Workshop

Protective / preventive role of bioactive food components in human health

Nutraceuticals in Cardioprotection

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Alma Mater Studiorum-University of Bologna (Italy)

Novi Sad, December 13-14, 2016

Quality of Life

WHO defines Quality of Life as individuals perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.

The concept of Health-Related Quality of Life (HRQOL) has evolved to encompass those aspects of overall QoL that can be clearly shown to affect health and is related to both chronic diseases and their risk factors

WHO defines health as "A state of complete physical, mental, and social well-being not merely the absence of disease"

World Health Organization

Well-being

The European Observatory on Health Systems and Polices definition of well-being is:

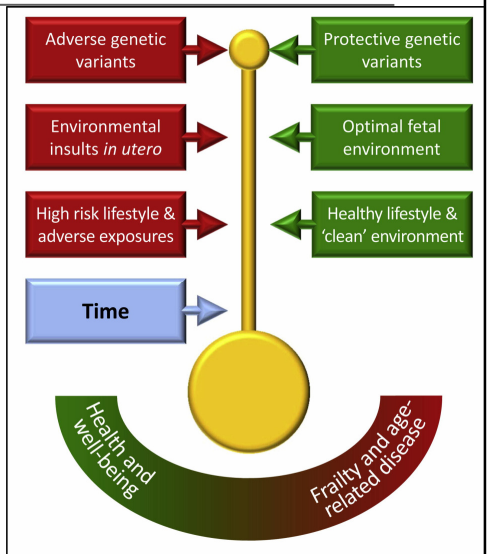
the emotional, mental, social and spiritual state that permits people to reach and maintain their personal potential in society

As age increases the role played by health tends to become more and more important until it was almost exclusively.

The health pendulum

Conceptual model of major influences which modulate the ageing trajectory and risk of development of frailty and age-related diseases.

Underpinning the "Health Pendulum" is the hypothesis that interactions between an individual's genotype and his/her environment influence the accumulation of molecular and cellular damage which is responsible for the ageing phenotype and contributes to the development of frailty and age-related diseases.



The desperate need for a definition of aging

Is aging a disease?

- NO, it is separate from age-related diseases
- NO, but it is a risk factor for age-related diseases
- **NO, it is the set of precursors of the age-related diseases**

Changes in Rankings for 15 Leading Causes of Death, 2002 and 2030

Disease or Injury	2002 Rank	2030 Ranks
Ischaemic heart disease	1	1
Cerebrovascular disease	2	2
Lower respiratory infections	3	5
HIV/AIDS	4	3
COPD	5	4
Perinatal conditions	6	9
Diarrhoeal diseases	7	16
Tuberculosis	8	23
Trachea, bronchus, lung cancers	9	6
Road traffic accidents	10	8
Diabetes mellitus	11	7
Malaria	12	22
Hypertensive heart disease	13	11
Self-inflicted injuries	14	12
Stomach cancer	15	10

Mathers CD, Loncar D. PLoS Med. 2006 Nov;3(11):442

Strategies to prevent heart disease

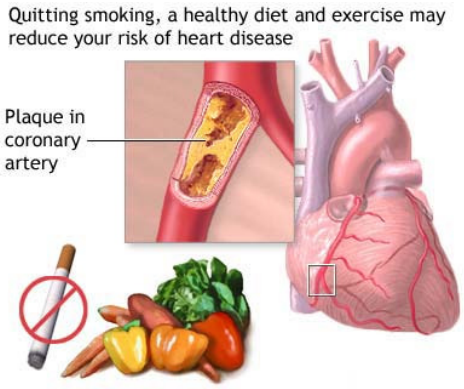
Heart disease may be a leading cause of death, but that **doesn't mean you have to accept it as your fate**.
Although you lack the power to change some risk factors such as family history, sex or age there are some key heart disease prevention steps you can take.

Don't smoke or use tobacco

Exercise for 30 minutes on most days of the week

Maintain a healthy weight

Eat a heart-healthy diet



Heart-healthy diet

Journal of Human Hypertension (2007) 21, 717–728

www.nature.com/jhh

ORIGINAL ARTICLE

Increased consumption of fruit and vegetables is related to a reduced risk of coronary heart disease: meta-analysis of cohort studies

FJ He[1], CA Nowson[2], M Lucas[2] and GA MacGregor[1]
[1]*Blood Pressure Unit, Cardiac and Vascular Sciences, St George's University of London, London, UK and*
[2]*Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Australia*

The analysis of data collected in 12 different studies, which enrolled 280000 subjects revealed that people consuming 3-5 or more than 5 servings/day had a risk reduction for coronary heart disease of 7% and 17%, respectively when compared with subjects who consumed less than 3 servings/day.

Springer European Journal of Nutrition
springer.com

Critical review: vegetables and fruit in the prevention of chronic diseases

Heiner Boeing et al. Eur J Nutr (2012) 51:637–663

For hypertension, CHD, and stroke, there is ***convincing evidence*** that increasing consumption of vegetables and fruit reduces the risk of disease.

There is ***probable evidence*** that the overall risk of cancer is inversely associated with the consumption of vegetables and fruit.

Data on dementia indicate ***possible evidence*** for a risk-reducing influence of increased vegetable and fruit consumption.

In addition, there is ***possible evidence*** that a diet with increased consumption of vegetables and fruit may prevent body weight gain. As overweight is the most important risk factor for type 2 diabetes mellitus, an increased consumption of vegetables and fruit might indirectly reduce the incidence of type 2 diabetes mellitus

Mediterranean Diet

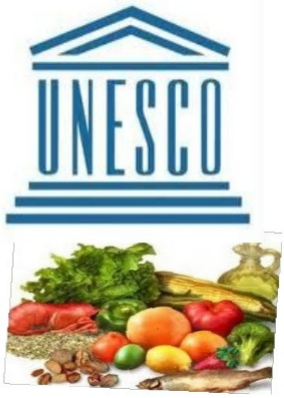
It was first publicized in 1945 by the American doctor Ancel Keys

Main characteristics: low consumption of meat and meat products, high consumption of vegetal foods rich in NUTRACEUTICAL bioactive compounds

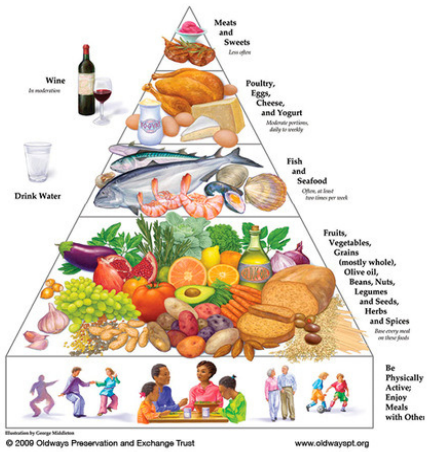
Mediterranean Diet

The Mediterranean diet involves a set of skills, knowledge, rituals, symbols and traditions concerning crops, harvesting, fishing, animal husbandry, conservation, processing, cooking, and particularly the sharing and consumption of food.

