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

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Blanka Klimova¹
Michal Novotný²
Kamil Kuca²⁻⁴
Martin Valis⁵

¹Department of Applied Linguistics, University of Hradec Kralove, Hradec Kralove 500 03, Czech Republic;

²Biomedical Research Centre, University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; ³Department of Chemistry, Faculty of Science, University of Hradec Kralove, Hradec Kralove, Czech Republic; ⁴Malaysia Japan International Institute of Technology (MJIIIT), Universiti Teknologi Malaysia Kuala Lumpur, Jalan Sultan Yahya Petra, Kuala Lumpur 54100, Malaysia;

⁵Department of Neurology, University Hospital Hradec Kralove, Hradec Kralove 500 05, Czech Republic

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.¹ This aging process is often connected with cognitive decline of some functions, such as memory or speed processing loss.² 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%.³ 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.^{4,5}

Correspondence: Kamil Kuca
University Hospital, Sokolska 581, Hradec Kralove, Czech Republic
Tel +420 603 289 166
Fax +420 495 835 200
Email kamil.kuca@fnhk.cz

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, research^{11–18} 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. 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 secoiridoid 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,

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.³⁵ 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 β aggregation, reduction of A β 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^{13,36} in which EVOO was tested against cognitive decline. They were both randomized controlled trials. The Italian study¹³ 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,³⁶ 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.¹³

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.^{13,36-42} This especially concerns memory functions and behavior.

Table 1 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 β aggregates. Another ability is to utilize the cytotoxicity of accumulated A β 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.⁴³ A great advantage is that EVOO does not show any adverse effects such as cell death or apoptosis (curcumin) or neurodegeneration (rapamycin).^{13,17,23,35,44}

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.³⁵

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 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 β -amyloid levels and plaque deposits; increase of autophagic markers expression through mTOR inhibition	38
TgCRND8 mice	Massive reduction of pyroglutamate-3 amyloid- β protein (major component of β -amyloid plaque) by reducing its aggregation	39
Wistar rat	Reduced the toxicity of A β aggregated; reduced the amount of soluble A β oligomers; no evident inflammatory reaction	40
CL2600 <i>Caenorhabditis elegans</i>	Reduction in the plaque deposition; less abundant toxic A β oligomers	41

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

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

- United Nations. Ageing. Available from: <http://www.un.org/en/sections/issues-depth/ageing/>. Accessed January 8, 2019.
- Klimova B, Valis M, Kuca K. Cognitive decline in normal aging and its prevention: A review on non-pharmacological lifestyle strategies. *Clin Interv Aging*. 2017;12:903–910. doi:10.2147/CIA.S132963
- Alzheimer's Association. 2014 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2014;10(2):e47–e92.
- Klimova B, Maresova P, Kuca K. Non-pharmacological approaches to the prevention and treatment of Alzheimer's disease with respect to the rising treatment costs. *Curr Alzheimer Res*. 2016;13(11):1249–1258.
- Klimova B, Maresova P, Valis M, Hort J, Kuca K. Alzheimer's disease and language impairments: social intervention and medical treatment. *Clin Interv Aging*. 2015;10:1401–1408. doi:10.2147/CIA.S89714
- Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. A randomised controlled trial investigating the effects of mediterranean diet and aerobic exercise on cognition in cognitively healthy older people living independently within aged care facilities: the Lifestyle Intervention in Independent Living Aged Care (LILAC) study protocol [ACTRN12614001133628]. *Nutr J*. 2015;14:53.
- Hardman RJ, Kennedy G, Macpherson H, Scholey AB, Pipingas A. Adherence to a Mediterranean-style diet and effects on cognition in adults: a qualitative evaluation and systematic review of longitudinal and prospective trials. *Front Nutr*. 2016;3:22. doi:10.3389/fnut.2016.00022
- Klimova B. Computer-based cognitive training in aging. *Front Aging Neurosci*. 2016;8:313. doi:10.3389/fnagi.2016.00313
- Kivipelto M, Solomon A, Ahliluo S, et al. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER): study design and progress. *Alzheimers Dement*. 2013;9(6):657–665. doi:10.1016/j.jalz.2012.09.012
- Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263. doi:10.1016/S0140-6736(15)60461-5
- Visioli F, Franco M, Toledo E, et al. Olive oil and prevention of chronic diseases: summary of an international conference. *Nutr Metab Cardiovasc Dis*. 2018;28(7):649–656. doi:10.1016/j.numecd.2018.04.004
- Locke A, Schneiderhan J, Zick SM. Diets for health: goals and guidelines. *Am Fam Physician*. 2018;97(11):721–728.
- Mazza E, Fava A, Ferro Y, et al. Effect of the replacement of dietary vegetable oils with a low dose of extravirgin olive oil in the mediterranean diet on cognitive functions in the elderly. *J Transl Med*. 2018;16(1):10. doi:10.1186/s12967-018-1386-x
- López-Miranda J, Pérez-Jiménez F, Ros E, et al. Olive oil and health: summary of the II international conference on olive oil and health consensus report, Jaén and Córdoba (Spain) 2008. *Nutr Metab Cardiovasc Dis*. 2010;20(4):284–294. doi:10.1016/j.numecd.2009.12.007

