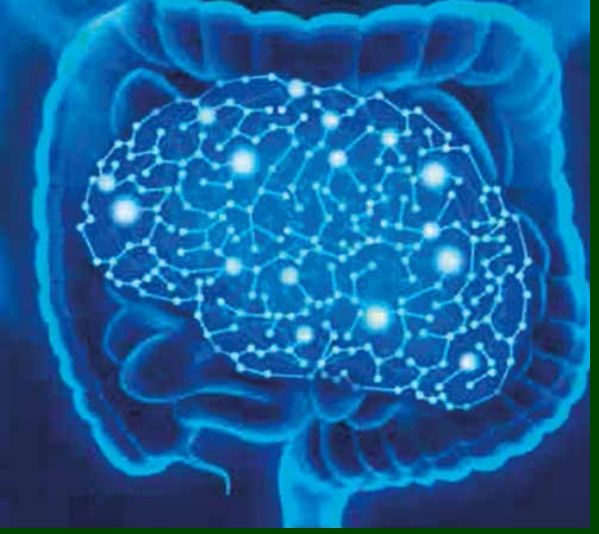

DAL BENESSERE DELL'INTESTINO
A QUELLO DELL'ORGANISMO:
QUALE RUOLO PER LA MEDICINA INTEGRATA?
11 maggio 2015, *Auditorium CAM Centro Analisi Monza*

Quali potenzialità per il resveratrolo?

Dalla sindrome metabolica alla neuroprotezione

Pietro Putignano

Responsabile Branca Medica
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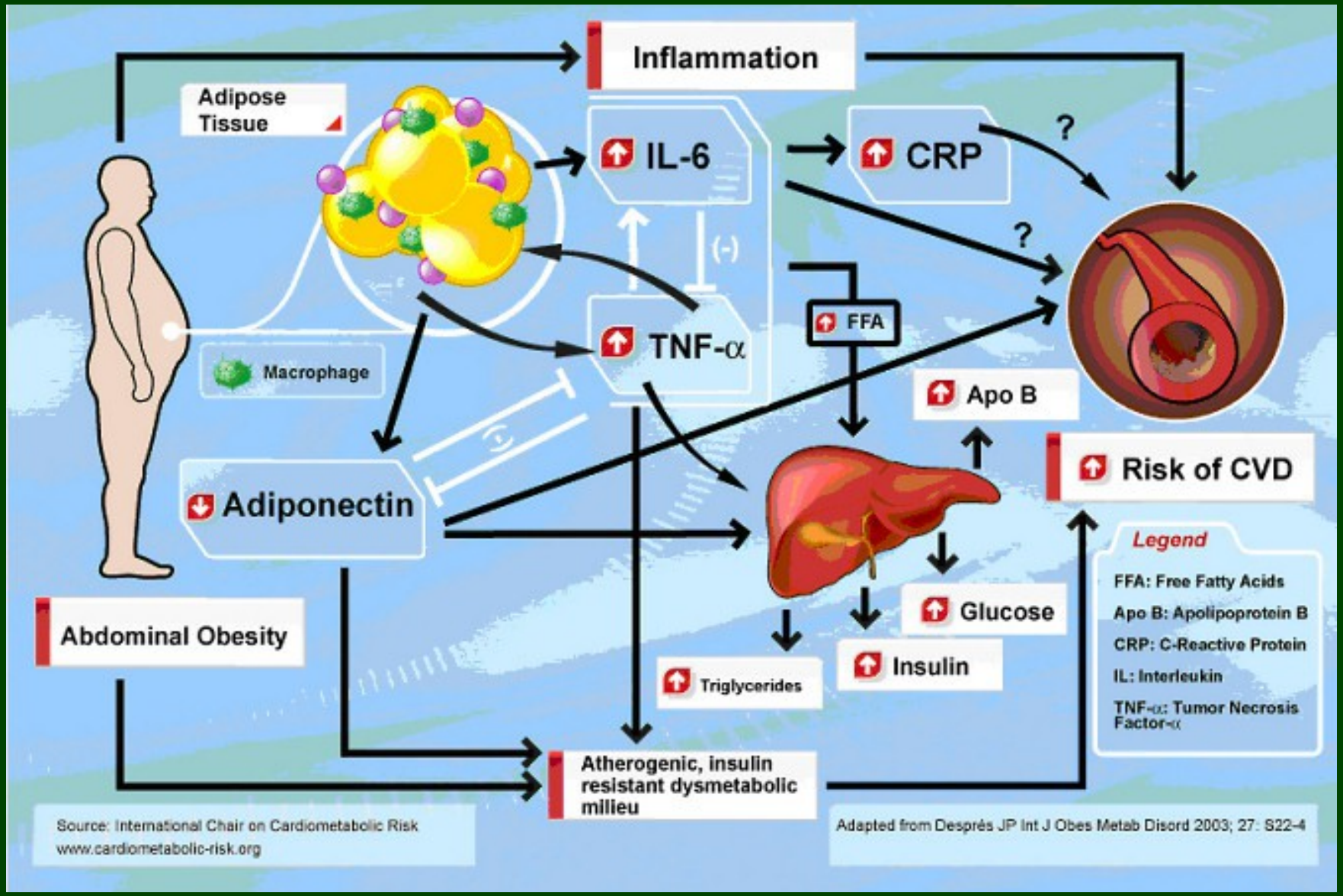
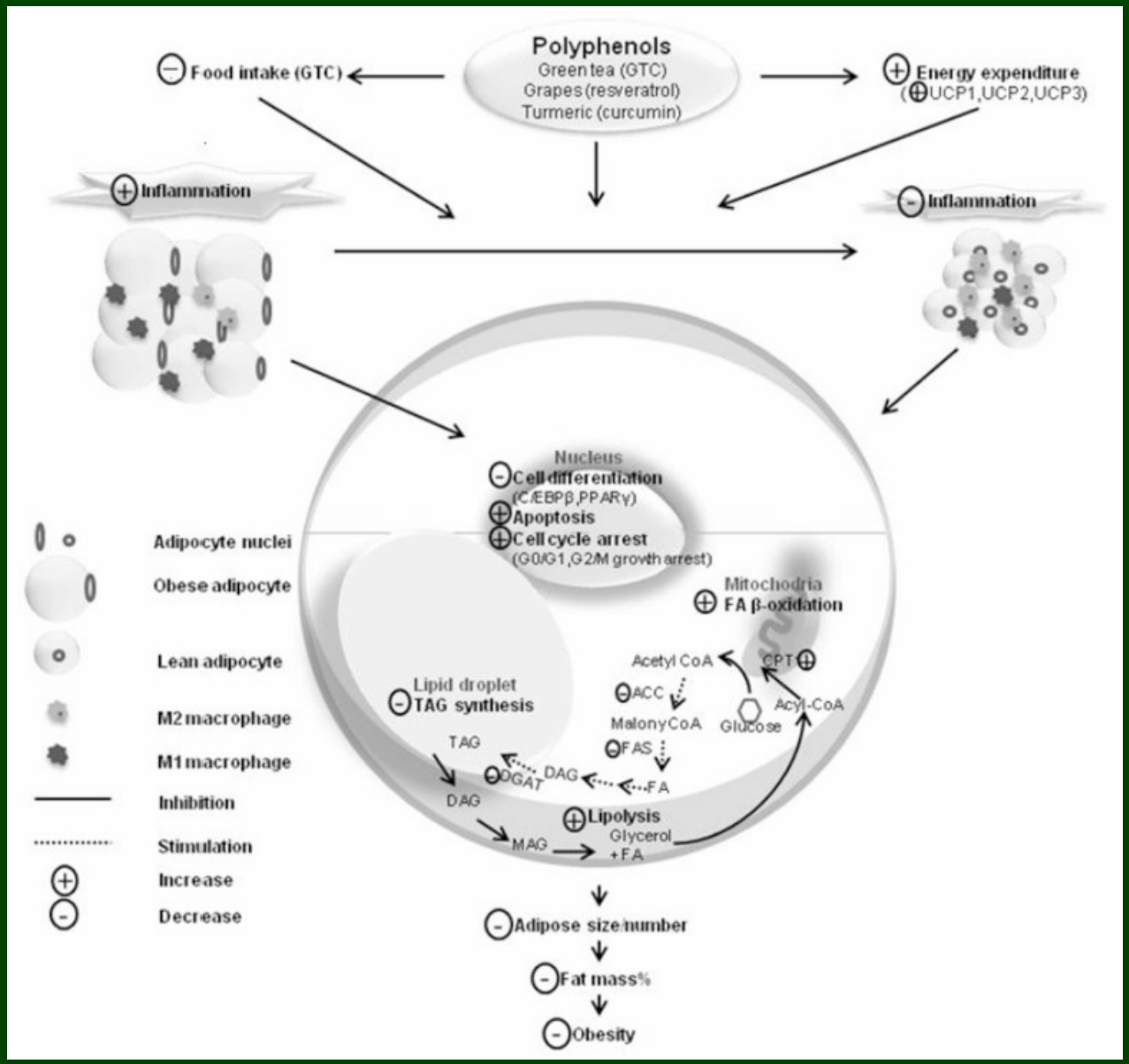
Presidio Territoriale
Ospedale San Gerardo di Monza