- On November 17th 2010, the **UNESCO** included the Mediterranean Diet on the Representative List of Intangible Cultural Heritage of Humanity during its meeting held in Nairobi, Kenya.



Mediterranean Diet Pyramid



Starting at the base of the pyramid, you'll find an emphasis on activity and social connections.

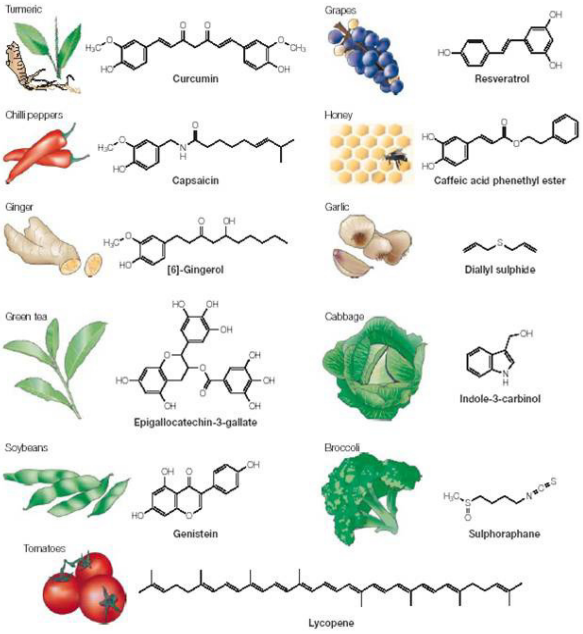
Moving upward, you'll see the core foods that you'll eat every day: whole grains, fruits, vegetables, beans, herbs, spices, nuts and healthy fats such as olive oil. Fish and seafood are typically eaten at least twice a week, and dairy foods – especially fermented dairy like yogurt and traditional cheese – are eaten frequently in moderate portions.

Eggs and occasional poultry are also part of the Mediterranean Diet, but red meat and sweets are rarely eaten. Water, and wine (for those who drink) are typical beverages

Nutraceuticals

- **Nutraceutical**, a term combining the words "**nutrition**" and "**pharmaceutical**", is a food constituent that provides health and medical benefits, including the prevention and treatment of disease
- The term nutraceutical was originally defined by Dr. Stephen L. DeFelice, founder and chairman of the Foundation of Innovation Medicine (FIM), Crawford, New Jersey (USA)

Institutions like FAO and WHO recommend a daily intake of at least 400 grams of fruits and vegetables a day, if possible in 5 different servings

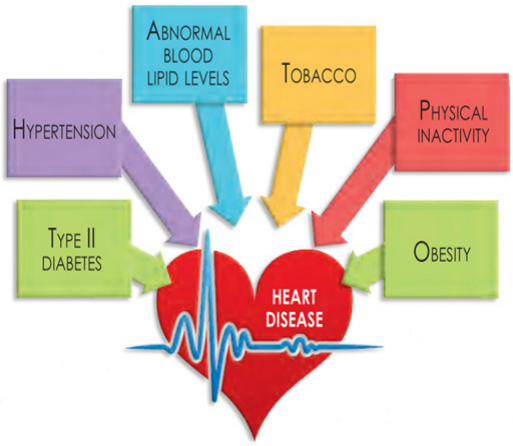


Cardiovascular diseases

More than any other disease, the etiology of cardiovascular disease reveals many risk factors that are amenable to nutraceutical intervention. Cardiovascular disease (CVD) is now the leading cause of death globally and is a growing health concern.

Lifestyle-related conditions, such as obesity, hyperlipidemia, type 2 diabetes, and hypertension, are also widespread and becoming more prevalent globally. Although the traditional cardiovascular risk factors have been extensively investigated, dietary factors are also important in the pathogenesis of CVD and may to a large degree determine CVD risk factors such as blood pressure and dyslipidaemia, but have been less extensively investigated.

Cardiovascular risk factors



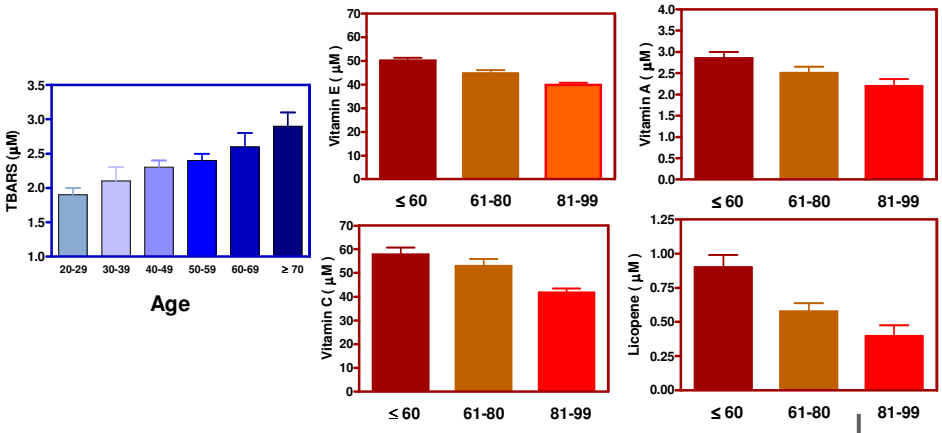
Although the traditional cardiovascular risk factors have been extensively investigated, dietary factors are also important in the pathogenesis of CVD and may to a large degree determine
CVD risk factors such as blood pressure and dyslipidaemia, but have been less extensively investigated.

