Effect Of An Extra-Virgin Olive Oil Intake On The Delay Of Cognitive Decline: Role Of Secoiridoid Oleuropein?

Abstract: Currently, there is an increase in the number of the world’s aging population. This aging process is often connected with cognitive decline of some functions such as memory or speed processing loss. Since Alzheimer’s disease cannot be cured yet, considerable efforts are being made to at least delay this cognitive decline among elderly in order to maintain and prolong the quality of their life. This can also be achieved by non-pharmacological approaches such as performing physical activities, cognitive training, or adhering to a Mediterranean Diet (MedDiet). One of the components of MedDiet – extra-virgin olive oil (EVOO) – has considerable health benefits. The purpose of this review is to examine the effect of EVOO intake on the delay of cognitive decline among the elderly. The methodology is based on a literature review of available sources found on the research topic in three acknowledged databases: Web of Science, Scopus, and PubMed. The results of in vitro and in vivo studies indicate that the regular intake of EVOO is associated with enhanced cognitive functions, which means that this oil may have a neuroprotective effect and could positively prevent the development of dementia, especially Alzheimer’s dementia. It is believed that secoiridoid oleuropein is responsible for this effectiveness. Furthermore, there is also a need of more randomized controlled studies or longitudinal observational studies to be performed to confirm the efficacy of the beneficial health effect of EVOO on the delay of cognitive decline.

Keywords: extra-virgin olive oil, oleuropein, oleuropein-aglycone, cognitive decline, Alzheimer disease, review

Introduction

As demographic trends indicate, there is an increase in the number of the world’s aging population. In 2017, there was almost one billion adults at the age of 60+ years. In 2050, this number should be 2-times higher. Europe has the largest share (25%) of this population group. This aging process is often connected with cognitive decline of some functions, such as memory or speed processing loss.

In some cases, cognitive decline can result in mild cognitive impairment (MCI) affecting everyday living. MCI is a forerunner of Alzheimer’s disease (AD). In fact, AD is the most common cause of cognitive decline among the elderly. Research shows that, at the age of 65, nearly 5% of older people suffer from AD and, by the age of 85, it is more than 40%. Thus, apart from cognitive decline, the main symptoms of AD include difficulties in orientation, language disorders, changes in mood, loss of motivation, inability to manage self-care, or behavioral disorders.
Since AD cannot be cured yet, considerable efforts are being made to at least delay this cognitive decline among elderly in order to maintain and prolong the quality of their life. This is done, for example, by non-pharmacological approaches such as performing physical activities, cognitive training, or adhering to a Mediterranean Diet (MedDiet).2,6–10

In addition, research11–18 reveals that one of the components of MedDiet (extra-virgin olive oil) has considerable health benefits. Apart from the protection against cardiovascular diseases, cancer, type 2 diabetes mellitus, or obesity, it plays an important role in the delay of the age-related cognitive decline. Recently, it has been published that poor adherence to the MedDiet may have a negative influence on academic performance in adolescents19 and contrary MedDiet well adherent female adolescents were associated with a reduced presence of depressive symptoms.20 Olive oil is a fatty acids and antioxidants-rich food, whose best quality form is extra-virgin olive oil (EVOO). Consumption of EVOO is connected with lower mitochondrial oxidative stress, which might counteract age-related cognitive decline.21–23 It seems that secoiridoid oleuropein, resp. oleuropein aglycone, is responsible for its neuroprotective effect.24

The purpose of this review is to examine the effect of EVOO intake on the delay of cognitive decline among elderly.

Methods

The methods are based on a literature review of available sources found on the research topic in three acknowledged databases: Web of Science, Scopus, and PubMed. The search was not limited by any time period. The oldest study dates back to 197325 and the latest to November 2018.26 The literature search was conducted between November 20, 2018, and December 20, 2018, to identify published peer-reviewed articles in English. The collocated keywords were as follows: olive oil AND cognitive decline, olive oil AND cognitive impairment, extra-virgin olive oil AND cognitive decline, extra-virgin olive oil AND cognitive impairment, extra-virgin olive oil AND cognitive impairment, extra-virgin olive oil AND cognitive impairment. The keywords were combined and integrated in database and journal searches. The terms used were searched using AND to combine the keywords listed and using OR to remove search duplication where possible. References of retrieved articles were assessed for relevant articles that authors’ searches may have missed. Both in vitro and in vivo studies were included.

