

# The anti-inflammation effects of olive oil extract in stroke model: a scoping review

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## ABSTRACT

Stroke is the second leading death in the world after cardiovascular disease. In 2016, globally, there were nearly 5.5 million deaths due to stroke. Recent studies found that an unhealthy diet is the most prevalent risk factor of stroke. Diets high in saturated fats, trans fat, and cholesterol results endothelial inflammation that affect the progression in mortality. Anti-inflammatory properties of olive oil have been considered as neuroprotective and cardioprotective in ischemic stroke prevention. This study aim is to discuss the effect of olive oil extract as an anti-inflammatory agent in experimental study performed by Mice and Rats. This search for scoping review on the role olive oil in stroke prevention was carried out in July-Agustus 2021 using three databases, namely: Google Scholar, PubMed, and ScienceDirect limited to the range of the last 10 years 2011 to 2021. The keyword combination used are: "Olive oil" and "inflammation or inflammatory" and "CVD" or "Stroke". Studies were excluded if they: (i) did not include mice or Rats; (ii) were a review, systematic review, or meta-analysis; (iii) were written in a language other than English; (iv) not available in full text. From 703 article that met the search criteria, 4 studies were found as inclusion criteria. The result shows comparing to Anti-inflammatory effect in olive oil, preventing the development atherosclerosis becomes one of the main factors of stroke progression. The association between CVD including stroke with olive oil intake were significant. Extract of olive oil has the potential effect as anti-inflammatory agent in Wistar rats and mice model of stroke.

Keywords: anti inflammatory, olive oil extract, stroke model, rats, mice

## 1. INTRODUCTION

Olive oil is a fruit that grow in Mediterranean region. There are types from olive oil that grow in asia and Europe is part of *Olea Europaea* L. Subspecies. The outspread of olive oil head to Greece, Italy, spain, Portugal dan France [1]. Olive oil is believed have benefits in health based on its component.

There are many types in olive oil production of of them Extra Virgin Olive Oil (EVOO) that usually used in Mediterranean diet. EVOO has bioactive component as anti-oxidant and anti-inflammation. An important com-

ponent in Virgin olive oil is phenolic, acid phenolic, phenolic alcohol, secoiridoids, hydroxy-isocromans, flavonoid and ligand [2]. These compound concentration of Phenolic includes (0.02 - 600mg/kg) [2]. Phenolic is derivate by hydro-cortisol, oleocanthal [2]

Unhealthy lifestyle one of the main leading. According to WHO, cerebrovascular disease is the second highest disease in the world after cardiovascular disease. There is an increase in the number of cerebrovascular diseases in the majority of the elderly, as a risk factor for cardiovascular disease [3] In addi-

tion, cerebrovascular disease is increasing due to the lack of complete investigations, especially in developing countries [4].

The occurrence of decreased consciousness in the presence of cerebrovascular occlusion is called stroke. This event is caused by metabolic stress on the brain resulting in arterial clots. Occlusion mostly occurs in the middle cerebral artery. Based on research [5] conducted on mice the damage to a specific location that is not handled properly leads to poor progression and increased mortality. In this state, glutamate release, calcium influx, oxidative stress, inflammation will affect the apoptosis microglial neuron lead to changes in cerebrovascular fluid, structural, neuronal. [6]

The risk factor of stroke is the consumption of foods that contain inflammatory effects that chronic inflammation occurs in the body [7]. This hyperlipidemia induces the risk factors for the metabolic syndrome and stroke. The outcome of the consumption in high-fat diet influences neuroinflammation. Based on the research conducted by de la cruz [8] the inflammatory mechanism of oxidative stress will increase the work of cytokines, especially IL-1 $\beta$ , prostaglandins and Nitric Oxide. In a study conducted by [6] shown the incidence of stroke can be caused by neuroinflammation

There are classifications in stroke, hemorrhagic and ischemic. Cellular mechanisms of free radical formation, neuronal apoptosis can lead to death. Hyperacute stroke occurs within 0 to 24 hours. The area surrounding the injury is called the penumbra. This area has the potential to provide the best treatment in the right time. Stroke treatment is effective in reducing the area of the lesion in the penumbra using neuroprotection to avoid apoptosis and neuronal death. In addition to providing neuroprotection, thrombolytic agents are used for reperfusion strat-

egies. Treatment focuses on minimizing stroke and its complications with neuroprotectants. However, most of the neuroprotective energy works to minimize the damage. There are many neuroprotective components that serve as safeguards against long-term damage. In addition, another study showed the presence of infarction in mice in the middle cerebral area [9]