Cardiovascular risk factors

Whilst epidemiological studies have identified a relationship between diet and CVD, there is still considerable scientific uncertainty about the relationship between specific dietary components and cardiovascular risk.
It has been suggested that oxidative stress is involved in the etiology of several chronic diseases including CVD, diabetes, stroke, some cancers, and neurodegenerative disorders.
Observational, prospective cohort studies suggest that a higher dietary intake or supplementation of antioxidants is associated with a lower risk of CVD and mortality, but the evidence from clinical trials is still largely negative
The conflicting results between the protective effects of antioxidants as part of dietary intake and the lack of effectiveness of single antioxidant supplementation in trials has led to a focus on whole foods or modified diets as protective against CVD.

Plasma antioxidant levels

Elderly people had lower circulating antioxidants and higher lipid peroxide levels than younger subjects, suggesting that advanced age is associated with systemic oxidative status



Mecocci et al. Free Radic. Biol. Med., 2000

RISTOMED
New e-Services for a Dietary Approach to the Elderly

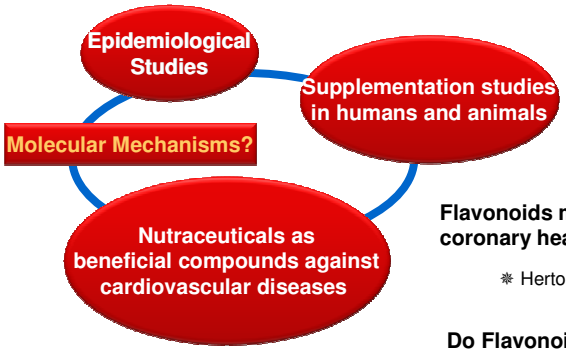
SEVENTH FRAMEWORK PROGRAMME

RISTOMED
New e-Services for a Dietary Approach to the Elderly

…The literature highlights that the ageing process and the pathogenesis of age-related diseases are influenced by oxidative stress, inflammation status, and gut microbiota. Thus, an healthy personalized dietetic approach specifically formulated for elderly people, with a defined pattern of nutrients, may represent a key strategy to improve the ageing process considering functional foods and/or nutraceutical supplements

The project allowed to analyse TAA, SOD, CAT, GR, GST, GPx activities and GSH levels in three hundred elderly European people (average age 70.43±3.9 y)

What we have yet to discover?



Flavonoids may reduce the risk of death from coronary heart disease and cancer

- Hertog et al. (2003) Lancet.

Do Flavonoids Reduce Cardiovascular Disease Incidence or Mortality in US and European Populations?

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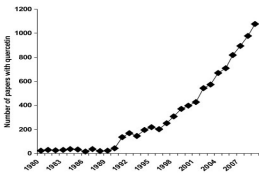
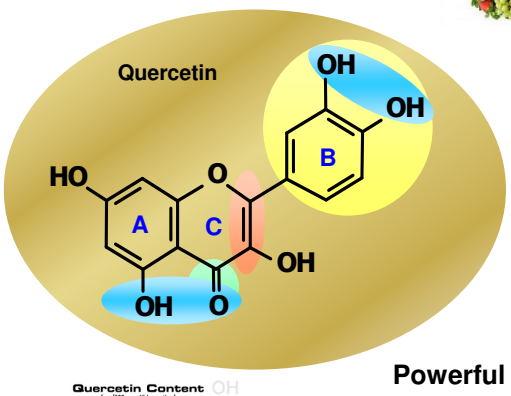
- Peterson et al. (2012) Nutr. Rev.

The "Quercetin" case



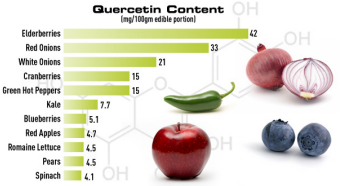


B-ring catechol group

Un-saturation in the C-ring

Carbonyl group

Presence of transition metal ion binding functions



Powerful scavenger of ROS and RNS:

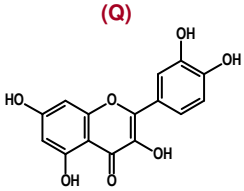
Fenton systems: Fe^{2+} Cu^{+} and peroxide
$ONOO^{-}$ and HOCl

Metal chelators

Major metabolites present in human plasma following Q ingestion

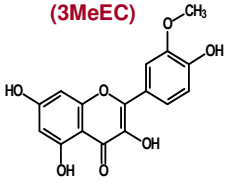
Quercetin

(Q)



3′-*O*-Me-quercetin

(3MeEC)



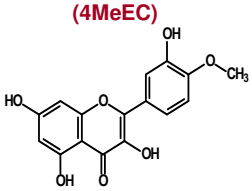
0.1-5 **0.9-5**

Plasma concentration µM

0.9-2 **0.1-3**

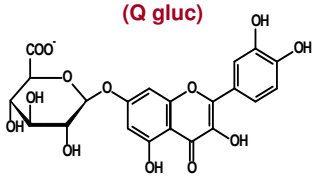
4′-*O*-Me-quercetin

(4MeEC)



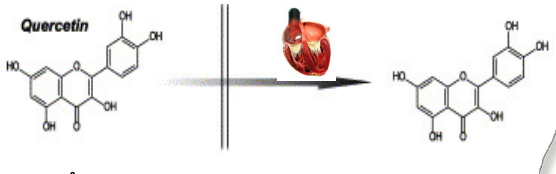
Quercetin-7-*O*-β-D-glucuronide

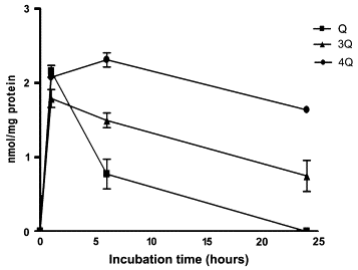
(Q gluc)

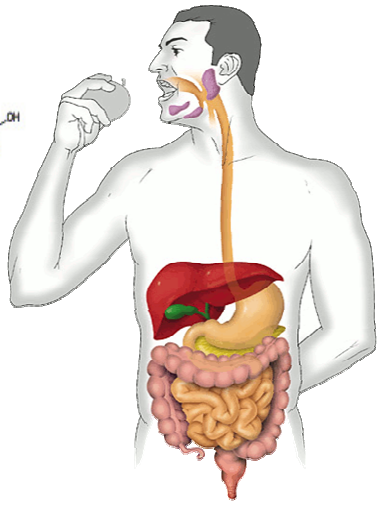


Hrelia and Angeloni. In: Bioactive Food as Dietary Interventions for CVD, pp. 217-228. San Diego: Academic Press.