Findings

Chemistry And Pharmacology Of Olive Oil – Oleuropein

The benefits of olives or olive oil have been observed on the basis of dietary effects on human health. The positive pharmacological properties of olive oil are mainly due to the phenolic content.27 The most significant representatives of the phenolic oleosides in Olea europaea are: oleuropein, dimethyl-oleuropein, ligstroside, and oleoside. Oleuropein has the largest proportion of them and its content in young olives can be as high as 140 mg/g of dry matter.28,29 Oleuropein (Figure 1) belongs to a group of polyphenols called secoiridoids. The molecule of oleuropein has three subunits: a polyphenol, namely 4-(2-hydroxyethyl) benzene-1,2-diol (also known as hydroxytyrosol), a secoiridoicd called elenolic acid, and a molecule of glucose.30 Oleuropein-aglycone (Figure 2) originates from it in the production of EVOO, where mechanical crushing and pressing takes place, as well as the physiological release of the β-glucosidase enzyme, which can cleave ester bonds.24,31 EVOO is the best form of olive oil and, thanks to its production technology (mechanical pressing of ripe olives), it retains most of its lipophilic components compared to ordinary olive oil (virgin and refined oil). It is believed that it is just oleuropein-aglycone, which has a neuroprotective effect.32–34

Several in vitro and in vivo studies have shown the pleiotropic effect of oleuropein and its derivatives. The positive properties of oleuropein included antioxidant,
antidiabetic, antimicrobial, antiviral, antitumor, hepatoprotective, cardioprotective, anti-aging, anti-inflammatory, and also neuroprotective effects. An overview of the most significant effects of oleuropein is provided in Table 1.

Clinical studies on olive oil, EVOO, or oleuropein studies, currently running, are described in Table 2 (Phase: recruiting or not yet recruiting, https://clinicaltrials.gov). It can be seen from the following that phenolic oleosides are a popular group of pharmacologically active substances among scientists, potentially suitable for affecting many different diseases (eg, hypertension, Alzheimer's disease, Ulcerative disease, DM2, …).

Animal Studies Of Oleuropein In Neuroprotection
The available data indicate that the administration of EVOO in particular oleuropein-aglycone intake has a neuroprotective effect in animal models. As is summarized in Table 3, memory functions and behavior are significantly improved. In terms of the protective action of oleuropein-aglycone, mechanisms are offered including: inhibition of Aβ aggregation, reduction of Aβ aggregate toxicity, promotion of natural autophagy, and lysosomal function. Equally important seems to be its anti-inflammatory properties.

Human Studies With EVOO As Neuroprotection
The authors detected only two studies in which EVOO was tested against cognitive decline. They were both randomized controlled trials. The Italian study examined whether the replacement of all vegetable oils with a lower amount of extra-virgin olive oil, in the contest of a MedDiet, would affect cognitive functions among the Italian elderly. It lasted for 1 year. In total, 110 healthy elderly subjects at the mean age of 70 participated. Fifty-five subjects were taking a Mediterranean diet (MedDiet) and 55 subjects in the experimental group were taking MedDiet plus EVOO. Extra-virgin Olive Oil intake was 30±12 g and 26±6 g in the MedDiet and MedDiet plus EVOO groups, respectively (p=0.044). The results revealed that the higher short-term improvement of cognitive functions scores was in subjects on a MedDiet plus low dose of extra-virgin olive oil rather than MedDiet alone. EVOO, thus, may have a neuroprotective effect.

The second, Spanish study evaluated the effect on cognition of a controlled intervention testing MedDiet. It lasted for 6.5 years. There were 285 non-demented subjects, out of which 44.8% were males and 55.2% were females. The mean age at cognitive evaluation was 74.1 ±5.7 years. The results showed that a long-term intervention with an EVOO-rich MedDiet resulted in a better cognitive function in comparison with a control diet. Subjects with an EVOO-rich MedDiet had less MCI than controls. Thus, the neuroprotective effect against cognitive decline was confirmed.

Discussion
EVOO is the best quality oil produced by mechanical pressing of ripe olives. Through this process, it is possible to retain most of the components with strong antioxidant and anti-inflammatory properties. Any industrial processing of olive oil (extraction and refining) makes it a lower quality oil. Comparing EVOO with refined olive oil, the refined form is less protective of oxidative lipid damage, free radical formation, and inflammatory activity. Oleuropein-aglycone, which is the chief phenolic substance of extra virgin olive oil, and the neuroprotective effect is thought to be associated with it.

The results of both in vitro and vivo studies show that oleuropein-aglycone, which is an important phenolic component of EVOO has a positive neuroprotective effect against cognitive decline. This especially concerns memory functions and behavior.
Animal model studies have suggested a possible mechanism of action associated with this improvement in cognitive function. It is an induction of autophagy, which in turn reduces the amount of Aβ aggregates. Another ability is to utilize the cytotoxicity of accumulated Aβ and reduce inflammation from activated astrocytes and microglia. One of the mechanisms by which the extra-virgin oil exerts this effect includes the increase in the antioxidant content of low density lipoproteins and the nutrigenomic effect.

