The neuroprotective effect of olive leaf extract is related to improved blood–brain barrier permeability and brain edema in rat with experimental focal cerebral ischemia

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**A R T I C L E   I N F O**

**Keywords:**
Neuroprotective
Olive leaf extract
Olea europea
Focal cerebral ischemia
Infarct volume
Brain edema
Blood–brain barrier permeability

**A B S T R A C T**

Recent studies suggest that olive extracts suppress inflammation and reduce stress oxidative injury. We sought to extend these observations in an in vivo study of rat cerebral ischemia-reperfusion injury.

Four groups, each of 18 Wister rats, were studied. One (control) group received distilled water, while three treatment groups received oral olive leaf extract (50, 75 and 100 mg/kg/day respectively). After 30 days, blood lipid profiles were determined, before a 60 min period of middle cerebral artery occlusion (MCAO). After 24 h reperfusion, neurological deficit scores, infarct volume, brain edema, and blood–brain barrier permeability were each assessed in subgroups of six animals drawn from each main group.

Olive leaf extract reduced the LDL/HDL ratio in doses 50, 75, and 100 mg/kg/day in comparison to the control group (\(P<0.001\)), and offered cerebroprotection from ischemia-reperfusion. For controls vs. doses of 50 mg/kg/day vs. 75 mg/kg/day vs. 100 mg/kg/day, attenuated corrected infarct volumes were 209.79 \(\pm\) 33.05 mm\(^3\) vs. 164.36 \(\pm\) 13.44 mm\(^3\) vs. 123.06 \(\pm\) 28.83 mm\(^3\) vs. 94.71 \(\pm\) 33.03 mm\(^3\); brain water content of the infarcted hemisphere 82.33 \(\pm\) 0.33\% vs. 81.33 \(\pm\) 0.66\% vs. 80.75 \(\pm\) 0.6\% vs. 80.16 \(\pm\) 0.47\% and blood–brain barrier permeability of the infarcted hemisphere 11.22 \(\pm\) 2.19 H\(9262\) g/g vs. 9.56 \(\pm\) 1.74 H\(9262\) g/g vs. 6.99 \(\pm\) 1.48 H\(9262\) g/g vs. 5.94 \(\pm\) 1.73 H\(9262\) g/g tissue (\(P<0.05\) and \(P<0.01\) for measures in doses 75 and 100 mg/kg/day vs. controls respectively).

Oral administration of olive leaf extract reduces infarct volume, brain edema, blood–brain barrier permeability, and improves neurologic deficit scores after transient middle cerebral artery occlusion in rats.

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**1. Introduction**

Brain ischemia induces the release of excitatory amino acids, with subsequent receptor activation leading to calcium influx, metabolic and electrophysiological dysfunction, and oxidative stress (including lipid peroxidation) (Lipton, 1999). Subsequent reperfusion worsens this oxidative stress, potentiating ischemic injury (Traystman et al., 1991). Diets rich in antioxidants might thus offer neuroprotection in cases of ischemic stroke.

The Mediterranean diet is powerfully antioxidant, and a number of international scientific organizations now recommend a modified version (Krauss et al., 2000) to prevent conditions in which oxidative stress may play an etiological role (Violi and Cangemi, 2005). Mediterranean diet contains high consumption of olive products constitute a rich source of polyphenols such as oleuropein and its derivatives, including hydroxytyrosol (HT), which scavenge free radicals and inhibit the chemical oxidation of LDL (Stupans et al., 2002; Visioli et al., 1998a).

HT administration enhances plasma antioxidant capacity and lowers production of pro-inflammatory and prothrombotic mediators in laboratory animals (Fki et al., 2007).

An HT extract prepared from olive mill wastewater reduces neuronal damage induced by chemical oxidative stress (from ferrous salts or sodium nitroprusside administration) (Schaffer et al., 2007).

The olive leaves have a hypoglycemic, hypotensive, vasodilatory and antiarrhythmic effect both in vitro and in vivo (Lasserre et al., 1983; Duarte et al., 1993; Zarzuelo et al., 1991; Occhiuto et al., 1990; Gonzalez et al., 1992). These effects are attributed
to oleuropein which has calcium antagonistic activity (Rauwald et al., 1994) and also enhances nitric oxide production by mouse macrophages (Visioli et al., 1998b).

