



Ruolo degli integratori nutrizionali nel trattamento del diabete mellito e dei dismetabolismi correlati: recenti acquisizioni dalla ricerca biochimica e clinica

Plant polyphenols: possible long-term treatments to reduce the risk of type 2 diabetes and the metabolic syndrome



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of Clinical Biochemistry
School of Human Health Sciences
University of Florence*





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Unified Criteria for Clinical Diagnosis of the Metabolic Syndrome

Increased waist circumference	Population-specific definition
Increased triglycerides (or medication)	≥ 150 mg/dl
Reduced HDL cholesterol (or medication)	<40 mg/dl in men <50 mg/dl in women
Increased blood pressure (or medication)	Systolic ≥ 130 or Diastolic ≥ 85 mmHg
Increased fasting blood glucose (or medication)	> 100 mg/dl



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Unifying theory

about central obesity and related type II diabetes mellitus (TIIDM), cardiovascular disease (CVD) and cancer. All conditions seem to be linked by the concept of the **metabolic syndrome**, but the underlying causes are not known. (McGill AT1 Causes of metabolic syndrome and obesity-related co-morbidities Part 1: A composite unifying theory review of human-specific co-adaptations to brain energy consumption. Arch Public Health. 2014 Sep 1;72(1):30)

Insufficient consumption of food micronutrients and plant chemicals with anti-oxidant activity

Excessive intake of energy-dense food

Dysfunction of NRF2 cellular protection system and of other metabolic pathways

Inefficient metabolism of excess energy forces central and non-adipose cells to store excess toxic lipids.

Oxidative stress and metabolic inflammation, allow susceptibility to infectious, degenerative atherosclerotic cardiovascular, autoimmune, neurodegenerative and dysplastic diseases



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Oxidative stress

Protein/peptide misfolding

Age-related
Degenerative diseases

Autophagy dis-regulation





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Clinical syndrome

Alzheimer's disease

Spongiform encephalopathies

Parkinson's disease

Familial Danish dementia

Familial British dementia

Fronto-temporal dementias

Hereditary cerebral amyloid angiopathy

Amyotrophic lateral sclerosis

Dentatorubro-pallido-Luysian atrophy

Huntington disease

Cerebellar ataxias

Kennedy disease

Spino cerebellar ataxia 17

Primary systemic amyloidosis

Secondary systemic amyloidosis

Senile systemic amyloidosis

Familial amyloid polyneurop./cardiomyopathy

Hemodialysis-related amyloidosis

Familial amyloid polyneuropathy III

Finnish hereditary systemic amyloidosis

Type II diabetes

Medullary carcinoma of the thyroid

Atrial amyloidosis

Hereditary non-neuropathic system. amyloidosis

Injection-localized amyloidosis

Hereditary renal amyloidosis

Fibril component

A β peptides (1-40, 1-41, 1-42, 1-43); *Ptau*

Prion (whole or fragments)

α -synuclein (wt or mutant)

ADan (34 AA fragment of Bri-277)

ABri (34 AA fragment of Bri-277)

Tau (wild-type or mutant)

Cystatin C (minus a 10-residue fragment)

Superoxide dismutase

Atrophia 1

Huntingtin (whole or poly(Q) fragment)

Ataxins (whole or poly(Q) fragments)

Androgen receptor (whole or poly(Q) fragment)

TATA box-binding protein (whole or poly(Q) fragments)

Ig light chains (whole or fragments)

Serum amyloid A (whole or 76-residue fragment)

Transthyretin (whole or fragments)

Transthyretin (over 45 variants)

β_2 -microglobulin

Apolipoprotein A1 (fragments)

Gelsolin (71 amino acid fragment)

IAPP (fragment) (***amylin***)

Calcitonin (fragment)

ANF

Lysozyme (whole or fragments)

Insulin

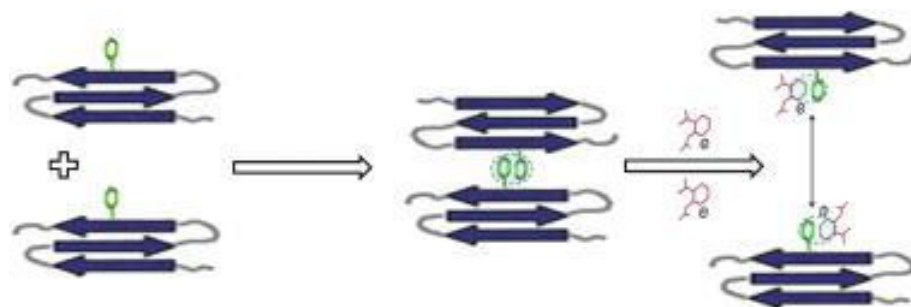
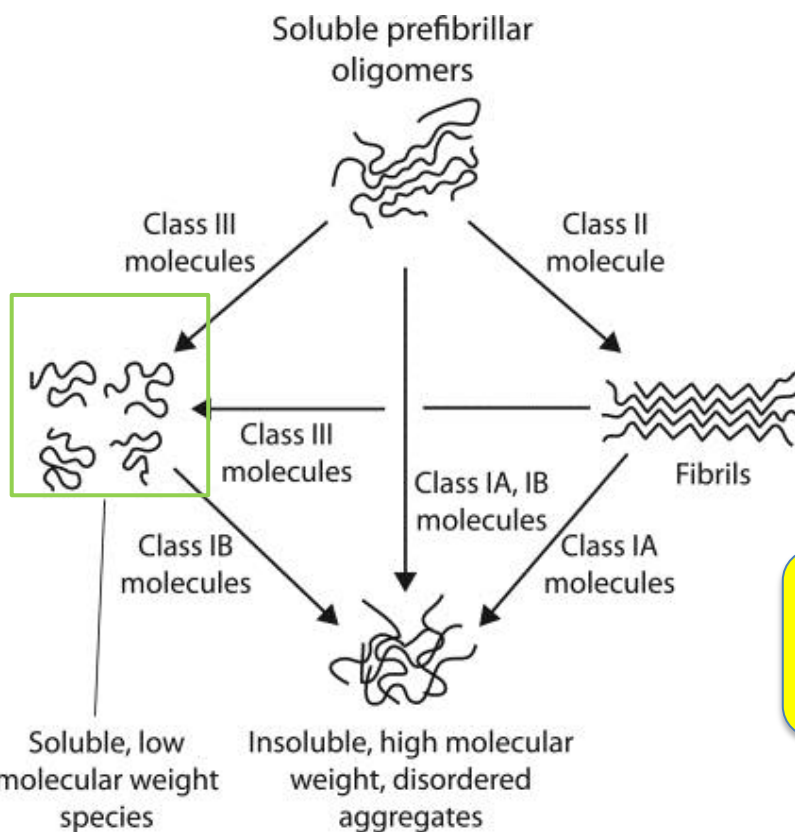
Fibrinogen (fragments)

Tissue deposits composed mainly of fibrillar polymers of specific peptides or proteins are the histopathological hallmark of amyloid diseases ...



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Small aromatic molecules, including **polyphenols**, can interfere in several ways with the aggregation of misfolded proteins favoring growth of non-toxic aggregates.