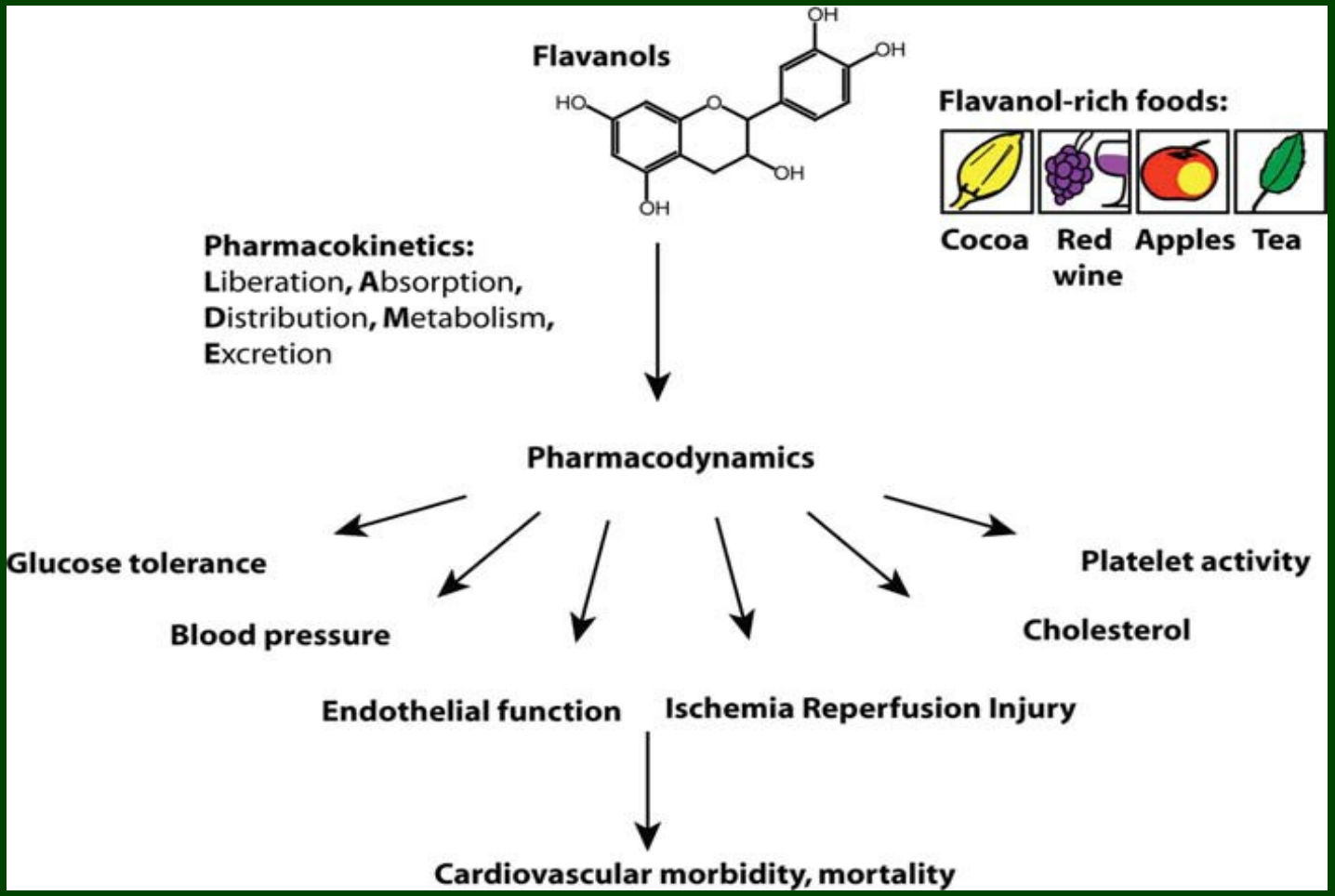
Azienda Ospedaliera
San Gerardo


Inflammation
Adipose Tissue
IL-6
CRP
?
?
(-)
TNF-α
FFA
Macrophage
Apo B
Risk of CVD
Adiponectin
(-)
Abdominal Obesity
Glucose
Insulin
Triglycerides
Atherogenic, insulin resistant dysmetabolic milieu
Legend
FFA: Free Fatty Acids
Apo B: Apolipoprotein B
CRP: C-Reactive Protein
IL: Interleukin
TNF-α: Tumor Necrosis Factor-α
Source: International Chair on Cardiometabolic Risk
www.cardiometabolic-risk.org
Adapted from Després JP Int J Obes Metab Disord 2003; 27: S22-4

Effetto dei polifenoli nell'obesità



Effetti cardiovascolari dei polifenoli



Heiss et al Eur Heart J 2010

Il resveratrolo

Physiol Rev
84: 1381–1478, 2004; 10.1152/physrev.00047.2003.

Role of Oxidative Modifications in Atherosclerosis

ROLAND STOCKER AND JOHN F. KEANEY, JR.

