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Short Communication

Olive Polyphenols: New Possible Tools against Type 2 Diabetes and Aging-Related Neurodegeneration

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Increasing evidence supports the idea that olive polyphenols are effective against several aging-associated diseases, including both systemic (type 2 diabetes, atherosclerosis, stroke, the metabolic syndrome, inflammatory diseases, cancer) and neurodegenerative (Alzheimer's and Parkinson diseases) pathologies, the latter still lacking an effective therapy [1-4]. The large literature in the field provides strong support to the benefits of the Mediterranean and Asian diets. In particular, increasing data are accumulating on the positive relation between type 2 diabetes and olive polyphenols, notably oleuropein (Ole) and its main metabolite, hydroxytyrosol (HT) [5]. On the other hand, more recently, a solid knowledge on a claimed protection by Ole, HT and oleocanthal, a third important olive polyphenol, against Aβ plaque deposition in Alzheimer's disease (AD) as well as on the molecular basis of the latter, has been accumulating [6].

The concomitant anti-diabetic and anti-neurodegenerative power of olive polyphenols is not surprising, when one considers the raising awareness that diabetes (notably type 2 diabetes) and AD are two degenerative conditions closely related to each other, such that the risk of dementia is claimed to be increased by 1.9-fold in diabetic people [7]. Actually, insulin-resistance is a common feature of the two pathologies [8]. In addition, increased circulating insulin has at least two outcomes. The first consequence is the increased incretion of amylin (IAPP) by pancreatic cells which, besides in pancreatic β cells, displays its tendency to aggregate into amyloid assemblies also in the brain tissue; there, often they are found as a minor component in AD plaque deposits. In addition, recent data highlight cross-seeding between amylin and Aβ aggregates, the main components of extracellular plaques in AD brain areas, leading to conclude that tiny amounts of amylin aggregates can seed extensive Aβ aggregation [9]. The second consequence stems from the known substrate preferences of insulin degrading enzyme (IDE) and nephrilysin, two proteases involved in degradation of both insulin, amylin and the Aβ peptide [7,10,11]. Accordingly, increased insulin/amylin may hinder efficient degradation of Aβ, resulting in raised levels of the latter, that, together with amylin seeding, can enhance Aβ tendency to aggregate inside the brain [7].

In the past, the anti-diabetic and anti-neurodegeneration effects of olive polyphenols have been traced back to the potent antioxidant power of these compounds, particularly HT, the main Ole metabolite [12]. However, recent investigations have highlighted a more complex interference of these compounds with cell and tissue physiology. In fact, similarly to other plant polyphenols, olive polyphenols also possess remarkable anti-inflammatory power elicited both in peripheral tissues and in the central nervous system [13,14]; in addition, they are able to reprogram cell metabolism by modulating cell signaling pathways involved in the regulation of the mTORC and AMPK metabolic hubs. The resulting mTORC inhibition and AMPK activation, eventually favors the catabolic, instead than the anabolic/proliferative, pathways [15,16]. One of the main outcomes of these modifications is the interference with the proteostasis balance, which results in a remarkable activation of autophagy, particularly macroautophagy [17]. The latter is a complex response to stress stimuli, such as nutrient deprivation, that helps the cells to clear, by lysosomal degradation, cellular components and undesired accumulating by-products for further use as building blocks; these materials also include intra- or extracellular protein aggregates of amyloid nature that stress and damage exposed cells [18]. On this aspect, it is of significance that brain autophagy is considerably decreased in neurodegenerative diseases, including AD [19].

Most of the biological effects of plant, notably olive, polyphenols result from their ability to modulate, in addition to proteostasis, the activity of transcription factors involved in the control of key cellular equilibria, such as the redox status. Several studies have reported that olive polyphenols modulate the activity of nrf-2, FOXO, TFEB or other transcription factor families that control the expression of genes whose products are involved in the redox, inflammatory or autophagic responses [20-23]. Even more importantly, these substances are starting to be described as important contributors to the epigenetic modifications involved in many of their activities. For example, we have recently reported that TgCRND8 mice, a murine model of Abeta plaque deposition, fed with a diet supplemented with Ole aglycone did not display the severe impairment of memory and cognitive performance displayed by normally fed littermates; rather, they cognitive behavior was undistinguishable from that recorded in w.t. mice. The strongly improved cognition, in these Ole-fed Tg mice, matched a remarkable reduction of neuroinflammation, Aβ levels and Aβ plaque load and consistence, together with improved neurogenesis and synaptic function (LTP) and an astonishing activation of the autophagic flux and autophagolysosome formation [24]. At least some of these effects were traced back to epigenetic modifications. In fact, Ole-fed Tg mice displayed increased histone acetylation, normally depressed in AD [25], which resulted from reduced levels of histone deacetylase 2 (HDAC2), normally upregulated in the AD brain [25] and, possibly, induced beclin-1/LC3 expression, whereas the expression of glutaminyl cyclase (QC) an enzyme abundantly expressed in brain cortex, hipothalamus and hippocampus was reduced. QC, whose mRNA is upregulated in the cortex and peripheral blood of AD patients [26] is involved in AD, where it is responsible for the generation of the pyroglutamylated $A\beta_{3\text{-}42}$. The latter, an Aβ derivative more resistant to proteases and with strong tendency to aggregate, is possibly involved in the onset of plaque deposition [27]. Overall, increasing data are accumulating on the polyphenol-epigenetics relation particularly in cancer [28,29]; however, more knowledge on this theme is needed, mainly for what olive polyphenols are concerned, to complete the picture of the cellular effects of these molecules at the molecular level.