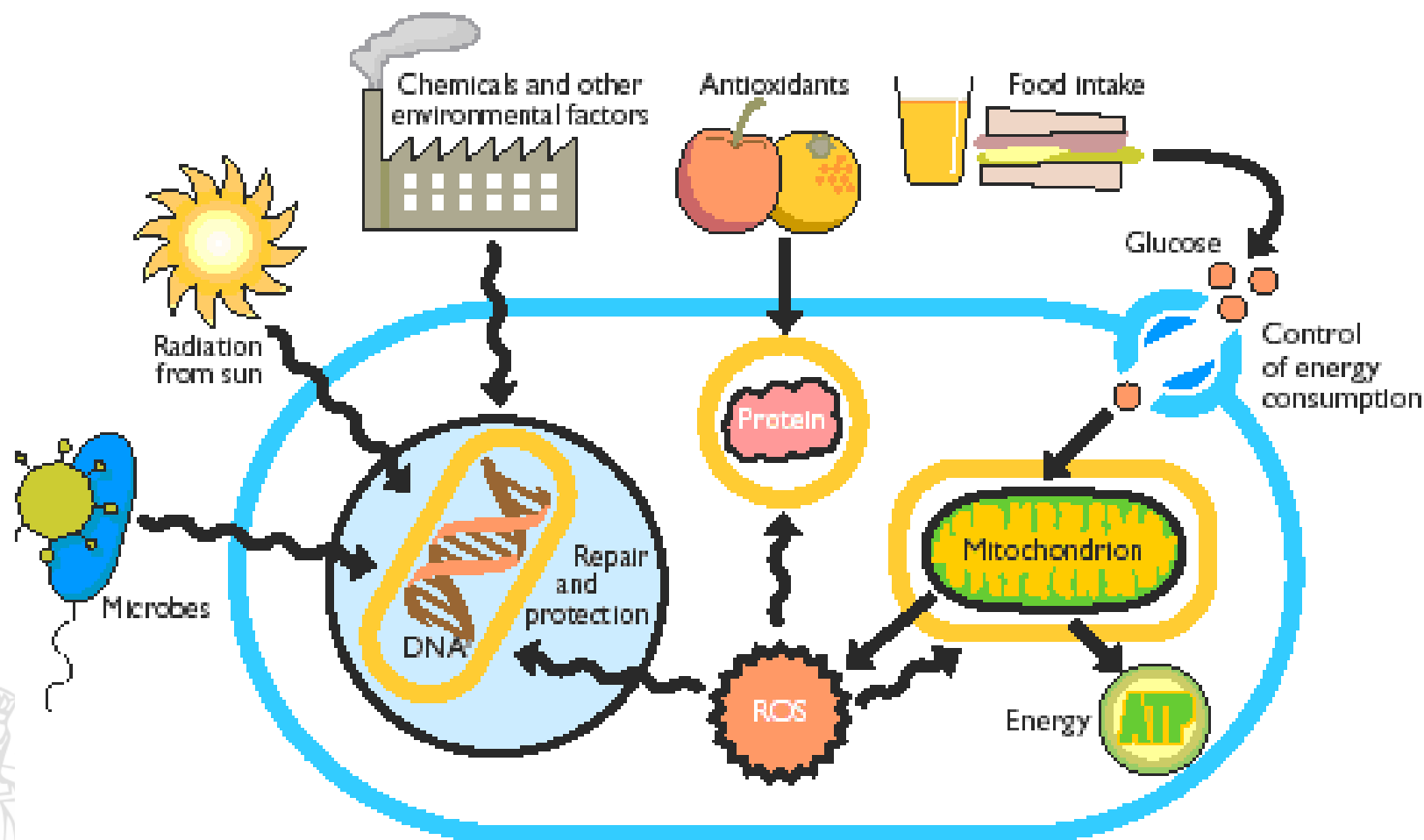


In particular, they can interfere with misfolded protein self-assembly and fibril stability by hindering π - π stacking, often skipping the growth of toxic pre-fibrillar oligomers.



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FONTI DI RADICALI LIBERI

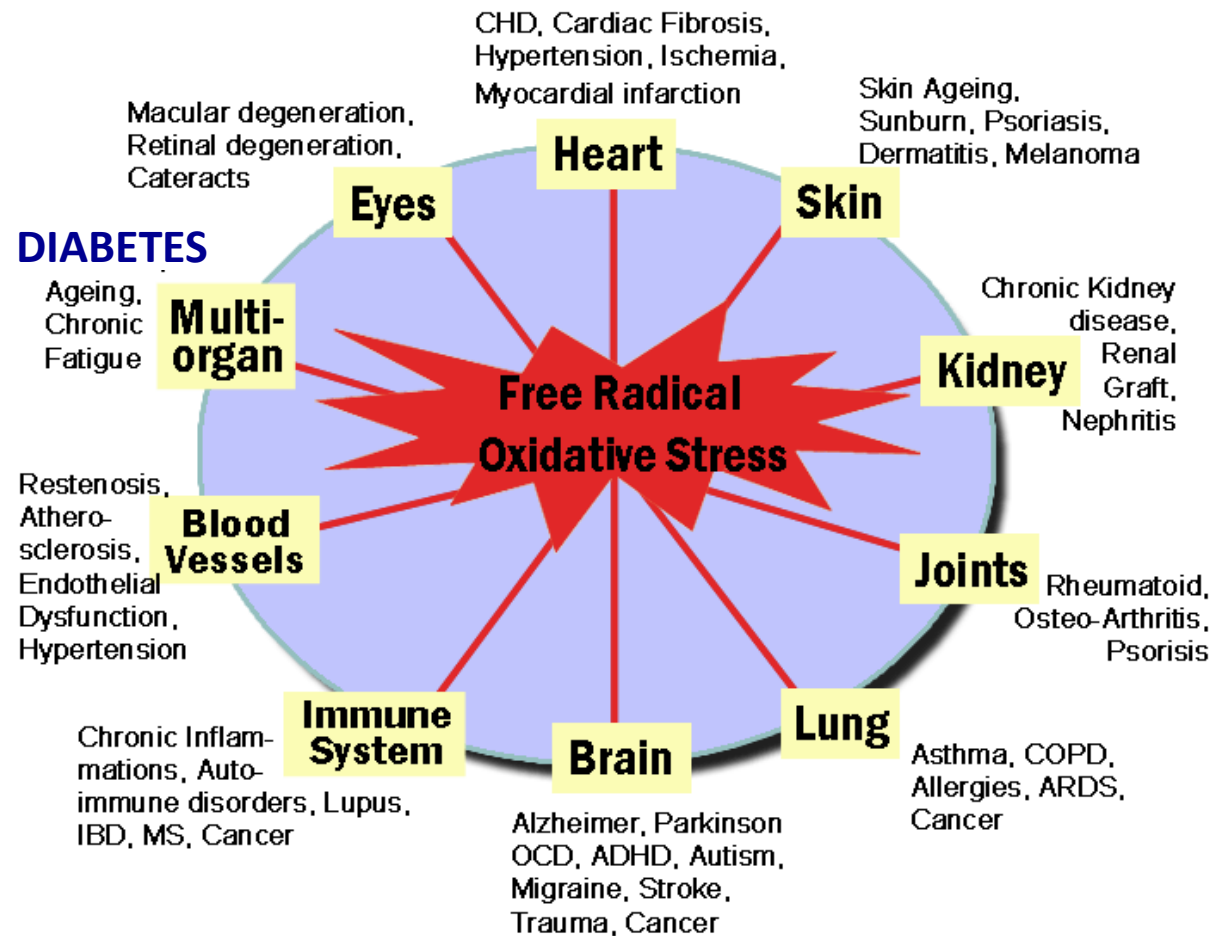




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Patologie caratterizzate da STRESS OSSIDATIVO

Uno squilibrio tra produzione di radicali liberi e difese antiossidanti a favore dei primi conduce ad uno stato di stress ossidativo, che numerosi studi indicano essere coinvolto nei processi di **invecchiamento**, nei tessuti esposti a **radiazioni ionizzanti** e anche nella patogenesi e nel decorso di diverse patologie degenerative (**morbo di Alzheimer, Parkinson, neoplasie, diabete mellito II, ecc.**).





