CORSO DI 2° LIVELLO
PER L'ORGANIZZAZIONE E LA GESTIONE
DI UN AMBULATORIO DEGLI STILI DI VITA

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Nutraceutica e nutrigenomica: nuove frontiere di intervento dietetico-nutrizionali

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Articolazione del Corso

- Parte generale-Definizioni, diagramma di flusso della ricerca in nutrigenomica

- Studi clinici-Studi di intervento

- Ricerca biomolecolare-Meccanismi di azione molecolare di componenti contenuti in alimenti funzionali

Obiettivi del corso

Fornire strumenti utili ad

- **Aumentare la conoscenza** dei principi di base della nutraceutica e della nutrigenomica e del complesso processo di studio e ricerca necessario a supportare qualsiasi nuova evidenza
- **Accrescere la capacità di giudicare** con competenza e senso critico i tanti messaggi, spesso privi di solide basi scientifiche, quotidianamente indirizzati ai cittadini così da indirizzare correttamente le loro scelte nutrizionali.

Nutrizione **Farmaceutica**

Nutraceutica

studio di alimenti che hanno una funzione benefica sulla salute umana.

European Commission Concerted Action on Functional Food Science in Europe – FUFOSE coordinata dal International Life Science Institute (ILSI) Europe (1995-1998)

Scientific Concepts of Functional Food in Europe: Consensus Document

A.T. Diplock, P.J. Aggett, M. Ashwell, F. Bornet, E.B. Fern & M.B. Roberfroid.

Brit. J. Nutr. (1999) Vol. 81, S1-S27

- Introduction
- Scientific basis
- Target functions
- Technological aspects
- Communication of health benefits (Health Claims)

Un alimento funzionale:

- Possiede effetti addizionali dovuti alla presenza di componenti, generalmente non-nutrienti, che interagiscono selettivamente con una o più funzioni fisiologiche dell'organismo (biomodulazione) in modo tale che risultino evidenti un miglioramento dello stato di salute e di benessere e/o una riduzione del rischio di malattia.
- E' un alimento, non una pillola, una capsula, o un integratore alimentare
- Esercita la sua funzione nelle quantità normalmente previste da una dieta equilibrata
- Deve dimostrare attraverso modelli e successivi trial clinici un effetto monitorabile sulla salute dell'uomo = Effetti funzionali scientificamente documentati e accettati

Nutraceutico= componente bioattivo contenuto in un alimento funzionale con proprietà curative di comprovata efficacia

- micronutrienti (vitamine e acidi grassi)
- non nutrienti (fitocomposti e probiotici)

Table 1

Functional foods classification, some sources, and examples of bioactive substances.

Functional food		Bioactive component (nutraceutic)	Source (s)
Micronutrients	Vitamins	Retinol (vitamin A) α-tocopherol (vitamin E) Calciferol (vitamin D3)	Walnuts, almonds, hazelnuts, spinach, fish oil
	Polyunsaturated fatty acids (PUFAs)	Omega 3 Fatty acids: eicosapentaenoic acid (EPA) docosahexaenoic acid (DHA)	Salmon, tuna and others fish oils
Nonnutrients Phytochemicals	Carotenoids	Beta-carotene lutein, zeaxanthin lycopene	Carrots, pumpkin, collards, kale, spinach, tomatoes, watermelon
	Phenolic acid derivatives	Caffeic acid Ferulic acid Gallic acid Curcumin	Coffee, pears, apples, corn, curcumin, vanilla
	Flavonoids	Flavonols (quercetin) Isoflavones Coumarins Anthocyanidines Stilbenes (resveratrol)	Berries, cherries, red grapes, tea, cocoa, apples, citrus fruits, onion, broccoli, cranberries, strawb
	Sulfides/thiols	Diallyl sulfide S-allyl cysteine sulfoxide 1,2-viniyldithiin	Garlic, onions, banana, cruciferous vegetables
	Dietary fiber (prebiotic)	Fructooligosaccharides Neoglicans	Whole grains, onions, chicory, agave, some fruits
Probiotics	PUFAs induction	*Saccharomyces cerevisiae* (var. *boulardii*) Bifidobacteria and *Lactobacillus* genus	Certain yogurts and other cultured dairy and no-dairy applications

TABLE 1 Recent observational studies on adherence to the Mediterranean diet and cardiovascular disease[1]

Study	Country	Sample size	Outcome	Events	Comment
Dilis et al., 2012 (12)	Greece	23,929	CHD incidence and death from CHD	636 CHD events and 240 CHD deaths	There was a stronger inverse association for mortality than for incidence.
Tognon et al., 2012 (13)	Sweden	77,151	CVD death	680 deaths	The inverse association was only significant among women. Effect of the dietary pattern (only present among women) was smaller than in studies conducted in Mediterranean countries.
Gardener et al., 2011 (14)	United States	2568	Stroke, myocardial infarction, and CVD death	518 events	In a multiethnic population, a dietary pattern resembling the Mediterranean diet was protective against the combined outcome of ischemic stroke, myocardial infarction, and vascular death.
Misirli et al., 2012 (15)	Greece	23,601	Stroke	395 incident cases and 196 stroke deaths	Inverse trends were stronger with respect to ischemic rather than hemorrhagic stroke.
Hoevenaar-Blom et al., 2012 (16)	The Netherlands	40,011	Fatal and nonfatal CVD events	4881 events, including 487 CVD deaths	There were significant inverse linear associations for fatal CVD, total CVD, myocardial infarction, and stroke.
Menotti et al., 2012 (17)	Italy	1139	CHD death	162 CHD deaths	There was an inverse association between an index of adequacy to the Mediterranean diet and total mortality in a male cohort.
Tognon et al., 2013 (18)	Denmark	1849	Fatal and nonfatal CVD events	755 CVD events and 223 CVD deaths	Higher adherence to a Mediterranean dietary score was inversely associated with CVD and myocardial infarction but not with stroke.

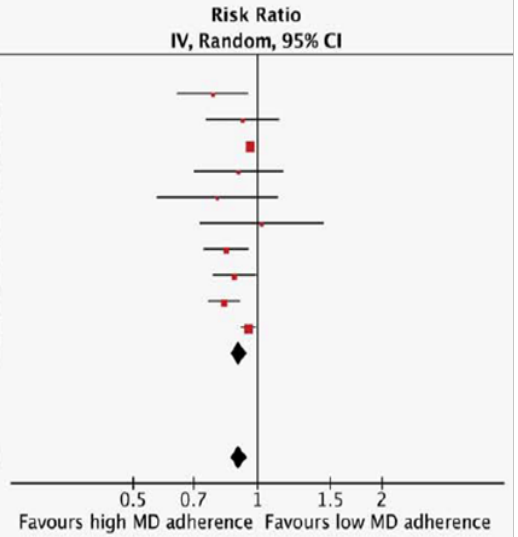
[1] Description of observational studies recently published but not included in the 2010 meta-analysis by Sofi et al. (8). CHD, coronary heart disease; CVD, cardiovascular disease.

International Journal of Cancer
Early View, Article first published online: 11 MAR 2014
Abstract | Full Article (HTML) | Enhanced Article (HTML) | References
Supporting Information | Cited By
Wiley Online Library

Adherence to Mediterranean diet and risk of cancer: A systematic review and meta-analysis of observational studies

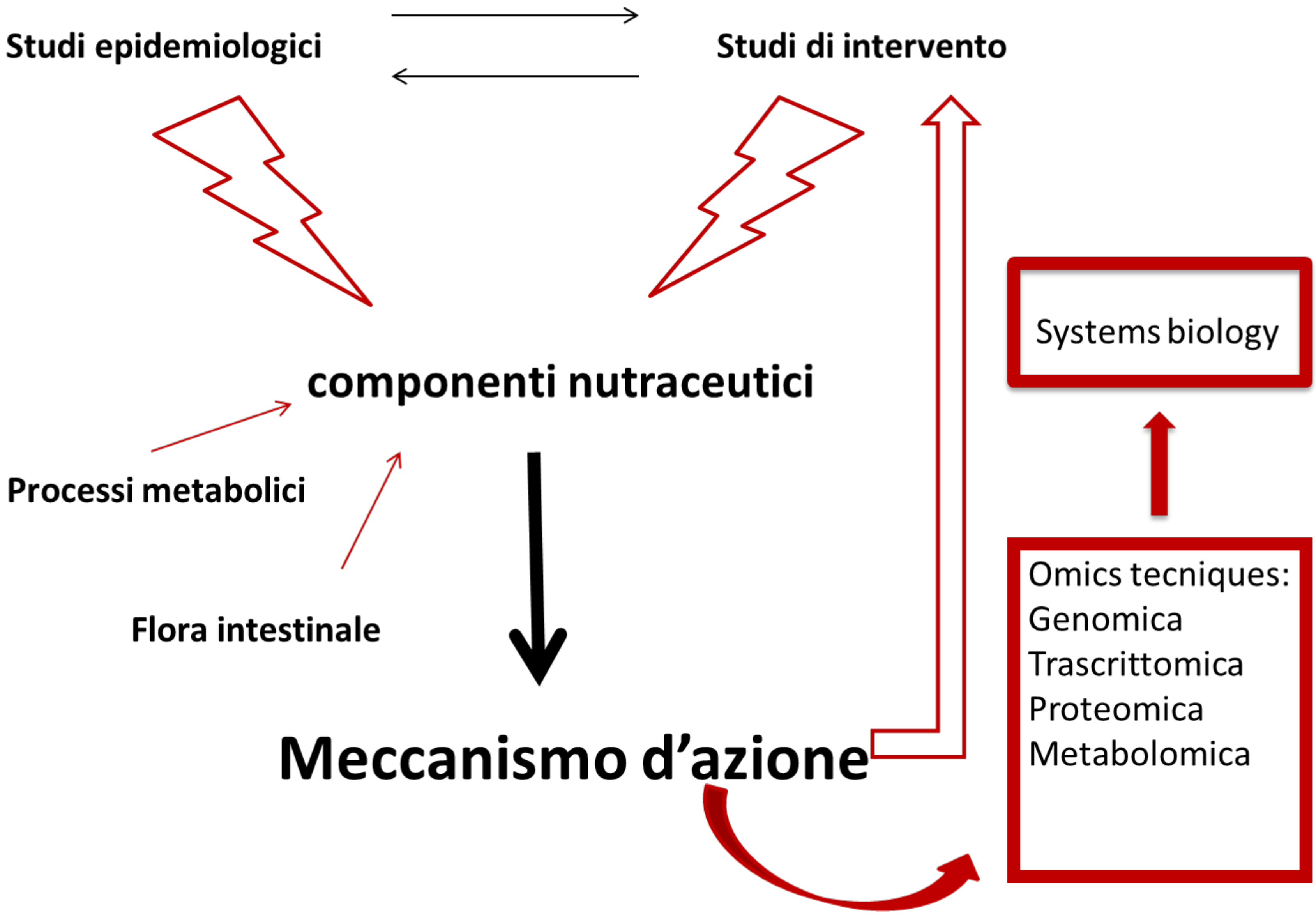
Lukas Schwingshackl and Georg Hoffmann

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI
cohort				
Benetou et al. 2008	-0.2485	0.1009	4.8%	0.78 [0.64, 0.95]
Buckland et al. 2011	-0.0834	0.1042	4.5%	0.92 [0.75, 1.13]
Couto et al. 2011	-0.0408	0.0107	27.0%	0.96 [0.94, 0.98]
Knoops et al. 2004	-0.1054	0.1282	3.2%	0.90 [0.70, 1.16]
Lagiou et al. 2006	-0.2231	0.1729	1.8%	0.80 [0.57, 1.12]
Martinez-Gonzalez 2010	0.0236	0.1757	1.8%	1.02 [0.73, 1.44]
Menotti et al. 2011	-0.1744	0.0647	9.4%	0.84 [0.74, 0.95]
Mitrou et al. 2007a	-0.1278	0.0615	10.0%	0.88 [0.78, 0.99]
Mitrou et al. 2007b	-0.1863	0.045	14.4%	0.83 [0.76, 0.91]
Tognon et al. 2012	-0.0513	0.0219	23.1%	0.95 [0.91, 0.99]
Subtotal (95% CI)			**100.0%**	**0.90 [0.86, 0.95]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 20.16$, df = 9 (P = 0.02); $I^2 = 55\%$				
Test for overall effect: Z = 4.20 (P < 0.0001)				
Total (95% CI)			**100.0%**	**0.90 [0.86, 0.95]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 20.16$, df = 9 (P = 0.02); $I^2 = 55\%$				
Test for overall effect: Z = 4.20 (P < 0.0001)				
Test for subgroup differences: Not applicable				



What's new?

Adherence to a "Mediterranean Diet" is associated with **significant improvements in health** status, including a **lower overall risk of cancer, especially colorectal and aerodigestive cancers.**


Studi epidemiologici
Studi di intervento
componenti nutraceutici
Processi metabolici
Flora intestinale
Meccanismo d'azione
Systems biology
Omics tecniques:
Genomica
Trascrittomica
Proteomica
Metabolomica

Nutrigenomica

Studia i meccanismi con i quali gli alimenti funzionali possono influenzare **l'espressione genica**

- **il transcrittoma → profilo degli RNA**
- **il proteoma → profilo delle proteine**
- **il metaboloma → profilo dei metaboliti**

Obiettivo finale: comprendere come il cibo interferisce con il codice genetico e come l'organismo risponde a queste interferenze modificando il fenotipo.