Centre for Vascular Research, University of New South Wales, and Department of Haematology, Prince of Wales Hospital, Sydney, New South Wales, Australia; and Whitaker Cardiovascular Institute, Evans Memorial Department of Medicine, Boston University Medical Center, Boston, Massachusetts

Stocker, Roland, and John F. Keaney, Jr. Role of Oxidative Modifications in Atherosclerosis. *Physiol Rev* 84: 1381–1478, 2004; 10.1152/physrev.00047.2003.—This review focuses on the role of oxidative processes in atherosclerosis and its resultant cardiovascular events. There is now a consensus that atherosclerosis represents a state of heightened oxidative stress characterized by lipid and protein oxidation in the vascular wall. The oxidative modification hypothesis of atherosclerosis predicts that low-density lipoprotein (LDL) oxidation is an early event in atherosclerosis and that oxidized LDL contributes to atherogenesis. In support of this hypothesis, oxidized LDL can support foam cell formation in vitro, the lipid in human lesions is substantially oxidized, there is evidence for the presence of oxidized LDL in vivo, oxidized LDL has a number of potentially proatherogenic activities, and several structurally unrelated antioxidants inhibit atherosclerosis in animals. An emerging consensus also underscores the importance in vascular disease of oxidative events in addition to LDL oxidation. These include the production of reactive oxygen and nitrogen species by vascular cells, as well as oxidative modifications contributing to important clinical manifestations of coronary artery disease such as endothelial dysfunction and plaque disruption. Despite these abundant data however, fundamental problems remain with implicating oxidative modification as a (requisite) pathophysiologically important cause for atherosclerosis. These include the poor performance of antioxidant strategies in limiting either atherosclerosis or cardiovascular events from atherosclerosis, and observations in

Arachis hypogea
Peanut

Morus rubra
Mulberry

Vitis vinifera
Grapes

Veratrum grandiflorum
White hellebore

Vaccinum sp.
Blueberry

Vaccinum sp.
Cranberry

Cassia sp.
Legumes

Artocarpus sp.
Jackfruit

Polygonum cuspidatum
Ko-jo-Kon (Japanese)

Rheum rhaponticum
Rheum

Eucalyptus

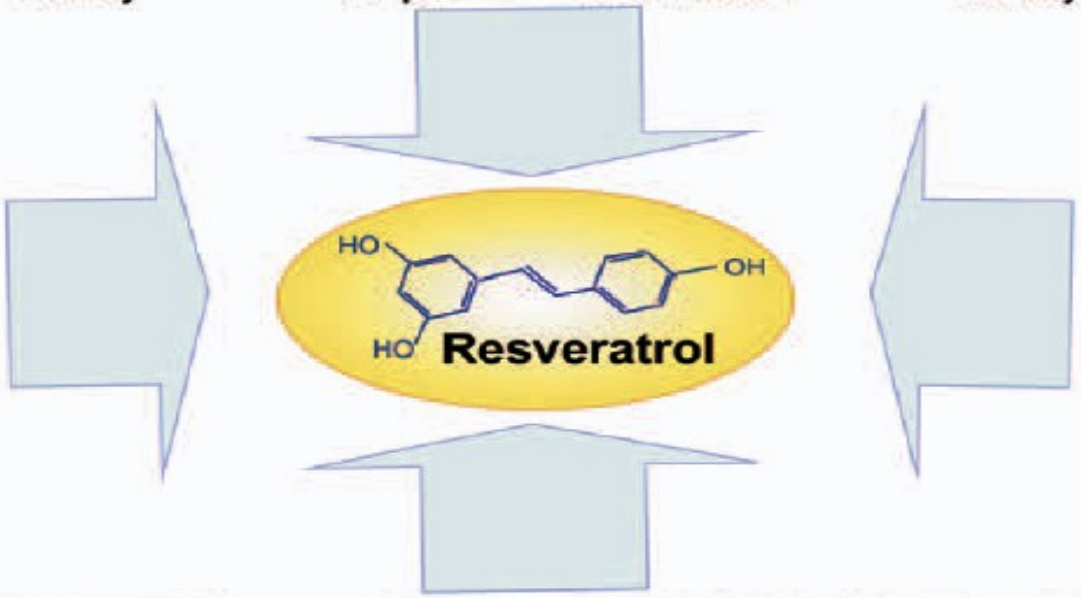
Gnetum montanum

Picea sp.
Spruce

Bauhinea sp.

Pinus sylvestris
Scots pine

Veratrum sp.
Corn lily



Amount of Resveratrol	Amount required to be equivalent	
		
	Red Wine	White Wine
10 mg	10 glasses (1500 ml)	40 glasses (6000 ml)

45 kg!

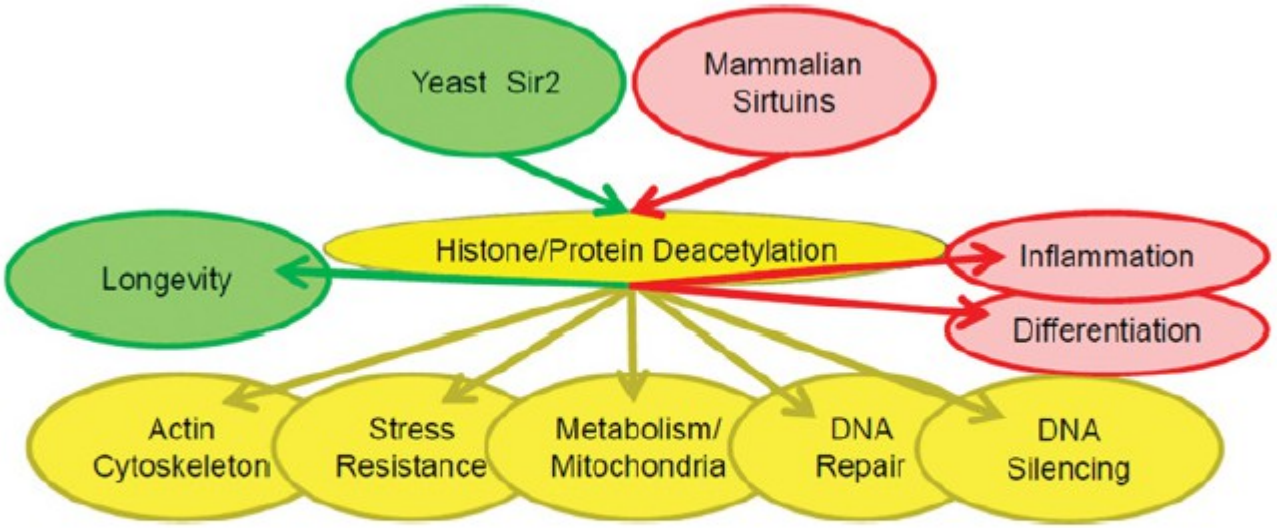


Figure 1 Common functions of yeast Sir2 and mammalian sirtuins

Sir2 and mammalian sirtuins deacetylate histones and various other proteins and affect physiological functions, many of which are common to both yeast and mammalian cells (yellow arrows). Green and red arrows indicate Sir2-specific and sirtuin-specific functions respectively.

effector	target	modulation	biological function
SIRT1	PPARγ	decrease activity	adipogenesis ↓
SIRT2	FOXO1	increase activity	adipogenesis ↓
SIRT1	SREBPs	increase ubiquitination	lipogenesis /cholesterogenesis ↓
SIRT1	PGC1α	increase activity	fatty acid oxidation ↑
SIRT1	PPARα	increase activity	fatty acid oxidation ↑
SIRT3	LCAD	increase activity	fatty acid oxidation ↑