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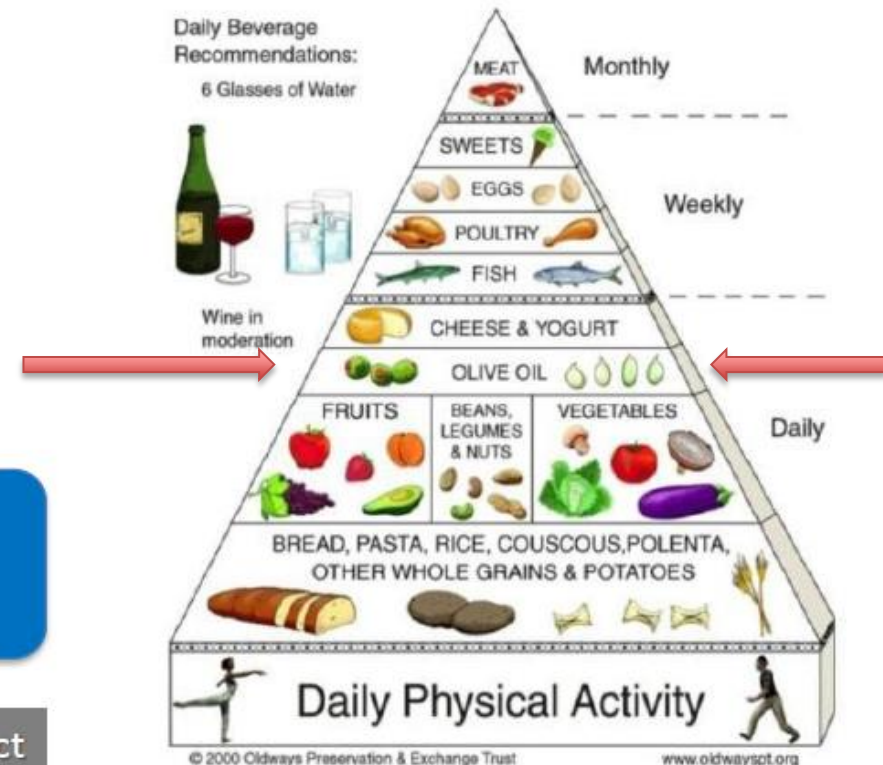
Beneficial effects of the Mediterranean/Asian diets

- high intake of vegetables
- fruits and nuts
- legumes, cereals
- fish
- olive oil
- spices
- relatively low intakes of meat and dairy products
- Moderate alcohol (red wine)

Polyphenols found in red wine, EVOO and other foods improve learning and behavioral deficits associated with aging and disease

Natural polyphenols are **phytoalexins** that protect plants against fungal and other microbial pathogens

The Traditional Healthy Mediterranean Diet Pyramid





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JOURNAL OF
**NATURAL
PRODUCTS**

Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010

David J. Newman* and Gordon M. Cragg

Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer

Institute–Frederick, P.O. Box B, Frederick, Maryland 21702, United States

...the utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well. Thus, in the area of cancer, over the time frame from around the 1940s to date, of the 175 small molecules, 131, or 74.8%, are other than “S” (synthetic), with 85, or 48.6%, actually being either natural products or directly derived therefrom. In other areas, the influence of natural product structures is quite marked, with, as expected from prior information, the anti-infective area being dependent on natural products and their structures.

[dx.doi.org/10.1021/np200906s](https://doi.org/10.1021/np200906s) | *J. Nat. Prod.* 2012, 75, 311–335



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Table 2 Plants with positive effects in experimental diabetes mellitus through their antioxidant properties [41].

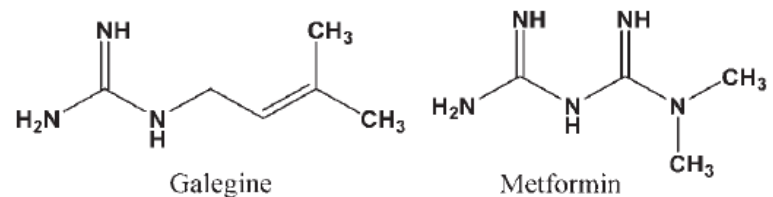
Plant species	Family
<i>Acanthopanax senticosus</i> Harms	Araliaceae
<i>Albizia lebbek</i> (L.) Benth.	Mimosaceae
<i>Allium sativum</i> L.	Alliaceae
<i>Amaranthus esculentus</i> Besser	Amaranthaceae
<i>Aralia taibaiensis</i> Z. Z. Wang & H. C. Zheng	Araliaceae
<i>Azadirachta indica</i> A. Juss.	Meliaceae
<i>Camellia sinensis</i> (L.) Kuntze	Theaceae
<i>Capparis decidua</i> Edgew.	Capparaceae
<i>Emblica officinalis</i> Gaertn.	Euphorbiaceae
<i>Ficus carica</i> L.	Moraceae
<i>Ficus bengalensis</i> L.	Moraceae
<i>Gentiana olivieri</i> Griseb	Gentianaceae
<i>Lycium barbarum</i> Lam.	Solanaceae
<i>Momordica charantia</i> L.	Cucurbitaceae
<i>Morinda officinalis</i> F. C. How	Rubiaceae
<i>Musa × sapientum</i> L.	Musaceae
<i>Ocimum sanctum</i> L.	Lamiaceae
<i>Panax ginseng</i> C. A. Meyer	Araliaceae
<i>Phyllanthus amarus</i> Schumacher	Euphorbiaceae
<i>Plantago depressa</i> Willd.	Plantaginaceae
<i>Pueraria lobata</i> (Willd.) Ohwi	Fabaceae
<i>Punica granatum</i> L.	Lythraceae
<i>Scutellaria baicalensis</i> Georgi	Lamiaceae
<i>Silybum marianum</i> (L.) Gaertn.	Asteraceae
<i>Strobilanthes crispus</i> T. Anderson	Acanthaceae
<i>Vaccinium arctostaphylos</i> L.	Ericaceae

Natural Products for the Treatment of Type 2 Diabetes Mellitus*

Authors

José Luis Ríos¹, Flavio Francini², Guillermo R. Schinella^{3,4}

Planta Med 2015; 81: 975–994



Da *Galega officinalis* (capraggine)



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mechanisms of natural products as antidiabetic agents.

- Inhibition of α -glucosidase and α -amylase,
- effects on glucose uptake and glucose transporters,
- modification of mechanisms mediated by the peroxisome proliferator-activated receptor,
- inhibition of protein tyrosine phosphatase 1B activity,
- modification of gene expression, and activities of hormones involved in glucose homeostasis such as:
 - adiponectin,
 - resistin,
 - incretin,
- reduction of oxidative stress are some of the mechanisms in which natural products are involved.





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Piante medicinali sottoposte a trial clinico per DMT2:

- aloe,
- banaba,
- bitter melon,
- caper,
- cinnamon,
- cocoa,
- coffee,
- fenugreek,
- garlic,
- guava,
- gymnema,
- nettle,
- sage,
- soybean,
- green and black tea,
- turmeric,
- walnut
- yerba mate.

