

# The Effects of Olive Oil in Neurovascular Disease : A Literature Review

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## Abstract

Olive oil is a fundamental component and the main source of fat in the Mediterranean diet, a dietary pattern that is considered as one of most healthy diet in the world. Olive oil contains high amount of MUFA and minor components such as phenolic compounds and others. Phenolic compounds have a lot of beneficial functions in the body including its neuroprotection effects. Neurovascular disease which is identical with ischemic stroke has limitation on its therapy choices. Current understanding of stroke pathogenesis has opened the way for newer therapies through neuroprotection approaches. Therefore, further studies regarding olive oil consumption and its mechanism of neuroprotection is needed.

Keywords : Olive oil; Mediterranean diet; Phenolic compounds; Neurovascular disease; Ischemic stroke

## 1. Introduction

The Mediterranean diet is considered as one of the most healthy diet predominantly because its ingredients that is rich in antioxidants and anti-inflammatory nutrients [1]. The Mediterranean diet is distinguished by a high consumption of organic plants like fruits and vegetables, grains and nuts, poultry and fish as the protein, and olive oil as the main source of fat. It also include consuming less meat, eggs, animal fats, dairy products, and discretionary foods that are not essentials for nutrition [2]. Therefore, olive oil is a fundamental nutraceutical component in Mediterranean diet. Several studies concluded that the Mediterranean diet could be beneficial for our health by reducing the risk of several pathological conditions such as cardiovascular and cerebrovascular diseases, metabolic syndromes such as diabetes mellitus, cancers, and neurodegenerative diseases [3].

Olive oil is made by mechanically extracting the fruit of *Olea europaea* L. It is mainly composed by glycerol fraction with the percentage of 90-99% and non-glycerol fraction with the percentage of 0,4-5% [4]. Oleic acid is one of mono unsaturated fatty acids (MUFA) that portrays 70-80% of fatty acids present in olive oil. High amount of MUFA has great nutritional implications and effects on oxidative stability in oils [5]. There are also minor components contained in extra virgin olive oil, for examples, hydrocarbons, tocopherols, phytosterols, and phenolic compounds [6]. The main antioxidant components of virgin olive oil are phenolic compounds and carotenoids. This could imply that the benefits of olive oil are not only due to its fatty acids, but also due to its phenolic compounds which act as an antioxidant [4].

There are simple phenolic compounds like gallic, vanillic, coumaric and caffeic acids, tyrosol and hydroxytyrosol in olive oil. The others are complex compounds like secoiridoids (ligstroside and oleuropein), and the lignans (pinosresinol and 1-acetoxypinosresinol) is also part of olive oil [4]. These have been widely identified as beneficial compounds that can effects the body in favorable way, especially if consumed in a long term [7]. Neuroprotective function is one of the most important function of phenolic compounds. It has been reported that olive polyphenols effect the reduction of neuroinflammation [8].

Neurovascular diseases fall into two categories, they either limit cerebral blood flow or cause bleeding within the brain vessels. Stroke is characterized as a neurological deficit associated with acute focal central nervous system (CNS) injury from vascular causes, including intracerebral hemorrhage (ICH), subarachnoid hemorrhage, and cerebral infarction [9]. Thrombosis, embolism, systemic hypoperfusion, or any kind of accidents which results in restricted blood flow of the brain could cause ischemic stroke and resulting in insufficient supply of oxygen and glucose that support cellular brain homeostasis [10]. According to WHO Global Health Estimate 2019 data, stroke with death rate of 11% is the second cause of death in the world. It also is the third cause of disability in the world [11].

The main goal of ischemic stroke management are revascularization and limitation of secondary neuronal injury [12]. Currently, there are two primary options for ischemic stroke therapy, IV thrombolysis and

endovascular thrombectomy with intravenous administration of tissue plasminogen activator (rtPA) [13]. With limitation of its therapy choices, current understanding of stroke pathogenesis has also opened the way for newer therapies through neuroprotection approaches. Neuroprotection approaches are any strategies or combinations which can antagonize, disrupt, or slow down the sequence of biochemical and molecular events that will result in injury and ischemic damages that are irreversible [14]. These therapies work by modulating the excitatory amino acid system, controlling calcium influx, working as metabolic activators, anti-edema agents, antioxidants, anti-apoptotic agents, and leukosine adhesion inhibitors [15]. Olive oil have been considered as a neuroprotective nutraceutical for use in the prevention and treatment of ischemic brain injury due to its antioxidant properties and antiapoptotic abilities [16]. This paper provides review on the beneficial neuroprotective agents of olive oil in neurovascular disease such as ischemic stroke.

## 2. Methods

The Pubmed database was searched up to January 2023 using the the keyword “olive oil”, “Mediterranean diet”, “phenolic compounds”, “neurovascular”, ‘neuroinflammation”, “cerebrovascular”, “stroke”. We also used our criteria for inclusion in choosing references. Criteria of inclusions are as follows: (1) Written in english; (2) full-length in a peer-reviewed journal; (3) directly addressed the topic of olive oil and its neuroprotective agents.

