aβ which spontaneously aggregates into soluble oligomers and combines to form insoluble fibrils which are eventually deposited in diffuse senile plaques. The neurotoxic effect of Aβ depends on its state of aggregation, in which oligomers and protofibrils are more toxic than soluble monomers and mature fibrils (Long et al., 2019).

A possible role of polyphenols in the formation of these protein aggregates has been investigated for many years. Then, more than 40 polyphenolic compounds act preventing Aβ polymerization or joining to certain ions, inhibiting the aggregation of this peptide (Velander, Wu, Henderson, Zhang, Bevan, & Xu, 2017). Leri et al (2019) demonstrated, by physical analysis experiments, that oleuropein inhibits the growth of oligomers Aβ1–42 and the formation of mature fibrils and, by chance, HT promotes the formation of non-toxic fibrils. Moreover, both polyphenols reduce the capacity of Aβ aggregates to interact with cell membranes and Aβ toxicity (Leri et al., 2019). Other important findings have been obtained from *in vivo* AD models, such in TgCRND8 mouse, in which oleuropein treatment reduce Aβ deposits in different cortical areas and in hippocampus, being this effect due to a positive action on autophagy process (Grossi et al., 2013; Luccarini et al., 2015). A study in molecular mechanism reveals that oleuropein improves the clearance of Aβ deposits from neurons by up-regulation of autophagy-related genes, human beclin 1 gene (BECN1), Atg8/microtubule-associated light chain 3C (LC3), p62 and cathepsin B to accelerate the autophagy process (Pantano, Luccarini, Nardiello, Servili, Stefani, & Casamenti, 2017).

3.1.2. Wine

The potential AD benefits of rat brain-targeted polyphenols, assessed after red wine oral administration, were evaluated in a primary neuron cultures originated from the AD-type amyloid-β neuropathology mouse model (Tg2576). Quercetin-3-O-glucuronide (0-5 μM) interfered with the early protein-protein interaction (Aβ1–40 and Aβ1–42), which promoted a decrease in the occurrence of neurotoxic oligomeric Aβ species (Ho et al., 2013). A different study showed that muscadine wine reduces Aβ neuropathology and attenuates Tg2576 spatial memory decline. The results suggest that muscadine wine

effects are associated with the decrease in the brain of soluble high molecular weight oligomeric Aβ species (Ho et al., 2009).

In vitro, amyloid β-protein aggregation into high-molecular-weight oligomers is also inhibited by grape seed polyphenolic extract (200 mg/kg/d). The same study showed that those oligomers are also reduced in the brain of Tg2576 mice when this grape extract is orally administered, which results in a decrease in AD-type cognitive decline. Particularly, authors found that grape seeds extract reduces the Aβ aggregate specifically associated to memory loss in rats (J. Wang et al., 2008). A different study showed, through a cytotoxicity assays, that grape seed polyphenolic extract has protective effects when mixed with Aβ prior to or after peptide assembly and just before peptide addition to cells (Ono et al., 2008). A posterior experimental trial showed that when APP_{Swe}/PS1dE9 transgenic AD mice model is fed for 9 months with polyphenol-rich grape seed extract, depending on the analysis methods used, total brain amyloid burden is reduced by 33–45% (Y. J. Wang et al., 2009).

Some *in vitro* studies report that resveratrol, the most famous wine polyphenol, has an anti-Aβ aggregation effect. In SH-SY5Y human neuroblastoma cells, resveratrol inhibits Aβ42 peptide fibrillization in a dose dependent way (10–100 μM), and depolymerize prebuilt fibrils, resulting in non-toxic oligomers (Feng et al., 2009). In an *in vitro* assay using the 25–35 Aβ peptide fragment, which preserves the properties of neurotoxicity and aggregation of the entire peptide, it was found that resveratrol inhibits fibril formation with a half maximal inhibitory concentration value of 5.6 μM (Riviere, Richard, Quentin, Krisa, Merillon, & Monti, 2007). The specific and decisive mechanism by which resveratrol blocks *in vitro* aggregation is unknown, however, several proposals have been made. Low molecular weight oligomers (20 kDa, tetramer) are stabilized when Aβ42 is co-incubated with resveratrol, and this remodelled resveratrol-capped oligomers has shown a reduced cell toxicity (Fu, Aucoin, Ahmed, Ziliox, Van Nostrand, & Smith, 2014). In this atomic force microscopy study, it was also observed that resveratrol binds to Aβ1–42 monomers in their N-terminus (Fu et al., 2014), which is consistent with studies showing that resveratrol can also bind directly to Aβ in different states, including monomer and fibril Aβ, inhibiting Aβ42 fibril formation (Feng et al., 2009; Ge, Qiao, Qi, Wang, & Zhou, 2012). A different study showed that resveratrol can remodel soluble prefibrillar oligomers, fibrillar intermediates, and fibrils into non-toxic alternative aggregated species (Ladiwala et al., 2010). Administration of resveratrol for 45 days diminishes β-amyloid plaque formation

in mice brain, with the largest decrease in the plaques area proportion in the medial cortex (48%), striatum (89%) and hypothalamus (90%) (Karuppagounder, Pinto, Xu, Chen, Beal, & Gibson, 2009). Resveratrol can protect against Aβ plaque formation in APP/PS1 mouse hippocampus and prevent memory loss (Porquet et al., 2014). The decrease of Aβ levels and its extracellular accumulation in animals treated with resveratrol can also be mediated by adenosine monophosphate-activated protein kinase (AMPK) (Porquet et al., 2013; Vingtdeux et al., 2010). Resveratrol can also avoid Aβ aggregation and storage through the stabilization of transthyretin, which increases its circulating levels and improves their assembly to Aβ peptide (Santos, Rodrigues, Alemi, Silva, Ribeiro, & Cardoso, 2016). Based on these studies, several derivatives of resveratrol were designed and synthesized as AD multi-targeted therapeutic agents (S. Y. Li, Wang, & Kong, 2014; Lu et al., 2013; Xu, Zhang, Sheng, & Ma, 2017).