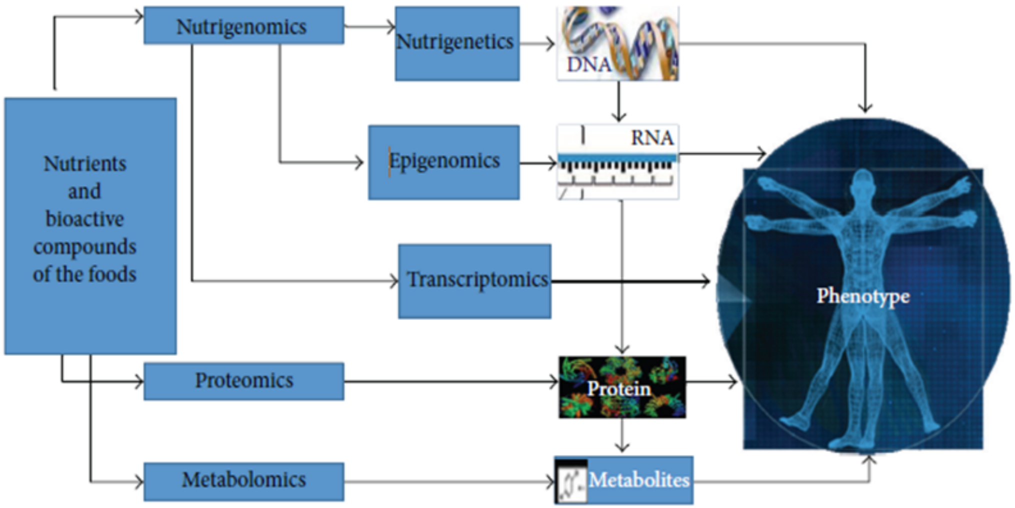
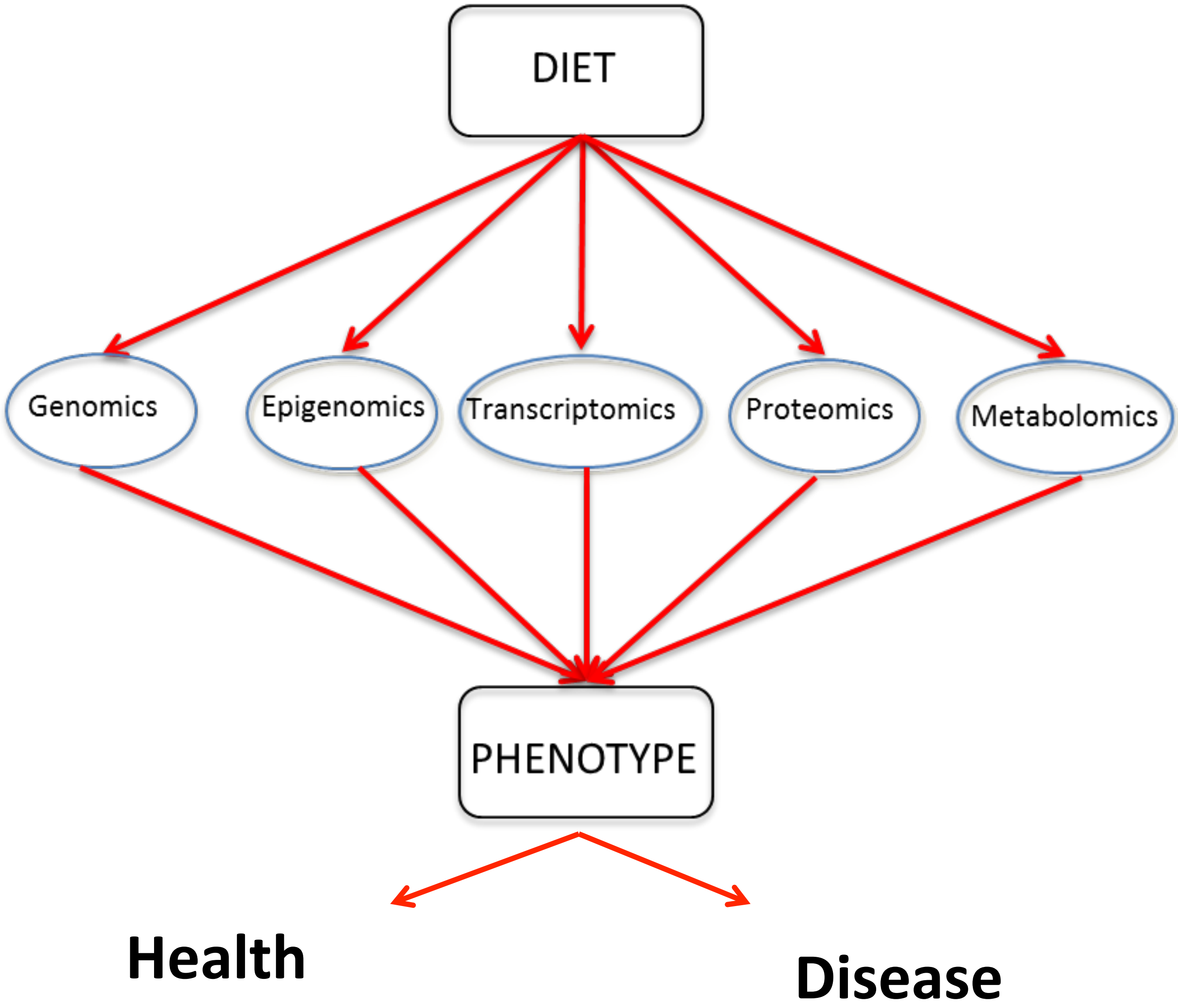
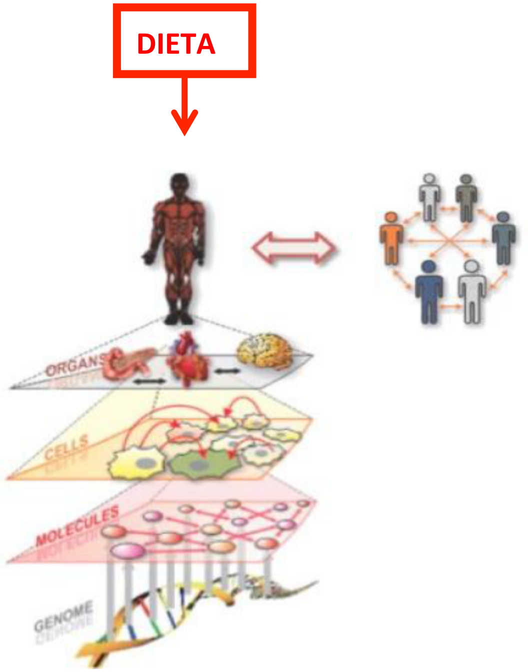


FIGURE 1: "Omics" sciences used in understanding the relationship between nutrition versus health versus disease (source: [4], with modifications; [9] with modifications).


DIET
Genomics
Epigenomics
Transcriptomics
Proteomics
Metabolomics
PHENOTYPE
Health
Disease



- **La dieta agisce sulle funzioni dell'organismo.**
- **L'individuo ha caratteristiche proprie che influenzano gli effetti della dieta**

→ **Nutrigenetica**

Table 2. Selected Studies Showing Statistically Significant Gene-Diet Interactions in Determining Intermediate CVD Phenotyes

Reference	Phenotype	Description of the Gene-Diet Interaction
Lopez-Miranda et al[60]*	Postprandial LDL-C	The −75G/A *APOA1* SNP influenced the postprandial LDL-C response to MUFA. After consumption of a high MUFA diet, significant increases in LDL-C were noted in carriers of the A alle but not in G/G subjects.
Jansen et al[61]*	Postprandial LDL-C	Postprandial LDL-C response to dietary fat is influenced by the 347Ser mutation of *APOA4*. Carriers of the 347Ser allele presented a greater decrease in LDL-C when they were switched from the SFA to the NCEP type 1 diet than homozygous the 347Thr allele.
D'Angelo et al[62]*	Plasma homocysteine	The C677T SNP in the *MTHFR* gene interacted with folate and vitamin B12 levels in determining plasma homocysteine concentrations.
Campos et al[63]	VLDL and HDL-C	The *APOE* genotype interacted with saturated fat in determining VLDL and HDL-C concentrations (higher VLDL and lower HDL-C in E2 carriers with a high fat).
Luan et al[64]	BMI and fasting insulin	An interaction was found between the PUFA:saturated fat ratio and the Pro12Ala *PPARG* polymorphism for both BMI and fasting insulin. With a low ratio, the BMI in Ala carriers was greater than that in Pro homozygotes, but when the dietary ratio was high, the opposite was seen.
Corella et al[65]	Fasting plasma LDL-C concentrations	Alcohol intake interacted with the *APOE* SNP in determining LDL-C in men. In E2 subjects, LDL-C was significantly lower in drinkers than in nondrinkers but was significantly higher in drinkers than in nondrinkers in E4 subjects.
Leeson et al[66]	Endothelium-dependent, flow-mediated brachial artery dilatation (FMD) and endothelium-independent dilatation response	An endothelial nitric oxide synthase (eNOS) SNP (Glu298Asp) interacted with dietary omega-3 in determining endothelial responses. Omega-3 was positively related to FMD in Asp298 carriers but not in Glu298 homozygotes.
Ordovas et al[67]	HDL-C concentrations and HDL particle size	The −514C>T *LIPC* polymorphism interacted with dietary fat in determining HDL-related measures. T allele was associated with significantly greater HDL-C concentrations and large HDL size only in subjects consuming <30% of energy from fat.

Circ Cardiovasc Genet. 2009;2:637-651.)

Capire come la dieta ed i suoi componenti possono interferire con questi meccanismi è un elemento chiave per la definizione di strategie di prevenzione nutrizionali efficaci e sostenibili che mirino alla cosiddetta

NUTRIZIONE PERSONALIZZATA → **AUMENTO DELL'EFFICACIA**

NUTRIZIONE PERSONALIZZATA → **DIMINUZIONE DEI COSTI**

Studi Nutrigenomici

- **Correlare modifiche dell'espressione genica a risultati sistemici**
- **Mettere insieme i risultati delle diverse tecniche «omiche» con lo studio classico dei biomarcatori**

↓

Visione olistica di come la dieta può influenzare i nostri geni

Evidence-based medicine → **High level of scientific evidence**

↓

Nutritional recommendation

Randomized, controlled double-bind, clinical intervention trials (level I of evidence)

Large cohort studies (level II of evidence)

Table 1. Summary of Dietary Recommendations to Participants in the Mediterranean-Diet Groups and the Control-Diet Group.

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<3 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day
Low-fat diet (control)	
Recommended	
Low-fat dairy products	≥3 servings/day
Bread, potatoes, pasta, rice	≥3 servings/day
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Lean fish and seafood	≥3 servings/wk
Discouraged	
Vegetable oils (including olive oil)	≤2 tbsp/day
Commercial bakery goods, sweets, and pastries§	≤1 serving/wk
Nuts and fried snacks	≤1 serving /wk
Red and processed fatty meats	≤1 serving/wk
Visible fat in meats and soups¶	Always remove
Fatty fish, seafood canned in oil	≤1 serving/wk
Spread fats	≤1 serving/wk
Sofrito‡	≤2 servings/wk

PREDIMED trial (Prevención con Dieta Mediterránea)

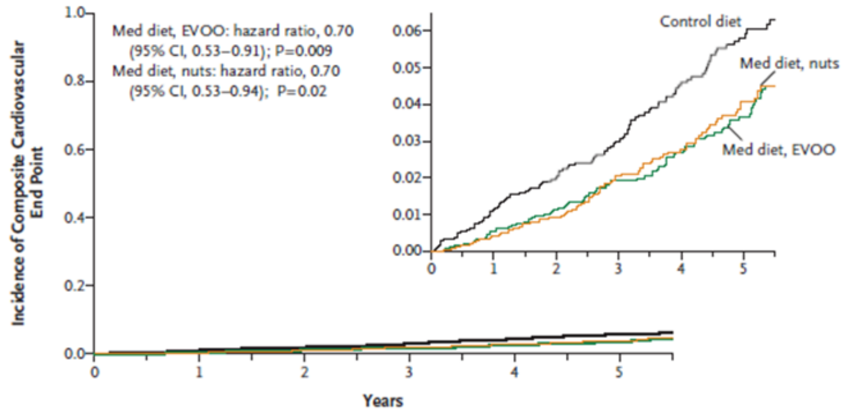
Studio a bracci paralleli, multicentrico, randomizzato

7447 soggetti (donne e uomini; 55-80 anni)

- No CVD al momento dell'arruolamento
- T2D o almeno 3 fattori di rischio (fumo, ipertensione, alto c-LDL, basso c-HDL, sovrappeso/obesità)

- Dieta mediterranea **+ EVOO** (1 lt/settimana)
- Dieta mediterranea + **noci/mandorle/nocciole** (30 gr/die)
- Dieta di controllo (**low fat**)

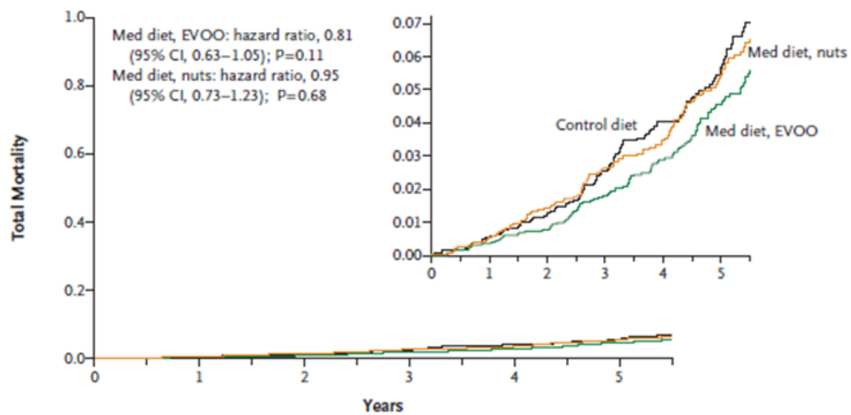
A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

B Total Mortality



No. at Risk

Control diet	2450	2268	2026	1585	1272	948
Med diet, EVOO	2543	2485	2322	1988	1690	1308
Med diet, nuts	2454	2345	2097	1662	1395	1037

Figure 1. **Kaplan–Meier Estimates of the Incidence of Outcome Events in the Total Study Population.**
Panel A shows the incidence of the primary end point (a composite of acute myocardial infarction, stroke, and death from cardiovascular causes), and Panel B shows total mortality. Hazard ratios were stratified according to center (Cox model with robust variance estimators). CI denotes confidence interval, EVOO extra-virgin olive oil, and Med Mediterranean.