Bioavailability



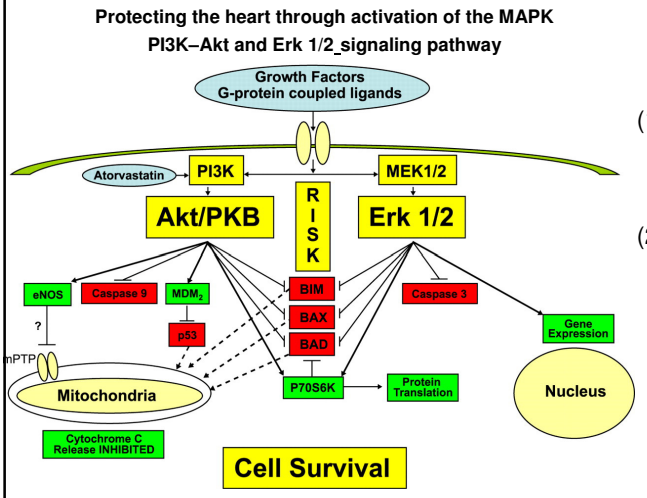




Uptake/association of quercetin, 3′-*O*-methyl quercetin, and 4′-*O*-methyl quercetin with H9c2 cells

C. Angeloni et al. Biochimie 89: 73 (2007)

Mechanism of action



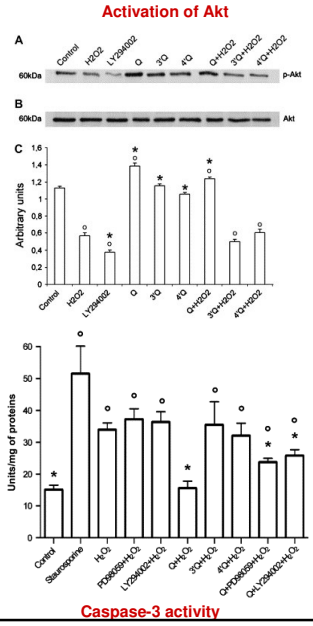
Signalling through the PI3K–Akt and/or the MEK1/2–Erk 1/2 cascades results in:

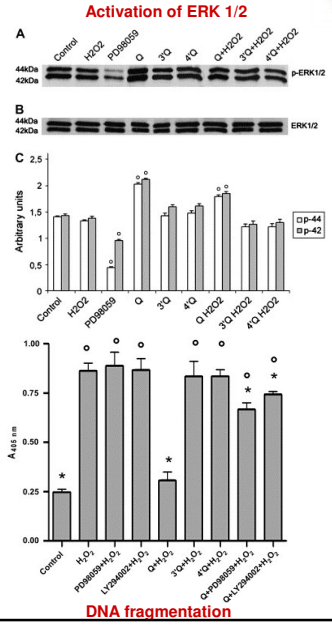
(1) phosphorylation and inactivation of caspases 3 and 9, which inhibits apoptosis;

(2) phosphorylation and inactivation of the pro-apoptotic proteins BIM, BAX, BAD and p53, one consequence of which is to prevent the release of mitochondrial cytochrome *c* in response to an apoptotic stimulus

Hausenloy et al.Cardiovasc Res 61:448 (2004)

Possible Mechanisms of Q Bioactivity

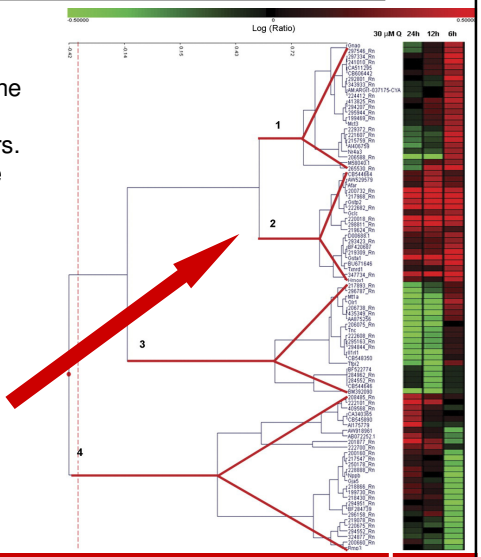




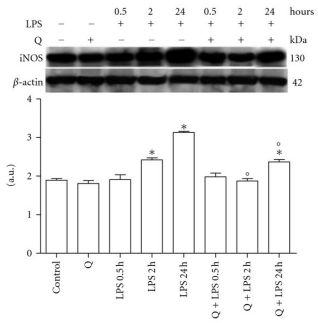
Q modulates gene expression profile in cardiomyocytes

Hierarchical clustering display of data in cardiomyocytes treated with Q based on the significant 91 genes. Each gene is represented by a single row of colored bars. The red color indicates upregulation of the gene expression, and the green color denotes the downregulation of the gene expression compared with the controls.

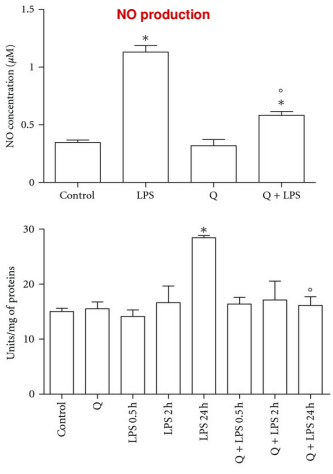
Cluster 2: genes critically involved in antioxidant/detoxification mechanisms related to cell survival: NQO1, HO-1, TR, GSTa3, and GSTp2 underlying a common functional regulation



Q reduces inflammatory responses in cardiac cells



Effect of Q on iNOS expression in LPS-stimulated cardiomyocytes

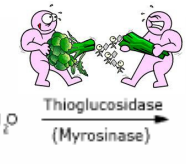


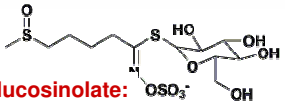
Proposed mechanisms underlying the cardioprotective effects of Q

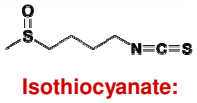
Q exerts its cardioprotective effects via:

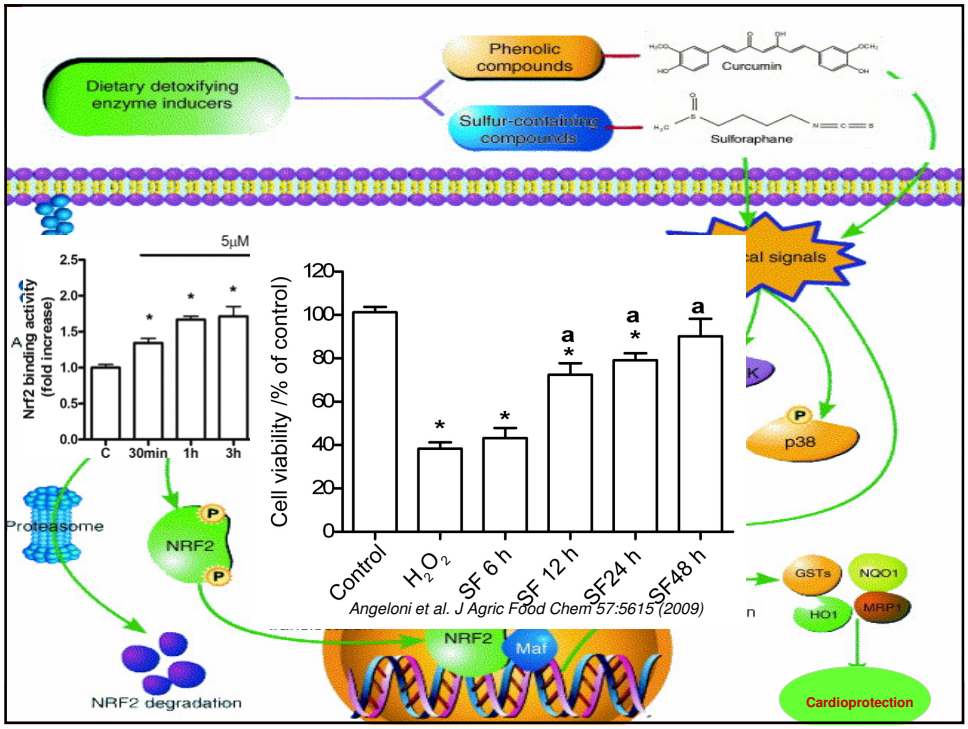
- its well know antioxidant activity
- through the modulation of intracellular signalling pathways (Akt, ERK1/2), and caspase-3 activity
- through changes in gene expression and a strong up-regulation of phase 2 enzymes, highlighting Q ability to act also with an indirect antioxidant mechanism
- through reduction of inflammatory responses by inhibiting iNOS induction in LPS-stimulated cardiac cells, reducing NO production, and counteracting LPS-induced apoptosis

The Sulforaphane case







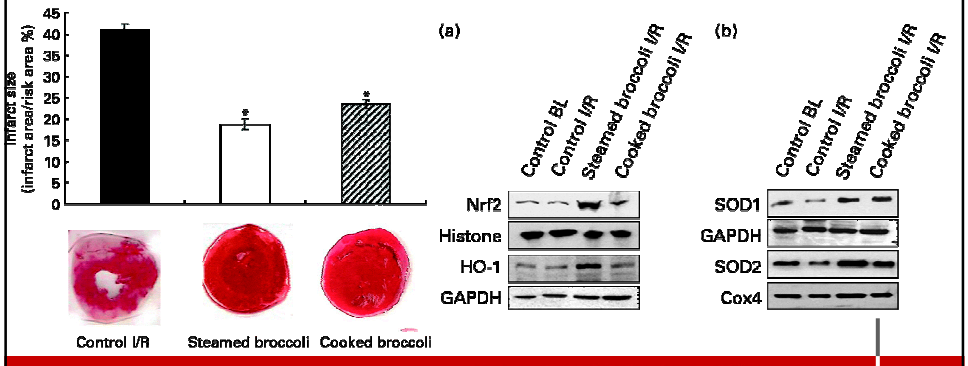


The Sulforaphane case

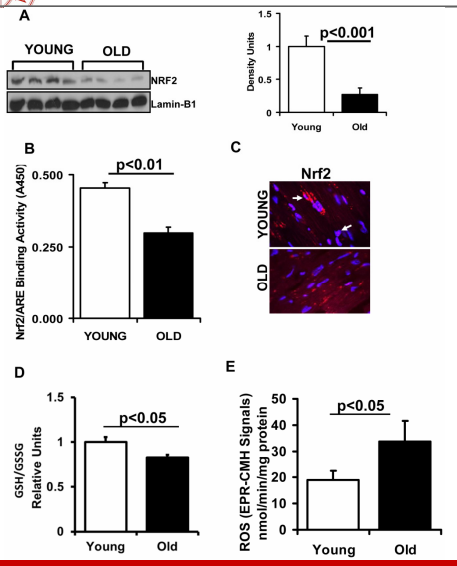
British Journal of Nutrition (2010), **103**, 815–823
doi:10.1017/S0007114509992492

Comparison of the protective effects of steamed and cooked broccolis on ischaemia–reperfusion-induced cardiac injury

Subhendu Mukherjee[1,2], Istvan Lekli[1], Diptarka Ray[1], Hiranmoy Gangopadhyay[2], Utpal Raychaudhuri[2] and Dipak K. Das[1]*



Nrf2 is impared in the aging heart



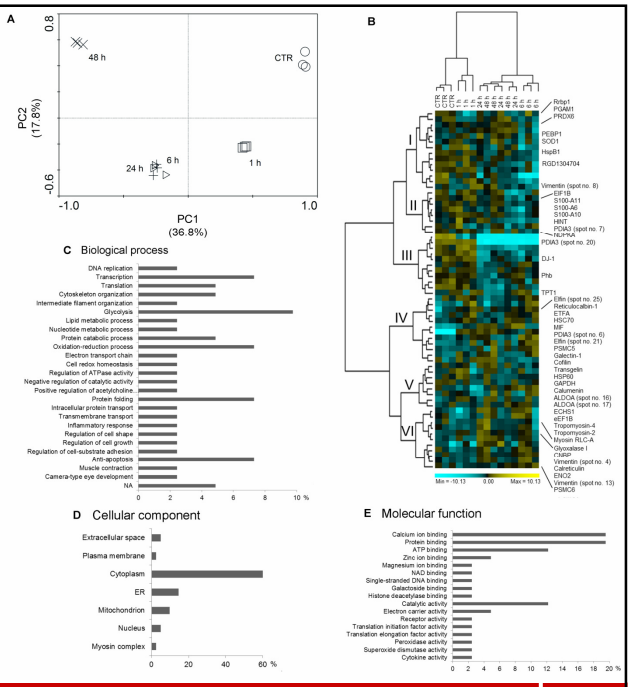
- Nrf2 levels in the nuclear extracts of myocardium are lower in aged (>23 months) than young (2 months) mice
- Nrf2-ARE-binding efficacy was significantly reduced (0.6 fold) in the aging heart.
- Immunofluorescence analysis using anti-Nrf2-Ab revealed decreased cytosolic and nuclear Nrf2 in old versus young myocardium

Gounder SS, PLoS One. 2012;7(9):e45697.