Oleuropein clears superoxide anions and hydroxyl radicals, and inhibits the respiratory burst of neutrophils and related radicals (Chimi et al., 1991; Visioli et al., 1998a).

Oleuropein exhibits anti-ischemic, antioxidant, hypolipidemic effects and therefore provides cardioprotection (Andreadou et al., 2006).

It has been shown that olive leaf extract (OLE) has antiatherogenesis effects that are related to the suppressed inflammatory response, which is an important mechanism in addition to the decrease of serum lipid levels (Aguilera et al., 2002; Cullinen, 2006; Wang et al., 2008).

In our laboratory, we have recently shown that pretreatment with various dietary doses of virgin olive oil induces ischemic tolerance and confers different degrees of neuroprotection in the rat brain (Mohagheghi et al., 2009, 2010).

In vivo neuroprotective effects of OLE from ischemia-reperfusion injury have yet to be clarified. We thus sought to characterize the impact of dietary OLE on brain infarct volume, brain edema, blood–brain barrier permeability, and neurological dysfunction resulting from transient middle cerebral artery occlusion (MCAO) in rats.

2. Materials and methods

A special preparation of OLE (Olea europaea; variety of Sevillano) extremely enriched in oleuropein, was provided by Herbal Medicine Institute (Lorestan, Iran). The OLE powder was dissolved in distilled water before use.

2.1. High-performance liquid chromatography (HPLC) procedure

HPLC analysis of the samples was conducted on a Shimadzu (model L-10AD) instrument consisting of two reciprocating pumps, a DGU-14A in-line degasser, a model CT10–10AC oven, a high pressure manual injection valve (20 μl injection loop) and a UV/VIS (model SPD-10A) detector. The software used for the data acquirement and processing was Class-vp v.R 6.1. The analytical column was a 25 cm × 4.6 mm i.d. RP-8 column (Shim-Pack CLC-C8) packed with 5 μm particles and equipped with a 1 cm guard column. A 25 μl HPLC microsyringe (F-LC, SGE, Australia) was used for the sample withdrawal and injection. A variable automatic pipette (ISOLAB, Gmbts) was used for the RP-DLLME procedure. A totally glass Fisons (UK) double distiller was used for preparation of doubly distilled water.

2.2. Quantification of some identified phenolic compounds by HPLC

For the HPLC separation and quantitation of oleuropein (Fig. 1), tyrosol, hydroxytyrosol and caffeic acid, a gradient elution with a mixture of solvents A (0.05 mol l⁻¹ acetate buffer pH 5.0 in water) and B (acetonitrile) with a flow rate of 1.0 ml min⁻¹ was used. The elution program was as follows: 0–8 min, 20–80% B; 8–11 min, 50–70% B; 11–13 min 70% B and 13–15 min, 70–20% B. The chromatograms were acquired at 240 nm (Hashemi et al., 2010). The main phenolic compositions of the olive leaf extract are oleuropein (356 mg/g), tyrosol (3.73 mg/g), hydroxytyrosol (4.89 mg/g), caffeic acid (49.41 mg/g) of the dry extract (Fig. 2).

2.3. Analysis of total phenolic compounds in the extract

The concentration of total phenolic compounds in olive leaf extract was determined using Folin–Ciocalteau assay (Folin and Ciocalteau, 1927) as described by Othman (Othman et al., 2009). Briefly, to 0.5 ml of a 5.5 g/l diluted extract, 2.5 ml of Folin–Ciocalteau reagent (diluted 10 times with water) was added. After about 3 min, 2 ml of Na₂CO₃ (75 g/l) was added and the sample was incubated for 5 min at 50 °C and then cooled. For the control sample, 0.5 ml of distilled water was used. The absorbance was measured at 760 nm. The results were expressed in mg of tyrosol per g of dry matter (De Marco et al., 2007). Total phenolic compounds are 349.4 that expressed as mg tyrosol per g of dry matter.