Composti con potenziale efficacia antidiabetica:

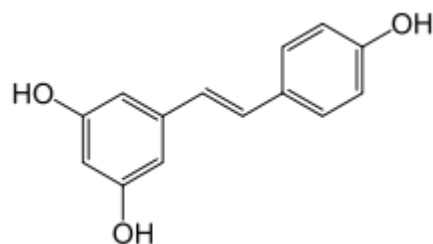
- fucugetina
- palmatina
- berberina
- onochiolo
- amorfrutine,
- trigonellina,
- acidi gimnemici,
- gurmarina
- florizina



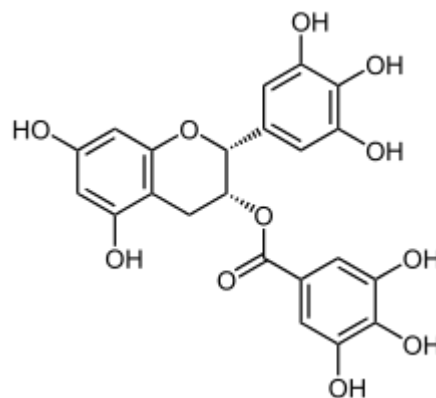


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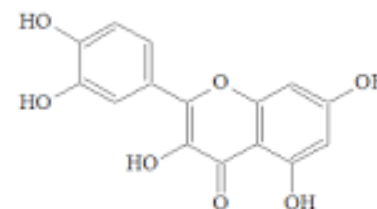
Natural polyphenols include many plant molecules (resveratrol, curcumin, epigallocatechin-3-gallate, quercetin, morin, etc.) whose beneficial properties against **ageing** as well as against many pathological conditions including oxidative stress, cancer, neurodegenerative and cardiovascular diseases, **type 2 diabetes** and the metabolic syndrome are known since long time and supported by many experimental data both in model animals and in humans.



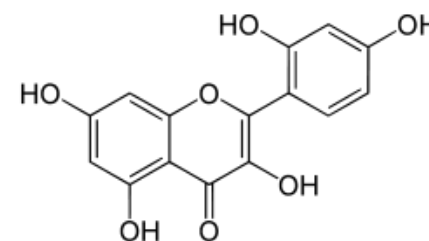
Resveratrolo



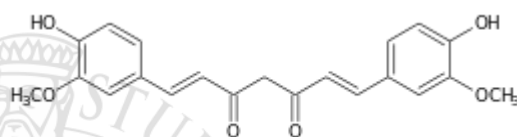
Epigallocatechina-3-gallato



Quercetina



Morina



Curcumina

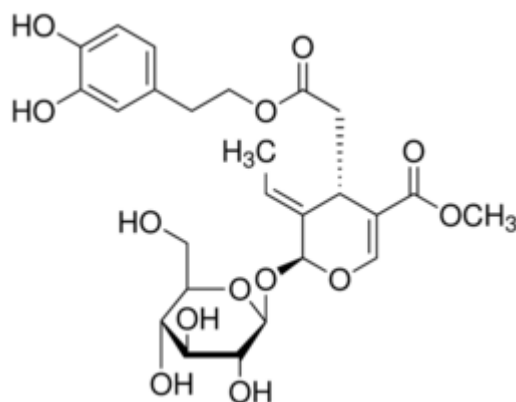


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Oleuropein

The major phenol in the extra virgin olive oil and in Olea europea leaves

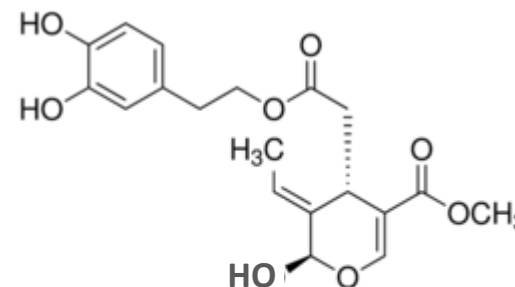
Glycated: Leaves, drupes



β -glucosidase



Aglycone: ripening olives and olive oil



Activities:

Antioxidant
Antitumoral
Anti-inflammatory

Prevention/treatment of:

- Hypertension
- Carcinogenesis
- Type II diabetes
- Atherosclerosis
- Risk of AD





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Dietary polyphenols, including oleuropein, are adsorbed both in rats and in humans

Mol. Nutr. Food Res. 2013, 57, 2079–2085

DOI 10.1002/mnfr.201200795

2079

FOOD & FUNCTION

Human absorption and metabolism of oleuropein and hydroxytyrosol ingested as olive (*Olea europaea* L.) leaf extract

Martin de Bock¹, Eric B. Thorstensen¹, José G. B. Derraik¹, Harold V. Henderson², Paul L. Hofman^{1,3} and Wayne S. Cutfield^{1,3}

Human Nutrition and Metabolism

Olive Oil Phenols Are Absorbed in Humans¹

Maud N. Vissers,* Peter L. Zock,* Annet J.C. Roodenburg,[†] Rianne Leenen[†] and Martijn B. Katan^{*2}

132:409-17, 2002



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A recent clinical trial has shown that intake of OLE and hydroxytyrosol improves insulin sensitivity in patient at risk for type 2 diabetes as well as pain in gonarthrosis

OPEN ACCESS Freely available online



Olive (*Olea europaea* L.) Leaf Polyphenols Improve Insulin Sensitivity in Middle-Aged Overweight Men: A Randomized, Placebo-Controlled, Crossover Trial

Martin de Bock¹, José G. B. Derraik¹, Christine M. Brennan¹, Janene B. Biggs¹, Philip E. Morgan², Steven C. Hodgkinson¹, Paul L. Hofman^{1,3}, Wayne S. Cutfield^{1,3*}

¹ Liggins Institute, University of Auckland, Auckland, New Zealand, ² Heart Research Institute, University of Sydney, Sydney, Australia, ³ Gravidia: National Centre for Growth and Development, Auckland, New Zealand

Phytomedicine 20 (2013) 861–864

Contents lists available at SciVerse ScienceDirect



Phytomedicine

journal homepage: www.elsevier.de/phymed



Double-blind placebo-controlled trial of hydroxytyrosol of *Olea europaea* on pain in gonarthrosis

Ryuji Takeda^a, Taisuke Koike^{b,*}, Itaru Taniguchi^b, Keiko Tanaka^c

^a Faculty of Agriculture, Kinki University, 3327-204 Nakamachi, Nara 631-8505, Japan

^b Planning & Development Department, Eisai Food & Chemical Co. Ltd., 13-10 Nihonbashi 2-Chome, Chuo-ku, Tokyo 103-0027, Japan

^c Kei Medical Clinic, Shiratori Building 3F, 1-4-2 Yamato-cho, Nakano-ku, Tokyo 164-0013, Japan





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Another previous study had shown that olive leaf extracts were effective to reduce glycaemia in subjects with type 2 diabetes

JOURNAL OF MEDICINAL FOOD

J Med Food 15 (7) 2012, 1–6

© Mary Ann Liebert, Inc. and Korean Society of Food Science and Nutrition

DOI: 10.1089/jmf.2011.0243

ORIGINAL ARTICLE

Olive Leaf Extract as a Hypoglycemic Agent in Both Human Diabetic Subjects and in Rats

Julio Wainstein,¹ Tali Ganz,¹ Mona Boaz,^{2,3} Yosefa Bar Dayan,¹
Eran Dolev,⁴ Zohar Kerem,⁵ and Zecharia Madar⁵

¹Diabetes Unit and ²Epidemiology and Research Unit, E. Wolfson Medical Center, Holon, Israel.

³Department of Nutrition, School of Health Sciences, Ariel University Center of Samaria, Ariel, Israel.