These observations suggest that enhancing Nrf2 function and endogenous cytoprotective mechanisms by SF, may combat age-induced ROS and protect the myocardium from oxidative stress diseases

Proteomic profiling of SF-treated cardiomyocytes

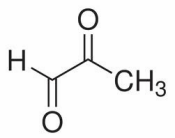
A 2-DE-based proteomics approach was employed to profile the proteins affected by SF, leading to the identification **of 41 distinct proteins with altered expression**, which were associated with diverse biological functions

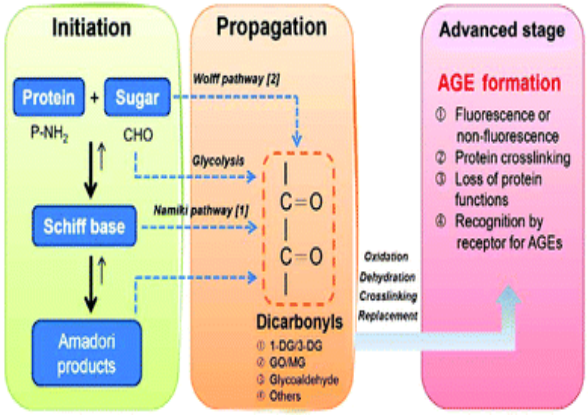


Angeloni et al..PloS One , 2013

Carbonyl and glycative stress

An imbalance between **pro-glycant species and anti-glycant enzymatic defenses,** in favor of the pro-glycant agents.
Reactive carbonyl compounds are constantly produced by the metabolism of carbohydrates, lipids, and aminoacids





MG is a potent dicarbonyl glycating agent formed by the degradation of triose-phosphate that accumulates in OS conditions and reacts with proteins, DNA and lipids to form AGE directly and relatively rapidly

AGEs

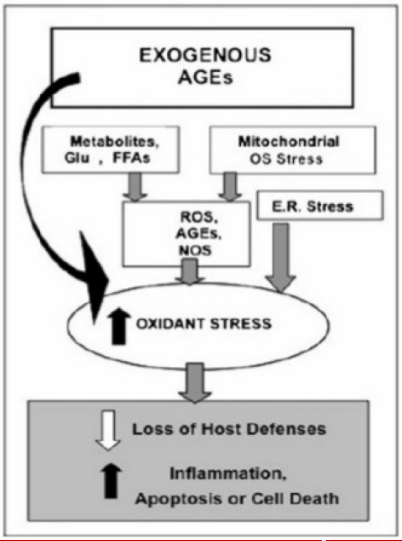
AGEs are generated in the late stages of Maillard reaction in foods and biological systems.

These products are mostly formed by the reactions of reducing sugar or degradation products of carbohydrates, lipids, and ascorbic acid.

AGEs exist in high concentration in foods, processed by common methods such as dry heat. Food processing - dry heat, ionization, or irradiation accelerates the generation of new AGEs whether done at industrial or commercial levels.

Heat and dehydration are also common in home cooking.

Human and animal studies demonstrated that about 10 % of AGEs contained in a meal can be absorbed into the circulation, of which two-thirds remain in the body for 72 hours, so they stay long enough to promote OS, more AGEs, and potentially more tissue injury.



Poulsen MW. Food Chem Toxicol 60:10-37 (2013)

AGEs

Glycation reactions also occur endogenously in all tissues and body fluids under physiological conditions and AGEs exist in relatively low concentrations in most of the biological systems.

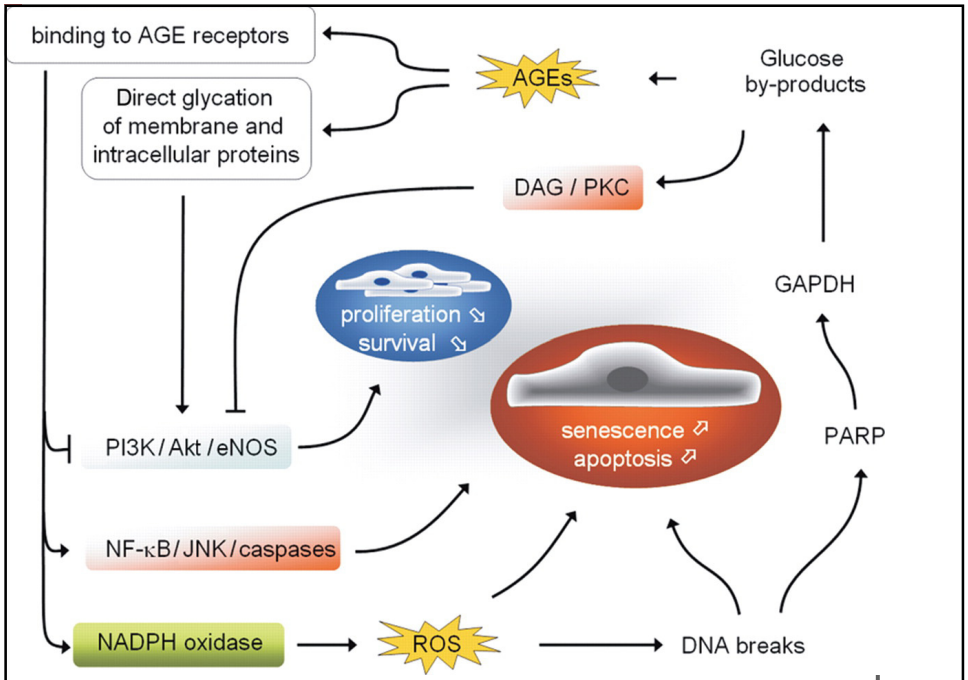
AGES levels increase in diabetes and also normal aging process.

Glucose is the most frequently found reducing sugar and also the most investigated carbonyl precursor under physiological conditions.