Quercetin has also a potent Aβ42 anti-aggregation power (75.4%), as shown in a study including both an *in vitro* cell-based and in silico approaches (Espargaro et al., 2017). A different *in vitro* study showed that the OH^- functional groups of quercetin B-ring is decisive for its potential to inhibit fibrils aggregation. According with this study results, quercetin also disrupts the mature fibrils (Suganthy, Devi, Nabavi, Braidy, & Nabavi, 2016). Quercetin decreases both number and area of amyloid plaques in the hippocampus and cortex of AD mice (D. M. Wang, Li, Wu, Zhu, Wang, & Yuan, 2014). Quercetin treatment (25 mg/kg) for three months decreases β-amyloidosis in 3xTg-AD model, contributing to cognitive protection and emotional function in animals (Sabogal-Guaqueta, Munoz-Manco, Ramirez-Pineda, Lamprea-Rodriguez, Osorio, & Cardona-Gomez, 2015). Quercetin orally administered to 5xFAD amyloid model mice reduces cortex insoluble Aβ levels (Zhang et al., 2016). Long-term (12 months) oral quercetin (100 mg/kg) administration to 3xTg-AD mouse model has significant effects on β-amyloidosis (Paula, Angelica Maria, Luis, & Gloria Patricia, 2019). To improve polyphenols bioavailability, stability, and ability to cross blood-brain barrier (BBB), nano-based delivery systems have been developed. Recently, the protective and therapeutic effects of quercetin nanoparticles (30 mg/kg) were investigated in aluminium chloride ($AlCl_3$) induced animal model of AD, and it was observed that they remarkably reduce the amyloid plaques development (Rifaai, Mokhemer, Saber, El-Aleem, & El-Tahawy, 2020).

Gallic acid has also alleviated cognitive decline of APP/PS1 double transgenic mice through reduction of Aβ1–42 aggregation and neurotoxicity (Yu et al., 2019).

3.2. Neurofibrillary tangles

3.2.1. Olive oil

The presence of intracellular NFTs is another of the pathological markers of AD. These NFTs are composed of tau protein in a hyperphosphorylated state. Under normal conditions, tau protein provides stability to the microtubules for the proper functioning of the neuron and its activity depends on its phosphorylation. In AD, tau is hyperphosphorylated and it appears in another different locations and not in the microtubules forming abnormal filaments, composed by tau and other microtubule associated with proteins. In this way, the microtubule is more unstable, so there are alterations in cellular transport and finally contributes to neuronal death. The cyclin-dependent kinase 5 (CDK5) and the glycogen synthase kinase 3β (GSK3β) phosphorylate tau and the protein phosphatase 2 A (PP2A) is the main phosphatase that dephosphorylates tau, acting on specific phospho-sites (Iqbal and Grundke-Iqbal., 2008). It has been demonstrated that oleuropein, oleocanthal and HT inhibit tau toxic aggregation demonstrated by physical assays *in vitro* (Rigacci & Stefani, 2016).

3.2.2. Wine

Resveratrol increases *in vitro* tau dephosphorylation through downregulation of extracellular signal-regulated kinases (ERK)1/2 and GSK3β, being the latter a key factor for tau protein hyperphosphorylation and NFTs genesis (Jhang, Park, Kim, & Chong, 2017). Resveratrol blocking of tau protein hyperphosphorylation, through the GSK3β inhibition, was also observed using a mouse neuroblastoma cell line widely used to study neurotoxicity (N2a cells) (He et al., 2016; Sun et al., 2019). Moreover, resveratrol (2.5 – 50 μM) could inhibit tau protein hyperphosphorylation both by the block of calmodulin-dependent protein kinase II (CaMKII), and trigger of protein PP2A (He et al., 2016). PP2A is the most important phosphatase that dephosphorylates tau, so its activation is a good strategy in the prevention and therapy of AD. It was shown that daily intraperitoneal injections of resveratrol (25 mg/ kg) in mice, for 2 weeks, increases PP2A activity by reducing microtubule-associated ubiquitin ligase (MID1) expression, through its proteasomal breakdown and subsequent destabilization of its mRNA (Schweiger et al., 2017). Recently, it was shown that resveratrol prevents caspase-3 activation, tau dephosphorylation at Ser^{422}, and genesis of misfolded protein aggregates, which protects optic nerve head astrocytes from oxidative stress-induced cell death

(Means, Lopez, & Koulen, 2020). When 6-month-old male PS19 mice (express mutant human microtubule-associated protein tau) were treated with resveratrol, orally administered (gavage) (40 mg/kg body weight) once a day for 5 weeks, it was observed that resveratrol suppresses tau assemblage and tau oligomer-induced cytotoxicity (Sun et al., 2019). Resveratrol decreases tau levels and improves cognitive function in rats (Al-Bishri, Hamza, & Farran, 2017; Y. T. Lin et al., 2018). Moreover, in rodents which early AD was induced by angiotensin-II, those results where related with the reducing activity of the Aβ–caspase3–Akt–GSK3β-tau pathway (Y. T. Lin et al., 2018). Both GSK3β and CDK5 activity decrease in resveratrol-fed senescence accelerated mouse (SAMP8), confirming that the inhibition these two major tau kinases in AD, prevents tau phosphorylation in the cortex and hippocampus of the animals (Porquet et al., 2013).