In vivo transcriptomic profile after a Mediterranean diet in high–cardiovascular risk patients: a randomized controlled trial[1–3]

Olga Castañer, Dolores Corella, Maria-Isabel Covas, José V Sorlí, Isaac Subirana, Gemma Flores-Mateo, Lara Nonell, Monica Bulló, Rafael de la Torre, Olga Portolés, and Montserrat Fitó for the PREDIMED study investigators

Am J Clin Nutr 2013;98:845–53

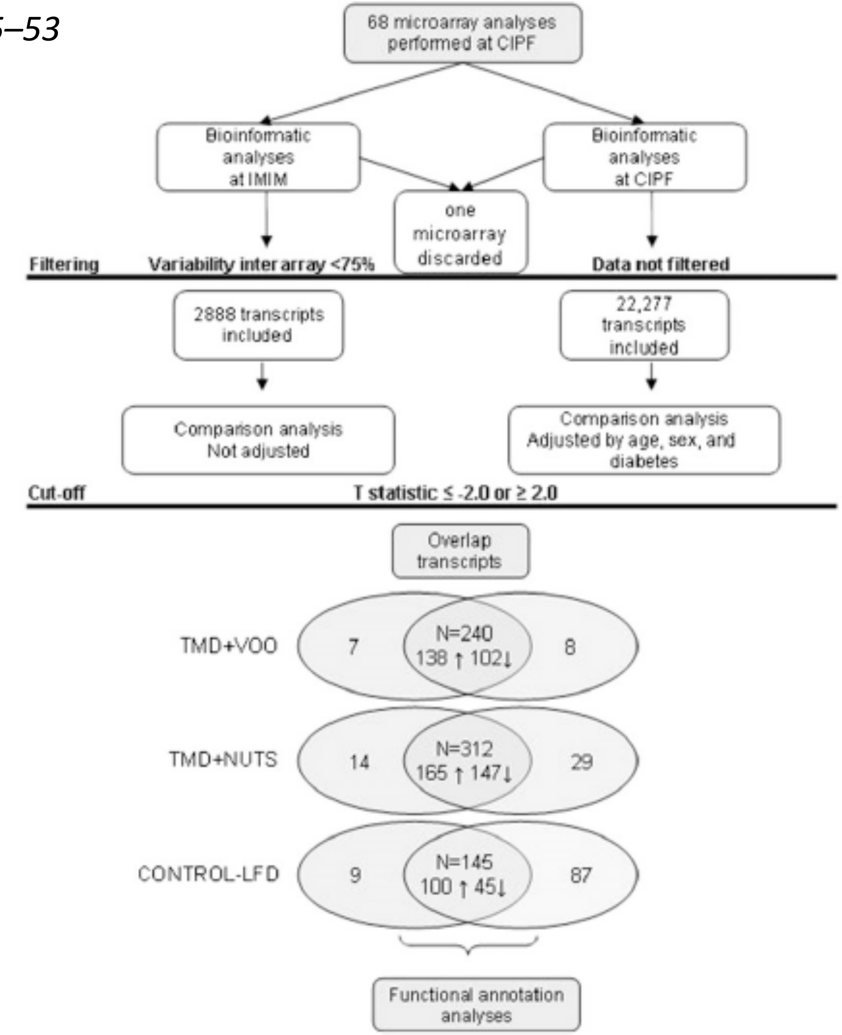
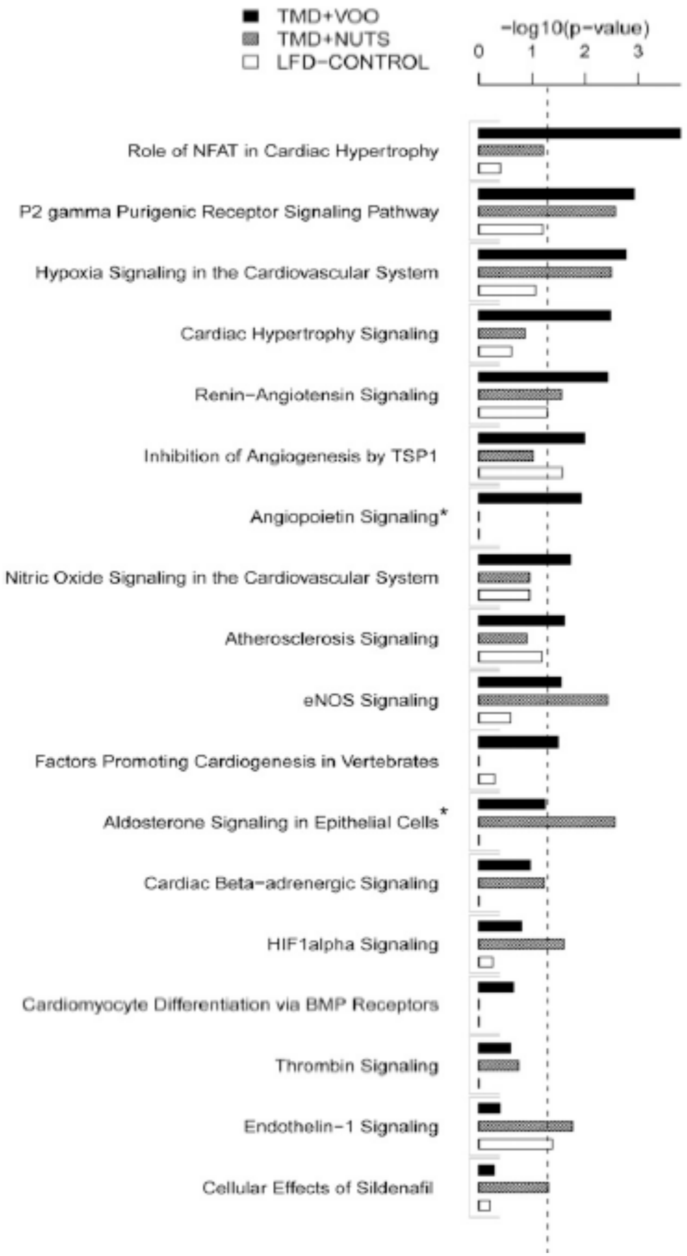


FIGURE 1. Flowchart of the 2 bioinformatics analysis approaches and procedures. CIPF, Príncipe Felipe Investigation Center; IMIM, Hospital del Mar Research Institute; LFD, low-fat diet; TMD+Nuts, traditional Mediterranean diet supplemented with nuts; TMD+VOO, traditional Mediterranean diet supplemented with virgin olive oil; ↓, downregulated; ↑, upregulated.

TRANSCRIPTOMIC PROFILE AFTER A MEDITERRANEAN DIET



Castagner et al. Am J Clin Nutr 2013;98:845–53

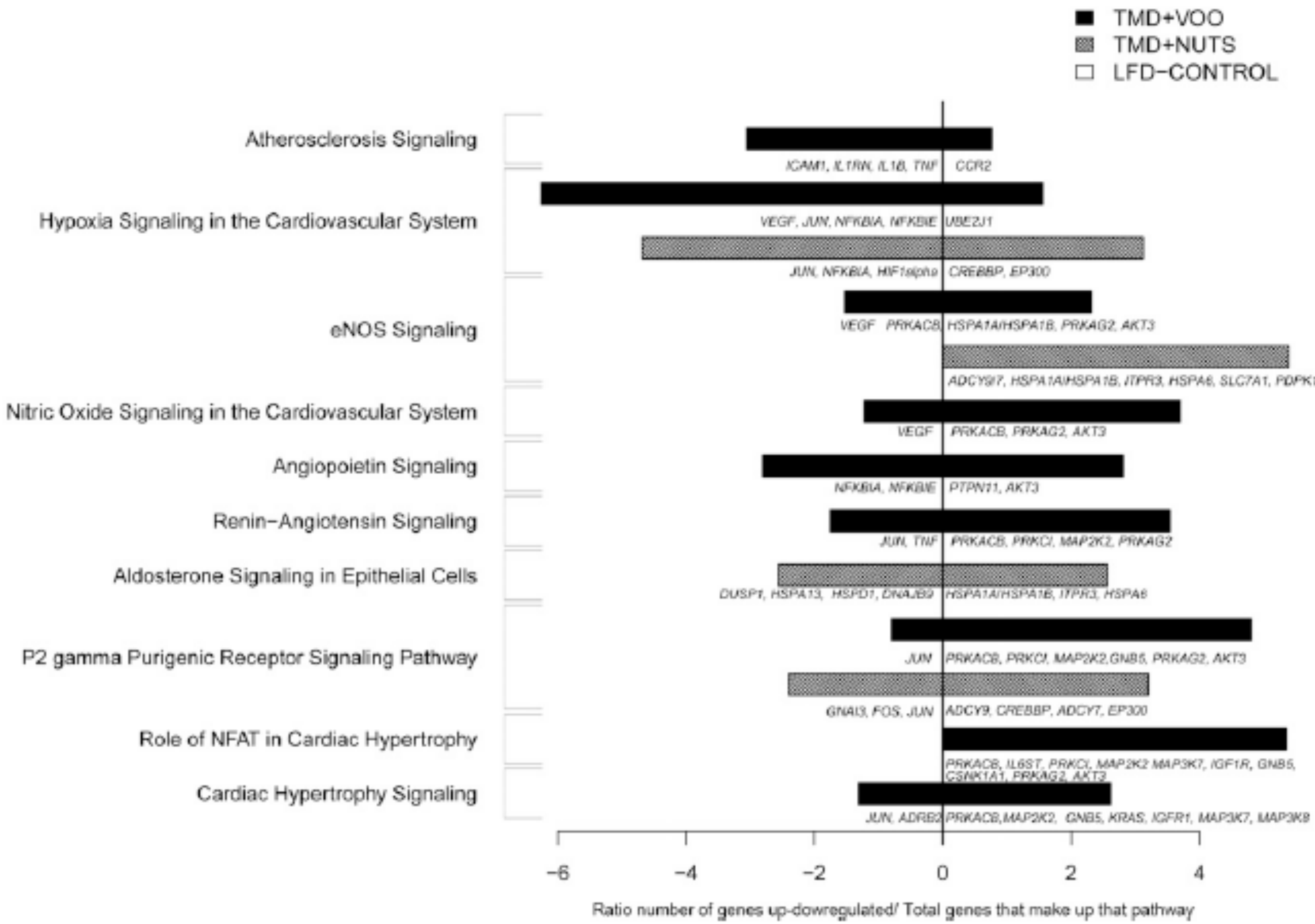


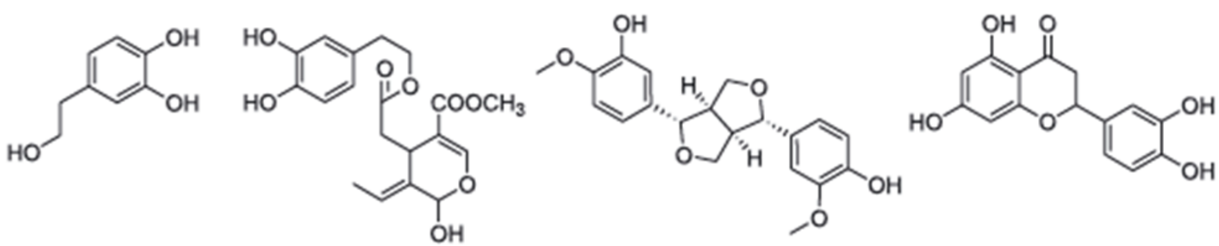
FIGURE 4. Cardiovascular canonical pathways significantly modulated after Benjamini-Hochberg correction and direction of the changes for the associated genes. TMD+VOO: $n = 11$; TMD+Nuts: $n = 11$; LFD, $n = 12$. eNOS, endothelial nitric oxide synthase; LFD, low-fat diet; NFAT, nuclear factor of activated T cells; TMD+Nuts, traditional Mediterranean diet supplemented with nuts; TMD+VOO, traditional Mediterranean diet supplemented with virgin olive oil.

