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Mini Review

Effect of Extra Virgin Olive Oil Consumption on Neurodegenerative Disease

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Abstract

Mediterranean diet (MeDi) is one of the most commonly described and studied dietary pattern in scientific literature and typically includes a diversity of foods, nutrients and constituents that are considered beneficial for the health. MeDi is robustly associated with lower risk of mortality, cardiovascular disease, metabolic disease, and cancer. Extra virgin olive oil (EVOO) is one of the most characteristic components of MeDi and is characterized by its antioxidant and anti-inflammatory activity. It has been reported that the consumption of EVOO is beneficial by reducing blood lipids content, inflammatory and oxidative stress markers. Moreover, EVOO consumption exerts an anti-inflammatory and antithrombotic function. This mini review summarizes all recent articles that have studied the effect of EVOO and its components on mental health and their impact on neurodegenerative disease. PubMed databases were examined from 2020 to 2024 by using the following key words: olive oil, mental health, neurodegeneration. This mini review focus on both established and less established mechanisms of action of EVOO and its components on neurodegenerative disorders. The following article types were considered eligible for inclusion in our study: studies carried out *in vitro, in vivo* and *in-silico*. All the reports analyzed are suggesting that EVOO consumption exhibits a protective role against neurodegenerative disorders.

Keywords: Extra virgin olive oil; Aging; Health; Neurodegeneration; Polyphenols; Anti-oxidant; Anti-inflammatory; Mediterranean diet

Introduction

Emerging studies plays attention to the diet's benefit on the human health, including the role of diet in promoting an enhanced lifespan. Several studies demonstrate that Mediterranean diet (MeDi) is strongly associated with lifespan extension as well as with healthy aging by reducing the progression of age-related pathologies [1-3]. In particular, EVOO ant its components play a key role in promoting an healthy aging [4,5].

The components of MeDi derive from various cultures present now and in the past in the Mediterranean region. MeDi is not only a dietary pattern, while it represents a defined lifestyle [3].

Clinical observational studies have demonstrated that high adherence to MeDi results in a better quality of life, enhanced longevity, reduced mortality and decreased risk of developing cardiovascular diseases, cancer, and other disorders [6-10].

Several investigations underline the important role of natural products present in the MeDi on the decreased risk of developing several chronic age-related illness [11]. These products exhibit antioxidative, anti-inflammatory, antithrombotic and anti-neoplastic effects [12].

Extra Virgin Olive oil (EVOO), the primary source of fat in MeDi, contains mostly monounsaturated fats, various antioxidant phenols and polyphenols, and other micronutrients [13].

Clinical and preclinical studies unveiled that EVOO promotes beneficial effects on brain aging and cognitive function, suggesting its neuroprotective effect and its role on the prevention of neurodegenerative disorders [14].

EVO is considered excellent because of its organoleptic and nutritional properties. According to the International Olive Council, EVOO production is tripled over the last 60 years and it is estimated that its production will reach 3,375,500 t (+32%) in the season 2024/25. The production of EVOO is concentrated in the Mediterranean area. EVOO produced by extraction from olives can be consumed directly as crude oil without any additional treatments. Several features related to EVOO organoleptic properties and nutritional quality have been extremely explored. EVOO composition changes with the different tree genotypes and oil extraction mechanisms. Major and minor fractions characterize the composition of EVOO. Glycerol, the major components, represent more than 98% of total EVOO weight. Minor components include more than 230 chemical compounds such as aliphatic and triterpenic alcohols, sterols, hydrocarbons, volatile compounds and antioxidants (carotenoids and polyphenols) [15]. Several clinical and epidemiological studies demonstrate the beneficial effects of EVOO. Indeed, EVOO exhibits antimicrobial, antioxidant, antihypertensive, hypoglycemic, antiproliferative and vasodilatory effects [16]. Macro- and micro-components of EVOO play a role in

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reducing the risk of several chronic diseases, such as cardiovascular diseases (CVD) [17,18], atherosclerosis [17], obesity and metabolic syndrome [19-21], Parkinson disease [22], Alzheimer disease [23], cancer [24-26], insulin resistance and diabetes [27,28], nonalcoholic fatty liver disease [29], and inflammatory diseases [30,31]. The aim of this mini review is to highlight the recent findings demonstrating the beneficial role of EVOO on degenerative disorders by summarizing the data present in pubmed database for articles published from 2020 to 2024.

Alzheimer Disease

AD is characterized by the presence of amyloid plaques, composed by the aggregated amyloid peptide (Aβ) and by the formation of neurofibrillary tangles constituted by hyperphosphorylated tau [32]. Alzheimer disease (AD) is a slowly progressive neurodegenerative disorder, characterized by a mixed proteinopathy, where amyloid pathology and tau-pathology act in concert to induce cognitive decline [32]. Many researchers have studied in vitro and in vivo the effect of different compounds present in EVOO on AD pathophysiology. EVOO exerts an anti- inflammatory function in an AD mice model by enhancing the production of IL-5 and reducing the levels of MIP-2, IL-17E, IL-23, and IL-12p70 [33]. Moreover, EVOO ameliorates the cognitive function, neuroinflammation and synaptic activity in a mice model of Down syndrome [34].

Polyphenols, such as tyrosol, hydroxytyrosol, secoiridoids, and lignans, confer to EVOO the typical pungent and bitter taste properties and also provide the chemical stability and resistance to lipid oxidation [35]. Recently it has been demonstrated that the polyphenols present in EVOO are beneficial against AD by reducing in vitro the toxicity induced by the amyloid peptide 1-40 (Aβ40). Indeed, low concentrations of EVOO extract reduce the rate of Aβ40 aggregation and fibril mass by binding preformed Aβ40 fibrils and soluble Aβ oligomers in SH-SY5Y cells [36].