## 3. Results

During ischemic stroke, cerebral blood flow is interrupted, making the brain cells short on the glucose and oxygen they needed to function, causing adenosine triphosphate (ATP) failure [15], [17]. ATP failure prevents plasma membrane  $\text{Ca}^{2+}$  ATPase from maintaining the normally low intracellular calcium concentration, cells then will produce adenosine biphosphate (ADP) as new source of energy. High levels of intracellular calcium, sodium, and adenosine diphosphate (ADP) cause mitochondria to produce reactive oxygen species (ROS) which excessive accumulation leads to a condition called oxidative stress and cause neuronal cell damaged [18].

There are reports that have shown olive polyphenols act against oxidative stress in brain tissues due to its antioxidant components through various mechanisms. Hydroxytyrosol and oleuropein has shown a strong radical-scavenging activity by exhibiting direct scavenging effect on superoxide anion production in vitro [19]. Another study reveals that virgin olive oil can avoid cell death by reducing NO production, brain prostaglandin E2, and lipid peroxidation as the effect of glutathione concentration upregulation [20].

Consumption of virgin olive oil 30 days prior to MCAO in mice also has an effect on lipidomics content in the brain. Virgin olive oil increases brain phosphatidylcholine, triglycerides, cholesterol esters and cholesterol, and cerebroside levels. It consumptions also decreases ceramide levels which high levels could induce apoptotic cell death in the brain [21], [22].

Virgin olive oil pretreatment can reduce infarction volume, brain edema, BBB (blood brain barrier) permeability, and neurobehavioral deficit scores in animal models of stroke followed by reperfusion [23]. Similar result also found in another study, oleuropein exerts neuroprotective activity by reducing brain infarct volume and improving neurobehavioral function after ischemic-reperfusion cerebral injury in rats. Quantitative analysis showed that OLE treatment significantly decreased caspase-3 and work as an anti-apoptotic agent. In addition, oleuropein exhibits an antiapoptotic effect by increasing the Bcl-2/Bax ratio. Oleuropein increases Bcl-2 expression, a prosurvival agent, and decreases Bax expression which is an apoptotic agent [24].

## 4. Conclusion

Olive oil has a potent neuroprotective effect on neurovascular disease such as ischemic stroke due to its fatty acid and phenolic compounds. Its fatty acid has effects on brain lipidomics which inhibit apoptotic pathway. Phenolic compounds of olive oil act as antioxidant and antiapoptotic agent and have proofed its ability to be a new therapeutic agent for ischemic stroke condition. Olive oil consumption before or after ischemic stroke incidence has the ability to reduce cell damage. However, the more effective way of olive oil consumption as pre-treatment or treatment is not yet known. Different mechanism of olive oil neuroprotective effect needs to be studied. Further studies on other olive oil componets is also needed.