15. Delgado-Lista J, Garcia-Rios A, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Olive oil and haemostasis: platelet function, thrombogenesis and fibrinolysis. *Curr Pharm Des*. 2011;17(8):778–785. doi:10.2174/138161211795428876
16. Perez-Jimenez F, Alvarez de Cienfuegos G, Badimon L, et al. International conference on the healthy effect of virgin olive oil. *Eur J Clin Invest*. 2005;35(7):421–424. doi:10.1111/j.1365-2362.2005.01516.x
17. Covas MI, de la Torre R, Fito M. Scientific evidence of the benefits of virgin olive oil for human health. *Med Balear*. 2014;29(2):39–46.
18. Martinez-Gonzalez MA, Martin-Calvo N. Mediterranean diet and life expectancy; beyond olive oil, fruits, and vegetables. *Curr Opin Clin Nutr Metab Care*. 2016;19(6):401–407. doi:10.1097/MCO.0000000000000316
19. Vassiloudis I, Yiannakouris N, Panagiotakos DB, Apostolopoulos K, Costarelli V. Adherence to the mediterranean diet and specific life-style habits are associated with academic performance in Greek adolescents. *MNM*. 2017;10(2):93–103. doi:10.3233/MNM-16133
20. Tehrani AN, Salehpour A, Beyzai B, et al. Adherence to Mediterranean dietary pattern and depression, anxiety and stress among high-school female adolescents. *MNM*. 2018;11(1):73–83. doi:10.3233/MNM-17192
21. Valls-Pedret C, Lamuela-Raventós RM, Medina-Remón A, et al. Polyphenol-rich foods in the mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J Alzheimers Dis*. 2012;29(4):773–782. doi:10.3233/JAD-2012-111799
22. Quiles JL, Barja G, Battino M, Mataix J, Solfrizzi V. Role of olive oil and monounsaturated fatty acids in mitochondrial oxidative stress and aging. *Nutr Rev*. 2006;64(s4):31–39. doi:10.1111/j.1753-4887.2006.tb00170.x
23. St-Laurent-Thibault C, Arseneault M, Longpré F, Ramassamy C. Tyrosol and hydroxytyrosol, two main components of olive oil, protect N2a cells against amyloid- β -induced toxicity. Involvement of the NF- κ B signaling. *Curr Alzheimer Res*. 2011;8(5):543–551.
24. Martorell M, Forman K, Castro N, Capó X, Tejada S, Sureda A. Potential therapeutic effects of oleuropein aglycone in Alzheimer's disease. *Curr Pharm Biotechnol*. 2016;17:994–1001. doi:10.2174/1389201017666160725120656
25. Fleming HP, Walter WM, Etchells JL. Antimicrobial properties of oleuropein and products of its hydrolysis from green olives. *Appl Microbiol*. 1973;26:777–782.
26. Morley JE. An overview of cognitive impairment. *Clin Geriatr Med*. 2018;34(4):505–513. doi:10.1016/j.cger.2018.06.003
27. Visioli F, Poli A, Gall C. Antioxidant and other biological activities of phenols from olives and olive oil. *Med Res Rev*. 2002;22:65–75.
