



# Olive Oil Polyphenols: Possible Tools to Prevent/Fight Alzheimer's Disease

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## Editorial

Alzheimer's disease (AD), the most common form of dementia affecting a large proportion of aged people, is considered a protein misfolding disease; accordingly, several therapeutic approaches, including the use of molecules enriched in the Mediterranean diet (MD) that are able to inhibit self-assembly into oligomers and fibrils of amyloidogenic proteins/peptides are under development. Many available data and population studies suggest that greater adherence to the MD enhances cognitive function, reduces both the risk of developing mild cognitive impairment and of its conversion to AD [1,2]. These studies have been better related to the presence of extra virgin olive oil (EVOO) and its polyphenols by the data arising from several population studies such as the Three-City Study Berr et al. and the PREDIMED-NAVARRA study [3,4] and several clinical trials; these include a study carried out in Australia and New Zealand (ACTRN12613000602729) which showed that a cause-effect relationship does exist between MD and aging-dependent cognition [5], and the Prevención con Dieta Mediterránea Nutrition Intervention Trial (ISRCTN35739639) which led to conclude that a MD supplemented with olive oil or nuts is associated with a significant improvement of cognitive behavior in a population of aged people [6]. Finally the PREDIMED-NAVARRA randomized trial indicated that a MD intervention modulates the way of genetic factors influence cognition [7]. Overall, these population studies and clinical trial support the idea that the MD, together with the intake of its polyphenols, provide consistent and effective protection that contributes to lower the risk of aging-associated neurodegeneration (reviewed in [8,9]. The beneficial effects of the MD against AD could result, at least in part, from the daily consumption of EVOO, particularly its polyphenols, that have been shown to possess beneficial effects against A $\beta$  and tau pathologies [10-13] and, possibly, Parkinson disease [14]. The polyphenols enriched in EVOO include oleocanthal, hydroxytyrosol and oleuropein, the latter both in the glycosylated and in the aglycone (OLE) forms.

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Increasing evidence has established a strong link between diabetes (mainly type 2) and AD-associated neurodegeneration [15,16]. Accordingly, most beneficial properties of EVOO polyphenols, notably OLE, have been associated, in addition to their well known antioxidant power, to the modulation of several types of signaling pathways involving insulin/IGF1/AKT, AMP-activated protein kinase (AMPK) and mTOR, whose inhibition favors longevity and reduces inflammatory states reviewed in [17]. mTOR is one of the most potent upstream regulators of autophagy, activation of the latter appears as one of the ways olive polyphenols can induce most of their beneficial effects against neurodegeneration [18]. In cultured neuronal cells, we have shown that OLE triggers autophagy, by AMPK activation through CAMKK $\beta$  and reduction of mTOR phosphorylation with mTOR inhibition [19]. These data support the idea that autophagy activation by OLE (and presumably other olive polyphenols) proceeds via the AMPK-mTOR signaling pathway, similarly to data reported for other plant polyphenols [20]. The involvement of autophagy activation in OLE protection against neurodegeneration has been extensively studied in a transgenic mouse model of A $\beta$  deposition, the TgCRND8 mouse, that carries the Indiana and the Swedish mutations in the APP gene and displays extensive plaque deposits since the age of three months [21]. We found that OLE administration to these mice also activates autophagy, reduces both the inflammatory response resulting from the accumulation of amyloid aggregates of A $\beta$  and its pyroglutamylated 3-42 derivative and the astrocyte reaction in the affected brain areas, with strong improvement of memory and behavioral performance to the levels recorded in wild-type mice; finally, these mice displayed increased hippocampal neurogenesis and improved synaptic behavior (increased LTP) [11,22].

Plant polyphenols can also counteract aging as well as many of its pathological consequences resulting from aberrant epigenetic mechanisms [23,24], and epigenetic issues targeted by diet polyphenols have become an attractive approach for the anti-neurodegeneration power of these substances. In the context of neurodegenerative diseases, the epigenetic modifications have been shown to induce effects similar to those provided by caloric restriction in humans reviewed [17]. In this context, we have recently shown that OLE administration downregulates the expression of histone deacetylase 2 (HDAC2), an enzyme known to be upregulated in AD [25], both in the hippocampus and in the cortex of TgCRND8 mice and that such decrease matched a significant increase in the level of histone H3 and H4 acetylation [22]. It must be stressed that histone acetylation has been reported to improve cognitive deficits in animal models of AD and its indication is considered a promising novel therapeutic strategy against AD [26]. Epigenetic involvement in some the aforementioned positive effects resulting from OLE administration is further supported by the reported modifications of the expression levels of effector proteins such as the glutaminyl cyclase and some autophagic players. It is also confirmed by a large wealth of data indicating the ability of many plant polyphenols to induce epigenetic modifications mainly in cancer [27], leading to the proposal of an epigenetic diet [28]. Thus, in spite of the limited information on the epigenetic effects of olive polyphenols presently available, modulation of epigenetic flaws by natural polyphenols appears as a promising subject for the discovery of new compounds effective against chronic diseases.

Finally, a problem associated with the use of olive and other plant polyphenols is their reduced bioavailability due both to incomplete intestinal absorption and to rapid biotransformation. However, many studies have clearly shown that OLE is indeed absorbed by humans and distributed, at least in part, to tissues before degradation and excretion [29-31], moreover, we have shown that some OLE metabolites, arising mainly from acid hydrolysis in the stomach, are found in the brain of TgCRND8 mice after an acute oral administration of OLE supporting the ability of some OLE derivatives, including hydroxytyrosol, to cross the blood-brain barrier [32]. In spite of the reduced available information on many aspects of plant polyphenol pharmacokinetics, pharmacodynamics and their metabolic modifications in the organism, also including the chemical modification by the gut microbiota, it is possible to consider that OLE and other olive, and more generally, plant polyphenols are absorbed, though in reduced amounts, and distributed to the whole organism reviewed in [9].

## Conclusion

The identification of novel effective molecules or molecular scaffolds able to contrast protein/peptide aggregation hindering the formation of the plaque deposits widely considered the main responsible for neuronal impairment in neurodegenerative diseases in a major, still unmet, medical need for the coming years. The studies carried out in the last decade have highlighted the beneficial effects of the MD against several aging-associated pathologies, including neurodegenerative diseases, thus providing strong value to this alimentary regimen. More recently, an increasing body of evidence has started to unravel the molecular basis of these beneficial effects, assigning a key role to the polyphenols enriched in the EVOO, a key component of the MD. These data are providing a strong rationale and a convincing scientific basis to the MD in general and, particularly, to

the use of nutraceuticals to supplement the dietary intake of these substances, also in the light of their reduced bioavailability. More knowledge is needed to fully confirm these considerations, mainly for what a deeper insight on the molecular and physiological basis of the claimed effects and a better knowledge of all the factors contributing to the effective bioavailability of these substances are concerned. However, the data presently available can be a strong starting point to definitely ascertain the real efficacy of any polyphenol-based nutraceutical treatment aimed at hindering the appearance of aging-associated neurodegeneration and its clinical signs.

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