2.4. Determination of radical scavenging activity of the extract

The radical scavenging activity of the extract was determined as described by Moon and Terao with little modification; based on the scavenging ability to 2,2-diphenyl-1-picrylhydrazyl (DPPH) stable radicals (Moon and Terao, 1998). Briefly, the samples (from 100 to 350 μg/ml) were mixed with 1 ml of 500 μmol/l DPPH solution and 0.8 μL Tris–HCl buffer (pH 7.4) and filled up with ethanol, to a final volume of 2 ml. The reaction mixture was shaken in a room temperature dark room for 40 min. Butylated hydroxytoluene (BHT) was used as a positive control. The control was prepared as the test samples and ethanol was used for the baseline correction. Absorbance at 517 nm was measured on a UV–Vis spectrophotometer (Biochrom Ltd, England). IC₅₀ values, which represent the concentration of the
extract or BHT that causes 50% neutralization of DPPH radicals, were calculated from the plot of inhibition percentage against concentration (Table 1). Inhibition of free radical by DPPH (%) was calculated as follows:

\[
I(\%) = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100
\]

### Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration (μg/ml)</th>
<th>DPPH radical scavenging activity (Inhibition %)</th>
<th>EC50 (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olive leaf extract</td>
<td>100</td>
<td>30.17 ± 2.25</td>
<td>231.62</td>
</tr>
<tr>
<td></td>
<td>150</td>
<td>33.58 ± 3.24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>38.21 ± 3.82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>250</td>
<td>55.97 ± 2.19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>63.35 ± 1.71</td>
<td></td>
</tr>
<tr>
<td></td>
<td>350</td>
<td>72.31 ± 2.24</td>
<td></td>
</tr>
<tr>
<td>BHT</td>
<td>10</td>
<td>24.34 ± 1.05</td>
<td>50.63</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>28.46 ± 1.55</td>
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<td></td>
<td>40</td>
<td>47.5 ± 2.05</td>
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<td>60</td>
<td>52.05 ± 1.97</td>
<td></td>
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<tr>
<td></td>
<td>80</td>
<td>74.21 ± 1.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>77.46 ± 1.89</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SEM.

### 2.5. Animals

All experimental animal procedures were conducted with the approval of the Ethics Committee of Shahid Beheshti University of Iran. Male Wistar rats (body weight 250–350 g) were housed under conditions of controlled temperature (22 ± 2 °C) and constant humidity, with 12 h light/dark cycle (light on 07:00–19:00). Food and water were available ad libitum.

### 2.6. Experimental protocol

Four groups, each of 18 animals, received a dietary intervention (10–11.00 h daily) for 30 days. A control received gastric gavage with daily distilled water. The other three groups received 50, 75 and 100 mg/kg/day p.o. OLE; doses identified using previously published data (Wang et al., 2008). Two hours after the last dose, the animals were subjected to 60 min of middle cerebral artery occlusion (MCAO). Twenty-four hours later, neurobehavioral studies were performed before each group was split into three subgroups of six, and sacrificed for study of infarct volume, brain edema, and blood–brain barrier (BBB) permeability respectively. In addition, another group (12 animals) was managed according to the control protocol, but underwent surgery without MCAO. When sacrificed, these sham-operated animal groups were divided into subgroups (n = 6 in each) for evaluation of brain edema, and BBB permeability respectively.

### 2.7. Lipid profiles

At the end of day 30, before surgery, all animals were anesthetized with chloral hydrate (400 mg/kg i.p.). A venous blood sample was drawn and centrifuged at 7000 × g for 10 min, and the supernatant (serum) frozen at −20 °C until assayed for HDL, triglyceride, and cholesterol content (Pars Azmun, Iran according to manufacturers instructions) and auto-analyzer (Liasys, Roma, Italy).