In conclusion, in addition to the population studies supporting the beneficial properties of olive oil [30,31], raising knowledge is focusing on its polyphenols, increasingly described as the main responsible for many virtues of the Mediterranean diet, including protection against type 2 diabetes, ageing and aging-related neurodegeneration. These studies are providing strong molecular support to the claimed effects of these substances. The resulting knowledge supports a positive modulation of the biochemical, physiological and epigenetic responses aimed at cell protection against the insult of various stressors responsible for cell impairment in several pathological conditions such as type 2 diabetes and AD. However, while Ole protection against type 2 diabetes has started to be supported not only mechanistically [32,33] but also by studies carried out in humans, yet to be confirmed in larger cohorts [34], Ole benefits against Aβ aggregation and plaque deposition in AD, increasingly proven *in vitro*, as well as in cell and animal models, still awaits confirmation in humans by appropriate clinical trials.

Bibliography

1. Stefani M and Rigacci S. "Beneficial properties of natural phenols: highlight on protection against pathological conditions associated with amyloid aggregation". *Bio Factors* 40.5 (2014): 482-493.

2. Tressera-Rimbau A., *et al*. "Dietary Polyphenols in the Prevention of Stroke". *Oxidative Medicine and Cellular Longevity* (2017): 7467962.

3. Santangelo C., *et al*. "Anti-inflammatory Activity of Extra Virgin Olive Oil Polyphenols: Which Role in the Prevention and Treatment of Immune-Mediated Inflammatory Diseases?". *Endocrine, Metabolic and Immune Disorders* 18.1 (2018): 36-50.

4. Stevens JF., *et al*. "Mitochondria-Centric Review of Polyphenol Bioactivity in Cancer Models". *Antioxidants and Redox Signaling* (2017).

5. Rigacci S and Stefani M. "Nutraceutical properties of olive oil polyphenols. An itinerary from cultured cells through animal models to humans". *International Journal of Molecular Sciences* 17.6 (2016) E843.

6. Casamenti F and Stefani M. "Olive polyphenols: new promising agents to combat aging-associated neurodegeneration". *Expert Review of Neurotherapeutics* 17.4 (2017): 345-356.

7. Schilling MA. "Unraveling Alzheimer's: making sense of the relationship between diabetes and Alzheimer's disease". *Journal of Alzheimer's Disease* 51.4 (2016): 961-977.

8. Jha NK., *et al*. "Impact of Insulin Degrading Enzyme and Neprilysin in Alzheimer's Disease Biology: Characterization of Putative Cognates for Therapeutic Applications". *Journal of Alzheimer's Disease* 48.4 (2015): 891-917.

9. Moreno-Gonzalez I., *et al*. "Molecular interaction between type 2 diabetes and Alzheimer's disease through cross-seeding of protein misfolding". *Molecular Psychiatry* 22.9 (2017): 1327-1334.

10. Guan H., *et al*. "Degradation of islet amyloid polypeptide by neprilysin". *Diabetologia* 55.11 (2012): 2989-2998.

11. Sexton T., *et al*. "site mutations change the cleavage specificity of neprilysin". *PLoS One* 7.2 (2012): e32343.

12. Bach-Faig A., *et al*. "Mediterranean Diet Foundation Expert Group. Mediterranean diet pyramid today Science and cultural updates". *Public Health Nutrition* 14.12A (2011): 2274-2284.

13. Cárdeno A., *et al*. "An up-date of olive oil phenols in inflammation and cancer: molecular mechanisms and clinical implications". *Current Medicinal Chemistry* 20.37 (2013): 4758-4776.