The incidence of cardiovascular disease is the highest cause of death in the western region. Cardiovascular disease is a non-communicable disease. This disease can be avoided with a lifestyle, where Mediterranean diet contains olive oil. A prospective study of patients who replaced their diet with margarine, mayonnaise and others with olive oil 5g/day for 10 years showed a non-fatal reduction in CVD in CVD patients [10]. In addition, based on PREDIMED consumption of the Mediterranean diet with VOO showed a reduction in cardiovascular risk of up to 31% [11] The components in olive oil, especially the phenolics, show significant results in anti-inflammatory action. Phenolic acids can reduce the action of NF- $\kappa$ B in activating B cells and reduce lipopolysaccharides, with plasma concentrations. In addition, research in on CVD Virgin olive oil can modulate inflammatory agents, namely thromboxane B2 and 6-keto-PG F1, Interleukin-6 and C-Reactive protein [6]

In modifying the diet that combine with olive oil has inversely proportional risk of stroke and has good results in lifestyle. Based on research Guasch 2021 [10] of extra-virgin olive oil can reduce the risk of CVD by almost 31%. Olive oil has an oleic acid component that can protect against brain damage.

Study [12] that conducted with a High-fat Diet with saturated fatty acids (HFD-SFA), with a refined high fat diet enriched in olive oil (HFD-OO) rich in MUFA, omega-3. Performed on rats that received 48 hours of

intervention. Where the results show that the size of the ischemia area given olive oil is smaller than (HFD-SFA) [12] Although, this study shows that the presence of a high-fat diet enriched in olive oil improves motor performance in rats who in receiving ischemic intervention. However, systematic review and meta – analysis that discuss anti-inflammation effect in olive oil are limited and still not updated in the recent years.

## 2. MATERIAL AND METHOD

### 2.1. Identification of relevant studies

The medical literature review was carried out on PubMed, Google Scholar and Science-Direct databases using the Boolean search used "Olive oil" and "inflammation or inflammatory or tumor necrosis factor or TNF or interleukin or IL" and "Stroke" and "model or Rat or Mice". The limits applied refer to the language (English) and years (2011 to 2021) of the articles of publication.

### 2.2. Study selection and eligibility criteria

For the analysis, all studies were selected independently by two researchers evaluating the anti-inflammation effects of olive oil extract in stroke model. All process was performed according to the PRISMA statement (Preferred Reporting Items Systematic Reviews and Meta-Analyses), as shown in the flow chart (Fig.1).

The selection process for the articles in this scoping review uses a screening method with predefined inclusion and exclusion criteria. The inclusion criteria of this study are; a) journal articles in English; b) journal articles in the type of original articles or research articles; c) the research method used in the selected articles is RCT or non-RCT; d) journal articles between 2011-2021; e) in terms

of intervention, the study involved intervention using the herbal compound Olive oil in any dosage form without any specific limitations on dosage.

Articles were excluded if studies: (i) did not include mice; (ii) were a review, systematic review, or meta-analysis; (iii) were written in a language other than English; (iv) not available in full text.

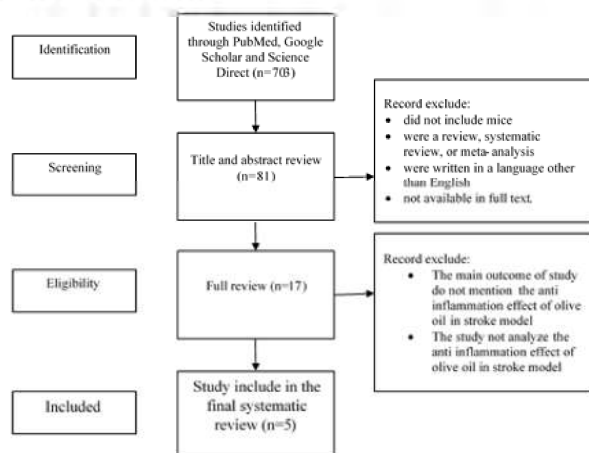


Figure 1. PRISMA Flowchart

### 2.3. Data Extraction

The data extraction process in the final reference of this study was carried out individually with one researcher. The results of data extraction as a whole will be carried out comprehensive data mapping in Microsoft Office Excel software (Table 1). The mapping process is needed to facilitate the stages of reading all variables from the final reference in this study.

## 3. RESULT

The initial search process is carried out using keywords that have been entered into scientific search engines such as PubMed, Google Scholar and ScienceDirect. In the initial search process for article journals, a total of 703 journal references were obtained. Then the identification process is continued by eliminating duplicate references obtained from different scientific search engines. This

stage is followed by two screening phases, phase one and phase two. In the first phase of screening, namely screening based on titles and abstracts on journal identities, 81 journals were excluded due to topics that did not meet the established exclusion criteria. Then in the second phase of screening, 17 journals were excluded due to the non-fulfillment of the inclusion criteria that had been set. So that the final references for 4 journals will be extracted for the next step.