Am J Clin Nutr 2013;98:845–53

- •Elevato contenuto di MUFA
- •Elevato contenuto di polifenoli

Mol. Nutr. Food Res. 2013, *57*, 760–771

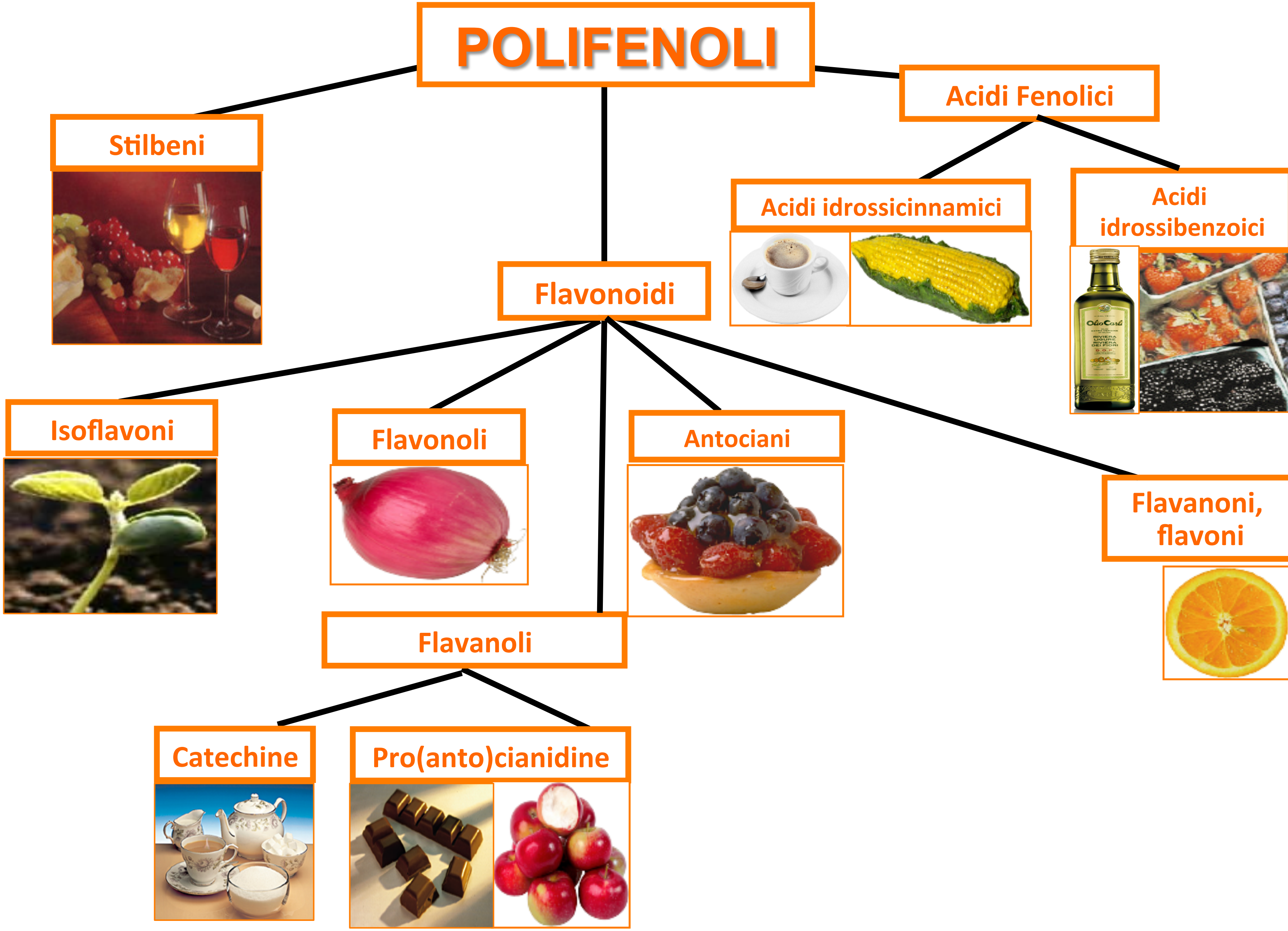
Simple phenols | Secoiridoids | Lignans | Flavonoids



Hydroxytyrosol (HT) | Oleuropein aglycon (3,4-DHPEA-EA) | (+)-Pinoresinol | Luteolin

Figure 1. Main classes of OOPC with representative compounds.

Attività antiossidante


POLIFENOLI
Stilbeni
Flavonoidi
Acidi Fenolici
Acidi idrossicinnamici
Acidi idrossibenzoici
Isoflavoni
Flavonoli
Antociani
Flavanoni, flavoni
Flavanoli
Catechine
Pro(anto)cianidine

I Polifenoli

- **Sono assorbiti in quantità piuttosto bassa ed i loro livelli ematici sono molto più bassi di quelli di vitamine come ascorbato e tocoferoli**

- **Sono modificati durante i processi metabolici**

Polifenoli

Antiossidanti e non solo….

Attività biologiche

Modulatori di → vie di segnale intracellulare
attività enzimatiche
recettoriale

Extra Virgin Olive Oil Biophenols Inhibit Cell-Mediated Oxidation of LDL by Increasing the mRNA Transcription of Glutathione-Related Enzymes[1]

R. Masella et al. J. Nutr 134: 785–791, 2004.

- Oleuropeina
- Acido protocatecuico

Macrofagi murini J774 A.1

I due polifenoli proteggono le LDL dall’ossidazione anche quando non sono presenti nel mezzo di coltura.

- **Diminuzione di radicali liberi prodotti**
- **Aumento del GSH**

Polifenoli dell’olio di oliva innescano processi cellulari di difesa.

Espressione di enzimi di fase 2

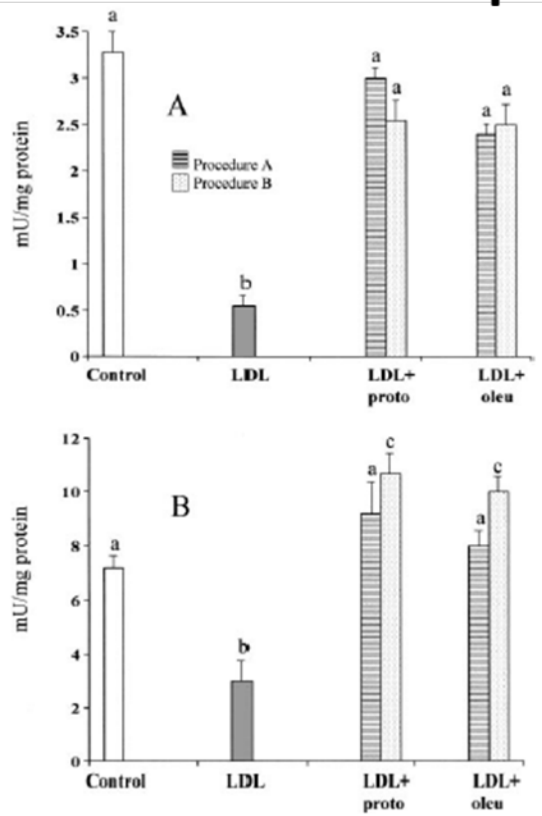


FIGURE 2 Biophenols restore GR (*A*) and GPx (*B*) activities in J774 A.1 macrophage-like cells following both procedure A or procedure B. Activities were measured after a 24-h incubation with LDL (0.2 g protein/L). Values are means ± SEM, *n* = 4. Bars without a common letter differ, $P < 0.05$. LDL = cell exposed to LDL; LDL + proto = cell exposed to LDL and protocatechuic acid; LDL + oleu = cell exposed to LDL and oleuropein.

GR

GPx

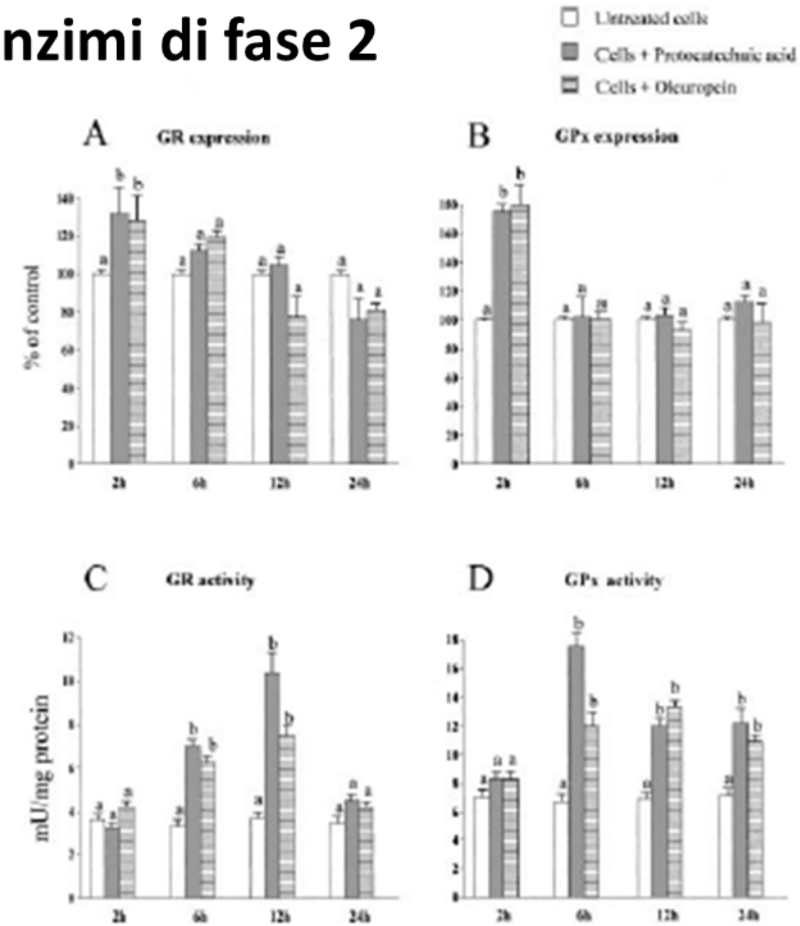
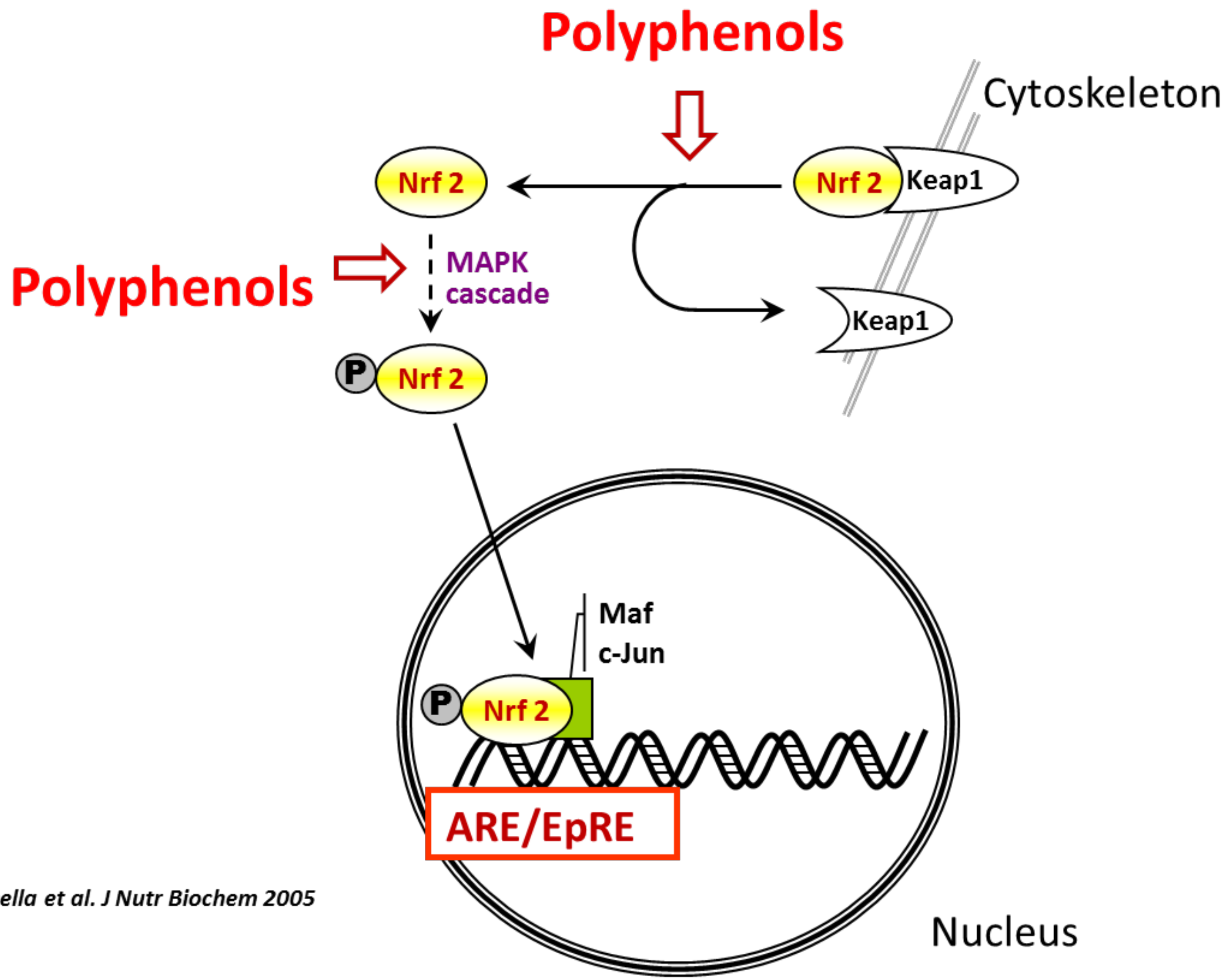
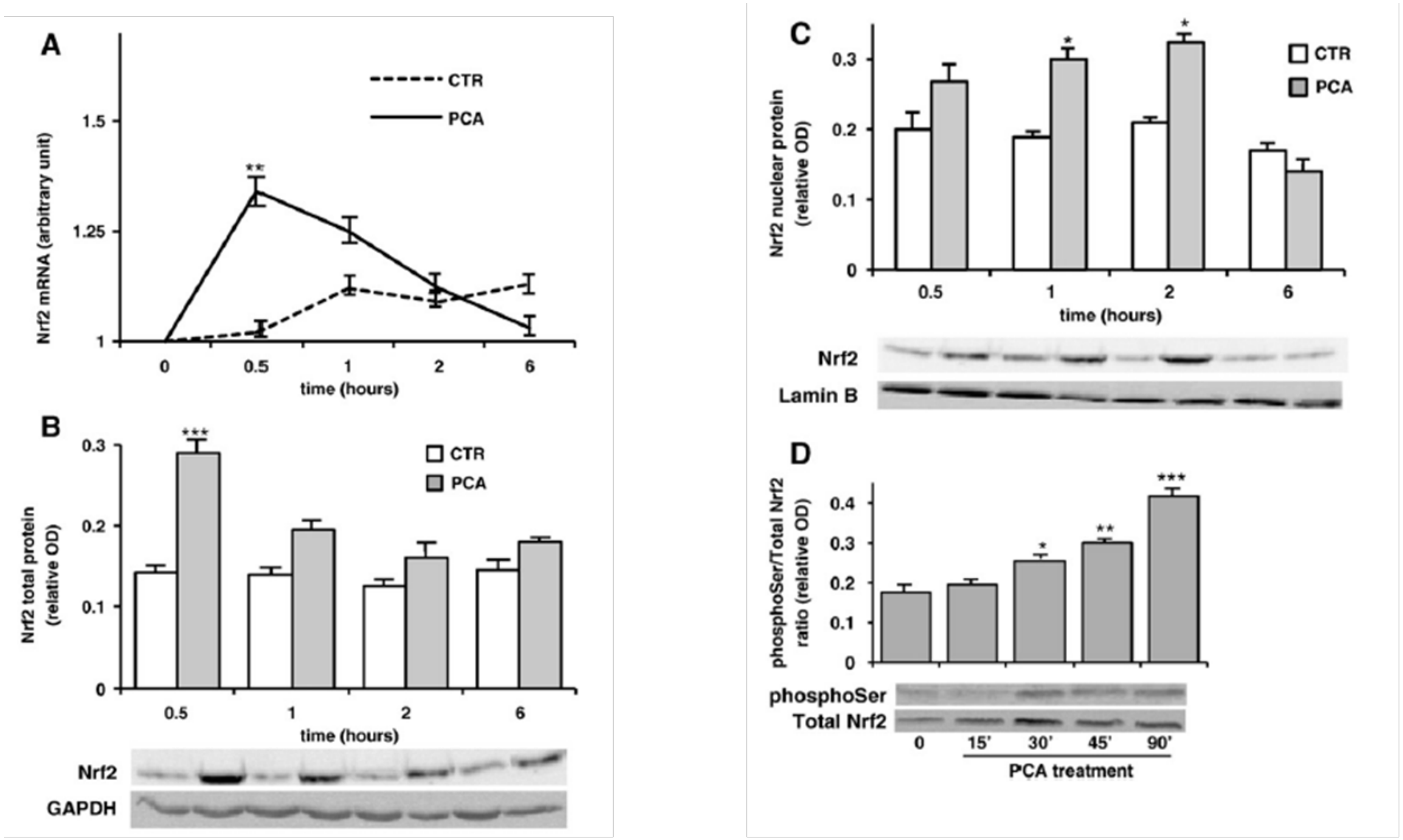