## 5. Acknowledgement

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## 6. References

- [1] M. C. Mentella, F. Scadaferri, C. Ricci, A. Gasbarrini, and G. A. D. Miggiano, "Cancer and mediterranean diet: A review," *Nutrients*, vol. 11, no. 9. MDPI AG, Sep. 01, 2019. doi: 10.3390/nu11092059.
- [2] E. M. Yubero-Serrano, J. Lopez-Moreno, F. Gomez-Delgado, and J. Lopez-Miranda, "Extra virgin olive oil: More than a healthy fat," *European Journal of Clinical Nutrition*, vol. 72. Springer Nature, pp. 8–17, Jul. 01, 2019. doi: 10.1038/s41430-018-0304-x.
- [3] F. Sofi, C. Macchi, R. Abbate, G. F. Gensini, and A. Casini, "Mediterranean diet and health," *BioFactors*, vol. 39, no. 4. Blackwell Publishing Inc., pp. 335–342, 2013. doi: 10.1002/biof.1096.
- [4] E. Tripoli, M. Giammanco, G. Tabacchi, D. di Majo, S. Giammanco, and M. la Guardia, "The phenolic compounds of olive oil: structure, biological activity and beneficial effects on human health," *Nutr Res Rev*, vol. 18, no. 1, pp. 98–112, Jun. 2005, doi: 10.1079/nrr200495.
- [5] G. di Loreto, L. Giansante, M. Pellegrino, R. Vito, and E. Perri, "Chemical and sensory characteristics of Italian virgin olive oils from Grossa di Gerace cv," *European Journal of Lipid Science and Technology*, vol. 118, no. 2, pp. 288–298, Feb. 2016, doi: 10.1002/ejlt.201400622.
- [6] C. (Claudio) Peri, *The extra virgin olive oil handbook*. 2014.
- [7] M. Bucciantini, M. Leri, P. Nardiello, F. Casamenti, and M. Stefani, "Olive polyphenols: Antioxidant and anti-inflammatory properties," *Antioxidants*, vol. 10, no. 7, Jul. 2021, doi: 10.3390/antiox10071044.
- [8] T. Grubić Kezele and B. Ćurko-Cofek, "Neuroprotective Panel of Olive Polyphenols: Mechanisms of Action, Anti-Demyelination, and Anti-Stroke Properties," *Nutrients*, vol. 14, no. 21, p. 4533, Oct. 2022, doi: 10.3390/nu14214533.
- [9] R. L. Sacco et al., "An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association," *Stroke*, vol. 44, no. 7, pp. 2064–2089, 2013, doi: 10.1161/STR.0b013e318296aeca.
- [10] N. Kanyal, "The science of ischemic stroke: Pathophysiology & pharmacological treatment," *Int J Pharma Res Rev*, vol. 4, no. 10, pp. 65–84, 2015.
- [11] World Health Organization, "Global Health Estimate 2019," <https://www.who.int/data/gho/data/themes/theme-details/GHO/mortality-and-global-health-estimates>, 2019.
- [12] F. Herpich and F. Rincon, "Management of acute ischemic stroke," *Critical Care Medicine*, vol. 48, no. 11. Lippincott Williams and Wilkins, pp. 1654–1663, Nov. 01, 2020. doi: 10.1097/CCM.0000000000004597.
- [13] M. S. Sun et al., "Free radical damage in ischemia-reperfusion injury: An obstacle in acute ischemic stroke after revascularization therapy," *Oxidative Medicine and Cellular Longevity*, vol. 2018. Hindawi Limited, 2018. doi: 10.1155/2018/3804979.
- [14] M. D. Ginsberg, "Neuroprotection for ischemic stroke: Past, present and future," *Neuropharmacology*, vol. 55, no. 3, pp. 363–389, Sep. 2008, doi: 10.1016/j.neuropharm.2007.12.007.
- [15] P. Deb, S. Sharma, and K. M. Hassan, "Pathophysiologic mechanisms of acute ischemic stroke: An overview with emphasis on therapeutic significance beyond thrombolysis," *Pathophysiology*, vol. 17, no. 3. pp. 197–218, Jun. 2010. doi: 10.1016/j.pathophys.2009.12.001.
- [16] C. Angeloni, M. Malaguti, M. C. Barbalace, and S. Hrelia, "Bioactivity of olive oil phenols in neuroprotection," *International Journal of Molecular Sciences*, vol. 18, no. 11. MDPI AG, Nov. 01, 2017. doi: 10.3390/ijms18112230.
- [17] J. Huang, U. M. Upadhyay, and R. J. Tamargo, "Inflammation in stroke and focal cerebral ischemia," *Surg Neurol*, vol. 66, no. 3, pp. 232–245, Sep. 2006, doi: 10.1016/j.surneu.2005.12.028.

- [18] K. P. Doyle, R. P. Simon, and M. P. Stenzel-Poore, "Mechanisms of ischemic brain damage," *Neuropharmacology*, vol. 55, no. 3, pp. 310–318, Sep. 2008, doi: 10.1016/j.neuropharm.2008.01.005.
- [19] F. Visioli, G. Bellomo, and C. Galli, "Free radical-scavenging properties of olive oil polyphenols," *Biochem Biophys Res Commun*, vol. 247, pp. 60–64, 1998.
- [20] J. A. González-Correa et al., "Dietary virgin olive oil reduces oxidative stress and cellular damage in rat brain slices subjected to hypoxia-reoxygenation," *Lipids*, vol. 42, no. 10, pp. 921–929, Oct. 2007, doi: 10.1007/s11745-007-3097-6.
- [21] Z. Rabiei, M. R. Bigdeli, B. Rasoulia, A. Ghassempour, and F. Mirzajani, "The neuroprotection effect of pretreatment with olive leaf extract on brain lipidomics in rat stroke model," *Phytomedicine*, vol. 19, no. 10, pp. 940–946, Jul. 2012, doi: 10.1016/j.phymed.2012.06.003.
- [22] S.-I. Yoshimura et al., "Ceramide formation leads to caspase-3 activation during hypoxic PC12 cell death inhibitory effects of Bcl-2 on ceramide formation and caspase-3 activation," 1998. [Online]. Available: <http://www.jbc.org/>
- [23] F. Mohagheghi, M. R. Bigdeli, B. Rasoulia, A. A. Zeinanloo, and A. Khoshbaten, "Dietary virgin olive oil reduces blood brain barrier permeability, brain edema, and brain injury in rats subjected to ischemia-reperfusion," *ScientificWorldJournal*, vol. 10, pp. 1180–1191, Jun. 2010, doi: 10.1100/tsw.2010.128.
- [24] H. Yu et al., "Oleuropein, a natural extract from plants, offers neuroprotection in focal cerebral ischemia/reperfusion injury in mice," *Eur J Pharmacol*, vol. 775, pp. 113–119, Mar. 2016, doi: 10.1016/j.ejphar.2016.02.027.