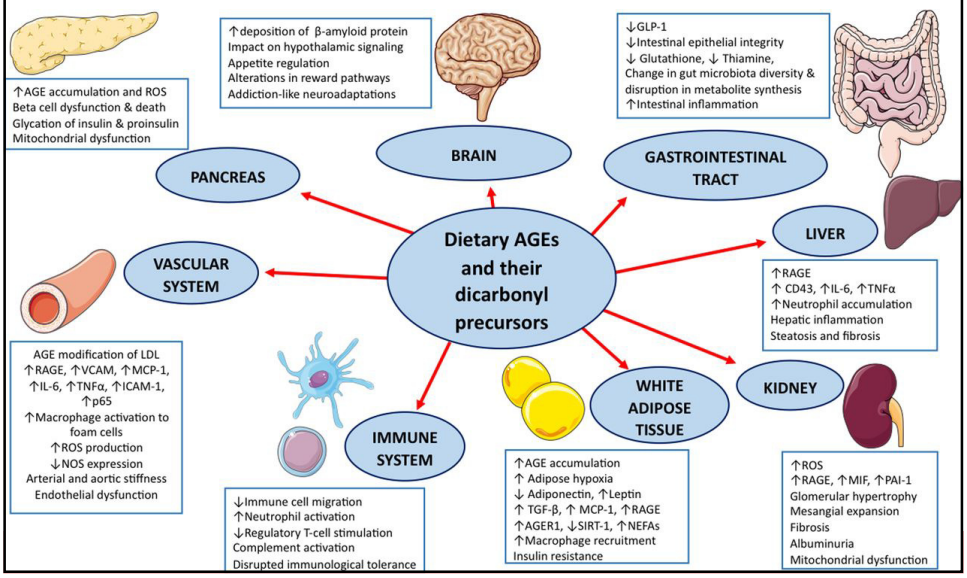
Physiologically formed AGEs are defined as the non-enzymatic reaction of glucose, a-oxoaldehydes, and other saccharide derivatives, with proteins, nucleotides, and lipids, in the human body

Receptors for AGEs (RAGEs) were believed to play a critical role in AGEs related biology and the pathology associated with diabetic complications and aging disorders.

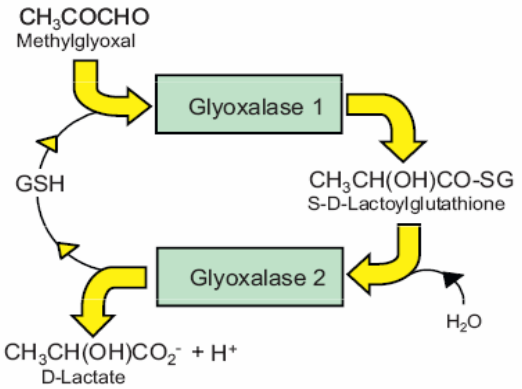
Consequently, defense mechanism against the Maillard reaction such as the deglycation of protein-bound Maillard products and the detoxification of dicarbonyl compounds to non-reactive compounds would be beneficial.



Effects of AGEs *in vivo*



The Glyoxalase system



MG is detoxified by the glyoxalase system.
The major physiological substrate for Glo1 is MG and this accumulates markedly by GSH depletion

OS is inextricably linked to glycation because the depletion of GSH in OS also decreases the activities of Glo1 and increases MG concentration and associated glycation reactions.

Glycation of proteins by Glo1 substrates may also increase ROS production, a further cause or contributory factor to OS.

Towards a nutraceutical approach

Food Chemistry 152 (2014) 323–330

Contents lists available at ScienceDirect

Food Chemistry

journal homepage: www.elsevier.com/locate/foodchem

Ellagitannin oligomers and a neolignan from pomegranate arils and their inhibitory effects on the formation of advanced glycation end products

Hideyuki Ito [a,b,*], Peng Li [b], Mayuko Koreishi [b], Akifumi Nagatomo [c], Norihisa Nishida [c], Takashi Yoshida [b]

Nutrition, Metabolism & Cardiovascular Diseases (2016) 26, 797–807

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Sulforaphane reduces advanced glycation end products (AGEs)-induced inflammation in endothelial cells and rat aorta

T. Matsui, N. Nakamura, A. Ojima, Y. Nishino, S.-i. Yamagishi*

Towards a nutraceutical approach

Chemico-Biological Interactions 227 (2015) 37–44

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Betanin reduces the accumulation and cross-links of collagen in high-fructose-fed rat heart through inhibiting non-enzymatic glycation

Junyan Han [a,*], Chang Tan [b], Yiheng Wang [a], Shaobin Yang [a], Dehong Tan [c,*]

OPEN ACCESS Freely available online

PLOS ONE

Novel Targets of Sulforaphane in Primary Cardiomyocytes Identified by Proteomic Analysis

Cristina Angeloni[1], Silvia Turroni[2], Laura Bianchi[3], Daniele Fabbri[1], Elisa Motori[1], Marco Malaguti[1], Emanuela Leoncini[1], Tullia Maraldi[4], Luca Bini[3], Patrizia Brigidi[2], Silvana Hrelia[1]*