FIGURE 4 Direct effect of the biophenols on DNA transcription of GSH-related enzymes in J774 A.1 cells incubated with protocatechuic acid and oleuropein following procedure B. (*A*) Semiquantitative RT-PCR time-course evaluation of *m*RNA for GR and GPx. (*B*) Time-course evaluation of GR and GPx activities. Values are means ± SEM, *n* = 4. Bars without a common letter differ, $P < 0.05$.

Meccanismi di regolazione dell'espressione di enzimi di fase 2



R. Masella et al. J Nutr Biochem 2005



R. Varì et al. J Nutr Biochem, 2011

Table 1. Randomized, crossover, controlled studies on the antioxidant effect of sustained consumption of phenolic compounds from olive oil on *in vivo* markers of lipid and DNA oxidation

	Olive oil intervention (time)	Daily olive oil dose	Subjects	Washout period	Oxidative markers	Effects
Vissiers *et al.* (2001) [79]	High-phenol vs Low-phenol (3 weeks)	69 g (in sauces, or baked products)	46 healthy (31 women, 15 men)	2 weeks without olives and olive oil	MDA, FRAP LP, PC LDL-resistance[a)] to oxidation	None
Moschandreas *et al.* (2002) [80]	High vs Low phenol (3 weeks)	70 g raw	25 healthy (14 women, 11 men)	2 weeks without olives and olive oil	MDA, FRAP LP, PC LDL resistance[a)] to oxidation	None
Marrugat *et al.* (2004) [66]	Virgin vs Common vs Refined (3 weeks with refined olive oil for cooking)	25 mL (22 g) raw	30 healthy men	2 weeks with refined olive oil for raw and cooking purposes	Plasma oxidized LDL LDL resistance[a)] to oxidation	Decrease with olive oil phenolics
					Antobodies against oxidized LDL	None
					HDL-cholesterol	Increase after virgin olive oil
Weinbrenner *et al.* (2004) [68]	High vs Meium vs Low phenol (4 days with low phenolic olive oil for raw and cooking	25 mL raw	12 healthy men	10 days: low phenol olive oil for raw and cooking; very-low antioxidant diet	Plasma oxidized LDL MDA in urine 8oxodG in urine and lymphoctyes	Decrease with olive oil phenolics
					F_2-isoprostanes	None
					GSH-Px HDL cholesterol	Increase with olive oil phenolics
Visioli *et al.* (2005) [81]	Virgin vs refined (raw)	40 mL raw	22 lipemic patients (12 men, 10 women)	4 weeks with	Plasma antioxidant capacity	Increase with olive oil phenolics
					F_2-isoprostanes	None
Fitó *et al.* (2005) [82]	Virgin vs Refined (raw) (3 weeks, refined olive oil for cooking)	50 mL, raw	Coronary heart disease patiens (40 men)	2 weeks with refined olive oil for all purposes	Plasma oxidized LDL, LP	Decrease with olive oil phenolics
					GSH-Px	Increase with olive oil phenolics
Salvini *et al.* (2006) [103]	High vs Low (8 weeks) phenolics	*ad libitum* in substitution of other fats	10 post-menopausal women	2 weeks (usual diet)	Comet assay for DNA oxidation	Decrease with olive oil
Covas *et al.* (2006) [84]	Virgin vs Common vs Refined (3 weks)	25 mL, raw	200 healthy men	2 weeks without olives and olive oil	Plasma oxidized LDL Uninduced dienes Hydroxy fatty acids	Decrease with olive oil phenolics
					Antiboides against oxidizee LDL F_2-isoprostans	None

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Journal of Nutritional Biochemistry 24 (2013) 1334–1339

Olive oil polyphenols enhance the expression of cholesterol efflux related genes *in vivo* in humans. A randomized controlled trial

Marta Farràs[a,b], Rosa M. Valls[c], Sara Fernández-Castillejo[c], Montserrat Giralt[c], Rosa Solà[c], Isaac Subirana[d], María-José Motilva[e], Valentini Konstantinidou[c], María-Isabel Covas[a,*,1], Montserrat Fitó[a,*,1]

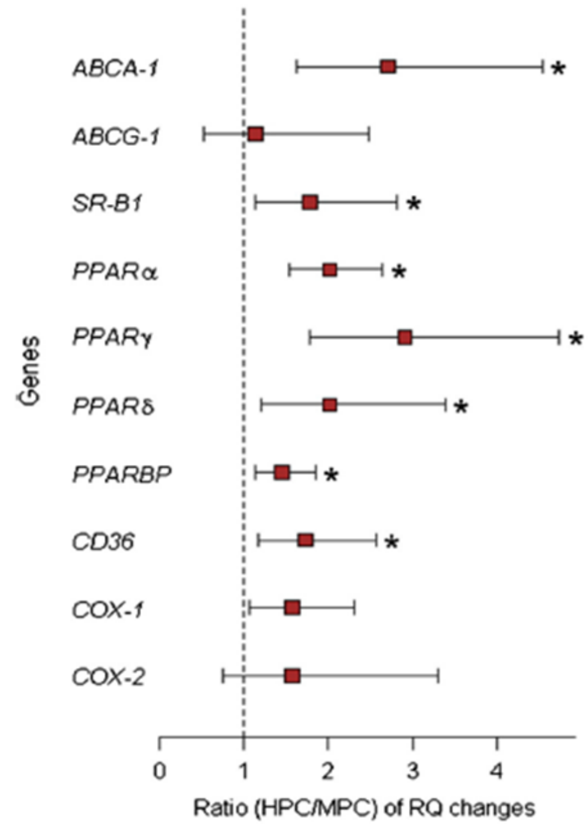
22 partecipanti ipertesi;
cross-over randomizzato; a doppio cieco.
30 ml di uno dei due olii di oliva :

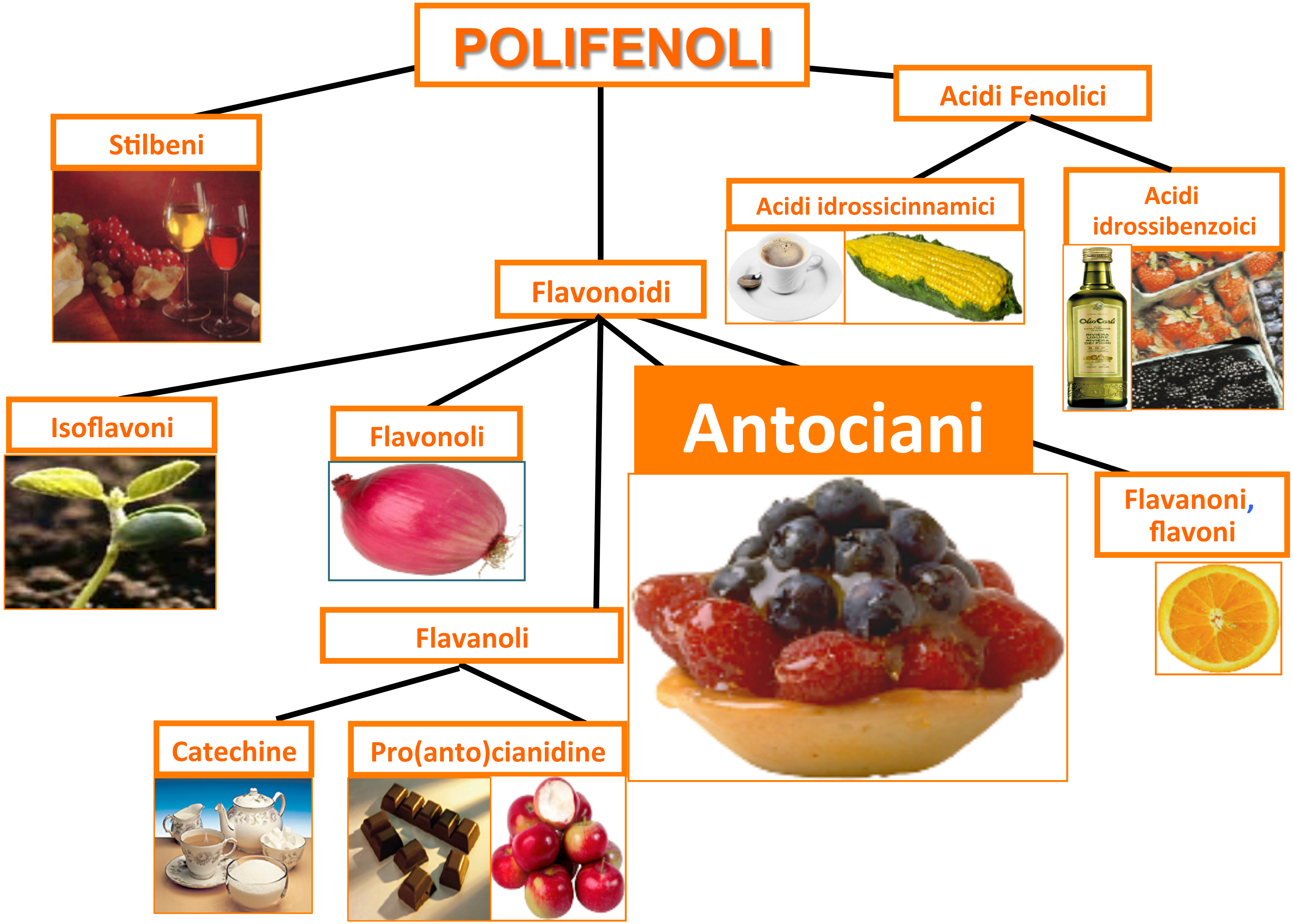
- **MPC**= a medio contenuto di poilifenoli

- **HPC** = MPC arricchito con un estratto di polifenoli (7 mg /ml di olio)

Dopo 5 h **mRNA** dei geni responsabili del trasporto di colesterolo dalle cellule alle HDL nelle cellule bianche del sangue

M. Farràs et al. / Journal of Nutrition




POLIFENOLI
Stilbeni
Acidi Fenolici
Acidi idrossicinnamici
Acidi idrossibenzoici
Flavonoidi
Isoflavoni
Flavonoli
Antociani
Flavanoni, flavoni
Flavanoli
Catechine
Pro(anto)cianidine

Dietary flavonoid intakes and risk of type 2 diabetes in US men and women[1–5]

Nicole M Wedick, An Pan, Aedín Cassidy, Eric B Rimm, Laura Sampson, Bernard Rosner, Walter Willett, Frank B Hu, Qi Sun, and Rob M van Dam

Am J Clin Nutr 2012;95:925–33.