Quercetin treatment attenuates tau phosphorylation via suppressing ER stress/NLRP3 (endoplasmic reticulum/ Nod-like receptor family pyrin domain containing 3) inflammasome trigger in SH-SY5Y cell line (Chen et al., 2016). Quercetin reduces okadaic acid-induced tau protein hyperphosphorylation, inhibits the activity of CDK5, and blocks the Ca^{2+}-calpain-p25-CDK5 signalling pathway in murine hippocampal neuronal HT22 cells (Shen et al., 2018). Decline of tauopathy in the hippocampus and amygdala of 3xTg-AD mouse model was observed after a 12 months treatment with quercetin (100 mg/kg) orally given, furthermore this polyphenol improves cognitive functional recovery without altering the emotional skills (Paula et al., 2019). Quercetin nanoparticles (30 mg/kg) reduce the neuronal degenerative changes by reducing NFTs (Rifaai et al., 2020).

Anthocyanin-loaded polyethylene glycol-gold nanoparticles administered to amyloid beta (Aβ)1–42 mouse model of Alzheimer's disease regulate the p-PI3K/p-Akt/p-GSK3β (phosphoinositide 3-kinase/phospho-protein kinase B/phospho-glycogen synthase kinase 3 beta) pathway and consequently prevent tau protein at serines 413 and 404 hyperphosphorylation (Ali, Kim, Rehman, Ahmad, & Kim, 2017).

Neuroprotective effects of gallic acid against $AlCl_3$-induced AD in adult Wistar rat were recently studied and histological analyses showed that NFTs and amyloid plaques in the external granular layer are protected by gallic acid (Ogunlade, Adelakun, & Agie, 2020).

In vitro studies, with pheochromocytoma cells (PC12), showed that caffeic acid inhibits calcium influx and tau phosphorylation and, therefore ameliorates Aβ-induced neurotoxicity (Sul, Kim, Lee, Joo, Hwang, & Park, 2009).

3.3. Autophagy

3.3.1. Olive oil

Autophagy is a ubiquitous physiological process is the process through which old, damaged, or poorly folded proteins or organelles are degraded in lysosomes. During aging, autophagic activity decreases and this fact has been linked to the onset of cancer, diabetes and various neuropathologies, including AD. In fact, it has been classified as a proteinopathy due to the existence of aggregated proteins abnormally accumulated, which occurs early in AD development, and it is related to neuron apoptosis (Q. Li et al., 2017). Therefore, autophagy is considered as a therapeutic target for this neuropathology. Many proteins mediate the autophagy process, one of them is the mammalian target of rapamycin complex 1 (mTORC1), which inhibits autophagy. This effect is due to a repressive effect of components such as unc-51-like autophagy-activating kinase 1 (ULK1) and autophagy-related proteins such ATG13 and ATG101, that play a key role in the start of the autophagic process (Q. Li et al., 2017).

Polyphenols modulate autophagy through different pathways and there are differences between each other in their mode of action (Benvenuto et al., 2020). Oleuropein reduces aggregated proteins by a positive effect on autophagy inhibiting AMPK/mTOR, activation of gene expression of protein related to autophagy and acetylation of histone or EB transcription factor. As mentioned above, in the AD mouse model TgCRND8, which overexpress the Swedish and Indiana mutations in the human amyloid precursor protein, oleuropein treatment reduces Aβ deposits in different brain areas. This effect is due to the activation of autophagy, by activating various genes related to the process such as, BECN1, LC3, p62 and cathepsin B, as well as the formation of autophagosome-lysosome to speed up the autophagy process (Pantano et al., 2017).

3.3.2. Wine

In SH-SY5Y cell model, minimal concentrations of resveratrol (2 μM) blocks, by an autophagy-dependent way, the effects of prion protein on mitochondrial transmembrane potential, Bcl-2-associated X protein (Bax) translocation to mitochondria, and cytochrome C release from the organelles (Jeong et al., 2012). Resveratrol induces autophagy, in dopaminergic SH-SY5Y cells challenged with rotenone via haem oxygenase (T. K. Lin et al., 2014) and AMPK/SIRT1 (sirtuin-1) signalling (Wu et al.,

2011). Moreover, neurotoxicity caused by Aβ25-35 in PC12 cells is attenuated by resveratrol, through inducing autophagy, which is partially mediated via activation of the TyrRS -PARP1-SIRT1 signalling pathway (Deng & Mi, 2016). A study with PC12 cells AD showed that resveratrol inhibits Aβ42-induced mitochondrial damage and increases mitophagy (H. Wang, Jiang, Li, Gao, & Zhang, 2018). In AD mouse models, resveratrol shows some protective effect against AD-like pathology through AMPK-mediated autophagy activation (Vingtdeux et al., 2010).

Liu et al. (2019) synthesized quercetin modified polysorbate 80 (P-80)-coated AuPd core-shell structure and find that they induce autophagy of SH-SY5Y cells. In this study, quercetin promotes the fusion of autophagosomes and lysosomes, speed up the Aβ clearance, and protect SH-SY5Y cells from Aβ-induced cytotoxicity injury (Liu et al., 2019).