Sirtuins and lipid metabolism

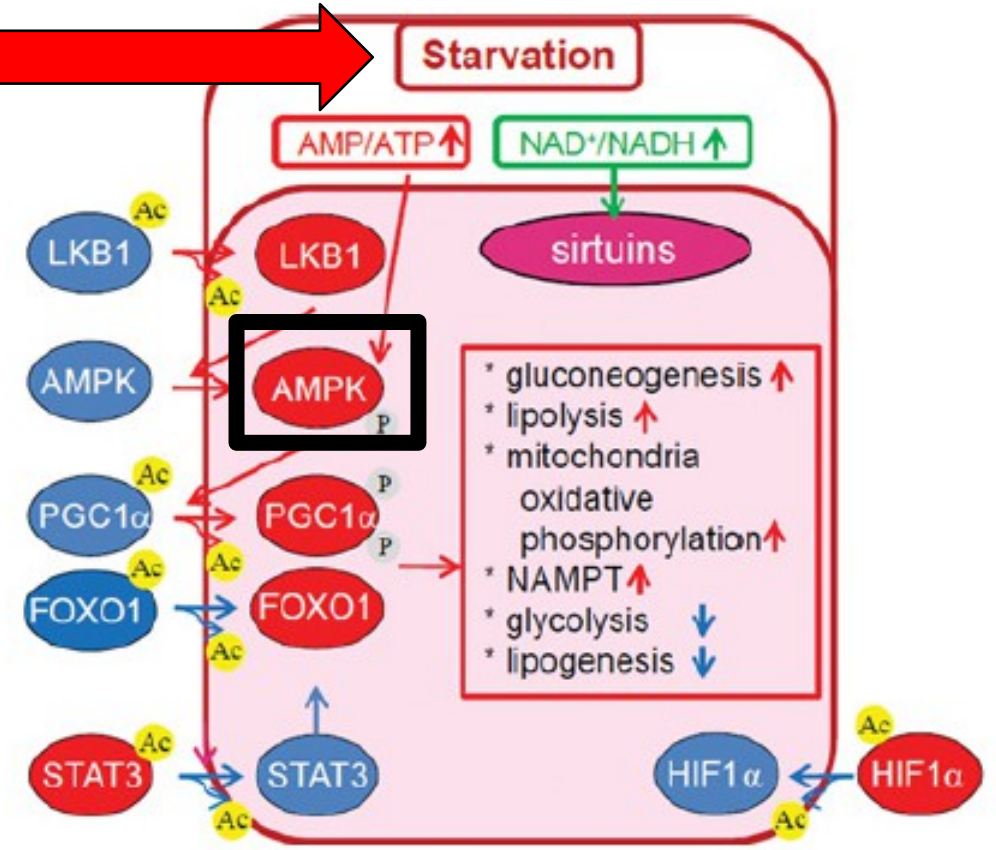
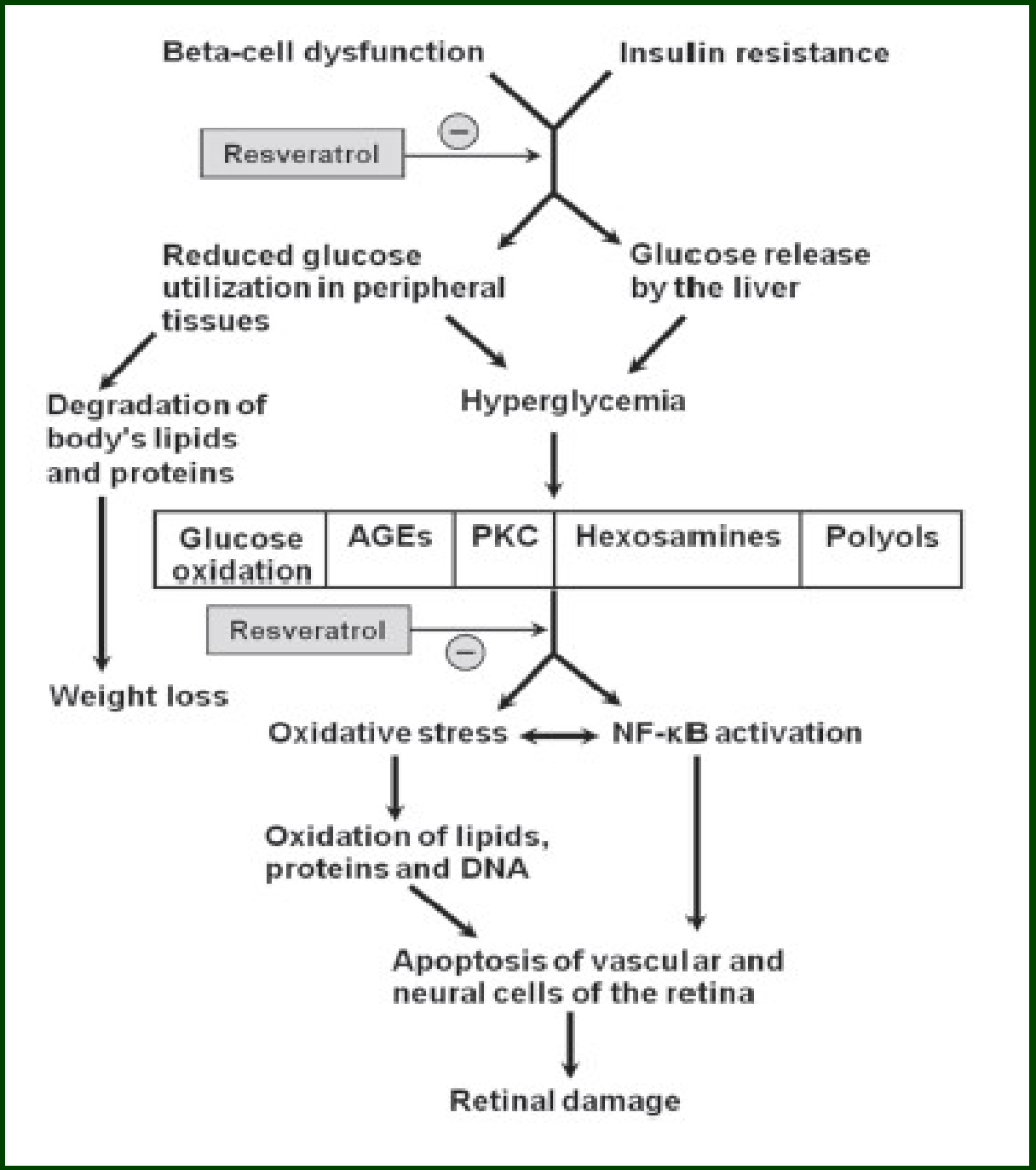


Figure 4 Metabolic functions of sirtuins

Starvation increases the SIRT1, AMP/ATP and NAD^+/NADH levels, resulting in activation of the LKB1/AMPK/PGC-1α pathway. SIRT3 also activates the pathway by LKB1 deacetylation. Red, active state; blue, inactive state; Ac, an acetyl-lysine residue; P, a phosphorylated residue.


Beta-cell dysfunction
Insulin resistance
Resveratrol
Reduced glucose utilization in peripheral tissues
Glucose release by the liver
Degradation of body's lipids and proteins
Hyperglycemia
Glucose oxidation
AGEs
PKC
Hexosamines
Polyols
Resveratrol
Weight loss
Oxidative stress
NF-κB activation
Oxidation of lipids, proteins and DNA
Apoptosis of vascular and neural cells of the retina
Retinal damage

Am J Cardiovasc Dis 2011;1(1):38-47
www.AJCD.us /ISSN: 2160-200X/AJCD1104001

Review Article

Cardioprotection by resveratrol: a review of effects/targets in cultured cells and animal tissues

Joseph M Wu[1], Tze-chen Hsieh[1], Zhirong Wang[2]

OPEN ACCESS Freely available online

PLOS | ONE

Chronic Resveratrol Treatment Protects Pancreatic Islets against Oxidative Stress in db/db Mice

Young-Eun Lee[1☯], Ji-Won Kim[1☯], Eun-Mi Lee[1], Yu-Bae Ahn[1], Ki-Ho Song[1], Kun-Ho Yoon[1], Hyung-Wook Kim[2], Cheol-Whee Park[2], Guolian Li[3], Zhenqi Liu[3], Seung-Hyun Ko[1]*

Chang *et al. Journal of Biomedical Science* 2011, **18**:47
http://www.jbiomedsci.com/content/18/1/47