TABLE 2 (*Continued*)

	Frequency of consumption					
	Q1	Q2	Q3	Q4	Q5	*P*-trend
NHS II						
Median value (mg/d)	9.0	16.5	27.7	56.2	148.4	
Cases/person-years	784/274,916	510/279,651	510/281,582	575/279,240	705/277,424	
Model 1[2]	1.00	0.78 (0.70, 0.87)	0.84 (0.75, 0.94)	0.86 (0.78, 0.96)	0.98 (0.88, 1.08)	0.06
Model 2[3]	1.00	0.91 (0.81, 1.02)	0.98 (0.87, 1.10)	0.96 (0.86, 1.07)	1.01 (0.91, 1.12)	0.40
HPFS						
Median value (mg/d)	9.0	16.7	25.4	43.9	103.9	
Cases/person-years	653/144,321	527/145,054	457/145,424	487/145,311	525/145,066	
Model 1[2]	1.00	0.84 (0.75, 0.94)	0.76 (0.68, 0.86)	0.82 (0.73, 0.93)	0.85 (0.76, 0.96)	0.25
Model 2[3]	1.00	0.90 (0.80, 1.02)	0.85 (0.75, 0.96)	0.91 (0.80, 1.02)	0.88 (0.78, 0.99)	0.22
Pooled results[4]						
Random-effects model	1.00	0.92 (0.87, 0.98)	0.91 (0.85, 0.98)	0.94 (0.89, 0.99)	0.91 (0.84, 1.00)	0.32
P-heterogeneity	—	0.80	0.27	0.78	0.07	0.03
Anthocyanins						
NHS						
Median value (mg/d)	2.2	4.7	8.1	13.1	22.3	
Cases/person-years	1688/286,253	1513/303,189	1293/314,489	1251/314,333	1133/309,332	
Model 1[2]	1.00	0.87 (0.81, 0.93)	0.75 (0.70, 0.81)	0.75 (0.70, 0.80)	0.69 (0.64, 0.74)	<0.001
Model 2[3]	1.00	0.93 (0.86, 0.99)	0.84 (0.78, 0.91)	0.85 (0.79, 0.92)	0.83 (0.77, 0.90)	<0.001
NHS II						
Median value (mg/d)	2.0	4.5	8.0	13.7	24.3	
Cases/person-years	898/270,677	702/277,111	513/281,465	515/281,334	456/282,225	
Model 1[2]	1.00	0.87 (0.79, 0.96)	0.72 (0.64, 0.80)	0.74 (0.66, 0.82)	0.68 (0.61, 0.76)	<0.001
Model 2[3]	1.00	0.98 (0.88, 1.08)	0.84 (0.75, 0.94)	0.88 (0.79, 0.99)	0.83 (0.73, 0.94)	0.002
HPFS						
Median value (mg/d)	2.3	4.9	8.3	14.0	24.2	
Cases/person-years	621/144,223	541/144,956	519/145,403	508/145,413	460/145,183	
Model 1[2]	1.00	0.90 (0.80, 1.01)	0.88 (0.78, 0.99)	0.87 (0.77, 0.98)	0.80 (0.70, 0.90)	<0.001
Model 2[3]	1.00	0.95 (0.84, 1.06)	0.96 (0.85, 1.08)	0.95 (0.84, 1.07)	0.93 (0.81, 1.05)	0.34
Pooled results[4]						
Random-effects model	1.00	0.94 (0.89, 0.99)	0.87 (0.80, 0.94)	0.88 (0.83, 0.94)	0.85 (0.80, 0.91)	<0.001
P for heterogeneity	—	0.69	0.15	0.33	0.34	0.20
Total flavonoids						

The Journal of Nutrition
Nutrition and Disease

J Nutr 2015;145:742–8.

Purified Anthocyanin Supplementation Reduces Dyslipidemia, Enhances Antioxidant Capacity, and Prevents Insulin Resistance in Diabetic Patients[1–3]

TABLE 2 Anthropometric data and lipid profiles of diabetic patients in the placebo and anthocyanin groups at baseline and after the 24-wk intervention[1]

	Placebo		Anthocyanin		
	Baseline	24 wk	Baseline	24 wk	P^2
Plasma anthocyanin (Cy3g and Dp3g), nmol/L	Not detectable	Not detectable	Not detectable	9.37 ± 1.06*	<0.01
Systolic blood pressure, mm Hg	128 ± 10	129 ± 9	130 ± 13	126 ± 11	0.034
Diastolic blood pressure, mm Hg	81 ± 9	82 ± 7	82 ± 8	80 ± 10	0.16
Serum total cholesterol, mmol/L	5.03 ± 0.78	4.99 ± 0.86	5.07 ± 0.89	4.88 ± 0.94*	0.041
Serum LDL cholesterol, mmol/L	3.19 ± 0.42	3.21 ± 0.48	3.17 ± 0.35	2.92 ± 0.54*	0.030
Serum HDL cholesterol, mmol/L	0.98 ± 0.08	0.95 ± 0.07	1.03 ± 0.11	1.23 ± 0.12*	0.012
Serum TGs, mmol/L	2.02 ± 0.36	1.96 ± 0.45	2.04 ± 0.41	1.57 ± 0.72**	<0.01
Serum apo A-I, g/L	1.35 ± 0.24	1.32 ± 0.36	1.33 ± 0.32	1.39 ± 0.43*	0.13
Serum apo B-48, mg/L	0.95 ± 0.17	0.93 ± 0.22	0.97 ± 0.20	0.81 ± 0.27*	0.017
Serum apo B-100, g/L	5.93 ± 1.44	5.85 ± 1.08	5.88 ± 1.37	5.66 ± 1.22	0.09
Serum apo C-III, mg/L	134 ± 15	136 ± 14	137 ± 18	122 ± 13*	<0.01
Serum FFAs, mmol/L	0.75 ± 0.19	0.77 ± 0.28	0.77 ± 0.16	0.73 ± 0.22	0.15

[1] Values are means ± SEMs, n = 29/group. No significant differences were found for any variable between the placebo and anthocyanin groups at baseline by unpaired Student's t test. *,**Different from baseline: *$P < 0.05$, **$P < 0.01$. Cy3g, cyanidin-3-O-β-glucoside; Dp3g, delphinidin-3-O-β-glucoside.

[2] P values for differences between placebo and anthocyanin groups after the 24-wk intervention.

TABLE 3 Antioxidant capacity of diabetic patients in the placebo and anthocyanin groups at baseline and after the 24-wk intervention[1]

	Placebo		Anthocyanin		
	Baseline	24 wk	Baseline	24 wk	P^2
Plasma FRAP, mmol Fe^{2+}/L	1.02 ± 0.13	1.04 ± 0.11	1.04 ± 0.08	1.35 ± 0.14*	0.013
Plasma TRAP, mmol/L	1.09 ± 0.06	1.12 ± 0.08	1.07 ± 0.09	1.33 ± 0.10*	0.017
Plasma 8-iso-$PGF_{2\alpha}$, pmol/mL	11.6 ± 2.78	11.4 ± 3.13	11.5 ± 3.55	8.73 ± 2.86**	<0.01
Plasma 13-HODE, pmol/mL	28.8 ± 4.87	27.9 ± 5.38	29.0 ± 6.25	20.7 ± 5.93**	<0.01
Plasma carbonylated protein, nmol/mg	0.68 ± 0.05	0.65 ± 0.03	0.67 ± 0.07	0.52 ± 0.03*	0.022

[1] Values are means ± SEMs, $n = 29$/group. No significant differences were found for any variable between placebo and anthocyanin groups at baseline by unpaired Student's *t* test. *,**Different from baseline: *$P < 0.05$, **$P < 0.01$. FRAP, ferric ion reducing antioxidant power; TRAP, total radical-trapping antioxidant parameter; 8-iso-$PGF_{2\alpha}$, 8-iso-prostaglandin F2α; 13-HODE, 13-hydroxyoctadecadienoic acid.
[2] *P* values for differences between placebo and anthocyanin groups at 24 wk.

TABLE 4 Serum adipokine and proinflammatory molecules in diabetic patients in the placebo and anthocyanin groups at baseline and after the 24-wk intervention[1]

	Placebo		Anthocyanin		
	Baseline	24 wk	Baseline	24 wk	P^2
BMI, kg/m^2	25.3 ± 2.5	25.4 ± 2.9	25.1 ± 2.7	25.0 ± 3.2	0.19
Fat mass, % (body weight)	35.2 ± 5.9	34.8 ± 5.3	35.4 ± 6.1	34.6 ± 6.5	0.13
Fasting plasma glucose, mmol/L	7.3 ± 1.7	7.1 ± 1.5	7.1 ± 2.2	6.5 ± 1.8*	0.042
Plasma insulin, mU/L	11.6 ± 4.13	11.7 ± 3.76	11.9 ± 4.30	11.1 ± 3.98	0.14
Plasma Hb A_{1c}, %	6.6 ± 1.5	6.5 ± 1.4	6.5 ± 1.7	6.2 ± 1.9	0.06
HOMA-IR	3.76 ± 0.53	3.69 ± 0.64	3.74 ± 0.55	3.21 ± 0.76*	0.035
Serum adiponectin, μg/mL	5.05 ± 0.79	5.09 ± 0.84	5.08 ± 0.92	6.28 ± 0.96**	<0.01
Serum HMW adiponectin, μg/mL	2.23 ± 0.56	2.16 ± 0.52	2.21 ± 0.67	3.26 ± 0.73**	<0.01
HMW:total adiponectin ratio, %	44.2 ± 6.52	42.6 ± 5.93	43.6 ± 6.79	51.9 ± 7.08*	0.024
Serum IL-6, pg/mL	3.26 ± 0.57	3.18 ± 0.63	3.23 ± 0.49	2.21 ± 0.42**	0.021
Serum TNF-α, pg/mL	16.2 ± 2.35	15.9 ± 2.67	16.2 ± 2.58	14.8 ± 2.13*	0.045
Plasma β-hydroxybutyrate, mg/dL	1.14 ± 0.37	1.18 ± 0.46	1.17 ± 0.42	1.68 ± 0.51**	0.010

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Nutrition, Metabolism and Cardiovascular Diseases

Volume 23, Issue 9, September 2013, Pages 843–849

150 soggetti,
ipercolesterolemici,
320 mg/die antociani in capsule
+ dieta abituale

Anti-inflammatory effect of purified dietary anthocyanin in adults with hypercholesterolemia: A randomized controlled trial

Y. Zhu[a,b], W. Ling[a], H. Guo[c], F. Song[a], Q. Ye[a], T. Zou[d], D. Li[a], Y. Zhang[a,e], G. Li[a], Y. Xiao[a], F. Liu[a], Z. Li[a], Z. Shi[a], Y. Yang[a]

Table 1 Changes in the lipids profile of the participants at baseline and at week 24 of the trial.[a]

	Placebo (n = 73)			Anthocyanin (n = 73)			P-value[c]
	Basseline	24 wk	Mean change, % (95%CI)[b]	Basseline	24 wk	Mean change, % (95%CI)	
Total cholesterol (mmol/L)	6.48 ± 0.84	6.25 ± 0.83	−3.6 (−7.8–0.6)	6.45 ± 1.02	6.18 ± 0.82	−2.9 (−6.3–0.5)	0.556
HDL-cholesterol (mmol/L)	1.24 ± 0.21	1.23 ± 0.20	−0.9 (−5.2–3.4)	1.22 ± 0.23	1.37 ± 0.22[d]	14.0 (7.9–20.2)[e]	0.036
LDL-cholesterol (mmol/L)	3.29 ± 0.47	3.30 ± 0.52	0.3 (−2.9–3.5)	3.36 ± 0.58	3.01 ± 0.41[d]	−10.4 (−14.8 to −6.0)[e]	0.030
Triacylglycerol (mmol/L)[f]	2.41 (1.47–2.70)	2.34 (1.35–2.62)	−3.2 (−7.6–1.2)	2.45 (1.53–2.74)	2.35 (1.37–2.61)	−4.8 (−9.8–0.2)	0.462

Table 2 Changes in the inflammatory cytokines of the participants at baseline and at weeks 12 and 24 of the trial.[a]

	Placebo (n = 73)				Anthocyanin (n = 73)				P-value[c]
	Basseline	12 wk	24 wk	Mean change, % (95%CI)[b]	Basseline	12 wk	24 wk	Mean change, % (95%CI)[b]	
hsCRP (mg/L)[d]	2.26 (0.97–3.72)	2.23 (1.08–3.76)	2.19 (0.93–3.82)	−2.5 (−7.0–2.1)	2.25 (1.06–4.25)	1.95 (0.92–2.84)[e]	1.74 (0.86–2.60)[e]	−21.6 (−37.5 to −5.7)[f]	0.001
sVCAM-1 (ng/mL)	544.2 ± 107.8	546.3 ± 106.9	547.6 ± 109.5	0.4 (−4.6–5.4)	542.9 ± 103.6	481.0 ± 91.8[e]	478.7 ± 97.8[e]	−12.3 (−21.5 to −3.1)[f]	0.005
TNF-α (pg/mL)	18.0 ± 6.0	19.1 ± 6.7	18.5 ± 5.4	2.8 (−3.4–9.1)	18.7 ± 6.4	17.9 ± 5.1	18.4 ± 5.6	−1.6 (−5.6–3.4)	0.673
IL-1β (pg/mL)	4.77 ± 1.71	4.23 ± 0.91	4.71 ± 1.60	−1.3 (−5.3–2.7)	5.18 ± 2.11	4.62 ± 1.20[e]	4.51 ± 1.60[e]	−12.8 (−24.4 to −1.2)[f]	0.019

[a] hsCRP: high-sensitive C-reactive protein. sVCAM-1: soluble vascular adhesion molecule-1. TNF-α: tumor necrosis factor-alpha. The data, unless otherwise specified, were expressed as mean ± SD. No significant differences were found for any variable between the two groups at baseline via the unpaired Student's t test.