### 2.8. MCA occlusion

The rats were weighed and intraperitoneally (i.p.) anesthetized with chloral hydrate (Merck, Germany) (400 mg/kg). MCAO was performed as described by Longa et al. (1989). Briefly, using microscopic surgery, a 3–0 silicone coated nylon suture was introduced through the external carotid artery stump. The occluder was advanced into the internal carotid artery (ICA) 20–22 mm beyond the carotid bifurcation until mild resistance indicated that the tip was lodged in the anterior cerebral artery and blocked the blood flow to the MCA (middle cerebral artery). Reperfusion was started by withdrawing the suture after 60 min of ischemia. Rectal temperature was monitored (Citizen-513w) and maintained at 37.0 °C by surface heating and cooling during surgery. A surface laser Doppler flowmeter (MBF3D, Moor instrument, Axminster, UK) was used to record regional cerebral blood flow (rCBF). Using a stereotaxic device and a low speed dental drill, a burr hole of 2 mm in diameter was made over the skull at 1 mm posterior and 5 mm lateral to the bregma on the right side. A needle shaped laser probe was placed on the dura away from visible cerebral vessels. Steady state baseline values were recorded before MCAO so that all rCBF data were expressed as percentages of the respective basal value (Bigdeli et al., 2008). Doppler flux was continuously measured from 30 min before MCAO to 30 min after reperfusion.

### 2.9. Assessment of neurobehavioral impact

After the suture was withdrawn, the rats were returned to their separate cages. 24 h later, the rats were assessed neurologically by an observer who was blind to the animal groups. The neurobehavioral scoring was performed using a six-point scale as previously described (Longa et al., 1989): normal motor function = 0; flexion of contralateral forelimb upon suspended vertically by tail or failure to extend forepaw = 1; circling to the contralateral side but have normal posture at rest = 2; loss of righting reflex = 3; no spontaneous motor activity = 4. Death was considered as score 5 only when a large infarct volume was present in the absence of subarachnoid hemorrhage. If the rats died due to subarachnoid hemorrhage or pulmonary insufficiency and asphyxia, they were eliminated from the study.

### 2.10. Assessment of infarct volume

After sacrifice with chloral hydrate (800 mg/kg), the animals were decapitated and the brains rapidly removed and cooled in saline at 4 °C for 15 min. Eight 2-mm thick coronal sections were then cut (Brain Matrix, Iran), beginning at the olfactory bulb. The slices were immersed in 2% 2,3,5-triphenyltetrazolium chloride solution (Merck, Germany), and kept at 37 °C in a water bath for 15 min. The slices were then digitally photographed (Lumix-Panasonic camera, Japan connected to a computer). Unstained areas were defined as infarct, and were measured using image analysis software (UTHSCSA Image Tool). The infarct volume was calculated by measuring the unstained and stained areas in each hemisphere slice, multiplying this by slice thickness (2 mm), and then summing all of the eight slices according to the method of Swanson et al. (1990): corrected infarct volume = left hemisphere volume – (right hemisphere volume – infarct volume).

### 2.11. Assessment of brain water content

After decapitation, the brain was removed. The cerebellum, pons, and olfactory bulb were separated and their wet weights (WW) measured (Bigdeli et al., 2007). Dry weights (DW) were assessed after 24 h at 120 °C. Brain water content (BWC) was calculated as \((\frac{\text{WW} - \text{DW}}{\text{WW}}) \times 100\).
2.12. Assessment of blood–brain barrier integrity

The integrity of BBB was evaluated by studying Evans Blue (EB, Sigma Chemicals, USA) extravasation. Briefly, the rats received 4 ml/kg of 2% EB solution in saline by tail vein injection 30 min after MCAO. 24 h after reperfusion, the thoracic cavity was opened under anesthesia. The rats were perfused with 250 ml saline transcardially to wash out intravascular EB until colorless perfusion fluid was obtained from the atrium. After decapitation, the brains were removed and the hemispheres were separately homogenized in 2.5 ml of 60% trichloroacetic acid was added and mixed by vortex for 3 min. The samples were then placed at 4 °C for 30 min and centrifuged for 30 min at 1000 g. The supernatants was measured at 610 nm using spectrophotometry (Perkin-Elmer, Illinois, USA). EB levels were expressed as μg/g of brain tissue against a standard curve (Bigdeli et al., 2007).

2.13. Statistical analysis

Infarct volume, brain water content, EB extravasation, blood flow, body weight, cholesterol, triglyceride, LDL, HDL, and VLDL were compared using one-way ANOVA test (post hoc LSD). The neurologic deficit scores were analyzed using the Mann–Whitney U test. Data were expressed as means ± SEM. P<0.05 was considered significant.