⁴Internal Medicine Unit E, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

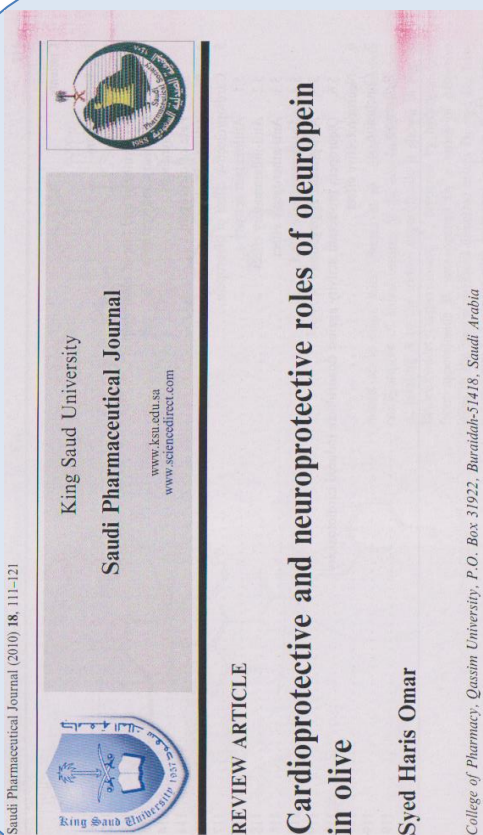
⁵Institute of Biochemistry, Food Science, and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot, Israel.





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Previous data have also shown that olive-leaf extracts and OLE protect against hepatic steatosis, obesity and drug-cardiotoxicity



Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2014, Article ID 971890, 12 pages
<http://dx.doi.org/10.1155/2014/971890>



Research Article

Olive Leaf Extract Attenuates Obesity in High-Fat Diet-Fed Mice by Modulating the Expression of Molecules Involved in Adipogenesis and Thermogenesis

Ying Shen, Su Jin Song, Narae Keum, and Taesun Park

Department of Food and Nutrition, Brain Korea 21 PLUS Project, Yonsei University, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-749, Republic of Korea

Research Article



Oleuropein attenuates hepatic steatosis induced by high-fat diet in mice

Soyoung Park¹, Youngshim Choi¹, Soo-Jong Um², Seung Kew Yoon³, Taesun Park^{1,*}

¹Department of Food and Nutrition, Brain Korea 21 Project, Yonsei University, 262 Seongsanno, Seodaemun-gu, Seoul 120-749, Republic of Korea; ²Department of Bioscience and Biotechnology/Institute of Bioscience, Sejong University, Republic of Korea; ³Department of Internal Medicine, College of Medicine, The Catholic University, Republic of Korea



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Finally, a very recent study from the Università la Sapienza has shown that administering a daily dose (10 g) of extra virgin olive oil to healthy subjects improves both glycemic and lipid profile, particularly increases post-prandial insulin and reduces glucose and LDL-cholesterol, an effect that may account for the antiatherosclerotic power of the Mediterranean diet.

OPEN

Citation: Nutrition & Diabetes (2015) 5, e172; doi:10.1038/nutd.2015.23



www.nature.com/nutd

ORIGINAL ARTICLE

Extra virgin olive oil use is associated with improved post-prandial blood glucose and LDL cholesterol in healthy subjects

F Violi¹, L Loffredo¹, P Pignatelli¹, F Angelico², S Bartimoccia¹, C Nocella¹, R Cangemi¹, A Petruccioli³, R Monticolo⁴, D Pastori¹ and R Carnevale^{1,4}





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In conclusion, a growing number of data obtained from clinical trials with human cohorts, animal models and cultured cells support the benefits of the EVOO as well as the utility of nutraceuticals based on pure oleuropein or on oleuropein-enriched olive leaf extracts in prevention and therapy of **type 2 diabetes** and its related syndromes, notably the **metabolic syndrome**.





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The **Mediterranean diet** is associated with a reduced risk of developing MCI and AD, as well as of MCI conversion to AD (*Singh et al., 2014*)

Proc Nutr Soc (2013) 140-152

Potential benefits of adherence to the Mediterranean diet on cognitive health

Feart C, Samieri C, Alles B and Barberger-Gateau P

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2009;28:357–364
DOI: 10.1159/000253483

Accept
Publ

Olive Oil and Cognition: Results from the Three-City Study

Claudine Berr^{a,b} Florence Portet^{a,b} Isabelle Carriere^a
Tasnim N. Akbaraly^{a,f} Catherine Feart^c Véronique Gourlet^d Nicole Combe^e
Pascale Barberger-Gateau^c Karen Ritchie^a

Journal of Alzheimer's Disease 29 (2012) 773–782

Polyphenol-Rich Foods in the Mediterranean Diet are Associated with Better Cognitive Function in Elderly Subjects at High Cardiovascular Risk

Cinta Valls-Pedret^{a,b}, Rosa Maria Lamuela-Raventós^{b,c,d}, Alexander Medina-Remón^{b,c,d}, Melibea Quintana^a, Dolores Corella^{b,e}, Xavier Pintó^{d,f}, Miguel Ángel Martínez-González^{d,g}, Ramon Estruch^{b,h} and Emilio Ros^{a,b,*}

Effects of dietary extra-virgin olive oil on behaviour and brain biochemical parameters in ageing rats

British Journal of Nutrition (2010), **103**, 1674–1683

Vanessa Pitozzi¹, Michela Jacomelli¹, Mohamed Zaid¹, Cristina Luceri¹, Elisabetta Bigagli¹, Maura Lodovici¹, Carla Ghelardini¹, Elisa Vivoli¹, Monica Norcini¹, Marco Gianfriddo², Sonia Esposto³, Maurizio Servili³, Guido Morozzi⁴, Elisabetta Baldi⁵, Corrado Bucherelli⁵, Piero Dolara¹ and Lisa Giovannelli^{1*}



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Natural compounds in clinical trial for Alzheimer's disease

Name	Synonyms	FDA status	Company	Target Type	Therapy Type
AC-1204	Caprylic triglyceride, Long-chain triglycerides	2/3	Accera, Inc.	Other	Dietary Supplement
Alpha-Tocopherol	Vitamin E	3		Other	Dietary Supplement
Resveratrol	trans-3,4',5-trihydroxystilbene	3,4 Not regulated		Other	Small Molecule
Curcumin	diferuloylmethane, Longvida™	2	Vendure Sciences	Other, Unknown	Dietary Supplement
Docosahexanoic acid (DHA)	Omega 3 fatty acid	3	Martek Biosciences Corporation	Other	Dietary Supplement
Epigallocatechin Gallate (EGCG)	Sunphenon EGCg	2/3, 2, 3	Taiyo International	APP and Amyloid-Related, Inflammation, Other	Dietary Supplement



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Other trials with resveratrol

Some of which with yet unpublished outcome....