[b] Calculated as (value at 24 wk − value at baseline)/value at baseline × 100.

[c] The effects of the intervention on these variables were tested by repeated-measures MANCOVA with the BMI and lipid profile (including HDL- and LDL-cholesterol, triacylglycerol and total cholesterol) values as covariates.

[d] Geometric mean; upper and lower quartiles in parentheses (all such values).

[e] $P < 0.05$ vs baseline, assessed by paired Student's t tests.

[f] $P < 0.05$ vs percentage changes in the placebo group, assessed by unpaired Student's t tests.

ORIGINAL ARTICLE

Cyanidin-3-*O*-β-Glucoside and Protocatechuic Acid Exert Insulin-Like Effects by Upregulating PPARγ Activity in Human Omental Adipocytes

Beatrice Scazzocchio,[1] Rosaria Varì,[1] Carmelina Filesi,[1] Massimo D'Archivio,[1] Carmela Santangelo,[1] Claudio Giovannini,[1] Annunziata Iacovelli,[2] Gianfranco Silecchia,[3] Giovanni Li Volti,[4,5] Fabio Galvano,[4] and Roberta Masella[1]

Diabetes, 2011; 60

1472 DOI 10.1002/mnfr.201400816 *Mol. Nutr. Food Res.* 2015, *59*, 1472–1481

RESEARCH ARTICLE

Protocatechuic acid activates key components of insulin signaling pathway mimicking insulin activity

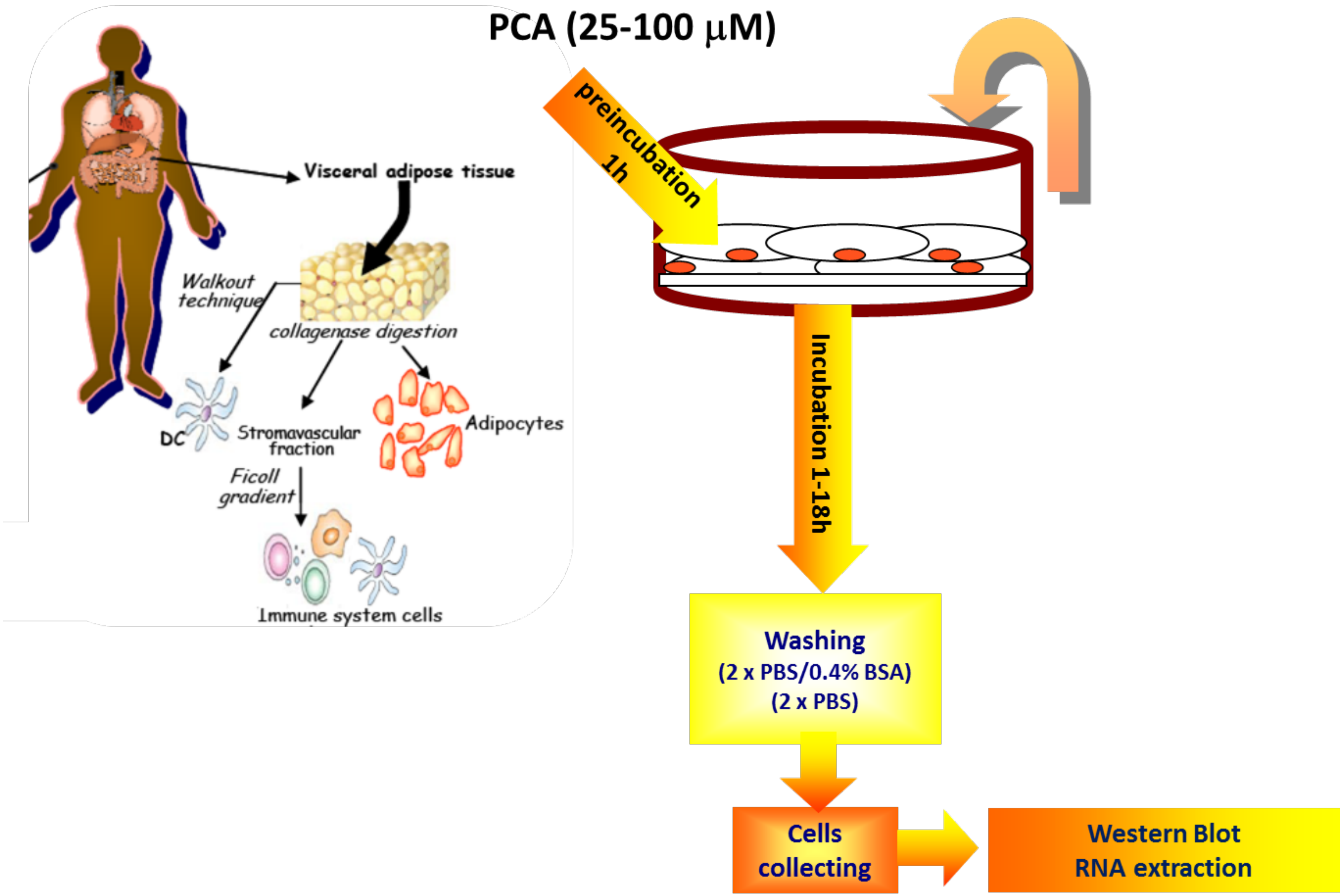
Beatrice Scazzocchio[1], Rosaria Varì[1], Carmelina Filesi[1], Ilaria Del Gaudio[1], Massimo D'Archivio[1], Carmela Santangelo[1], Annunziata Iacovelli[2], Fabio Galvano[3], Francesca Romana Pluchinotta[4], Claudio Giovannini[1] and Roberta Masella[1]

Research Article

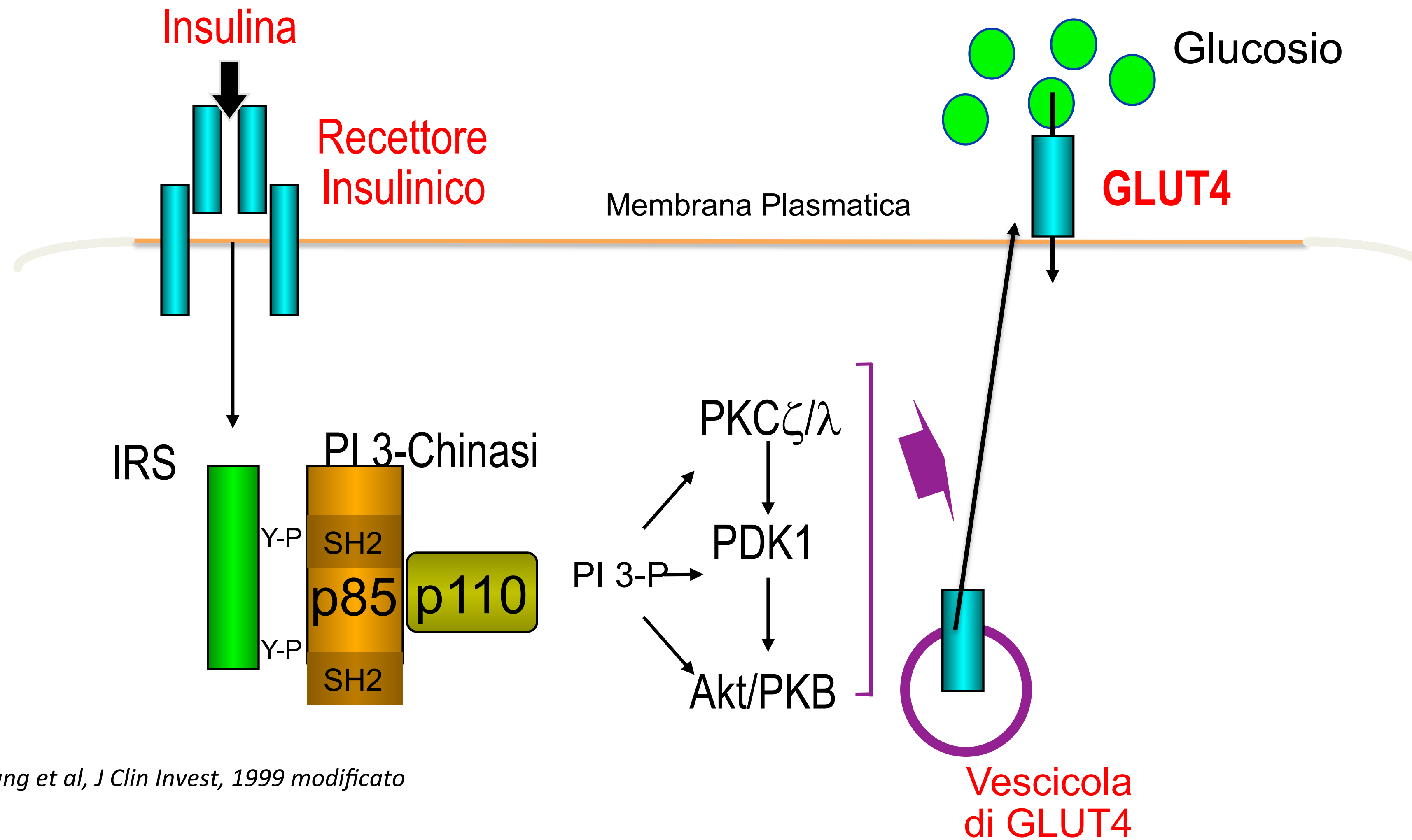
Oxidative Medicine and Cellular Longevity. Volume 2015, Article ID 351827

Protocatechuic Acid Prevents oxLDL-Induced Apoptosis by Activating JNK/Nrf2 Survival Signals in Macrophages

Rosaria Varì,[1] Beatrice Scazzocchio,[1] Carmela Santangelo,[1] Carmelina Filesi,[1] Fabio Galvano,[2] Massimo D'Archivio,[1] Roberta Masella,[1] and Claudio Giovannini[1]


PCA (25-100 μM)
preincubation 1h
Visceral adipose tissue
Walkout technique
collagenase digestion
DC
Stromavascular fraction
Adipocytes
Ficoll gradient
Immune system cells
Incubation 1-18h
Washing
(2 x PBS/0.4% BSA)
(2 x PBS)
Cells collecting
Western Blot
RNA extraction

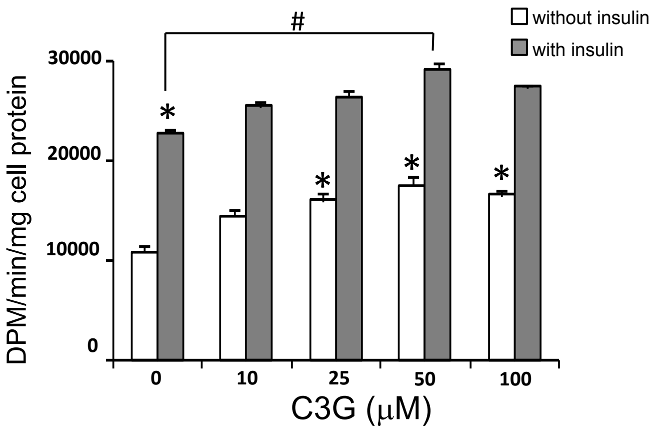
Insulina e uptake del glucosio

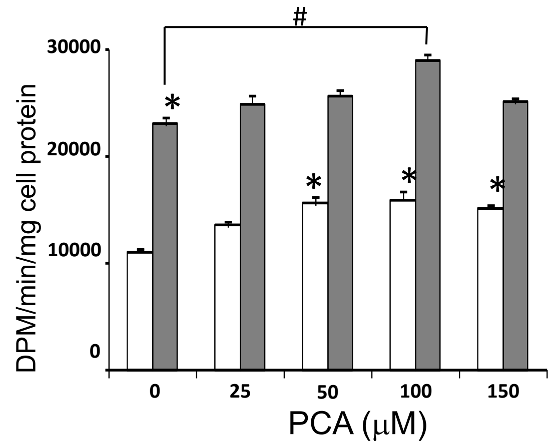


Jiang et al, J Clin Invest, 1999 modificato

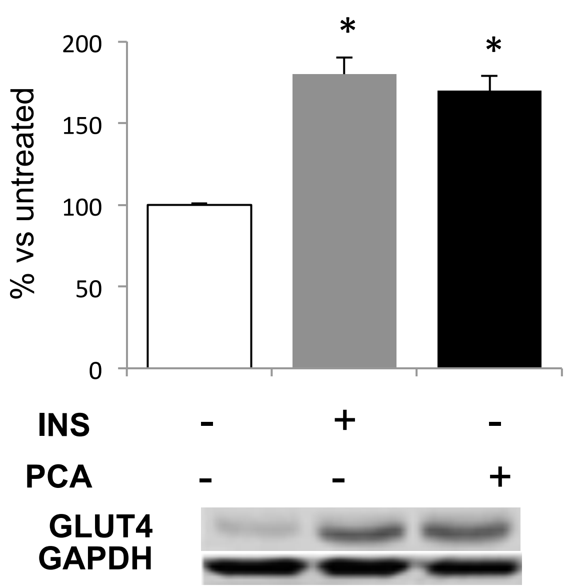
C3G e PCA hanno un'azione insulino-mimetica