NSC
The cost of publication in *Journal of Biomedical Science* is borne by the National Science Council, Taiwan

JBS JOURNAL OF BIOMEDICAL SCIENCE

RESEARCH Open Access

Resveratrol retards progression of diabetic nephropathy through modulations of oxidative stress, proinflammatory cytokines, and AMP-activated protein kinase

Chih-Chun Chang[1], Chieh-Yu Chang[1], Yang-Tzu Wu[1], Jiung-Pang Huang[1], Tzung-Hai Yen[2] and Li-M

Resveratrol improves diabetic retinopathy possibly through oxidative stress – nuclear factor κB – apoptosis pathway

Farhad Ghadiri Soufi[1], Daryoush Mohammad-nejad[2], Hamid Ahmadieh[3]

Cell Metabolism
Article

Calorie Restriction-like Effects of 30 Days of Resveratrol Supplementation on Energy Metabolism and Metabolic Profile in Obese Humans

Silvie Timmers,[1,2,8] Ellen Konings,[2,8] Lena Bilet,[2] Riekelt H. Houtkooper,[5] Tineke van de Weijer,[2] Gijs H. Goossens,[2] Joris Hoeks,[2] Sophie van der Krieken,[2] Dongryeol Ryu,[5] Sander Kersten,[6] Esther Moonen-Kornips,[2] Matthijs K.C. Hesselink,[3] Iris Kunz,[7] Vera B. Schrauwen-Hinderling,[4] Ellen E. Blaak,[2] Johan Auwerx,[5] and Patrick Schrauwen[1,2,*]

[1]Top Institute Food and Nutrition (TIFN), 6700 Wageningen, The Netherlands
[2]Department of Human Biology
[3]Department of Human Movement Sciences
[4]Department of Radiology
NUTRIM School for Nutrition, Toxicology and Metabolism, Maastricht University Medical Center, 6200 Maastricht, The Netherlands
[5]Laboratory for Integrative and Systems Physiology, Ecole Polytechnique Fédérale de Lausanne (EPFL), 1015 Lausanne, Switzerland
[6]Nutrition, Metabolism, and Genomics Group, Division of Human Nutrition, Wageningen University, 6700 Wageningen, The Netherlands
[7]DSM Nutritional Products Ltd., 4303 Kaiseraugst, Switzerland
[8]These authors contributed equally to this work
*Correspondence: p.schrauwen@maastrichtuniversity.nl
DOI 10.1016/j.cmet.2011.10.002

healthy, obese men
placebo and 150 mg/day resveratrol
randomized double-blind crossover study for 30 days

Resveratrol significantly:

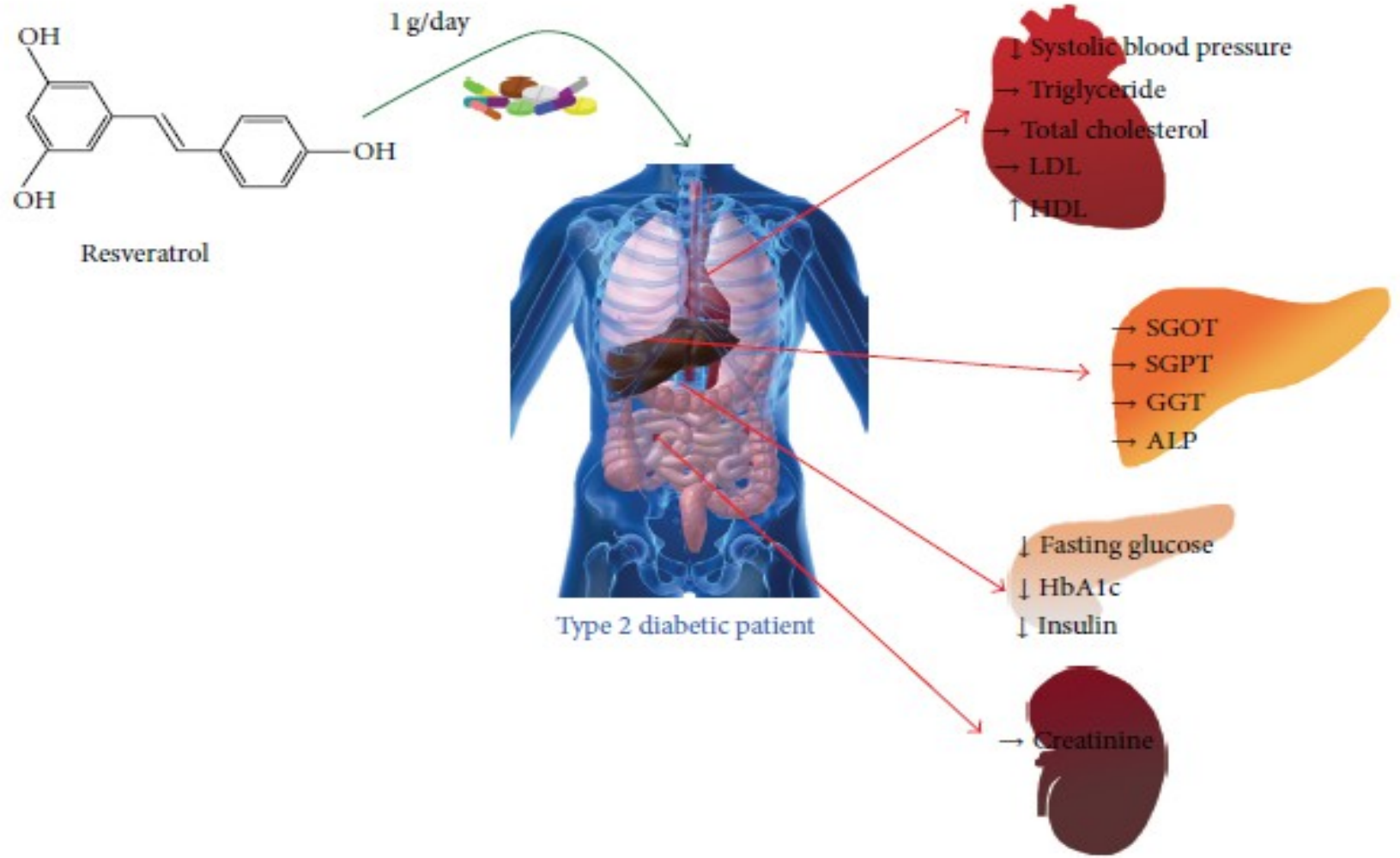
reduced sleeping and resting metabolic rate
activated AMPK,
increased SIRT1 and PGC-1α protein levels
increased citrate synthase activity without change in mitochondrial content
improved muscle mitochondrial respiration on a fatty acid-derived substrate
elevated intracellular lipid levels
decreased intrahepatic lipid content
decreased circulating glucose
decreased triglycerides
reduced inflammatory interleuchins
reduced alanine-aminotransferase and inflammation markers
dropped Systolic blood pressure
reduced HOMA index improved after resveratrol

30 days of resveratrol supplementation induces metabolic changes in obese humans, mimicking the effects of calorie restriction

Research Article

Antihyperglycemic Effects of Short Term Resveratrol Supplementation in Type 2 Diabetic Patients