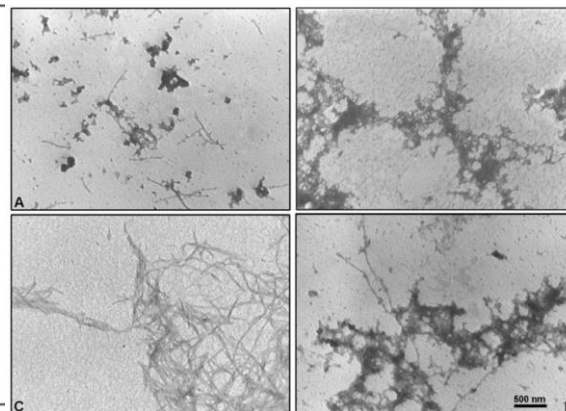
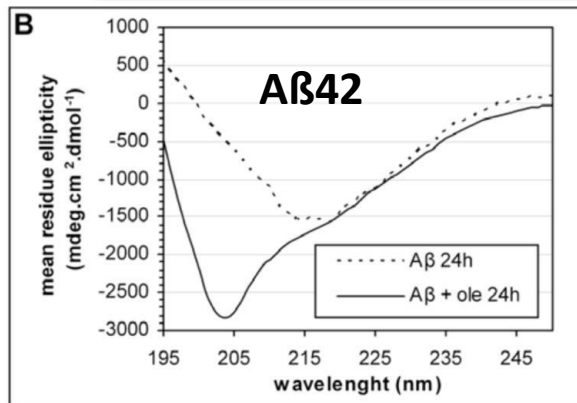
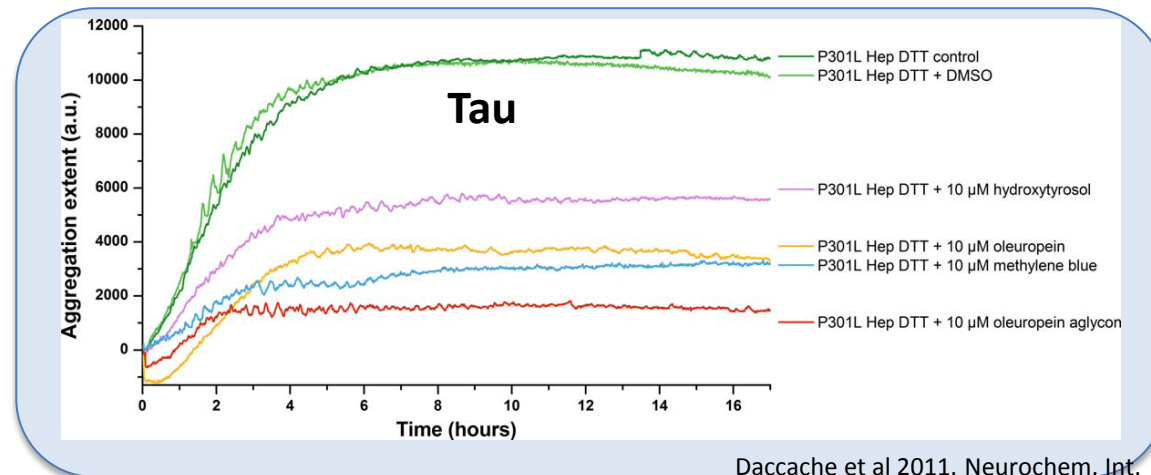
26 Alzheimer's Disease Cooperative Study (ADCS) clinical centers under R.S. Turner direction are conducting a Phase 2 trial of **resveratrol** to assess whether it slows disease progression in people with mild to moderate dementia. The group has just finished collecting data on **120 people who took 0.5 g of resveratrol once in a day steadily increased to 1 g, equivalent to hundreds of bottles of wine, twice daily for a year. "The preliminary results will be presented in November at the Clinical Trials on Alzheimer's Disease (CTAD) meeting"**.

Primary outcomes were change in **CSF A β and tau biomarkers, safety and tolerability, and change in brain and hippocampal volume as measured by MRI.**

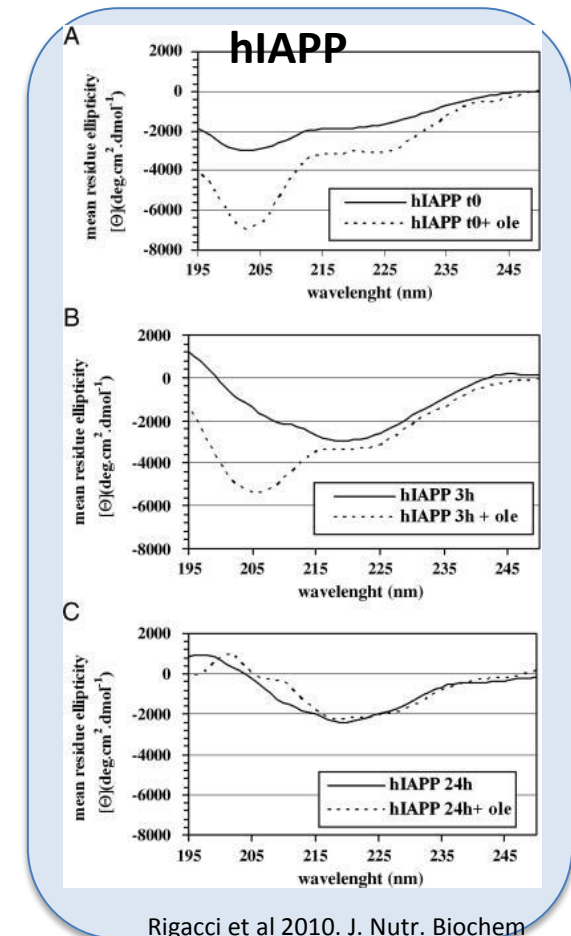


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OLE redirects *in vitro* amyloid aggregation of peptides and proteins skipping the formation of toxic oligomers and favoring the growth of disordered aggregates...



Rigacci et al 2011. Curr. Alz. Res.

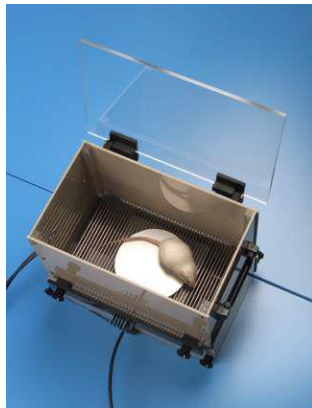




Ruolo degli integratori nutrizionali nel trattamento del diabete mellito e dei dismetabolismi correlati: recenti acquisizioni dalla ricerca biochimica e clinica

Oleuropein aglycone ameliorates cognitive functions in young/middle aged TgCNRD8 mice

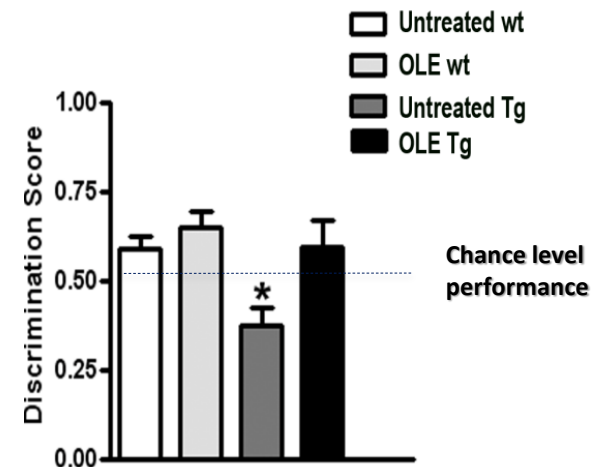
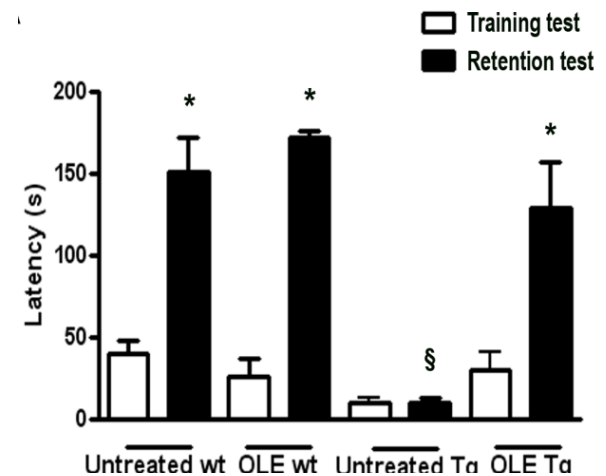
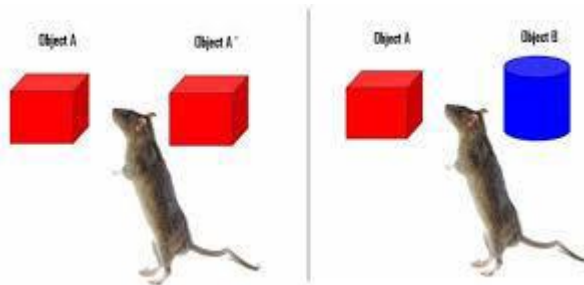
STEP DOWN