3. Results

3.1. Cerebral blood flow

In each group, MCAO reduced cerebral blood flow to less than 24% of that at baseline (Fig. 3).

![Fig. 3. Regional cerebral blood flow (rCBF) before and during middle cerebral artery occlusion (MCAO), and after reperfusion (*P = 0.000, n = 6).](image)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Serum lipids levels at the end of olive leaf extract (OLE) pretreatment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 0</td>
<td>Dose 50</td>
</tr>
<tr>
<td>Chol</td>
<td>84.33 ± 3.45</td>
</tr>
<tr>
<td>TG</td>
<td>106.5 ± 4.55</td>
</tr>
<tr>
<td>HDL</td>
<td>6.16 ± 0.3</td>
</tr>
<tr>
<td>LDL</td>
<td>57 ± 2.67</td>
</tr>
<tr>
<td>VLDL</td>
<td>21 ± 0.99</td>
</tr>
</tbody>
</table>

** = P<0.05; *** = P<0.01; **** = P<0.001; n = 6.

3.2. Effects of OLE on body weight

Body weight were not increased by OLE in the 50, 75, and 100 mg/kg/day (difference between first day and thirtieth day: 41.22 ± 3.95, 37.72 ± 3.54, and 30.88 ± 1.79 g respectively), vs. control group (36.83 ± 2.67 g) significantly.

3.3. Effects of OLE on serum lipids levels

Serum cholesterol levels were lower in the 50, 75, and 100 mg/kg/day group vs. control group (P=0.006, P=0.01, and P=0.001 respectively, Table 2). Serum triglyceride levels were similar in the control and all OLE groups. The HDL levels in the control group were 6.16 ± 0.3 mg/dl, but higher in the 50, 75, and 100 mg/kg/day OLE groups (15.33 ± 0.21, 15.33 ± 0.21, and 13.66 ± 0.42 mg/dl, P=0.000, P=0.000, and P=0.000, respectively, Table 2). The LDL levels were reduced in the 50, 75, and 100 mg/kg/day group vs. control group (P=0.000, P=0.001, and P=0.000 respectively, Table 2). The LDL/HDL ratio was 9.55 ± 0.59 in the control group, but 1.74 ± 0.48, 1.86 ± 0.23, and 1.66 ± 0.46 in the 50, 75, and 100 mg/kg/day groups respectively (P=0.000, P=0.000, and P=0.000, Table 2).

3.4. Effects of OLE on neurologic deficit scores

Median neurologic deficit scores (NDS) were reduced by OLE, being 1 (range: 0–3), 1 (range: 0–2), 1 (range: 0–2) and 2 (range: 0–4) in the 50, 75, 100 mg/kg/day, and control group, respectively (Table 3). The putative beneficial effects of OLE were confirmed by a reduction in infarct volume (Fig. 4).

3.5. Effects of OLE on infarct volume

Pretreatment with 75 and 100 mg/kg/day OLE for 30 days and 2 h before MCAO resulted in a reduction of infarct volume, while was slightly observed in the infarct core. The protection exerted by OLE was mainly seen in the penumbra (cortex), while was slightly observed in the infarct core.

3.6. Effects of OLE on brain edema

Focal cerebral ischemia significantly increased the brain water content in the ischemic hemisphere in control groups (P<0.001). The dose of 75 and 100 mg/kg/day reduced the post-ischemic brain edema (P<0.001).
Fig. 4. Photographs showing the neuroprotective effect of olive leaf extract (OLE) on focal cerebral ischemia. All sections of the brain were stained with TTC at 24 h after 60 min of ischemia. Each column presents the series of rat brain coronal sections: (a) Brain sections of control rat (b), (c), and (d) Brain sections of 50, 75, and 100 mg/kg/day pretreated rats, respectively (A). The graph shows the effects of various doses (0, 50, 75, and 100 mg/kg) of olive leaf extract (OLE) on infarct volume in different experimental groups in cortex (C), subcortex (Su), and total (T) area of brain (B) (*P<0.05; **P<0.01; n=6).