#### 4. DISCUSSION

The research that discussed olive oil, fo-

cused research on polyphenols can reduce the incidence of cardiovascular risk. This can be characterized by inflammatory markers in several studies. Hydro-cortisol is a major phenolic metabolite which has antioxidant action obtained from olive oil. Based on this research the table the benefits of hydro-cortisol to prevent stroke. Supported by research conducted in Boutin where Translocator 18kDa Protein (TSPO) with PET imaging as a sign of brain damage due to neuroinflammation produced by microglia [13]. In a study conducted by Barca [5] that TSPO was not detected in the first post-ischemia in rats receiving hydro-cortisol. In this case,

Table 1. Characteristics of the included studies.

| Author                         | Population  | Intervention  | Results   | Conclusion  |
|--------------------------------|---|---|---|---|
| Natalia Lausada et al (2015)   | Male Wistar rats (three weeks old, $48 \pm 3$ g/animal) were used. Animals were randomly assigned to four experimental groups (twelve animals for each experiment) and fed after weaning on specific diets for 35 days. | Wistar rats were fed on diets containing 7 % commercial oils (S, soybean; O, olive; C, coconut; G, grape seed) for 35 days. Stroke was induced by permanent middle cerebral artery occlusion.   | Olive oil was protective in terms of redox homeostatic balance, minor increase in lipid and protein damage, conservation of reduced glutathione, protective activation of NOS in penumbra, and net ratio of anti- to pro-inflammatory cytokines. Apoptosis (caspase-3, milli- and micro-calpains) was less activated by Olive oil than by any other diet. | Olive oil appears to be a biological source for the isolation of protective agents that block the expansion of brain core at the expense of penumbra neurons.   |
| Jamileh Mardhooki et al (2016) | 58 male Wistar rats were totally divided into six groups including sham, control (intact), control (middle cerebral artery occlusion, MCAO), and treatments.  | The treatment groups received different doses (0.25, 0.50, and 0.75 ml/kg) of olive oil by gastric gavage for 30 days. Two hours after the last gavage, the Wistar rats were subjected to 60 min MCAO surgery.  | Mice fed with HFD-OO-w3 displayed better histological outcomes after cerebral ischemia than mice that received an HFD-SFA or LFD. Furthermore, PUFA- and MUFA-enriched diets improved the motor function and neurological performance of ischemic mice relative to those fed with an LFD or HFD-SFA.  | These findings support the use of DHA/EPA-in olive oil as dietary source of MUFAs in order to reduce the damage and protect the brain when a stroke occurs. Work as well in Omega-3 in fish fatty acid. |
| Gonzalo-Gobernado et al (2019) | Male C57BL/6J mice were divided into four groups.   | Mice were fed for 4 weeks with a standard low-fat diet (LFD), a high-fat diet (HFD) rich in saturated fatty acids (HFD-SFA), an HFD containing monounsaturated fatty acids (MUFAs) from olive oil (HFD-OO), or an HFD containing MUFAs from olive oil plus polyunsaturated fatty acids (PUFAs) docosahexaenoic acid/eicosapentaenoic acid (DHA/EPA) (HFD-OO-w3). These mice were subjected to transient middle cerebral artery occlusion (tMCAo). | Mice fed with HFD-OO-w3 displayed better histological outcomes after cerebral ischemia than mice that received an HFD-SFA or LFD. Furthermore, PUFA- and MUFA-enriched diets improved the motor function and neurological performance of ischemic mice relative to those fed with an LFD or HFD-SFA.  | These findings support the use of DHA/EPA-in olive oil as dietary source of MUFAs in order to reduce the damage and protect the brain when a stroke occurs. Work as well in Omega-3 in fish fatty acid. |