Taken together these results confirm that wine polyphenols can activate and/or promote autophagy to stimulate clearance of unwanted protein aggregates, and therefore they are a promising therapeutic approach against AD.

3.4. Mitochondrial function

3.4.1. Olive oil

In the pathophysiological frame of AD, the mitochondrial energetic deficit is one of the early damage/events involved in the advance of disease. Specifically, a decreased mitochondrial ATP production, as well as an unbalancedmitochondrial dynamics, have been showed *in vitro* and *in vivo* studies of AD (Reddy & Oliver, 2019). These mitochondrial damages/alterations are clinically translated to an early memory loss, because there is not enough energetic support to carried out the neurological processes. Recent studies have suggested that polyphenols from EVOO could ameliorate and/or revert the mitochondrial dysfunction characteristic of AD. Grewal et al. (2020), have reported that oleuroside, oleacein, ligstroside and oleocanthal elevated the ATP production in SH-SY5-APP659 cells and in brain of an animal model of early AD. Moreover, other *in vitro* studies have demonstrated that oleocanthal and ligstroside induced an increase of the mitochondrial biogenesis. These beneficial results were reflected on an improved spatial working memory and cognitive function in ligstroside fed aged mice (Grewal et al., 2020). In this same line, it is also noteworthy that the beneficial and hopeful properties of HT, the foremost phenolic component of EVOO, on

cerebral mitochondrial dysfunction. Visioli and collaborators have currently demonstrated that HT increased ATP production, the mitochondriogenesis and mitochondrial fusion in 7PA2 cells, one cellular model of AD with a well-characterized mitochondrial dysfunction (Visioli, Rodríguez-Pérez, Gómez-Torres, Pintado-Losa, & Burgos-Ramos, 2020). Other study reported that HT ameliorated mitochondrial dysfunction and cognitive behaviour in the brain of APP/PS1. However, they only analysed mitochondrial markers related to oxidative stress and inflammatory response Aβ-induced and not the cellular energetic production (Peng et al., 2016). Additionally, it has shown that the intake of a mixture of highly purified secoiridoid polyphenols improved energy metabolism in the brain of aged mice (Reutzel et al., 2018). Up to the present date, all investigations seem to point that EVOO polyphenols exert remarkable neuroprotective effects on damaged cerebral mitochondria in AD, appropriate clinical trials should be carried out to confirm these preclinical findings.

3.4.2. Wine

Resveratrol has some indirect mitochondrial effects, including decrease of oxidative stress and induction of mitochondrial biogenesis, through the activation of peroxisome proliferator-activated receptor gamma coactivator 1α (PGC1α). After the work of Howitz et al., published in 2003, resveratrol is one of the most SIRT1 activators molecules studied (Howitz et al., 2003). The mechanism of action is not fully elucidated, although several studies indicate that SIRTs mediate some of resveratrol effects (Sanchez-Fidalgo, Villegas, Sanchez-Hidalgo, & de la Lastra, 2012). Resveratrol upregulates SIRT1-mediated mitochondrial biogenesis and stimulate AMPK and PGC-1α functions. In cell culture, activation of AMPK by resveratrol occurs by increasing cytosolic calcium levels, and by promoting phosphorylation of AMPK trough calcium/calmodulin-dependent protein kinase kinase β (CaMKK β) pathway. When orally administered, resveratrol crosses the mice BBB and activates brain AMPK (Vingtdeux et al., 2010). In SH-SY5Y neuronal cells, resveratrol ameliorates mitochondria oxidative stress, apoptosis and cell death induced by hypoxia by improving transient receptor potential melastatin 2 (TRPM2) channel activation, decreasing mitochondrial oxidative stress, and protecting glutathione (GSH) and glutathione peroxidase (GPx) thiol redox system. This outcome result from an increase in the mitochondrial function restore via modulation of TRPM2 channel and calcium signalling (Akyuva & Nazıroğlu, 2020).

Quercetin (40 mg/kg) alleviates Aβ-induced mitochondrial dysfunction as evidenced by mitochondrial membrane potential recovery in APPswe/PS1dE9 transgenic mice. The results suggest that quercetin activates AMPK which improves cognitive functioning in this animal model (D. M. Wang et al., 2014).

3.5. Cerebral Insulin resistance

3.5.1. Olive Oil

Recently, epidemiological evidence has found insulin resistance in brain of AD patients because the insulin signalling pathway is blocked at levels of the insulin-receptor substrate 1(IRS1) by Aβ-induced hyperphosphorylation (Diehl, Mullins, & Kapogiannis, 2017). Consequently, at cellular level, astrocytes do not capture glucose and no transform it into lactate, main fuel for neurons, exacerbating neuronal damage. A recent study has demonstrated that HT protects Aβ-treated astrocytes by improving insulin sensitivity, what suggested that HT as nutritional supplement could reduce insulin resistance associated with AD (Crespo, Tomé-Carneiro, Pintado, Dávalos, Visioli, & Burgos-Ramos, 2017). HT administration for 30 days, also activated hippocampal neurogenesis and increased neuronal survival in aged mice (D'Andrea et al., 2020). In the same stage, oleocanthal revert the Aβ-induced glucose transporter type 1 (GLUT1) down-regulation in astrocytes, favoring the astrocytic glucose uptake (Batarseh et al., 2017). Many other polyphenols, as oleacein, play a protective role in peripheral insulin resistance in obesity mice (Cao et al., 2014; Lombardo et al., 2018; Lepore et al., 2019). Nevertheless, the effects on cerebral insulin resistance have not been analyzed yet. On the whole, these evidence suggest that EVOO polyphenols could be used to improve the cerebral insulin resistance associated with AD. However, more *in vitro* and *in vivo* studies should be carried out to deeply explain their action mechanism.