Water content increment (P=0.017, and P=0.001 respectively), while the lower dose (50 mg/kg/day) was without effect (Fig. 5).

3.7. Effects of OLE on blood–brain barrier permeability

Brain edema formation was associated with increased BBB permeability at 24 h. In the control group, EB concentration in ischemic cerebral tissue was 11.22±2.19 and 6.28±1.03 μg/g tissue in the non-ischemic left hemisphere. Administration of OLE at doses of 75 and 100 mg/kg/day was associated with a reduction in EB extravasation in the ischemic brain (the dose of 75 mg/kg/day: left hemisphere = 5.11±0.79, right hemisphere = 6.99±1.48 μg/g tissue; the dose of 100 mg/kg/day: left hemisphere = 4.55±0.92, right hemisphere = 5.94±1.73 μg/g tissue). BBB permeability in the contralateral hemisphere was not significantly affected in the brain pretreated with OLE (Fig. 6). This effect was not observed at the lower OLE dose of 50 mg/kg/day: left hemisphere = 5.07±0.6 μg/g, right hemisphere = 9.56±1.74 μg/g tissue in 75 and 100 mg/kg/day groups.

4. Discussion

This is the first study to directly assess OLE in focal cerebral ischemia animal model. We report that pretreatment with dietary OLE may reduce infarct volume, brain edema, BBB permeability, and neurobehavioral deficit scores in a reliable and reproducible animal model of stroke followed by reperfusion (Longa et al., 1989). Although this response is conserved in the circulation (Wang et al., 2008), the focal cerebral ischemia rat model was used for proof-of-concept for ischemic tolerance because it is well established for illustrating neuroprotection. These data are partly supported by recent study suggesting that OLE have anti-atherosclerotic effects via suppression of inflammatory response (Wang et al., 2008).

Our findings indicate that OLE may influence brain water content and brain water homeostasis by increasing BBB integrity, modulating the cell volume of neurons and astrocytes directly. The neuroprotection exerted by OLE was mainly seen in the penumbra (cortex). The lack of protective effects in the subcortical area could be due to the more severe damage in the subcortical area than cortex. It has been shown that neuronal injury after transient MCAO is more severe in the subcortex than in the cortex (Garcia et al., 1997). Although our data suggest that OLE-mediated neuroprotection is due to the reduction of postischemic infarct volume and brain edema, other mechanisms may be at work.

It has been shown that the administration of OLE downregulates the expression of TNF-α. Thus, NF-κB activation and the formation of lipid peroxidation are inhibited. Oxidative stress via increased production of ROS and LDL oxidation induces inflammatory response; olive phenols with high antioxidant capacity can thus inhibit LDL oxidation and block inflammatory response (Wang et al., 2008).
This study focused on the effects of OLE on vascular permeability and infarct volume, which is far more important in neuroprotection assessments. Although the mechanism of neuroprotection-induced by OLE requires further elucidation, it has been shown that oleuropein, the main constituent of the leaves of *O. europaea*, has high antioxidant activity in vitro, comparable to a hydrosoluble analog of tocopherol (Speroni et al., 1998). In myocardium, prolonged ischemia and reperfusion reduce the antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) (Das et al., 1986) and it has been demonstrated that pretreatment with oleuropein keep the superoxide dismutase activity stable at ischemia-reperfusion (Andreadou et al., 2006).

In our study, OLE improved the LDL/HDL ratio – a finding in keeping with the findings of others. It has been shown that the administration of OLE can reduce serum levels of lipid and suppress the development of atherosclerosis (Wang et al., 2008). Moreover, an olive extract rich in oleuropein decreases cholesterol levels in rats, an effect attributed to its ability to slow down the lipid peroxidation process and to enhance antioxidant enzymes activity (Fki et al., 2005).

In conclusion, our data suggest that OLE may be cerebroprotective in a rat model of ischemia-reperfusion. Further work is required to extend these observations. Ultimately, it is hoped that novel cerebroprotective strategies may be developed for those at risk of stroke, or in whom cerebral perfusion is electively reduced perhaps at the time of surgery.

References