Uptake del glucosio

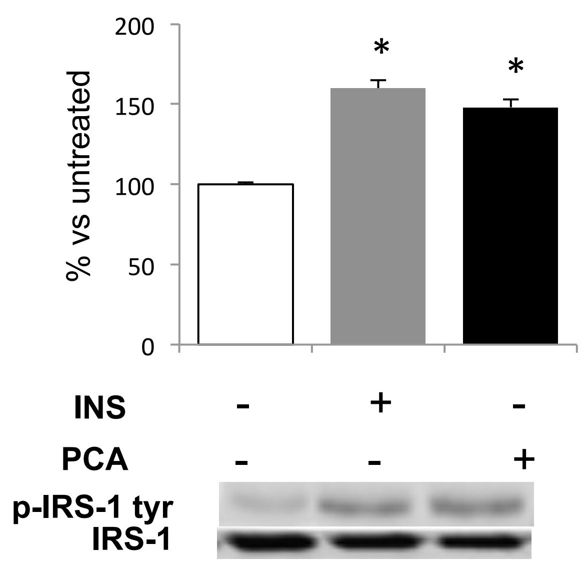




Translocazione del GLUT4



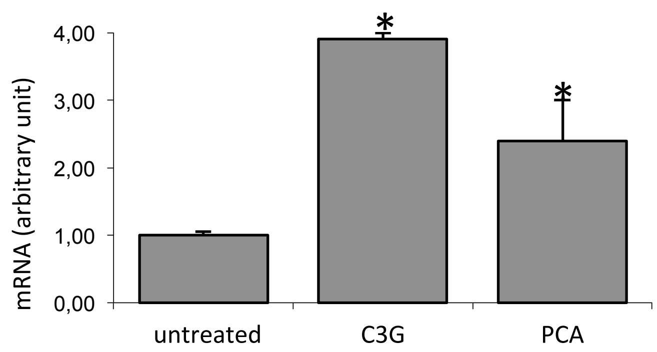
IRS-1 attivato

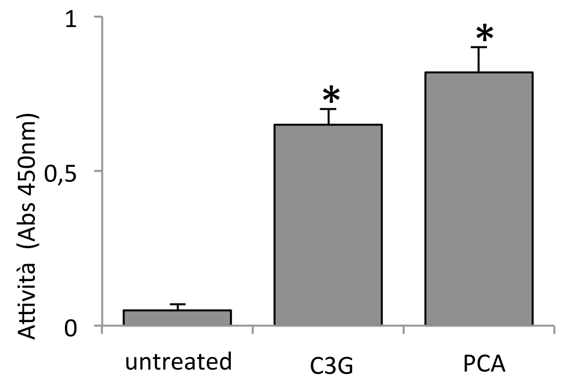


B.Scazzocchio et al. Diabetes 60:2234–2244, 2011

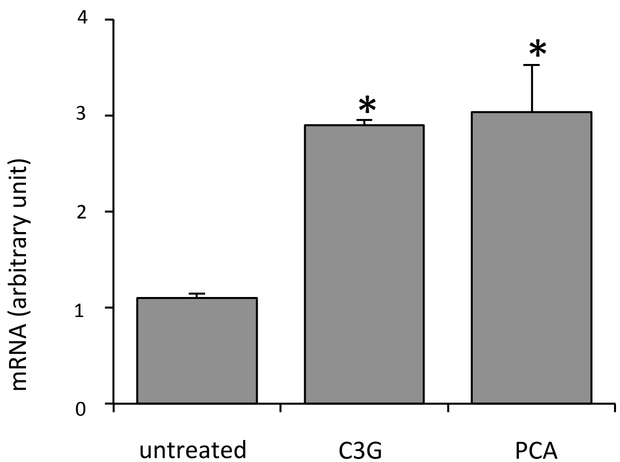
L'attività insulino-mimetica di C3G e PCA è mediata dall'aumento dell'espressione e dell' attività di PPARϒ e di adiponectina

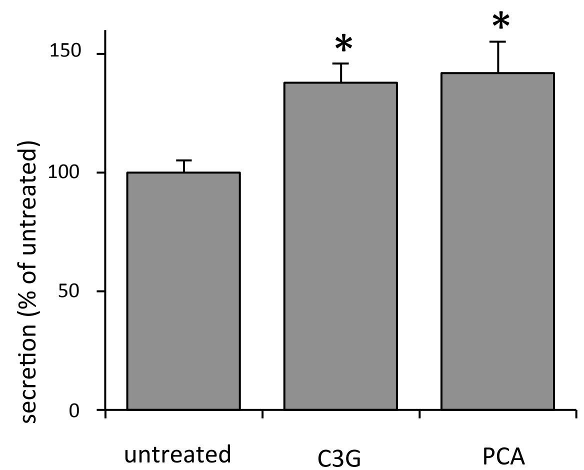
PPARγ



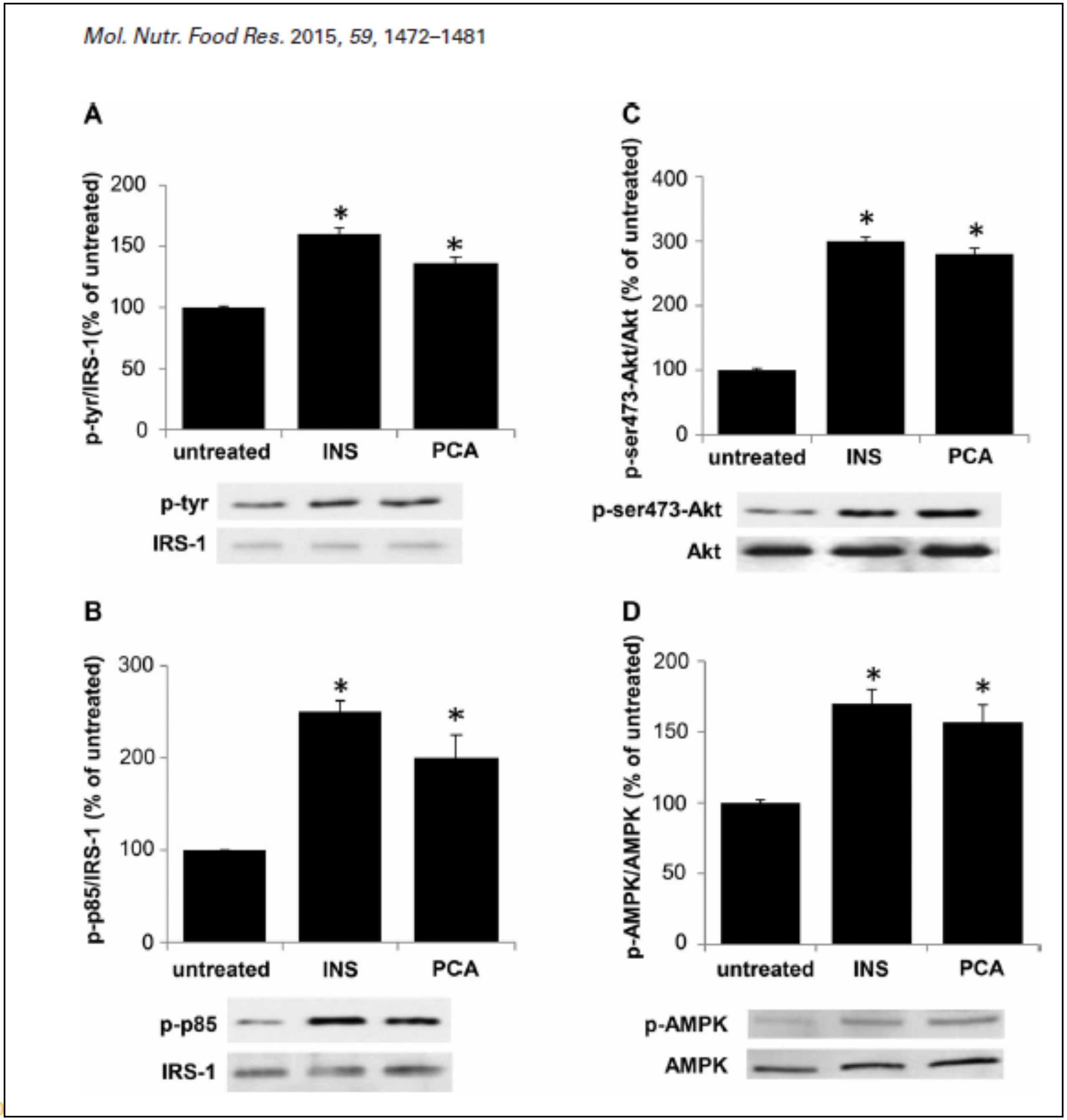


ADIPONECTINA

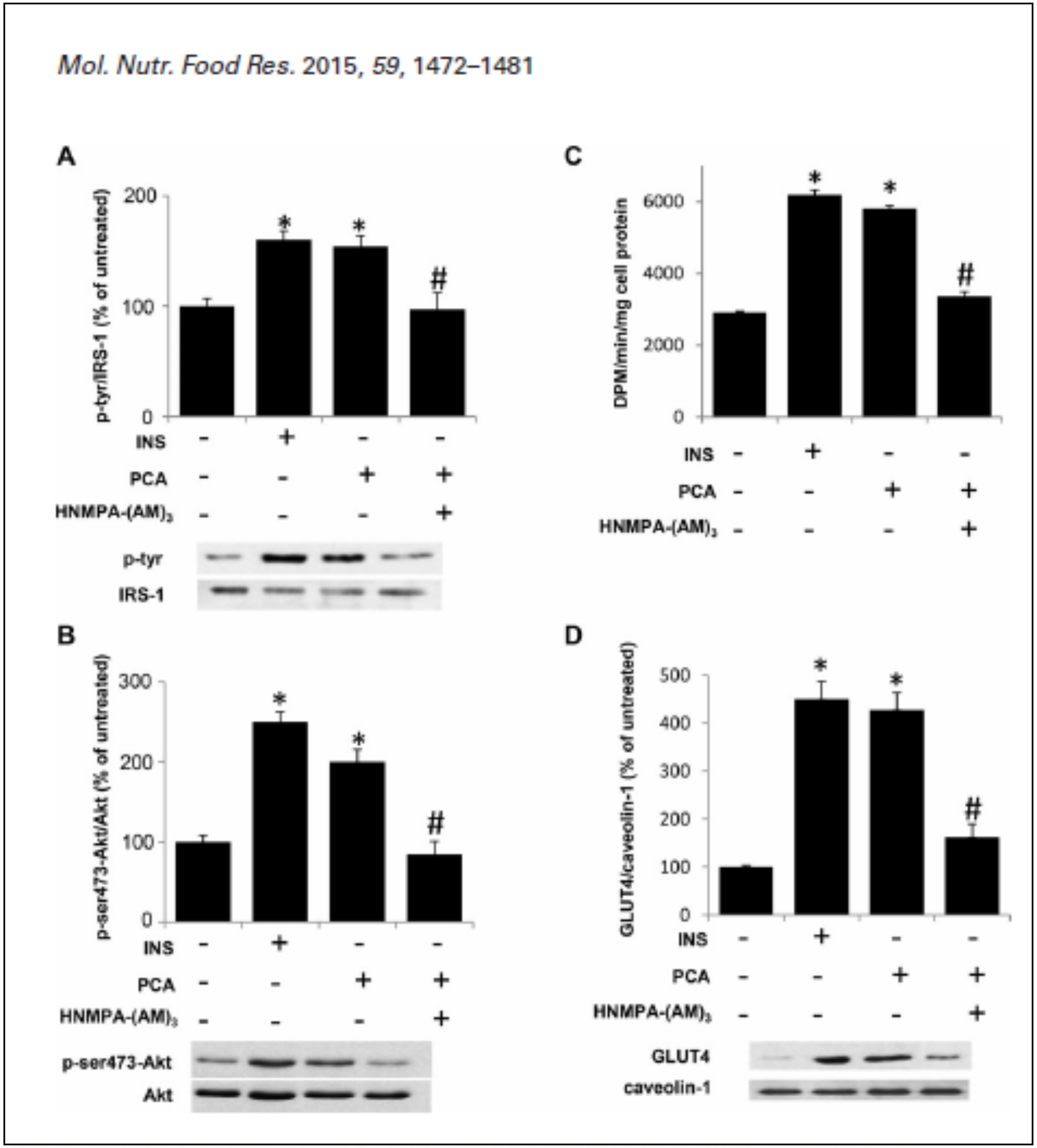




B.Scazzocchio et al. Diabetes 60:2234–2244, 2011



PCA attiva i componenti della via di segnale insulinico



PCA esercita i suoi effetti attraverso il recettore per l'insulina


Grazie per l'attenzione