Due to the complexity and possible distance of these studies, there are no direct studies of the mechanism of action and physiological effect of EVOO on the human body. All available human data are based on extrapolation from animal models. However, it is seriously assumed that EVOO is a useful food to prevent and alleviate the symptoms associated with AD. However, more studies are needed to test human effects, particularly in terms of metabolic pathways and bioavailability. The fact is that the effects of EVOO on gene expression have not yet been studied.

As general recommendations state, the protective effect of virgin olive oil can be most important in the first decades of life, which suggests that the health benefit of virgin olive oil intake should start before puberty, and maintained through life.11,16

The limitations of this review are related to a relatively small number of the studies with humans, their different methodologies, and studying the effect of EVOO together with the MedDiet. All this can lead to the overestimation of the discussed results.

### Conclusion

Much evidence shows the beneficial effects of Mediterranean diet as an effective prevention of neurodegenerative diseases. As Mediterranean diet is characterized by high consumption of extra virgin olive oil, it is believed that the complex of biomolecules, led by oleuropein-aglycon, contained in EVOO, may be responsible for the beneficial effect of Mediterranean diet. The beneficial effects of olive oil and its biomolecules on neurological disorders have been extensively investigated from the perspective of different cell pathways. Studies demonstrating the protective activity of oleuropein-aglycone include: against LDL oxidation,45

### Table 1 The Most Important Effects Of Oleuropein

<table>
<thead>
<tr>
<th>Property</th>
<th>Observed Effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antioxidant</td>
<td>Inhibits oxidation of low-density lipoproteins (LDL)</td>
<td>54,55</td>
</tr>
<tr>
<td></td>
<td>Scavenges nitric oxide; increase inducible nitric oxide synthase expression</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>Induction of the inducible nitric oxide synthase in macrophages</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Increases the ability of LDL to resist oxidation; reduces the plasma levels of</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>total, free, and esterified cholesterol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antioxidant effects in leukocytes</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Lower lipid peroxidation</td>
<td>57</td>
</tr>
<tr>
<td>Anti-inflammatory</td>
<td>Inhibits lipoxygenase activity and the production of leukotriene B4</td>
<td>59</td>
</tr>
<tr>
<td>Anti-atherogenic</td>
<td>Reduces monocyte adhesion to endothelium and reduces cell adhesion molecule-1</td>
<td>60</td>
</tr>
<tr>
<td>Anti-cancer</td>
<td>Inhibits growth cancer cells (LN-18, TF-1a, 786-O, T-47D, RPMI-7951, LoVo)</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>Decreases breast cancer cell viability</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Reduces the viability of MCF-7 by inducing cell apoptosis</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Inhibits cell proliferation (MCF-7, T-24, BBCE)</td>
<td>64</td>
</tr>
<tr>
<td>Anti-microbial</td>
<td>Strong antimicrobial activity against gram-negative and gram-positive bacteria</td>
<td>65,66</td>
</tr>
<tr>
<td></td>
<td>Antimicrobial activity against mycoplasma</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>Able to inhibit the development of: Staphylococcus aureus, Salmonella enteritidis, Bacillus cereus, Klebsiella pneumoniae, Escherichia coli, Campylobacter jejuni, Helicobacter pylori</td>
<td>68–72</td>
</tr>
<tr>
<td>Antiviral</td>
<td>Antiviral against: herpes mononucleosis, hepatitis virus, rotavirus, bovine rhinovirus, canine parvovirus, feline leukemia virus</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Antiviral against: respiratory syncytial virus and para-influenza type 3 virus</td>
<td>74</td>
</tr>
</tbody>
</table>
Table 2: Currently Ongoing Studies Of Olive Oil, EVOO, Or Oleuropein (https://clinicaltrials.gov)