3.5.2. Wine

Memory-impairing effects of diet-induced obesity may be mediated by neuroepigenetic dysregulation of SIRT1 in the hippocampus. Resveratrol was administrated to a rat model of brain insulin resistance with intracerebroventricular injection of streptozotocin (ICV-STZ; 3 mg/kg, twice with an interval of 48 h) for 8 weeks (30 mg/kg, once per day). At the end, it was concluded that resveratrol was able to reverse the ICV-STZ-

induced decrease in SIRT1 activity, the increase in both ERK1/2 phosphorylation and tau phosphorylation. Consequently, resveratrol also reversed the impairment of cognitive capability (Du et al., 2014). Similarly, in obese mice fed a diet supplemented with resveratrol exhibit increased hippocampal SIRT1 activity and preserved hippocampus-dependent memory (Heyward et al., 2016). In summary, resveratrol can prevent cognitive impairment induced by brain insulin resistance, by protecting hippocampus neurons from tau hyperphosphorylation through SIRT1 pathway and decrease in hippocampus ERK1/2 activity. In a recent study, supplementation with 0.1% resveratrol, over 16 weeks, protects against high fat diet (HFD)-induced memory loss in male wild type mice and prevents memory loss in 5XFAD mice. These results confirm the potential of resveratrol to counteract the deleterious effects of the diet, by decreasing the excessive activation of proteasome and immunoproteasome, probably caused by the metabolic stress (Sarroca et al., 2021).

3.6. Clinical trials

3.6.1. Olive Oil

In the 60's, the population studies showed that inhabitants of Mediterranean arch had a minor risk of developing AD and other associated-aging disorder. Successive studies have demonstrated that consumption of Mediterranean diet is the responsible for this population fact/evidence (Manach et al., 2004; Scarmeas et al., 2006; Estruch et al., 2015). Specifically, the randomized clinical trial PREDIMED-NAVARRA (ISRCTN:35739639) showed that a Mediterranean diet supplemented with EVOO (50g per day) improved the cognitive function in 552 participants in comparison with a low-fat control diet, after 6,5 years of intervention (Martínez-Lapiscina et al., 2013). All evidence suggested that the foods of Mediterranean diet, rich in polyphenols, are the most suitable for improving the cognitive function and stopping or preventing the onset of neurodegenerative disorders as AD. To date, a clinical trial aimed to evaluate the effect of EVOO (10 mg daily for one year) on AD is now recruiting (NCT: 04229186) patients between 50-70 years old, with mild cognitive impairment diagnosed One group will receive EVOO and the other an olive oil poor in polyphenols for 12 months. They will exanimate biomarkers of neurodegeneration in cerebrospinal fluid (CSF), changes of cortical thickness, brain amyloid plaque load and neurological and neuropsychological features. A recent clinical trial (NCT03362996) has reported that EVOO annual consumption (50ml daily) on older patients with mild cognitive

impairment, prevents progression of AD (Tzekai et al., 2021). However, few nutritional intervention studies have been carried out to investigate the possible neuroprotective role of each one of existing phenolic components in EVOO. In this regard, we have identified two ongoing clinical trials, one will evaluate HT (NCT:04440020) effects and other oleocanthal (NCT:03824197) in patients with some clinical cognitive alteration diagnosed, such as memory loss or dementia. In both studies, they will carry out cognitive and neuroimaging studies and several markers of neurodegeneration will be measured to demonstrate the neuroprotective effect of the polyphenol from olive oil cited. Currently, both clinical trials are recruiting patients between 55 and 85 years old, of both genders, with some clinical dementia diagnosed.

3.6.2. Wine

Regular wine consumption has been linked with a reduced risk of AD. The Canadian Study of Health and Aging showed that moderate wine consumption halved the risk of AD after 5 years follow up (Lindsay, 2002). In the Italian Longitudinal Study on Aging, the influence of wine consumption on the incidence of mild cognitive impairment was evaluated in cognitively normal individuals and on its advance to dementia in 121 patients with mild cognitive impairment (65 - 84 years). The consumption of less than one drink of wine per day by patients with mild cognitive impairment decreased the rate of progression to dementia (Solfrizzi et al., 2007). Comparing current alcohol drinkers versus former or never drinkers, it was found that wine was also protective for dementia, being this effect greatest among women who drank wine only (Göteborg Study) (Mehlig et al., 2007). Moderate wine consumption was also independently associated with better cognitive results on all tests, after 7 years of follow up, compared with low alcohol intake (Tromsø Study) (Arntzen, Schirmer, Wilsgaard, & Mathiesen, 2010).

Table grapes twice-daily consumed (72 g), over 6 months, protected cerebral metabolism, which was correlated with improvement in attention/working memory performances as showed by a double-blind placebo-controlled longitudinal pilot study (Lee, Torosyan, & Silverman, 2017).