Grossi et al. 2013,
PlosOne, 8:e71702

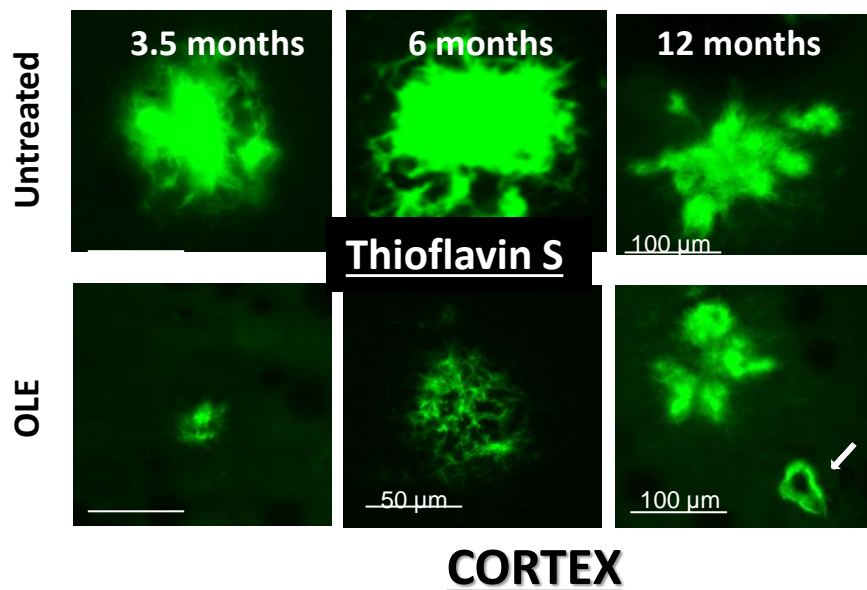
ORT

1 h
Training Test → Retention Test

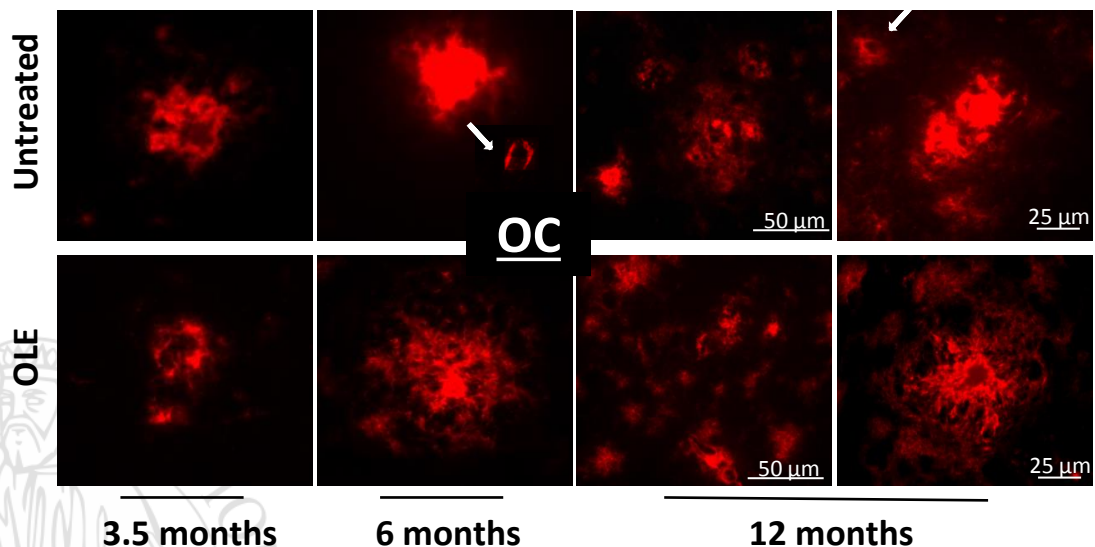




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**OLE administration
results in Aβ42
plaque disaggregation**





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Dysfunction of autophagy is a key element in the development and progression of AD

Autophagy (2009)

Autophagy protects neuron from A β -induced cytotoxicity

Shih-Ya Hung,¹ Wei-Pang Huang,³ Hsiung-Chi Liou¹ and Wen-Mei Fu^{1,2,*}

Induction of autophagy might be useful to protect against the toxicity of A β peptides

Journal of Alzheimer's Disease (2014)

Stimulation of Autophagy Prevents Amyloid- β Peptide-Induced Neuritic Degeneration in PC12 Cells

Yang Y¹, Chen S², Zhang J³, Li C³, Sun Y², Zhang L³ and Zheng X⁴

The autophagy-related protein beclin 1 shows reduced expression in early Alzheimer disease and regulates amyloid β accumulation in mice Pickford, et al *J Clin Invest.* 2008 118: 2190–2199.

Autophagy, 7:8,1-2

The unfolded protein response and proteostasis in Alzheimer's disease. Preferential activation of autophagy by endoplasmic reticulum stress.

Scheper et al 2011,

Nat Rev Drug Discov. 2012 September ; 11(9): 709–730. doi:10.1038/nrd3802.

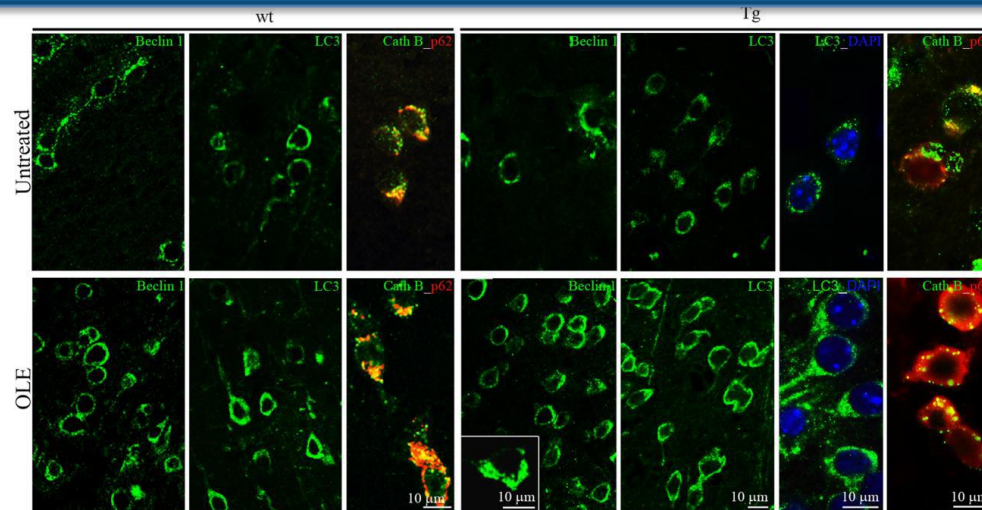
Autophagy modulation as a potential therapeutic target for diverse diseases