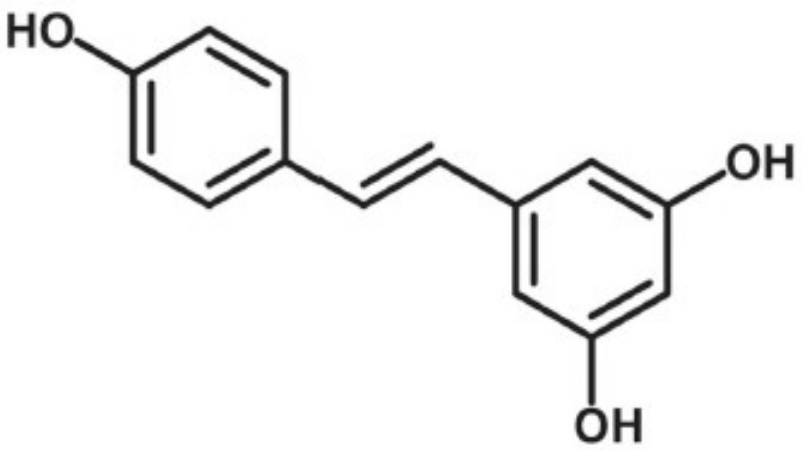
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 851267, 11 pages



	Control/placebo group			Intervention/resveratrol group		
	Baseline	After 45 days	*P* value	Baseline treatment	After treatment	*P* value
Body weight (kg)	76.60 ± 14.27	76.60 ± 14.16	0.809	74.26 ± 11.39	74.48 ± 11.34	0.712
BMI (kg/m^2)	27.83 ± 4.21	27.69 ± 4.15	0.332	27.05 ± 3.13	27.16 ± 3.13	0.395
Systolic blood pressure (mmHg)	129.31 ± 15.16	130.68 ± 13.21	0.147	129.03 ± 14.91	121.45 ± 10.26	<0.0001*
Diastolic blood pressure (mmHg)	78.58 ± 15.39	81.55 ± 5.84	0.279	76.93 ± 19.54	78.54 ± 6.35	0.169
Fasting glucose (mg/dL)	151.24 ± 51.52	161.13 ± 53.16	0.002*	175.74 ± 49.63	140.80 ± 39.74	<0.0001*
Insulin (μIU/mL)	9.04 ± 5.35	8.77 ± 4.16	0.642	10.20 ± 4.33	5.37 ± 2.62	<0.0001*
HbA1c	8.30 ± 1.43	8.50 ± 2.46	0.764	8.6 ± 1.390	7.60 ± 1.32	<0.0001*
HOMA-IR	3.20 ± 2.37	3.43 ± 1.83	0.423	4.61 ± 2.77	1.91 ± 1.17	<0.0001*
HOMA-β	36.13 ± 8.45	35.68 ± 7.95	0.039	32.15 ± 5.32	25.80 ± 4.43	0.009*
Triglyceride (mg/dL)	134.69 ± 45.61	123.13 ± 43.27	0.145	160.1 ± 58.96	142.28 ± 52.61	0.051
Total cholesterol (mg/dL)	168 ± 41.97	175.34 ± 41.31	0.424	203.61 ± 52.70	192.28 ± 53.13	0.156
HDL-cholesterol (mg/dL)	41.73 ± 9.52	39.69 ± 10.83	0.133	41.40 ± 8.35	46.15 ± 8.40	0.001*
LDL-cholesterol (mg/dL)	107.95 ± 31.67	117.18 ± 29.88	0.003*	134.04 ± 36.18	122.71 ± 38.19	0.106
SGOT (IU/L)	24.0 ± 5.47	25.0 ± 6.71	0.212	26.0 ± 5.87	26.0 ± 7.56	0.837
SGPT (IU/L)	19.44 ± 8.79	21.65 ± 8.67	0.202	21.45 ± 7.91	22.61 ± 9.74	0.365
GGT (IU/L)	30.82 ± 17.79	29.93 ± 17.01	0.545	32.12 ± 15.32	33.38 ± 17.92	0.441
ALP (IU/L)	169.37 ± 52.63	189.41 ± 48.38	0.001*	185.29 ± 59.35	190.64 ± 47.55	0.372
Creatinine (mg/dL)	0.92 ± 0.24	0.97 ± 0.25	0.281	0.96 ± 0.24	0.90 ± 0.21	0.098

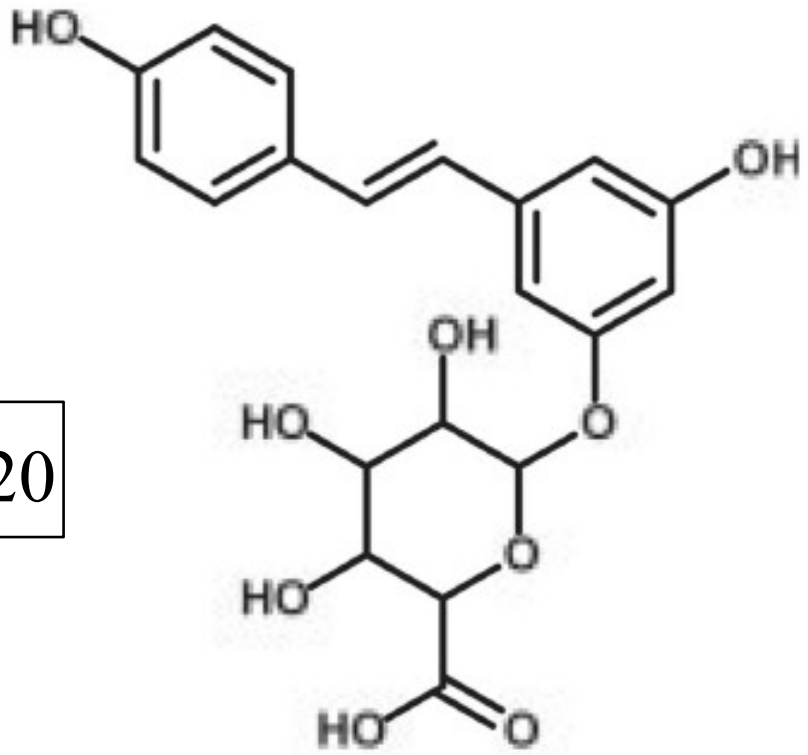

Restrizione calorica
RESVERATROLO
Attivazione SIRTUINE
AMPK
Insulino-sensibilità
Lipolisi
Insulino-sensibilità
SIRT-1

Resveratrol



1 : 20

Resveratrol-3-O-β-D-glucuronide



Published in final edited form as:
Mol Nutr Food Res. 2011 August ; 55(8): 1169–1176. doi:10.1002/mnfr.201100117.

Enhancing the bioavailability of resveratrol by combining it with piperine

Jeremy J. Johnson[1], **Minakshi Nihal**[2], **Imtiaz A. Siddiqui**[2], **Cameron O. Scarlett**[3], **Howard H. Bailey**[4,5], **Hasan Mukhtar**[2,5], and **Nihal Ahmad**[2,5]

[1]Department of Pharmacy Practice, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, USA

The Journal of Nutrition
Nutrient Physiology, Metabolism, and Nutrient-Nutrient Interactions