Resveratrol administrated in single oral doses (250 and 500 mg) to healthy adults improved cerebral blood flow, however, had no effect in short-term cognitive performance (Kennedy et al., 2010). In healthy overweight older participants of a double-blind placebo-controlled interventional study, resveratrol supplementation (200

mg/d) over 26 weeks, improved their memory performance and functional connectivity of the hippocampus. It was concluded that resveratrol induces positive effects on glucose metabolism and subsequent neuronal function and cognitive performance (Witte, Kerti, Margulies, & Floel, 2014). In a clinical phase 2 trial, 119 patients with mild to moderate AD, received 500 mg resveratrol per day for 52 weeks and the dose was increased by 500 mg every 13 weeks. Compared with placebo, resveratrol promoted an increase in ventricular volume and a decrease in brain volume. Resveratrol also promoted a decrease of Aβ40 levels in plasma and CSF (Turner et al., 2015). Resveratrol modulated neuro-inflammation and induce adaptive immunity in AD patients (Moussa et al., 2017). A non-significant decrease in glycated haemoglobin A1c (HbA1c), which is a long-term marker of glucose control, was observed with a daily supplementation with 200 mg resveratrol over 26 weeks. Additionally, supplementation significantly increased resting-state functional connectivity between the right hippocampus and the right angular cortex and preserved the volume of the left, particularly anterior, hippocampus with a moderate effect size (non-significant). Memory performance and hippocampus microstructure did not beneficiate with resveratrol supplementation (Köbe et al., 2017). Resveratrol administration to post-menopausal women (45–85 years) for 14 weeks improved the performance of cognitive tasks in the domain of verbal memory and in overall cognitive performance (Evans, Howe, & Wong, 2017). In a more recent randomized placebo-controlled crossover trial, with postmenopausal women in the same age range, the consumption of 75 mg resveratrol twice-daily for 12 months resulted in a 33% improvement in overall cognitive performance. Moreover, resveratrol improved cerebrovascular function and insulin sensitivity in postmenopausal women (Thaung Zaw, Howe, & Wong, 2020). A double-blind randomized controlled trial, in which elderly participants (60–79 years) received either resveratrol (200 mg/day) or placebo for 26 weeks, failed to show significant improvements in verbal memory (Huhn et al., 2018). Resveratrol neuroprotective benefits were not also detected in a multicentric placebo-controlled phase II trial, in which AD patients were randomized to receive a dose of 500 mg of resveratrol every 13 weeks, up to 52 weeks (Zhu et al., 2018). These clinical trials show that resveratrol, at the doses administered, is safe and well-tolerated, however, the benefit effects of resveratrol in human clinical trials are far away from the ones observed in animal models. In general, there are no or small effects of resveratrol in human cognition. Several reasons can explain this difference namely resveratrol

dose/body weight and trials duration. In the future, better designed long term trials must be done to evaluate the resveratrol efficacy. In table 1, we recapitulate all the clinical trials mentioned above.

4. Conclusions

Numerous studies show us the beneficial effects of Mediterranean diet, not only for health but also in the therapeutic and preventive framework of the neurodegenerative diseases. In this work, we have focused on reviewing the state of the art of polyphenols from olive oil and wine on prevention and/or treatment of AD. It is well known that life expectancy is progressively increasing along time, however, this fact carries a negative point, major prevalence of neurodegenerative aging-associated disease like AD. Therefore, the national public health systems have had to increase the budgetary spending for caring and mitigating the symptoms in patients with AD. Preclinical and clinical studies carried out for last five years, have reported that polyphenols from olive oil and wine are active components which exert a noteworthy neuroprotective effect. These polyphenols reduce the Aβ aggregation and tau-protein hyperphosphorylation, promoting autophagy and improving the damaged mitochondrial function and cerebral insulin resistance related to AD. Therefore, all these evidence could conclude that intake of polyphenols from EVOO and or wine could be a great therapeutic tool to prevent or delay the neurodegeneration present in AD. However, some limitations must be considered in future studies. Defining the bioavailability of polyphenols clearly would help to describe action mechanisms of these molecules because current data are still limited.

Another unclear issue is whether the polyphenols from daily consumption olive oil and wine are enough or conversely, a nutritional supplement enriched with polyphenols would be more efficient to exert their neuroprotective effects. In order to elucidate this limitation, we consider that future interventional trials, with an accurate dose of polyphenols, should be carried out. In addition, we must take into account that recruiting a homogenous cohort of patients with the same degree of cognitive decline is very difficult.

Therefore, more longitudinal studies in humans are necessary to corroborate the efficacy of these nutraceuticals, as well as analyze which is the most appropriate dose for this purpose. In summary, with this review we would like to highlight that a moderate consumption of wine and olive oil could be beneficial for our brain, thanks to their polyphenols.

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Conflict of Interest

None.

Authorship

P.S. and E. BR designed and planned the manuscript. M.RP, O. GT and E.BR wrote what related with olive oil and P.S. of the wine. P.S. designed the figures and EBR the table. All authors provided critical feedback and helped shape the work and approved the submission of the final version.