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Status</th>
<th>Conditions</th>
<th>Enrollment</th>
<th>Start Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03779529</td>
<td>EVOO Coratina Intervention on Lipids in Non-diabetic Hypertensive Patients Undergoing Hemodialysis</td>
<td>Recruiting</td>
<td>Chronic Kidney Disease Stage V</td>
<td>24</td>
<td>July 1, 2018</td>
</tr>
<tr>
<td>NCT03820336</td>
<td>Cardiovascular Effects of EVOO in Healthy Reproductive-aged Women</td>
<td>Not yet recruiting</td>
<td>Hypertension; Vascular Stiffness</td>
<td>40</td>
<td>February 2019</td>
</tr>
<tr>
<td>NCT03824197</td>
<td>Auburn University Research on Olive Oil for Alzheimer’s Disease</td>
<td>Not yet recruiting</td>
<td>Alzheimer Disease; Cerebral Amyloid Angiopathy</td>
<td>30</td>
<td>February 2019</td>
</tr>
<tr>
<td>NCT03408847</td>
<td>Monocultivar Coratina Extra Virgin Olive Oil in UC Patients</td>
<td>Recruiting</td>
<td>Ulcerative Colitis Chronic Mild</td>
<td>30</td>
<td>November 20, 2017</td>
</tr>
<tr>
<td>NCT03528603</td>
<td>Acute Assessment of Platelet Reactivity After the Intake of Oleocanthal</td>
<td>Recruiting</td>
<td>Platelet Aggregation; Nutritional and Metabolic Disease; Cardiovascular Diseases</td>
<td>50</td>
<td>April 2, 2018</td>
</tr>
<tr>
<td>NCT03053843</td>
<td>Mediterranean Diet Plus Extra-virgin Olive Oil in the Prevention of Recurrent Arrhythmias</td>
<td>Recruiting</td>
<td>Atrial Fibrillation; Atrial Arrhythmia</td>
<td>640</td>
<td>March 22, 2017</td>
</tr>
<tr>
<td>NCT03891927</td>
<td>Extra Virgin Olive Oil on Glycemic Control, Insulin Resistance and Insulin Secretion</td>
<td>Not yet recruiting</td>
<td>Insulin Resistance</td>
<td>80</td>
<td>May 1, 2019</td>
</tr>
<tr>
<td>NCT03081065</td>
<td>Mediterranean Diet and Recurrence of Depression</td>
<td>Not yet recruiting</td>
<td>Depression</td>
<td>750</td>
<td>March 20, 2017</td>
</tr>
<tr>
<td>NCT03447301</td>
<td>The Effect of Daily Consumption of Extra Virgin Olive Oil on Blood Glucose Among Diabetic Patients</td>
<td>Not yet recruiting</td>
<td>Type 2 Diabetes Mellitus</td>
<td>400</td>
<td>February 25, 2018</td>
</tr>
<tr>
<td>NCT03796780</td>
<td>Comparison of Extra-Virgin and Refined Olive Oil on Some Cardiovascular Risk Factors</td>
<td>Recruiting</td>
<td>Cardiovascular Risk Factor</td>
<td>40</td>
<td>January 1, 2019</td>
</tr>
<tr>
<td>NCT03024359</td>
<td>Monounsaturated Fatty Acids and Brown/Beige Adipose Tissue in Humans</td>
<td>Recruiting</td>
<td>Obese</td>
<td>50</td>
<td>January 2017</td>
</tr>
</tbody>
</table>
against oxidative stress at the brain level, to reduce the volume of cerebral infarction after cerebral ischemia/reperfusion injury in mice, reduction of inflammatory biomarkers (TNF-α, IL-1α, iNOS, COX-2) after spinal cord injury (animal model), interference with amyloid aggregation (in vitro), reduction in Aβ42 deposits (animal models), suppression of pE3-Aβ production, and reduction of oxidative stress and apoptosis induced by 6-OHDA (in vitro).

Moreover results of this study show that the use of secoiridoid oleuropein-aglycone which is present in EVOO in diet has a positive impact on the delay of cognitive decline among non-demented older individuals. In addition, there is a longitudinal association between this oil consumption and cognitive decline.

Furthermore, there is a need of more randomized controlled studies or longitudinal observational studies to be performed to confirm the efficacy of the beneficial health effect of oleuropein-aglycone respective EVOO on the delay of cognitive decline.

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Disclosure
The authors have no conflicts of interest to report in this work.

References

Table 3 Animal Studies Of Oleuropein In Neuroprotection

<table>
<thead>
<tr>
<th>Animal</th>
<th>Result</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57Bl/6j mice</td>
<td>Enhanced contextual memory; reduced age-related impairment in motor coordination; lipid peroxidation and inflammation markers were decreased in brain areas connected with motor control</td>
<td>37</td>
</tr>
<tr>
<td>TgCRND8 mice</td>
<td>Ameliorated memory dysfunction; reduced β-amyloid levels and plaque deposits; increase of autophagic markers expression through mTOR inhibition</td>
<td>38</td>
</tr>
<tr>
<td>TgCRND8 mice</td>
<td>Massive reduction of pyroglutamate-3 amyloid-β protein (major component of β-amyloid plaque) by reducing its aggregation</td>
<td>39</td>
</tr>
<tr>
<td>Wistar rat</td>
<td>Reduced the toxicity of Aβ aggregated; reduced the amount of soluble Aβ oligomers; no evident inflammatory reaction</td>
<td>40</td>
</tr>
<tr>
<td>CL2600 Caenorhabditis elegans</td>
<td>Reduction in the plaque deposition; less abundant toxic Aβ oligomers</td>
<td>41</td>
</tr>
</tbody>
</table>


71. Tassou CC, Nychas GJE. Inhibition of staphylococcus aureus by olive phenolics in broth and in a model food system. *J Food Prot*. 1994;57:120–124. doi:10.4315/0362-028X-57.2.120