14. Cabrerizo S., *et al*. "Role of the inhibition of oxidative stress and inflammatory mediators in the neuroprotective effects of hydroxytyrosol in rat brain slices subjected to hypoxia reoxygenation". *The Journal of Nutritional Biochemistry* 24.12 (2013): 2152-2157.

15. Hadrich F., *et al*. "Oleuropein activated AMPK and induced insulin sensitivity in C2C12 muscle cells". *Life Sciences* 151 (2016): 167-173.

16. Rigacci S., *et al*. "Oleuropein aglycone induces autophagy via the AMPK/mTOR signalling pathway: a mechanistic insight". *Oncotarget* 6 (2015): 35344-35357.

17. Grossi C., *et al*. "The polyphenol oleuropein aglycone protects TgCRND8 mice against Aβ plaque pathology". *PLoS One* 8.8 (2013): e71702.

18. Rubinsztein DC., *et al*. "Autophagy and aging". *Cell* 146.5 (2011): 682-695.

19. Menzies FM., *et al*. "Compromised autophagy and neurodegenerative diseases". *Nature Reviews Neuroscience* 16.6 (2015): 345-357.

20. Aparicio-Soto M., *et al*. "Dietary extra virgin olive oil attenuates kidney injury in pristane-induced SLE model via activation of HO-1/Nrf-2 antioxidant pathway and suppression of JAK/STAT, NF-κB and MAPK activation". *The Journal of Nutritional Biochemistry* 27 (2016): 278-288.

21. Peng S., *et al*. "Dual protection of hydroxytyrosol, an olive oil polyphenol, against oxidative damage in PC12 cells". *Food and Function* 6.6 (2015): 2091-2100.

22. Chu AJ. "Antagonism by bioactive polyphenols against inflammation: a systematic view". *Inflammation and Allergy Drug Targets* 13.1 (2014): 34-64.

23. Settembre C., *et al*. "TFEB links autophagy to lysosomal biogenesis". *Science* 332.6036 (2011): 1429-1433.

24. Luccarini I., *et al*. "Oleuropein aglycone protects against pyroglutamylated-3 amyloid-β toxicity: biochemical, epigenetic correlates". *Neurobiology of Aging* 36.2 (2015): 648-663.

25. Gräf J., *et al*. "An epigenetic plackade of cognitive functions in the neurodegenerating brain". *Nature* 483 (2012): 222-226.

26. Valenti MT., *et al*. "Increased glutaminyl cyclase expression in peripheral blood of Alzheimer's disease patients". *The Journal of Alzheimer's Disease* 34.1 (2013): 263-271.

27. Pivtoraiko VN., *et al*. "Cortical pyroglutamate amyloid-β levels and cognitive decline in Alzheimer's disease". *Neurobiology of Aging* 36.1 (2015):12-19.

28. Giudice A., *et al*. "Epigenetic changes induced by green tea catechins are associated with prostate cancer". *Current Molecular Medicine* 17.6 (2017): 405-420.

29. Ferraresi A., *et al*. "Resveratrol inhibits IL-6-induced ovarian cancer cell migration through epigenetic up-regulation of autophagy". *Molecular Carcinogenesis* 56.3 (2017): 1164-1181.

30. Valls-Pedret C., *et al*. "Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk". *Journal of Alzheimer's Disease* 29.4 (2012): 773-782.

31. Soriguer S., *et al*. "Olive oil has a beneficial effect on impaired glucose regulation and other cardiometabolic risk factors. Di@betes study". *European Journal of Clinical Nutrition* 67.9 (2013): 911-916.

32. Fujiwara Y., *et al*. "Oleuropein improves insulin resistance in skeletal muscle by promoting the translocation of GLUT4". *Journal of Clinical Biochemistry and Nutrition* 61.3 (2017): 196-202.

33. Hadrich F., *et al*. "Oleuropein activated AMPK and induced insulin sensitivity in C2C12 muscle cells". *Life Science* 151 (2016): 167-173.

34. de Bock M., *et al*. "Olive (Olea europaea L.) leaf polyphenols improve insulin sensitivity in middle-aged overweight men: a randomized, placebo-controlled, crossover trial". *PLoS One* 8.3 (2013): e57622.

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1. Dunne C and Meriano A. "Acute postpartum pulmonary edema in a 23-year-old woman 5 day after cesarean delivery". *Canadian Journal of Emergency Medicine* 11.2 (2009): 178-181.

2. Vigil-De Gracia P. "Pregnancy and severe chronic hypertension: maternal outcome". *Hypertension in Pregnancy* 23.3 (2004): 285-293.