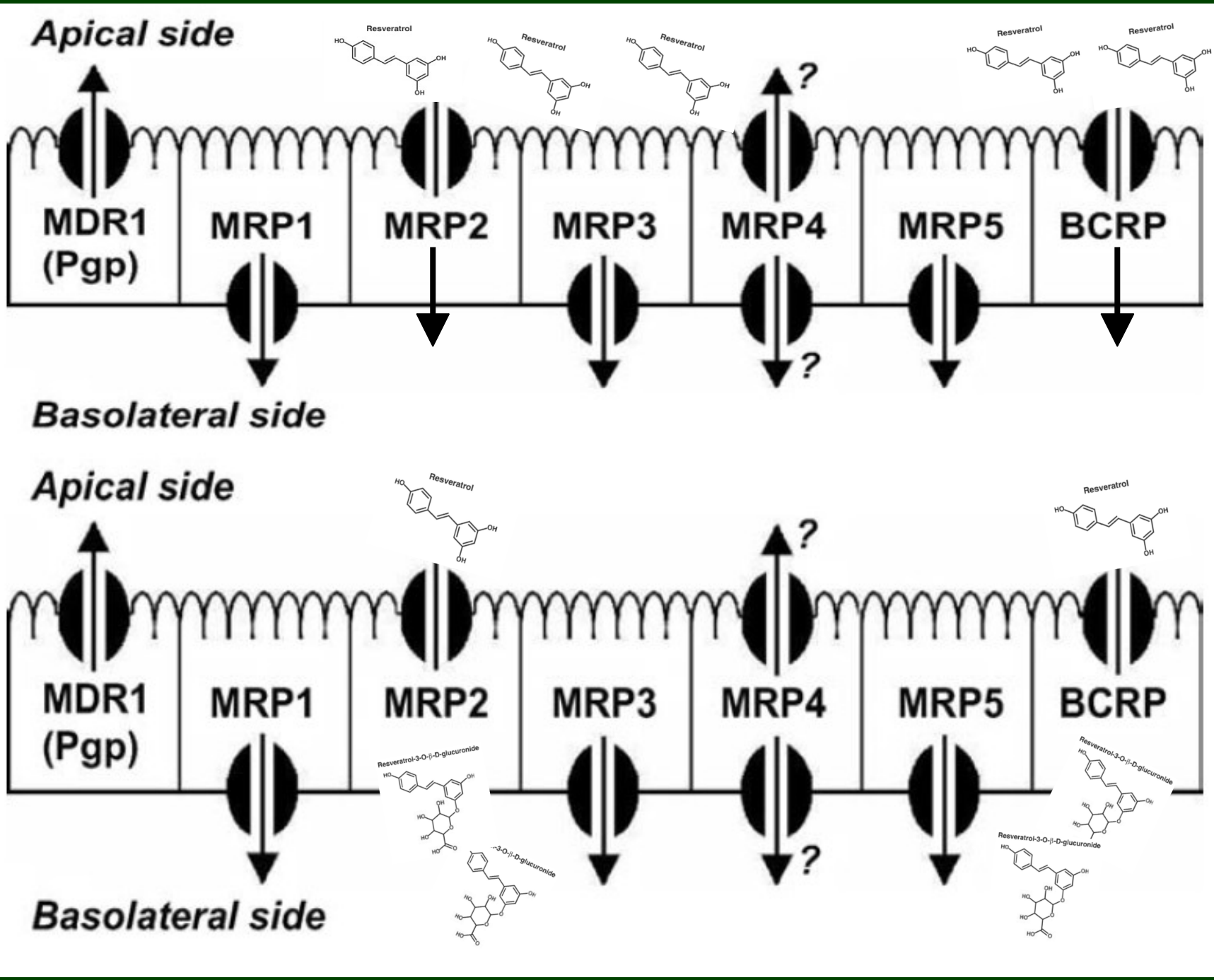
Multidrug Resistance Proteins Restrain the Intestinal Absorption of *trans*-Resveratrol in Rats[1–3]

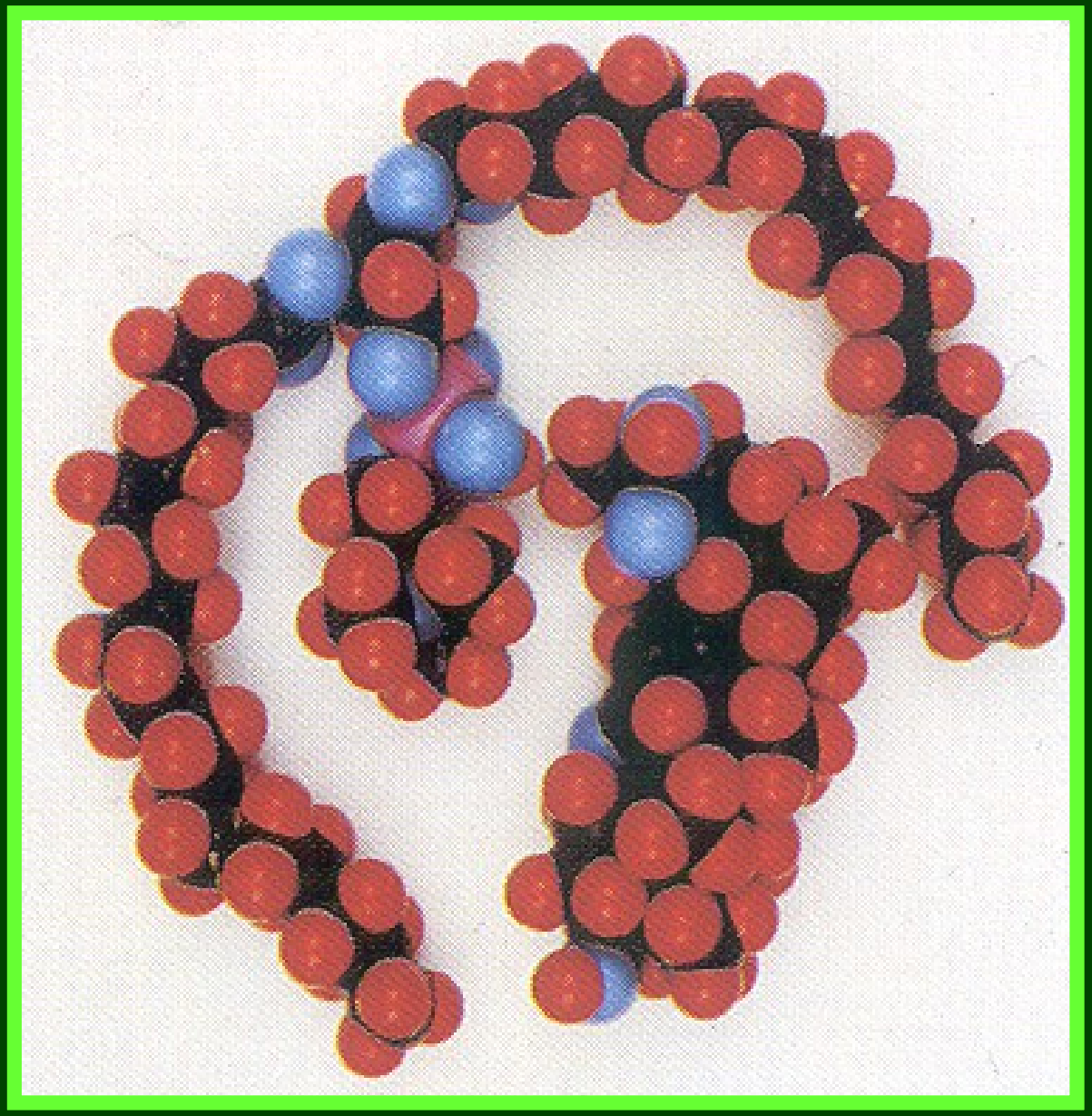
M. Emília Juan,[4]* Eulalia González-Pons,[4] and Joana M. Planas

Departament de Fisiologia (Farmàcia) and Institut de Recerca en Nutrició i Seguretat Alimentària, Universitat de Barcelona, Barcelona E-08028, Spain