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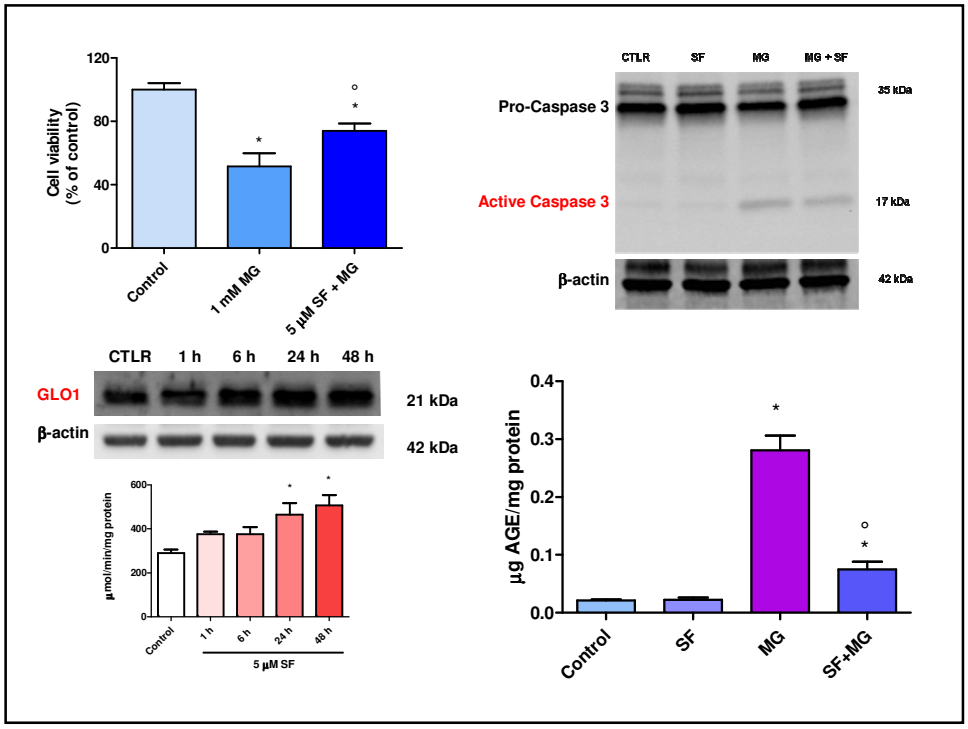
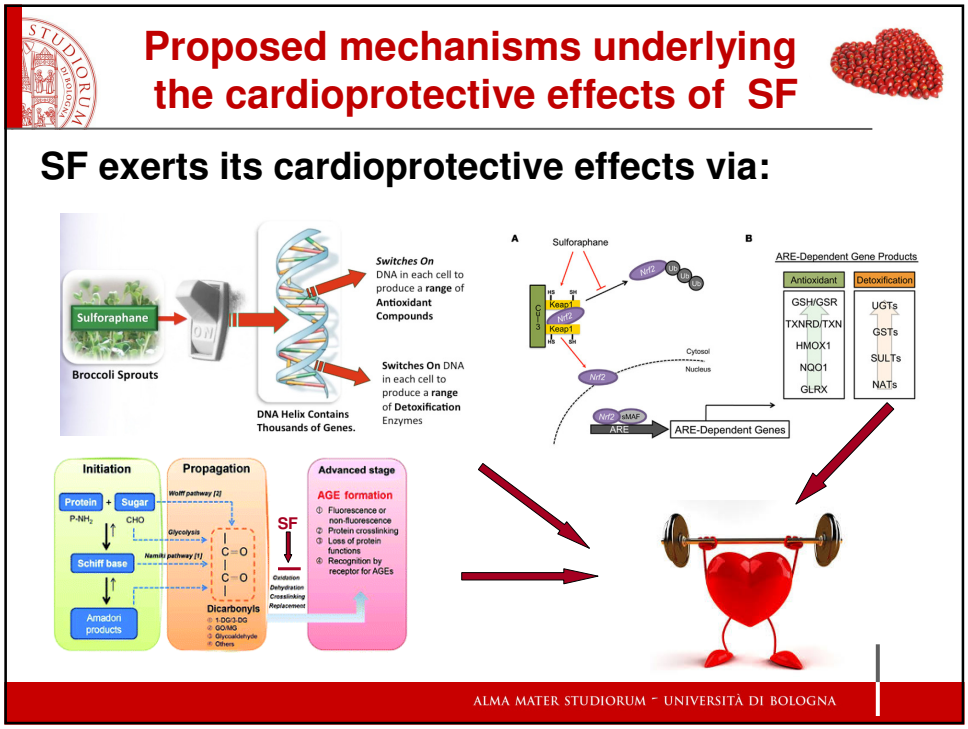

Cell viability (% of control)
120
80
40
0
Control
1 mM MG
5 µM SF + MG
CTLR
SF
MG
MG + SF
Pro-Caspase 3
Active Caspase 3
β-actin
35 kDa
17 kDa
42 kDa
CTLR 1 h 6 h 24 h 48 h
GLO1
β-actin
21 kDa
42 kDa
µmol/min/mg protein
600
400
200
0
Control
1 h
6 h
24 h
48 h
5 µM SF
µg AGE/mg protein
0.4
0.3
0.2
0.1
0.0
Control
SF
MG
SF+MG


Proposed mechanisms underlying the cardioprotective effects of SF
SF exerts its cardioprotective effects via:
Sulforaphane
Broccoli Sprouts
ON
DNA Helix Contains Thousands of Genes.
Switches On DNA in each cell to produce a range of Antioxidant Compounds
Switches On DNA in each cell to produce a range of Detoxification Enzymes
A
Sulforaphane
Keap1
Nrf2
Cytosol
Nucleus
ARE
ARE-Dependent Genes
B
ARE-Dependent Gene Products
Antioxidant
Detoxification
GSH/GSR
TXNRD/TXN
HMOX1
NQO1
GLRX
UGTs
GSTs
SULTs
NATs
Initiation
Protein
Sugar
Schiff base
Amadori products
Propagation
Wolff pathway [3]
Glycolysis
Namiki pathway [1]
Dicarbonyls
SF
Advanced stage
AGE formation
① Fluorescence or non-fluorescence
② Protein crosslinking
③ Loss of protein functions
④ Recognition by receptor for AGEs
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- New nutritional strategies intend to identify nutraceutical bioactive compounds with the ability to directly target and enhance intrinsic cytoprotective mechanisms
- Individual nutraceuticals can have greater or lesser effects on specific Nrf2- and inflammation-related genes in various tissues and experimental models.
- Only using a combination of nutraceuticals, **as those naturally present in fruits and vegetables**, it would be possible to modulate the greatest diversity of Nrf2- and inflammation related genes in the greatest number of tissues **to achieve the most dramatic protective effects** against oxidative damage, toxicants, and inflammation, and **to provide the most robust preventive/protective and anti-aging benefits.**

- There is intriguing but not yet compelling evidence that relatively small amounts of certain of the dietary nutraceuticals may lower risk of coronary heart disease mortality in European and US countries.
- More research is needed to establish that cardioprotective relationships exist with these bioactive compounds and, if they prove to be protective, what consumption levels may be required to achieve health benefits.
- Future studies are needed that allow for more direct comparison of research findings using more complete and comprehensive nutraceutical databases, more standardized and comprehensive dietary assessment methods, more information on the age, sex, health status and other characteristics of populations studied, more complete cardiovascular outcome measures, and longer lengths of follow-up that will allow for more direct comparison of research findings

The Med-Italian Diet

Italians do EAT better

Thanks for your attention

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

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Department for Life Quality
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IL PRESENTE MATERIALE È RISERVATO AL PERSONALE DELL'UNIVERSITÀ DI BOLOGNA E NON PUÒ ESSERE UTILIZZATO AI TERMINI DI LEGGE DA ALTRE PERSONE O PER FINI NON ISTITUZIONALI