

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

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**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.<sup>1</sup> This aging process is often connected with cognitive decline of some functions, such as memory or speed processing loss.<sup>2</sup> 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%.<sup>3</sup> 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.<sup>4,5</sup>

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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).<sup>2,6–10</sup>

In addition, research<sup>11–18</sup> 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 adolescents<sup>19</sup> and contrary MedDiet well adherent female adolescents were associated with a reduced presence of depressive symptoms.<sup>20</sup> 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.<sup>21–23</sup> It seems that secoiridoid oleuropein, resp. oleuropein aglycone, is responsible for its neuroprotective effect.<sup>24</sup>

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

## Methods

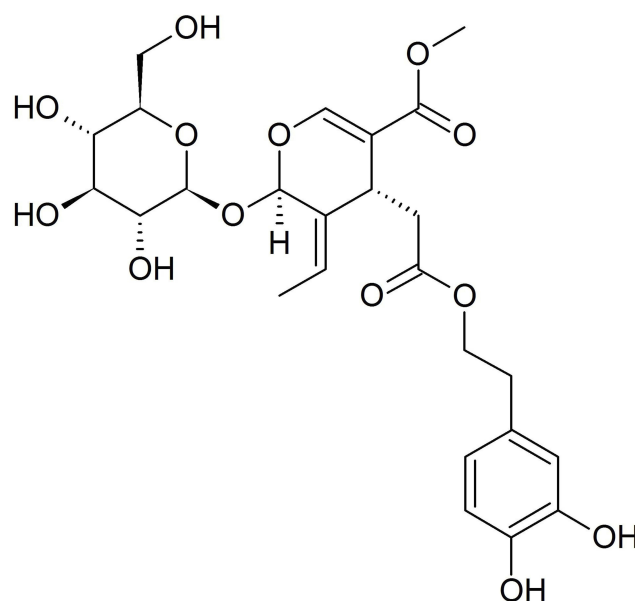
The methods are based on a literature review of available sources found on the research topic in three acknowledged databases: Web of Science, Scopus, and PubMed. The search was not limited by any time period. The oldest study dates back to 1973<sup>25</sup> and the latest to November 2018.<sup>26</sup> 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. 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

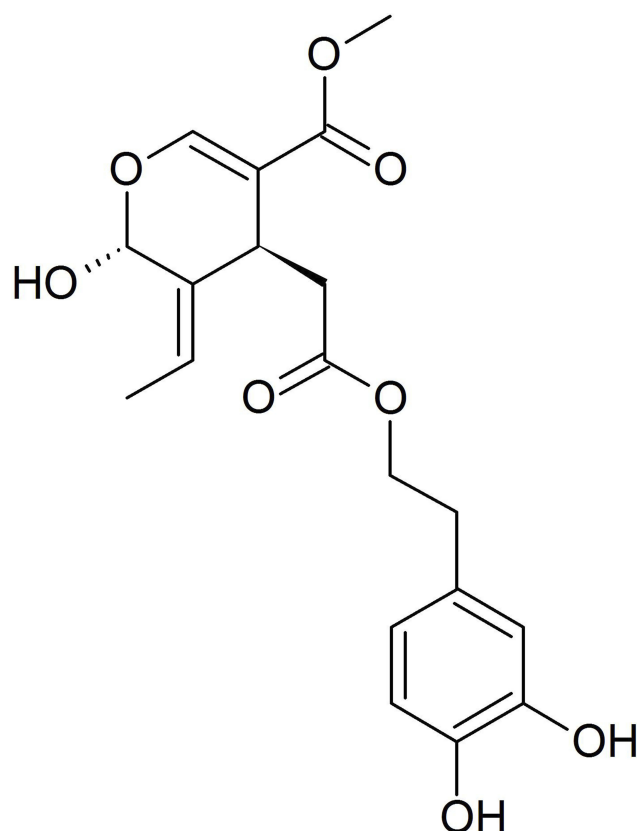
### Chemistry And Pharmacology Of Olive Oil – Oleuropein

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.<sup>27</sup> 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.<sup>28,29</sup> 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 secoiridoid called elenolic acid, and a molecule of glucose.<sup>30</sup> 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  $\beta$ -glucosidase enzyme, which can cleave ester bonds.<sup>24,31</sup> 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.<sup>32–34</sup>

Several in vitro and in vivo studies have shown the pleiotropic effect of oleuropein and its derivatives. The positive properties of oleuropein included antioxidant,