28. Soler-Rivas C, Espín JC, Wichers HJ. Oleuropein and related compounds. *J Sci Food Agric*. 2000;80:1013–1023. doi:10.1002/(SICI)1097-0010(20000515)80:7<1013::AID-JSFA571>3.0.CO;2-C
29. Amiot MJ, Fleuriot A, Macheix JJ. Accumulation of oleuropein derivatives during olive maturation. *Phytochemistry*. 1989;28:67–69. doi:10.1016/0031-9422(89)85009-5
30. Omar SH. Cardioprotective and neuroprotective roles of oleuropein in olive. *Saudi Pharm J*. 2010;18(3):111–121. doi:10.1016/j.jsps.2010.05.005
31. Rigacci S. Olive oil phenols as promising multi-targeting agents against Alzheimer's disease. *Adv Exp Med Biol*. 2005;863:1–20.
32. Barbaro B, Toietta G, Maggio R, et al. Effects of the olive-derived polyphenol oleuropein on human health. *IJMS*. 2014;15(10):18508–18524.
33. Xu F, Li Y, Zheng M, Xi X, Zhang X, Han C. Structure properties, acquisition protocols, and biological activities of oleuropein aglycone. *Front Chem*. 2018;6:239. doi:10.3389/fchem.2018.00239
34. Angeloni C, Malaguti M, Barbalace M, Hrelia S. Bioactivity of olive oil phenols in neuroprotection. *IJMS*. 2017;18(11):2230. doi:10.3390/ijms18112230
35. Cordero JG, García-Escudero R, Avila J, Gargini R, García-Escudero V. Benefit of oleuropein aglycone for Alzheimer's disease by promoting autophagy. *Oxid Med Cell Longev*. 2018;2018:5010741. doi:10.1155/2018/5010741
36. Martínez-Lapiscina EH, Clavero P, Toledo E, et al. Virgin olive oil supplementation and long-term cognition: the PREDIMED-NAVARRA randomized, trial. *J Nutr Health Aging*. 2013;17(6):544–552. doi:10.1007/s12603-013-0027-6
37. Pitozzi V, Jacomelli M, Catelan D, et al. Long-term dietary extra-virgin olive oil rich in polyphenols reverses age-related dysfunctions in motor coordination and contextual memory in mice: role of oxidative stress. *Rejuvenation Res*. 2012;15:601–612. doi:10.1089/rej.2012.1346
38. Grossi C, Rigacci S, Ambrosini S, et al. The polyphenol oleuropein aglycone protects TgCRND8 mice against A β plaque pathology. *PLoS One*. 2013;8:e71702. doi:10.1371/journal.pone.0071702
39. Grossi C, Dami TE, Rigacci S, Stefani M, Luccarini I, Casamenti F. Employing Alzheimer disease animal models for translational research: focus on dietary components. *Neurodegener Dis*. 2014;13:131–134. doi:10.1159/000355461
40. Luccarini I, Dami TE, Grossi C, Rigacci S, Stefani M, Casamenti F. Oleuropein aglycone counteracts A β 42 toxicity in the rat brain. *Neurosci Lett*. 2014;558:67–72. doi:10.1016/j.neulet.2013.10.062
