

# Oleuropein aglycone and polyphenols from olive mill wastewater ameliorate cognitive deficits and neuropathology

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Alzheimer's disease (AD) is the most common form of dementia presently affecting, in the developed countries, approximately 30 million aged people. AD brain is characterized by the presence of intracellular tangles of hyperphosphorylated tau protein and of extracellular diffuse and senile plaques of fibrillar A $\beta$ .

The Mediterranean and Asian diets are claimed to reduce age-related dysfunctions including AD. One of the dietary habits that characterize the Mediterranean countries is the daily consumption of extra-virgin olive oil (EVOO). Oleuropein and its aglycone (OLE) are the major polyphenols present in the EVOO.

We investigated, the effects of OLE and of a mix of polyphenol extract from a concentrate of olive mill waste water on cognitive functions and neuropathology in the TgCRND8 (Tg) mouse model of A $\beta$  deposition.

4-month-old Tg and wild type (wt) mice (n = 6/group/genotype, equally divided for sex) were equally divided into four groups and treated for 8 weeks with a modified low-fat (5.0%) AIN-76A diet (10 g/day/ mouse) as such, supplemented with OLE (50, 12.5 or 0.5 mg/kg of diet, high, intermediate and low dose, respectively,) or with a mix of polyphenol extract (50 mg/kg of diet).

The administration of the high and intermediate dose of OLE and of a mix of polyphenols significantly improved the performance of Tg mice to the level of wt mice, evaluated by the step down test (P<0.0001). The same mice were also tested for object recognition test (ORT); the ability of polyphenols-fed and OLE-fed (50 mg/Kg) Tg mice to discriminate between the familiar and novel object appeared significantly improved respect to that of untreated Tg mice (P<0.001).

At the end of behavioural performance we checked whether the treatment resulted from any altered amyloid load with respect to untreated animals. Amyloid- $\beta$ 1-42 (A $\beta$ 42) and 3-42 pyroglutamylated A $\beta$  (pE3-A $\beta$ ) plaque area and number were significantly reduced in the cortex by administration of the intermediate dose of OLE (P<0.01) and in the cortex and hippocampus by OLE at the high dose and by a mix of polyphenols (P<0.0001). Behavioral impairment and A $\beta$  deposition were unaffected by the low dose of OLE. In addition, an intense activation of autophagy was found in the cortex of all treated groups. Our data indicate that the beneficial effects of OLE are dose-related and that the remarkable effect of OLE at the high dose is reproduced by the same dose of a mix of polyphenols found in olive mill waste water. In conclusion, olive polyphenols are beneficial either when administered as pure components (OLE) or as a mixture.