**Figure 1** Chemical formula of oleuropein.



**Figure 2** Chemical formula of oleuropein-aglycone.

antidiabetic, antimicrobial, antiviral, antitumor, hepatoprotective, cardioprotective, anti-aging, anti-inflammatory, and also neuroprotective effects.<sup>35</sup> 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 A $\beta$  aggregation, reduction of A $\beta$  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<sup>13,36</sup> in which EVOO was tested against cognitive decline. They were both randomized controlled trials. The Italian study<sup>13</sup> 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 $\pm$ 12 g and 26 $\pm$ 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,<sup>36</sup> 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  $\pm$  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.<sup>13</sup>

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.<sup>13,36-42</sup> This especially concerns memory functions and behavior.

**Table I** The Most Important Effects Of Oleuropein

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

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 A $\beta$  aggregates. Another ability is to utilize the cytotoxicity of accumulated A $\beta$  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.<sup>43</sup> A great advantage is that EVOO does not show any adverse effects such as cell death or apoptosis (curcumin) or neurodegeneration (rapamycin).<sup>13,17,23,35,44</sup>

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.<sup>35</sup>

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.<sup>11,16</sup>

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,<sup>45</sup>

**Table 2** Currently Ongoing Studies Of Olive Oil, EVOO, Or Oleuropein (<https://clinicaltrials.gov>)

NCT Number	Title	Status	Conditions	Enrollment	Start Date
NCT03779529	EVOO Coratina Intervention on Lipids in Non-diabetic Hypertensive Patients Undergoing Hemodialysis	Recruiting	Chronic Kidney Disease Stage V	24	July 1, 2018
NCT03820336	Cardiovascular Effects of EVOO in Healthy Reproductive-aged Women	Not yet recruiting	Hypertension; Vascular Stiffness	40	February 2019
NCT03824197	Auburn University Research on Olive Oil for Alzheimer's Disease	Not yet recruiting	Alzheimer Disease; Cerebral Amyloid Angiopathy	30	February 2019
NCT03408847	Monocultivar Coratina Extra Virgin Olive Oil in UC Patients	Recruiting	Ulcerative Colitis Chronic Mild	30	November 20, 2017
NCT03528603	Acute Assessment of Platelet Reactivity After the Intake of Oleocanthal	Recruiting	Platelet Aggregation; Nutritional and Metabolic Disease; Cardiovascular Diseases	50	April 2, 2018
NCT03053843	Mediterranean Diet Plus Extra-virgin Olive Oil in the Prevention of Recurrent Arrhythmias	Recruiting	Atrial Fibrillation; Atrial Arrhythmia	640	March 22, 2017
NCT03891927	Extra Virgin Olive Oil on Glycemic Control, Insulin Resistance and Insulin Secretion	Not yet recruiting	Insulin Resistance	80	May 1, 2019
NCT03081065	Mediterranean Diet and Recurrence of Depression	Not yet recruiting	Depression	750	March 20, 2017
NCT03447301	The Effect of Daily Consumption of Extra Virgin Olive Oil on Blood Glucose Among Diabetic Patients	Not yet recruiting	Type 2 Diabetes Mellitus	400	February 25, 2018
NCT03362996	Management of Mild Cognitive Impairment Patients With Extra Virgin Olive Oil	Recruiting	Mild Cognitive Impairment	150	November 9, 2016
NCT03796780	Comparison of Extra-Virgin and Refined Olive Oil on Some Cardiovascular Risk Factors	Recruiting	Cardiovascular Risk Factor	40	January 1, 2019
NCT03024359	Monounsaturated Fatty Acids and Brown/Beige Adipose Tissue in Humans	Recruiting	Obese	50	January 2017



**Table 3** Animal Studies Of Oleuropein In Neuroprotection

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

against oxidative stress at the brain level,<sup>46,47</sup> to reduce the volume of cerebral infarction after cerebral ischemia/reperfusion injury in mice,<sup>48</sup> reduction of inflammatory biomarkers (TNF- $\alpha$ , IL-1 $\alpha$ , iNOS, COX-2) after spinal cord injury (animal model),<sup>49,50</sup> interference with amyloid aggregation (in vitro),<sup>51</sup> reduction in A $\beta$ 42 deposits (animal models),<sup>41</sup> suppression of pE3-A $\beta$  production,<sup>52</sup> and reduction of oxidative stress and apoptosis induced by 6-OHDA (in vitro).<sup>53</sup>

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.

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