Pro-inflammatory S100A9 protein plays an important role on AD by co-aggregating with Aβ and contributing to amyloid plaque formation, providing a link between the neuroinflammatory cascades and Aβ-induced neurodegeneration. S100A9 co- aggregates with other proteins in AD, contributing to amyloid plaque formation and neurotoxicity. The amyloidogenic nature of S100A9 and its role in chronic neuroinflammation suggest that it may play a key function in AD pathophysiology. Leri and colleagues reveal that hydroxytyrosol (HT), present in EVOO, modulates S100A9 and amyloid co-aggregation and S100A9 self-assembly, suggesting that EVOO consumption may be considered as a preventive treatment against AD [37]. Oleuropein (Ole), the major polyphenols contained in EVOO, presents beneficial properties against various diseases through different mechanisms. Tau aggregation is characterized by the self-assembly of its hexapeptide domain, paired helical filament 6 (PHF6). The inhibition of tau aggregation is considered a therapeutic strategy for AD and other tauopathies. Srijita Paul and Parbati Biswas, using computational modeling and molecular dynamics simulations, demonstrate that PHF6 monomers collapse in water to form β-sheet rich structures. Notably, the polyphenol oleuropein aglycone (OleA) derived from EVOO, can significantly inhibit PHF6 aggregation, suggesting a therapeutic effect of OleA against AD and tauopathies [38].

EVOO exerts an anti-inflammatory function that is promoted by polyphenols, oleuropein aglycone (OleA) and hydroxytyrosol (HT) present in EVOO.

In vitro studies analyzing carried out in human neuronal (SH-SY5Y) and microglial (BV2 and C13NJ) cells activated by LPS reveal that treatment with EVOO-derived molecules reduce the release of pro-inflammatory cytokines (IL-6, IL-8, IP-10 and RANTES) and induce the activation in microglia of the TREM2-dependent anti-inflammatory pathway, which promotes the formation of protective microglia by favoring the M2 polarization microglia phenotype [39]. Moreover, the phenolic fraction of EVOO reduces the expression of pro-inflammatory cytokine in Aβ1-42- treated neutrophils and the pretreatment with the EVOO phenolic fraction prevent neutrophil activation [39].

Interestingly, in silico studies aimed to predict the similarities between existing drugs against AD and known EVOO-derived molecules reveal that ten EVOO-derived molecules show a high similarity in the mechanism of action with anti-AD drugs. These findings open the way to future clinical trials assessing the efficacy of EVOO- derived molecules as therapeutic agents for AD [40].

EVOO also exhibits an anti-inflammatory function. Indeed, EVOO-derived Oleocanthal, a phenolic compound, inhibits the pro-inflammatory nuclear factor-κB (NF-κB) pathway and reduces the activation of NOD-, LRR- and pyrin domain- containing protein 3 (NLRP3) inflammasomes [41].

Parkinson Disease

Parkinson disease (PD) is a neurodegenerative disease characterized by the formation of aggregates constituted by alpha-synuclein. In PD, S100A9 co- aggregates with α-synuclein (α-Syn). As reported above, Leri and colleagues reveal that hydroxytyrosol (HT) interact with S100A9 and blocks its self-assembly as vwell as its expression, suggesting the potential role of HT against S100A9 aggregation and its use as nutraceuticals for the prevention of neurodegenerative diseases characterized by the co-aggregation of S100A9 (37). Indeed, HT considerably reduces the conformational changes of α-Syn and the formation of β-sheet, promoting its aggregation. Moreover, HT increases the coil content of α-Syn trimer, confirming the role of HT in inhibiting the conformational changes and the aggregation of various molecules [42]. In addition, HT is able to reduce α-synuclein- induced inflammation. This effect seems to be mediated by MAPKs and the generation of ROS through the NADPH oxidase.

In vivo and in vitro studies demonstrate the beneficial role of EVOO-derived polyphenols in PD. Hydroxytyrosol acetate (HTA) and dihydroxyphenyl acetic acid (DOPAC) completely inhibit α-Syn aggregation in vitro and in vivo in a Caenorhabditis elegans model of PD [43].

Huntington Disease

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder. It occurs as a result of the expansion of cytosine, adenine, and guanine (CAG) trinucleotide repeats on the short arm of chromosome 4p16.3, which encodes the Huntingtin (HTT) gene. The expansion of this three-nucleotide repeat leads to an

abnormally long polyglutamine domain in huntingtin (htt) protein, which promotes neurodegeneration [44].

Several studies attribute the healthy properties of EVOO and its role on the prevention of HD to its peculiar fatty acid composition. Oleuropein, present in olive leaves and EVOO, promotes cell viability and reduces the formation of soluble and aggregated forms of mutant huntingtin (mHtt) protein in an HD cell models constituted by striatal neuronal cells carrying and expressing the mHtt ($STHdh^{Q7/Q7}$). The reduction of mHtt aggregates was associated to enhanced proteasome activity, which degrades mHtt. Moreover, EVOO-derived oleuropein modulates the proteasome activity through an unidentified pathway, which do not alter the 20S proteasome catalytic β subunits, the proteasome regulator PA28γ, or multiple MAPK pathways [45].

Conclusion

In summary, EVOO plays an important role on the human health. EVOO consumption could protect the nervous system and decrease the occurrence of neurodegenerative disease. Future research including mammalian models and clinical trials are needed to uncover the full potential of EVOO and EVO-derived molecules.

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