David C. Rubinsztein^{1,*}, Patrice Codogno^{2,*}, and Beth Levine^{3,*}

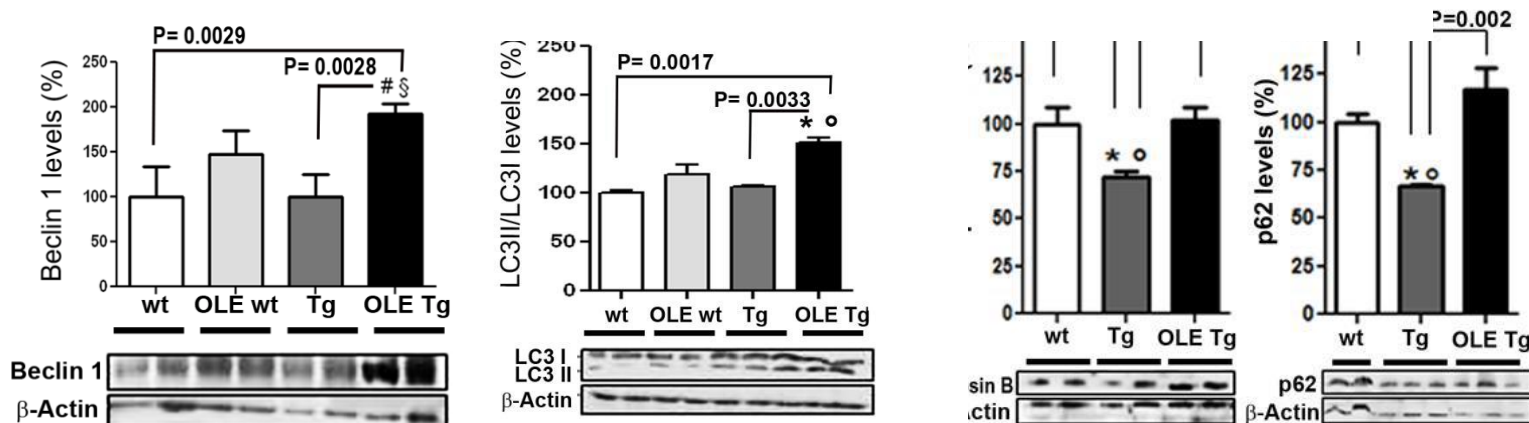


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OLE rescues autophagy in 12 month-old Tg mice...



Luccarini et al., Neurobiol. Aging., 2014 in press.



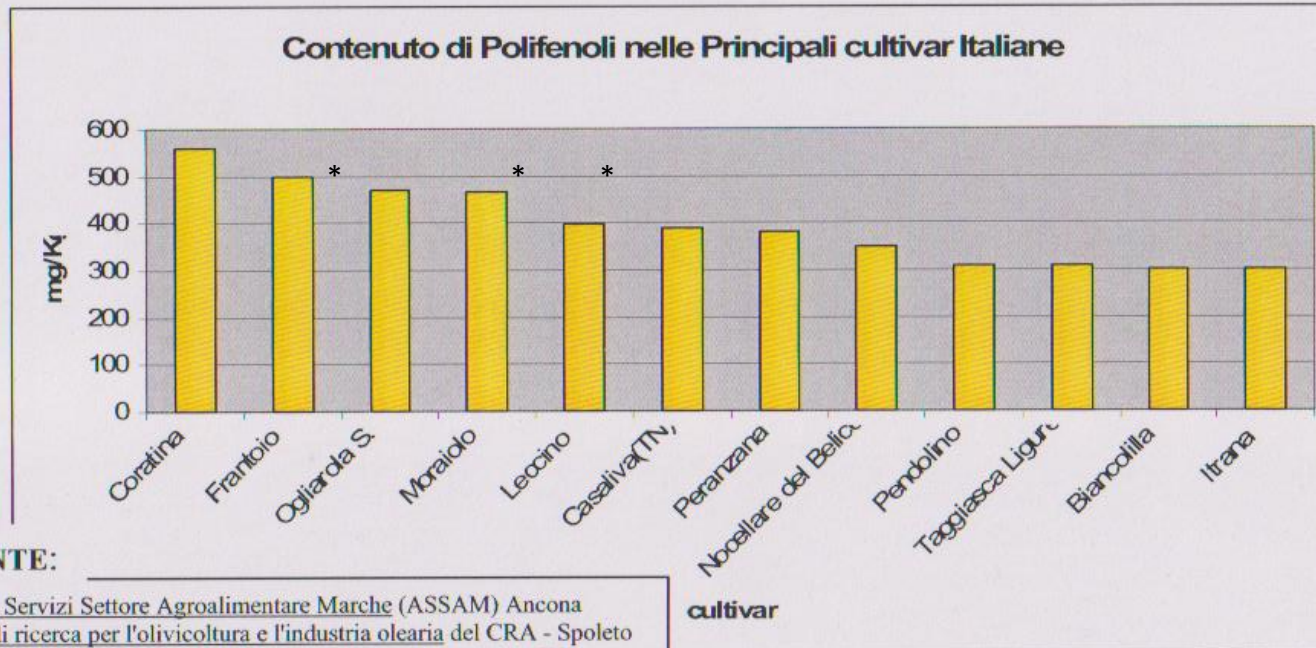
Grossi et al. 2013 PLoS ONE 8(8): e71702.

...as previously shown for 3.5 and 6 month-old Tg mice



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The content of oleuropein aglycone in the extra virgin olive oil depends on cultivar, fruit growth and maturation, type of squeezing, conservation, etc.

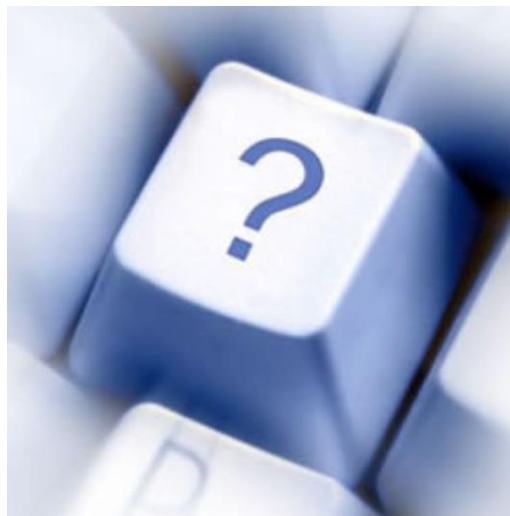


Le cultivar presenti nelle principali DOP Italiane:

DOP Chianti Classico: 80% Frantoio, Correggiolo, Moraiolo, Leccino; 20% varietà autoctone



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30 capsule retard

INTEGRATORE A BASE DI OLEUROPEINA,
OLIGOELEMENTI E VITAMINE D e E

Capsule contenenti 130 mg di Oleuropeina





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- Brevetto/i internazionale/i già concessi (no P/P !!)
- Uno o più claims ufficiali EFSA/FDA
- Evidenze cliniche di efficacia da più gruppi internazionali indipendenti
- Presentazione aderente a claims/guidelines
- Assenza di toxic effect / Chemical of concern





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Alcuni attivi base di integratori in commercio con indicazione di efficacia nella disregolazione del metabolismo glicidico

	Oleuropeine	Berberine	Oligofructose*
- Brevetto/i internazionale/I <u>d'uso</u> già concesso/i (no Patent/Pending !!)	X		
- Uno o più claims ufficiali EFSA/FDA	X		X
- Evidenze cliniche di efficacia da più gruppi di ricerca internazionali indipendenti	X	X	X
- Presentazione professionale	X	X	
- Assenza di toxic effect / Chemical of concern (EFSA)	X		X

* Preprobiotic fibre derived from chicory



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**EAT GOOD
FOOD**

AND

THANK YOU

FOR YOUR ATTENTION