3. Sciscione AC., *et al*. "Acute pulmonary edema in pregnancy". *Obstetrics and Gynecology* 101.3 (2003): 511-515.

4. Grobman WA., *et al*. "Frequency of and factors associated with severe maternal morbidity". *Obstetrics and Gynecology* 123.4 (2014): 804-810.

5. Dennis AT and Solnordal CB. "Acute pulmonary oedema in pregnant women". *Anaesthesia* 67.6 (2012): 646-659.

6. Gebhardt GS., *et al*. "National Committee for Confidential Enquiries into Maternal Deaths in South A. Maternal death and caesarean section in South Africa: Results from the 2011-2013 Saving Mothers Report of the National Committee for Confidential Enquiries into Maternal Deaths". *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde*. 105.4 (2015): 287-291.

7. Murray JF. "Pulmonary edema: pathophysiology and diagnosis". The International Journal of Tuberculosis And Lung Disease15.2 (2011):155-160.

8. Thornton CE., *et al*. "Acute pulmonary oedema as a complication of hypertension during pregnancy". *Hypertension in Pregnancy* 30.2 (2011): 169-179.

9. Yeast JD., *et al*. "The risk of pulmonary edema and colloid osmotic pressure changes during magnesium sulfate infusion". *American Journal of Obstetrics and Gynecology* 169.6 (1993): 1566-1571.

10. Tuffnell DJ., *et al*. "Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003". *BJOG : An International Journal of Obstetrics and Gynaecology* 112.7 (2005): 875-880.

11. Vaast P., *et al*. "Acute pulmonary oedema during nicardipine therapy for premature labour; Report of five cases". *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 113.1 (2004): 98-99.

12. Le Bret F., *et al*. "Transesophageal echocardiographic assessment of left ventricular function in response to labetalol for control of postoperative hypertension". *Journal of Cardiothoracic and Vascular Anesthesia* 6.4 (1992): 433-437.

13. Gul A., *et al*. "Maternal and fetal outcomes in HELLP syndrome complicated with acute renal failure". *Renal Failure* 26.5 (2004): 557-562.

14. Tomimatsu T., *et al*. "Pathophysiology of preeclampsia: an angiogenic imbalance and long-lasting systemic vascular dysfunction". *Hypertension research: official journal of the Japanese Society of Hypertension* 40.4 (2017): 305-310.

15. Chaiworapongsa T., *et al*. "Pre-eclampsia part 1: current understanding of its pathophysiology. Nature reviews". *Nephrology* 10.8 (2014): 466-480.

16. Publications Committee SfM-FM and Sibai BM. "Evaluation and management of severe preeclampsia before 34 weeks' gestation". *American Journal of Obstetrics and Gynecology* 205.3 (2011): 191-198.

17. Roberts JM., *et al*. "Sera from preeclamptic women specifically activate human umbilical vein endothelial cells in vitro: morphological and biochemical evidence". *American Journal of Reproductive Immunology* 27.3-4 (1992): 101-108.

18. Redman CW., *et al*. "Preeclampsia: an excessive maternal inflammatory response to pregnancy". *American Journal of Obstetrics and Gynaecology* 180 (1999): 499-506.

19. Ware LB and Matthay MA. "Clinical practice. Acute pulmonary edema". *The New England Journal of Medicine*. 353.26 (2005): 2788-2796.

20. Kindermann M., *et al*. "Heart failure with normal left ventricular ejection fraction: what is the evidence?". *Trends in cardiovascular medicine* 18.8 (2008): 280-292.

21. Andrew P. "Diastolic heart failure demystified". *Chest* 124.2 (2003): 744-753.

22. MacIver and Clark AL. "The vital role of the right ventricle in the pathogenesis of acute pulmonary edema". *The American Journal of Cardiology* 115.7 (2015): 992-1000.

23. Tariq S and Aronow WS. "Use of Inotropic Agents in Treatment of Systolic Heart Failure". *International Journal of Molecular Sciences* 16.12 (2015): 29060-29068.

24. Christiansen LR and Collins KA. "Pregnancy-associated deaths: a 15-year retrospective study and overall review of maternal pathophysiology". *The American Journal of Forensic Medicine and Pathology* 27.1 (2006): 11-19.

25. Samol JM and Lambers DS. "Magnesium sulfate tocolysis and pulmonary edema: the drug or the vehicle?". *American journal of obstetrics and gynecology* 192.5 (2005): 1430-1432.

26. Dogdu O., *et al*. "Fatal pulmonary oedema following oxytocin administration in a pregnant woman with acute myocardial infarction". *Cardiovascular Toxicology* 11.1 (2011): 74-77.