

# Oleuropein aglycone efficacy against Alzheimer's disease: an advanced biological preclinical investigation

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The Mediterranean and Asian diets are claimed to reduce age-related dysfunctions including Alzheimer's disease (AD) possibly due to the presence of substantial amounts of polyphenols whose beneficial properties include anti-amyloid aggregation power. Oleuropein and its aglycone (OLE) are the major polyphenols in the extra virgin olives oil. In TgCRND8 mice and w.t. control littermates of different ages, from pre-A $\beta$  (1.5-month-old) to the late stage (12-month-old) of A $\beta$  deposits, fed or not for 8 weeks with different amounts of OLE (0.5, 12.5, 50 mg/kg of diet) (8-10 mice/group) we investigated, by means of step-down inhibitory passive avoidance and object recognition test, the effects of OLE on cognitive functions, and by immunohistochemistry and Western Blotting, whether and how, OLE modulates the presence in the plaques of glutaminyl cyclase (QC)-produced pE(3-42)A $\beta$  and QC activity/expression. It was also checked if OLE affects synaptic morphology and function by stimulating adult hippocampal neurogenesis in the dentate gyrus SGZ. We report here that OLE (50 mg/kg of diet) supplementation with diet significantly protects against cognitive deterioration, remarkably reduces  $\beta$ -amyloid levels and plaque deposits, which appeared less compact and "fluffy", is active against QC-catalyzed pE3-A $\beta$  generation reducing enzyme expression and interferes both with A $\beta$ 42 and pE3-A $\beta$  aggregation. Moreover, the phenol astonishingly activates neuronal autophagy even in mice at advanced stage of pathology, where it increases histone 3 and 4 acetylation, which matches both a decrease of histone deacetylase 2 expression and a significant improvement of synaptic function. The occurrence of these functional, epigenetic and histopathological beneficial effects even at a late stage of the pathology suggests that the phenol could be beneficial at the therapeutic, in addition to the prevention, level. The dose-response relation of OLE on cognitive functions and neuropathology is undergoing.

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