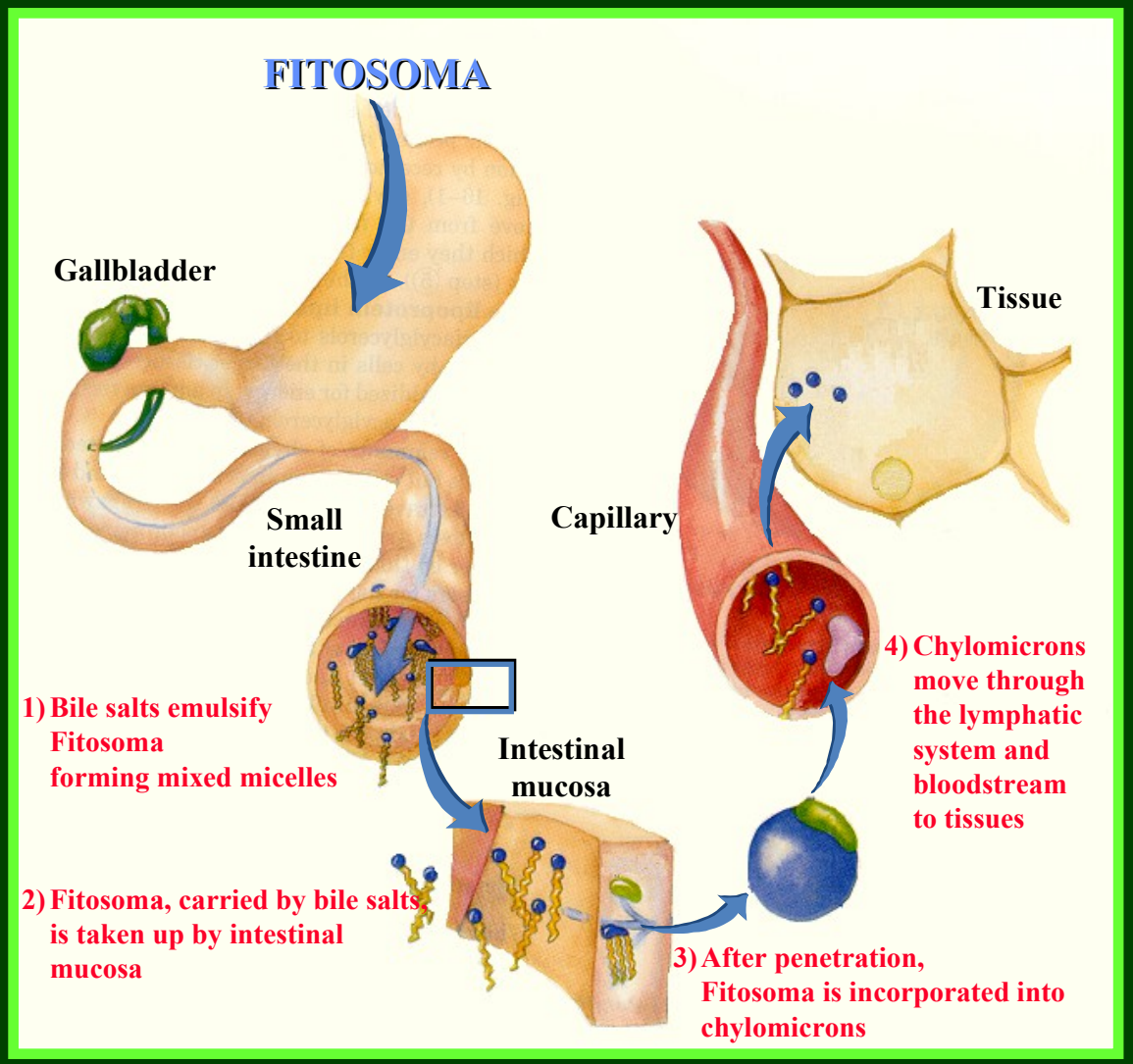
Abstract

trans-Resveratrol, a natural antioxidant, has been described as a nutraceutic compound with important beneficial effects on health, but its low oral bioavailability hinders its therapeutic activity. Here, we studied the mechanisms of apical transport of *trans*-resveratrol in enterocytes and the role of ATP-binding cassette (ABC) transporters in the secretion of resveratrol glucuronide and sulfate resulting from the rapid intracellular metabolism. An intestinal perfusion method with recirculation in vivo was used in rats. Jejunal loops were perfused with increasing concentrations of *trans*-resveratrol and results showed that its uptake occurs by simple diffusion without the participation of a mediated transport. The apparent diffusion constant was 8.1 ± 0.3 μL/(5 min·mg dry weight). The glycoprotein-P (Pgp, ABCB1), multidrug resistance-associated protein 2 (MRP2, ABCC2), and breast cancer resistance protein (BCRP, ABCG2) located in the apical membrane of enterocytes were investigated using specific inhibitors. The Pgp inhibitors verapamil (5 μmol/L) and cyclosporin A (5 μmol/L) did not affect the efflux of *trans*-resveratrol and its conjugates. The MRP2 inhibitors probenecid (2 mmol/L) and MK571 (10 μmol/L) reduced the efflux of glucuronide by 61 and 55%, respectively, and of sulfate by 43 and 28%, respectively. The BCRP inhibitor Ko143 (0.5 μmol/L) decreased the secretion of glucuronide by 64% and of sulfate by 46%. Our experiments identify MRP2 and BCRP as the 2 apical transporters involved in the efflux of resveratrol conjugates. J. Nutr. 140: 489–495, 2010.


Apical side
Resveratrol
Resveratrol
Resveratrol
Resveratrol
Resveratrol
?
MDR1
(Pgp)
MRP1
MRP2
MRP3
MRP4
MRP5
BCRP
?
Basolateral side
Apical side
Resveratrol
Resveratrol
?
MDR1
(Pgp)
MRP1
MRP2
MRP3
MRP4
MRP5
BCRP
Resveratrol-3-O-β-D-glucuronide
Resveratrol-3-O-β-D-glucuronide
Resveratrol-3-O-β-D-glucuronide
?
Basolateral side



INTESTINAL ABSORPTION OF PHYTOSOME



From : Principles of Biochemistry, by A.L. Lehninger (adapted)

RESVERATROLO: POTENZIALI MECCANISMI DI NEUROPROTEZIONE

- Protezione da stress ossidativo
- Riduzione beta amiloide (aumento della degradazione e stimolazione dell'autofagia via HEME-1)
- Riduzione insulinoresistenza
- Attivazione AMP-kinasi
- Attivazione sirtuine
- Potenziamento preconditioning post-ischemico
- Inibizione NfKb
- Riduzione citochine proinfiammatorie (inib neuroinfiammazione)
- Inibizione formazione AGE (inib glicazione membrane biologiche)
- Riduzione dell'apoptosi
- Riduzione FRCV (PA, colesterolo LDL, trigliceridi, Insulina)
- Aumento dell'ossidazione neuronale degli acidi grassi (maggiore efficienza energetica del neurone)


Poche aziende investono nello sviluppo clinico
Non rimborsabilità: accettazione dei costi cronici da parte del paziente e del medico
Cultura nutraceutica limitata nella classe medica
Variabilità della qualità degli estratti erbali e dell'affidabilità delle aziende del settore
Resveratrolo nell'uomo:
Il problema principale:
Bassissima biodisponibilità
Diffidenza da parte della medicina ufficiale/tradizionale
Considerati solo alternativi e non anche complementari ai farmaci
EBM e nutraceutica: qualità degli studi nell'uomo
Sicurezza:possibili interazioni farmacocinetiche con OAD, antipertensivi, statine
Farmacovigilanza e aspetti normativi

Vi ringrazio per l'attenzione !