41. Diomedea L, Rigacci S, Romeo M, Stefani M, Salmona M. Oleuropein aglycone protects transgenic C. elegans strains expressing A β 42 by reducing plaque load and motor deficit. *PLoS One*. 2013;8:e58893. doi:10.1371/journal.pone.0058893
42. Lauretti E, Iuliano L, Praticò D. Extra-virgin olive oil ameliorates cognition and neuropathology of the 3xTg mice: role of autophagy. *Ann Clin Transl Neurol*. 2017;4(8):564–574. doi:10.1002/acn3.431
43. Gorzynik-Debicka M, Przychozden P, Cappello F, et al. Potential health benefits of olive oil and plant polyphenols. *Int J Mol Sci*. 2018;19(3):pii,E6. doi:10.3390/ijms19030686
44. Rigacci S. Olive oil phenols as promising multi-targeting agents against Alzheimer's disease. *Adv Exp Med Biol*. 2015;863:1–20. doi:10.1007/978-3-319-18365-7_1
45. Visioli F, Galli C. Oleuropein protects low density lipoprotein from oxidation. *Life Sci*. 1994;55(24):1965–1971. doi:10.1016/0024-3205(94)00529-x
46. Ogun M, Ozcan A, Karaman M, et al. Oleuropein ameliorates arsenic induced oxidative stress in mice. *J Trace Elem Med Biol*. 2016;36:1–6. doi:10.1016/j.jtemb.2016.03.006
47. Peng S, Zhang B, Yao J, Duan D, Fang J. Dual protection of hydroxytyrosol, an olive oil polyphenol, against oxidative damage in PC12 cells. *Food Funct*. 2015;6(6):2091–2100. doi:10.1039/c5fo00097a
48. Yu H, Liu P, Tang H, et al. Oleuropein, a natural extract from plants, offers neuroprotection in focal cerebral ischemia/reperfusion injury in mice. *Eur J Pharmacol*. 2016;775:113–119. doi:10.1016/j.ejphar.2016.02.027
49. Impellizzeri D, Esposito E, Mazzon E, et al. The effects of a polyphenol present in olive oil, oleuropein aglycone, in an experimental model of spinal cord injury in mice. *Biochem Pharmacol*. 2012;83(10):1413–1426. doi:10.1016/j.bcp.2012.02.001
50. Khalatbary AR, Ahmadvand H. Neuroprotective effect of oleuropein following spinal cord injury in rats. *Neurol Res*. 2012;34(1):44–51. doi:10.1179/1743132811Y.0000000058
51. Rigacci S, Guidotti V, Bucciantini M, et al. Oleuropein aglycone prevents cytotoxic amyloid aggregation of human amylin. *J Nutr Biochem*. 2010;21(8):726–735. doi:10.1016/j.jnutbio.2009.04.010
52. Luccarini I, Grossi C, Rigacci S, et al. Oleuropein aglycone protects against pyroglutamylation-3 amyloid- β toxicity: biochemical, epigenetic and functional correlates. *Neurobiol Aging*. 2015;36(2):648–663. doi:10.1016/j.neurobiolaging.2014.08.029
53. Pasban-Aliabadi H, Esmaeili-Mahani S, Sheibani V, Abbasnejad M, Mehdizadeh A, Yaghoobi MM. Inhibition of 6-hydroxydopamine-induced PC12 cell apoptosis by olive (*Olea europaea* L.) leaf extract is performed by its main component oleuropein. *Rejuvenation Res*. 2013;16(2):134–142. doi:10.1089/rej.2012.1384