Abbreviations

AD, Alzheimer disease

AICD, Amyloid protein precursor intracellular domain

AMPK, Adenosine monophosphate-activated protein kinase

APP, Amyloid protein precursor

ATG, Autophagy-related protein 13 / 101

Aβ, Amyloid beta peptide

BACE-1,β-site amyloid precursor protein cleaving enzyme-1;

BBB, Blood-brain barrier

BECN, Human beclin 1 gene

CaMKII, Calmodulin-dependent protein kinase II

CaMKK β, Calcium/calmodulin-dependent protein kinase kinase β

CDK5, Cyclin-dependent kinase 5

CSF, Cerebrospinal fluid

ER, Endoplasmic reticulum

ERK, Extracellular signal-regulated kinases

EVOO, Extra virgin olive oil

GLUT1, Glucose transporter type 1

GPx, Glutathione peroxidase

GSH, Glutathione

GSK3β, Glycogen synthase kinase 3β

HT, Hydroxytyrosol

HT22, Murine hippocampal neuronal cell line

IRS1, Insulin-receptor substrate 1

LC3, Microtubule-associated protein 1A/1B-light chain 3

MID1, Microtubule-associated ubiquitin ligase

mTOR, Mammalian target of rapamycin

mTORC1, Mammalian target of rapamycin complex 1

MUFAs, Monounsaturated fatty acids

N2a, Mouse neuroblastoma cell line

NF-B, Nuclear factor-kappa beta

NFTs, Neurofibrillary tangles

NLRP3, Nod-like receptor family pyrin domain containing 3

p-Akt, Phospho-protein kinase B

PARP1, Poly(ADPribose) polymerase I

PC12, Pheochromocytoma cells

PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1α

p-GSK3β, Phospho-glycogen synthase kinase 3 beta

PI3K, Phosphatidylinositol-3-Kinase

PP2A, Protein phosphatase 2 A

PS1, Presenilin-1

PUFAs, Polyunsaturated fatty acids

SAMP8, Senescence accelerated mouse

SH-SY5Y, Human neuroblastoma cells

SIRT1, Sirtuin-1

TRPM2, Transient receptor potential melastatin 2

ULK1, unc-51-like kinase 1

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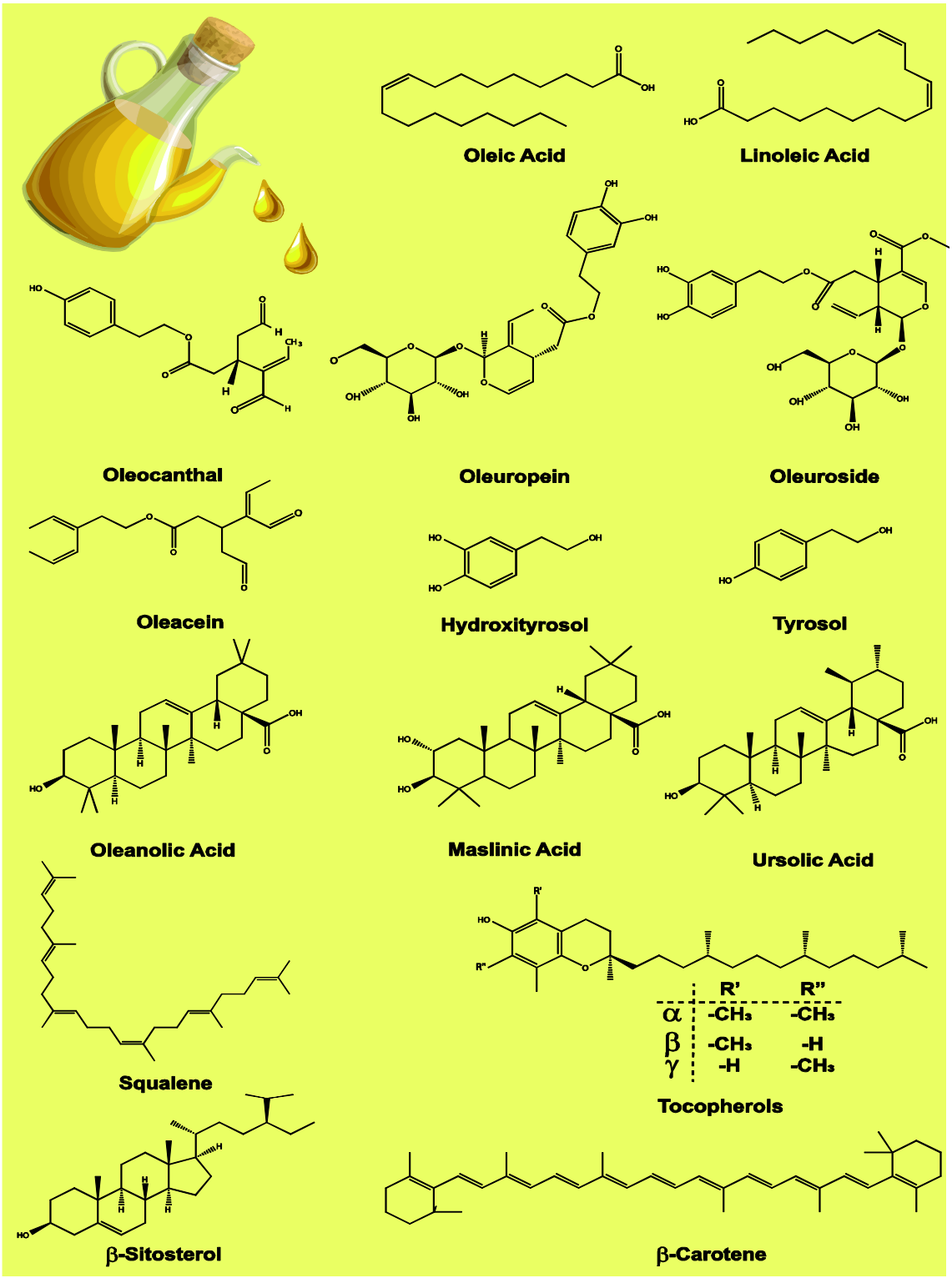

Figure 1. Representative chemical structures of some relevant compounds present in extra virgin olive oil.