|                             |   |   |   |  |
|-----------------------------|---|---|---|--|
| Cristina Barca et al (2021) | 22 male C57BL/6 mice were divided into two groups, standard chow or HT (hydroxytyrosol) enriched diet.  | Mice were fed with either a standard chow (n = 11) or a HT (hydroxytyrosol) enriched diet (n = 11) for 35 days, following 30 min transient middle cerebral artery occlusion (tMCAo). Hydroxytyrosol (HT) enriched diet contains the main phenolic component of the extra virgin olive oil (EVOO).   | Quantification of the percentage of TSPO+ area by immunoreactivity indicated a slight 2-fold increase in TSPO expression within the infarct region in HT-fed mice at day 35 post ischemia (p = 0.011) correlating with a 2-3-fold increase in Iba-1+ cell population expressing CD163 as anti-inflammatory marker (R2 = 0.80).  | An HT-enriched diet significantly increased the number of Iba-1+ microglia/macrophages in the post-ischemic area, inducing higher expression of anti-inflammatory markers.   |
| Masayuki Ueda et al (2013)  | Male Sprague-Dawley rats 250-300g (n=105) divided into groups vehicle treatment, vehicle pretreatment and post treatment of focal brain ischemia. | Male Sprague-Dawley rats (n=105) subjected 90 min focal brain ischemia. (Eicosapentaenic Acid) EPA-E (100 and 300 /mg/kg/day) in experiment 1 rats administered with 3, 5, and 7 days prior to ischemia then subjected to ischemia in 24 h. Experiment 2 group in 3, 5 and 7-days prior ischemia and subjected ischemia in 7 days. Experiment 3 given EPA-E (100-600/mg/kg/day) post-ischemia in 72h. | Plasma EPA levels were elevated after 7-day pretreatment compared with control. Other group that was given EPA for more than 5 days did not show any difference between groups.<br>MRI study show decrease in Apparent Diffusion Coefficient (ADC) area in EPA-E treatment compare with control. Immunohistochemical analyses show that EPA-E treated show decreased in 8-OHdG-, 4-HNE-, p-adduction and vWF positive cell in cortical ischemia | Pre-treatment of EPA-E show significant reduction in infarct volume and neurological improvements. However Post-treatment of EPA-E did not show improvements.<br>It is concluded that EPA-E work as neuroprotection. |

it shows an activation relationship in post-stroke retrograde degeneration.

In addition, the Barca [5] study based on the effectiveness of Hydro-cortisol working as an anti-inflammatory, where the study showed a decrease in CBF on days 1, 3, and 7 and showed significant results in the activation of Iba-1+ CD163+ cells.

Based on research by Fucelli [14] in rats Hydro-cortisol works in reducing the inflammatory marker Cyclooxygenase (COX2) and Tumor Necrosis Factor (TNF-alpha). This reduces the incidence of chronic degenerative diseases. This study showed that mice that did not get Hydro-cortisol caused an increase in pro-inflammatory in addition to the dose (40-80 mg/kgW) will still have an effect on reducing inflammation.

Research conducted by [15] on olive oil reagent on Hydro-Cortisol with PGE2 that there is a decrease in macrophages. Research on [16] An inflammatory production of NO are causing a cell injury in cerebral Cortex of mice, thus using the specific blockers of Pro-inflammatory cytokines, such as iNOS

containing in hydro-cortisol preventing stress in mice. The content of phenol can affect endothelial function or inhibit the work of platelets. Lussada [17] NO work as protection in penumbra by inhibiting the work of anti-cytokine pro-inflammation, in antioxidant use.

In a study [6] olive oil has the power to reduce NF-κB in the striatum cortex. Other experiment by [18] NF-κB transcription will increase neuroinflammation and neurotoxicity. Giving olive oil with phenolic content can avoid free radicals from the blood-brain barrier. Another study proves that the anti-inflammatory properties of olive oil reduce the action of TNFR1 on cerebral ischemia. Research [6] showed the use of a dose of 0.75ml/kgBW in rats can reduce the incidence of infarction by reducing the role of neuroinflammation.

In this review the composition of diet can affect the cerebral ischemia in mice. Study from Gonzales [12] show that Mice fed with HFD-OO-w3 displayed better histological outcomes after cerebral ischemia than mice

that received an HFD-SFA or LFD. Based on research [19] given fatty acid improve cerebral infarction. These supplementation of PUFA. DHA also show can decrease in BBB Permeability In Proinflammatory agents such as IL-6 and NF- $\kappa$ B. In [19] shows that injection of DHA after ischemia reduce brain injury. This experimental show clinical observation will reduce stroke severity. However, research in [20] EPA and DHA on hippocampal in rats worked as antioxidant enzymatic in ischemia. [12] MUFAs (from olive oil) motor deficit in rats shows reversed motor deficit with improvement in neurological score. Based on stroke prevention it is important to take saturated fat.

From this 4 research that olive oil contains many active compounds in reducing cardiovascular disease. MUFA in olive oil show permeability in decrease BBB. Although, the active compound of olive oil, hydro-cortisol and phenolic acid work as antioxidant trough pro-inflammatory marker that causes ischemia in brain. The toxicity happens in ischemic brain can be saved in penumbra. Olive oil compound eventually inhibit neuroinflammation in apoptosis of neuron in penumbra. Thus, based on research Lussada [17] and Barca [5] can be found a retrograde degeneration by saving penumbra.

Olive oil in Mediterranean diet contain, is a healthy diet contain anti-inflammatories and also high in Monosaturated Fatty Acid in reducing the risk of stroke and increase the severity of stroke. These can predict, in the future review other than stroke the anti-inflammatory can also help to increase cognitive in dementia related to apoptosis of cell.

## 5. CONCLUSION

This research has shown an effective of olive oil *Olea European* in chronic disease. The compound of olive oil has many benefits in decreasing the pro-inflammatory especially

in ischemic stroke.

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