54. Visioli F, Galli C, Galli G, Caruso D. Biological activities and metabolic fate of olive oil phenols. *Eur J Lipid Sci Tech*. 2002;104:677–684. doi:10.1002/1438-9312(200210)104:9/10<677::AID-EJLT677>3.0.CO;2-M
55. Boskou D. *Olive Oil: Chemistry and Technology*. 2nd ed. AOCS Publishing; 2006.
56. de la Puerta R, MEM D, Ruiz-Gutierrez V, Flavill JA, Hoult JRS. Effects of virgin olive oil phenolics on scavenging of reactive nitrogen species and upon nitrenergic neurotransmission. *Life Sci*. 2001;69:1213–1222. doi:10.1016/s0024-3205(01)01218-8
57. Visioli F, Caruso D, Galli C, Viappiani S, Galli G, Sala A. Olive oils rich in natural catecholic phenols decrease isoprostane excretion in humans. *Biochem Biophys Res Commun*. 2000;278:797–799. doi:10.1006/bbrc.2000.3879
58. Coni E, Di Benedetto R, Di Pasquale M, et al. Protective effect of oleuropein, an olive oil biophenol, on low density lipoprotein oxidizability in rabbits. *Lipids*. 2000;35:45–54. doi:10.1007/s11745-000-0493-2
59. de la Puerta R, Gutierrez VR, Hoult JRS. Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol*. 1999;57:445–449. doi:10.1016/s0006-2952(98)00320-7
60. Carluccio MA, Siculella L, Ancora MA, et al. Olive oil and red wine antioxidant polyphenols inhibit endothelial activation: antiatherogenic properties of Mediterranean diet phytochemicals. *Arterioscler Thromb Vasc Biol*. 2003;23:622–629. doi:10.1161/01.ATV.0000062884.69432.A0
61. Hamdi HK, Castellon R. Oleuropein, a non-toxic olive iridoid, is an anti-tumor agent and cytoskeleton disruptor. *Biochem Biophys Res Commun*. 2005;334:769–778. doi:10.1016/j.bbrc.2005.06.161
62. Menendez JA, Vazquez-Martin A, Colomer R, et al. Olive oil's bitter principle reverses acquired autoresistance to trastuzumab (Herceptin™) in HER2-overexpressing breast cancer cells. *BMC Cancer*. 2007;7:80. doi:10.1186/1471-2407-7-80
63. Han J, Talorete TPN, Yamada P, Isoda H. Anti-proliferative and apoptotic effects of oleuropein and hydroxytyrosol on human breast cancer MCF-7 cells. *Cytochemistry*. 2009;59:45–53. doi:10.1007/s10616-009-9191-2
64. Goulas V, Exarchou V, Troganis AN, et al. Phytochemicals in olive-leaf extracts and their antiproliferative activity against cancer and endothelial cells. *Mol Nutr Food Res*. 2009;53:600–608. doi:10.1002/mnfr.200800204
65. Bisignano G, Tomaino A, Cascio RL, Crisafi G, Uccella N, Saija A. On the in-vitro antimicrobial activity of oleuropein and hydroxytyrosol. *J Pharm Pharmacol*. 1999;51:971–974. doi:10.1211/0022357991773258
66. Aziz NH, Farag SE, Mousa LA, Abo-Zaid MA. Comparative antibacterial and antifungal effects of some phenolic compounds. *Microbios*. 1998;93:43–54.
67. Furneri PM, Marino A, Saija A, Uccella N, Bisignano G. In vitro antimycoplasmal activity of oleuropein. *Int J Antimicrob Agents*. 2002;20:293–296. doi:10.1016/s0924-8579(02)00181-4
68. Sudjana AN, D'Orazio C, Ryan V, et al. Antimicrobial activity of commercial Olea europaea (olive) leaf extract. *Int J Antimicrob Agents*. 2009;33:461–463. doi:10.1016/j.ijantimicag.2008.10.026
69. Tassou CC, Nychas GJ, Board RG. Effect of phenolic compounds and oleuropein on the germination of bacillus cereus T spores. *Biotechnol Appl Biochem*. 1991;13:231–237.
70. Tassou CC, Nychas GJE. Inhibition of salmonella enteritidis by oleuropein in broth and in a model food system. *Lett Appl Microbiol*. 1995;20:120–124. doi:10.1111/j.1472-765x.1995.tb01301.x
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
72. Tranter HS, Tassou SC, Nychas GJ. The effect of the olive phenolic compound, oleuropein, on growth and enterotoxin B production by staphylococcus aureus. *J Appl Bacteriol*. 1993;74:253–259. doi:10.1111/j.1365-2672.1993.tb03023.x
73. Fredrickson WRF, S Group, Inc. Method and composition for antiviral therapy with olive leaves. U.S. Patent. 2000;6:117:884.
74. Ma SC, He ZD, Deng XL, et al. In vitro evaluation of secoiridoid glucosides from the fruits of ligustrum lucidum as antiviral agents. *Chem Pharm Bull (Tokyo)*. 2001;49:1471–1473. doi:10.1248/cpb.49.1471

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