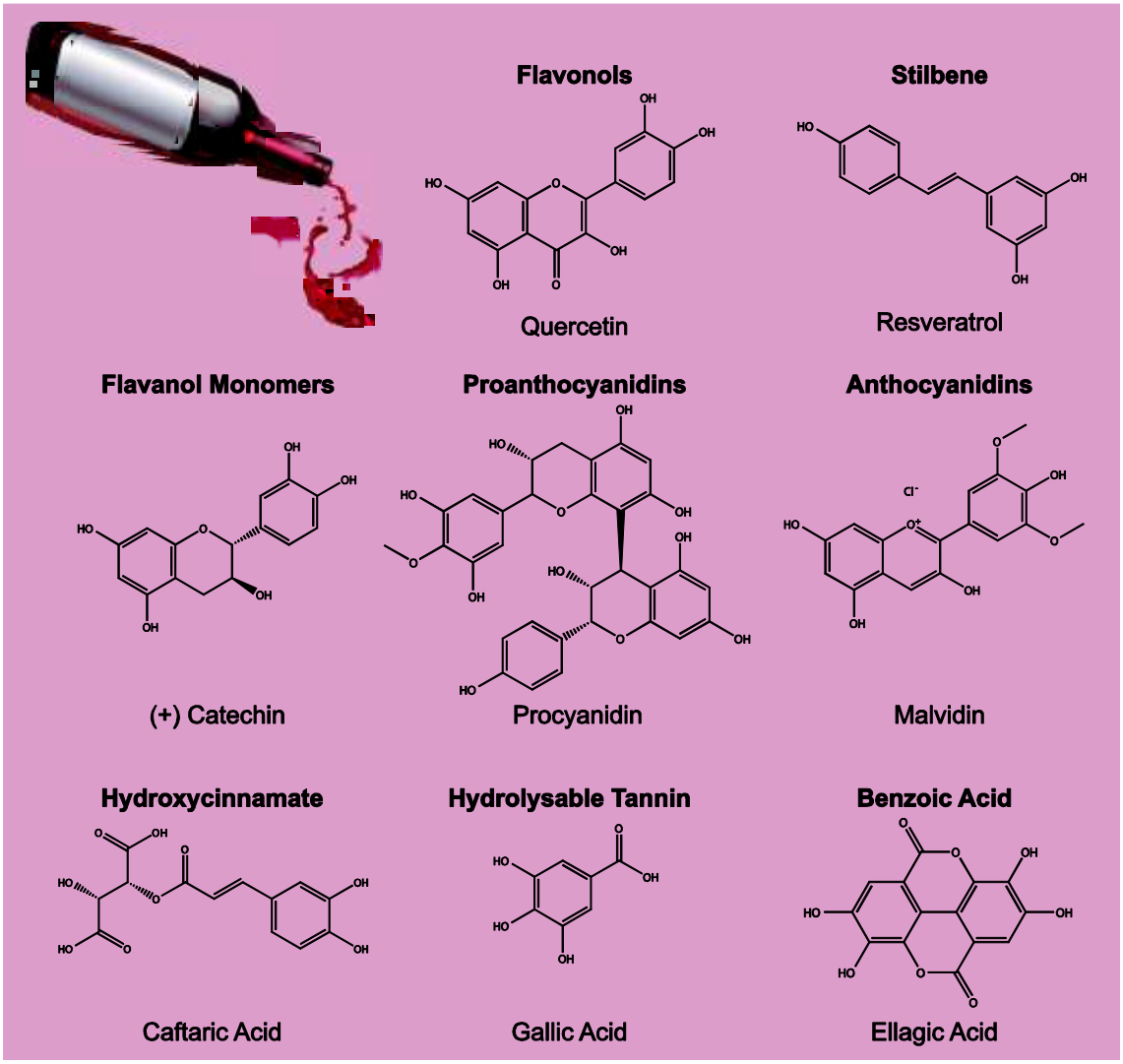

Figure 2. Representative chemical structures of some relevant compounds present in wine.

Table 1: Summarize of the cited clinical trials in this review about polyphenols of EVOO and wine on AD.

Clinical trials EVOO		
EVOO		
Reference or number clinical trail	Treatment dose daily	Time of follow up
Martinez-Lapiscina et al.,2013	50g	6,5 years
NCT: 04229186	10mg	1 year
NCT:04440020	----	----
NCT: 0324197	----	----
Tzekaki et al., 2021	50ml	1 year
WINE		
Wine		
Lindsay, 2002	---	5 years
Solfrizzi et al., 2007	< 1 drink/day (approximately 15 g of alcohol)	3,5 years
Mehlig et al., 2007	---	34 years
Arntzen et al., 2010	---	7 years
Grapes		
Lee et al., 2017	72 g/day	0,5 years
Resveratrol		
Witte et al., 2014	200 mg/d	26 weeks
Turner et al., 2015	500 mg resveratrol per day for 52 weeks and the dose was increased by 500 mg every 13 weeks	65 weeks
Moussa et al., 2017	500 mg/day (with a dose escalation by 500-mg increments every 13 weeks, ending with 1000 mg twice daily).	52 weeks
Köbe et al., 2017	200 mg/d	40 weeks
Evans et al., 2017	75 mg twice daily	14 weeks
Thaung et al., 2020	75 mg twice daily	12 weeks
Huhn et al., 2018	200 mg/day	26 weeks
Zhu et al., 2018	500 mg of resveratrol every 13 weeks	52 weeks

EVOO; extra virgin olive oil. --- missing data/ recruiting patients