ANTIOSSIDANTI NATURALI

ANTIOSSIDANTI

Sostanze che rallentano o prevengono l'ossidazione di substrati a causa dell'azione di molecole "ossidanti" (radicali liberi)

RADICALI LIBERI

Specie molecolari o atomiche reattive a causa di 1 o più elettroni spaiati

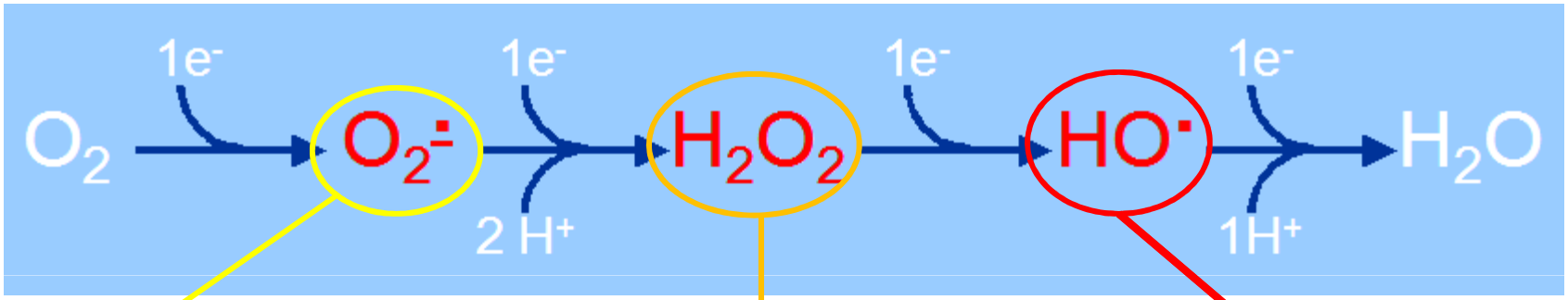
MECCANISMI DI PRODUZIONE

PRODUZIONE ENDOGENA

Mitocondri	• Respirazione cellulare (processo ossidativo con trasporto di elettroni), dove l'ossigeno funge da accettore finale per la produzione di elettroni
Acidi grassi polinsaturi	• Produzione prostaglandine, trombossani , leucotrieni
Macrofagi	• Produzione molecole per la distruzione dei microrganismi patogeni

PRODUZIONE ENDOGENA

SPECIE REATTIVE DELL' OSSIGENO



ANIONE SUPEROSSIDO
Reattività bassa
SOD

PEROSSIDO DI IDROGENO
Tossico
CAT e GSPHx

RADICALE OSSIDRILE
Haber-Weiss (Fe^{2+}, Cu^{+})
Fenton
Molecola più tossica

OSSIGENO SINGOLETTO ($^1O_2$)
non è un vero e proprio radicale!

PRODUZIONE ESOGENA

- STRESS NERVOSO
- ALIMENTAZIONE
- INGESTIONE ECCESSIVA DI ALCOL
- FUMO DI SIGARETTA
- INQUINAMENTO ATMOSFERICO
- ESPOSIZIONE ECCESSIVA AI RAGGI SOLARI
- ESERCIZIO FISICO INTENSO

PRINCIPALI BERSAGLI

DNA	• DANNO STRUTTURA • PERDITA INFORMAZIONE - INFORMAZIONE ERRATA
mtDNA	• DANNO STRUTTURA • PERDITA INFORMAZIONE - INFORMAZIONE ERRATA
LIPIDI	• DANNO DI MEMBRANA • FORMAZIONE DI MALLONDIALDEIDE / EFF. TOSSICI
PROTEINE	• COMPROMISSIONE FUNZIONALE • DENATURAZIONE

Antiossidanti

Vitamine (A, C, E)
Carotenoidi (beta-carotene, licopene, etc.)
Minerali (rame, zinco)
Enzimi (SOD, perossidasi, etc.)
Oligopeptidi (GSH)
Altre molecole endogene (CoQ10, acido lipoico, etc.)
Polifenoli
Omega 3-6

Forza anti-ossidativa (TE, ORAC, TRAP)

Licopene
Resveratrolo
OPC
PAC
Catechine gallate
CoQ10
Acido alfa-lipoico
GSH
Vitamina E
Vitamina C

LIMITI E PROBLEMATICHE

1°: gli antiossidanti pro-ossidano

- ✓ Radicale tocoferoxile
- ✓ Diidro-ascorbato
- ✓ Beta-carotene

2° azione attesa dopo decenni

- ✓ Epidemiologia (frutta e verdura)!

3°: scarsa biodisponibilità

- ✓ Polifenoli
- ✓ Licopene

LIMITI E PROBLEMATICHE

4°: enormi difficoltà formulative

- ✓ Gli antiox si ossidano nella fase industriale!
- ✓ (PAC, SAMe, GSH, CoQ10, Licopene)

5°: assenza di correlazione tra in vitro e conseguenze cliniche

- ✓ Beta-carotene (antiox dannoso)
- ✓ Vitamina E (antiox inefficace anche se biodisponibile)
- ✓ Polifenoli (antiox inefficaci perché poco biodisponibili)

CHE COS'E' NATURALE ?

NATURALE: Che riguarda la natura, che deriva dalla natura o che è conforme ai suoi principi:

Se un fenomeno si realizza sia biochimicamente all'interno di un organismo vivente o chimicamente in un laboratorio è perché avviene nel rispetto delle LEGGI NATURALI DELLA FISICA che stabiliscono a cascata il funzionamento di tutti gli altri fenomeni

CHE COS'E' NATURALE ?

SE UNA SOSTANZA FUNZIONA E' PERCHE' HA UN EFFETTO FARMACOLOGICO BEN PRECISO !

PER CORRETTEZZA DOBBIAMO PARLARE QUINDI DI SOSTANZE:

- **XENOBIOTICHE – BIOTICHE**
- **PARTE DEL PATRIMONIO ALIMENTARE DI UN ORGANISMO O NO**

N.B.: ALCUNI TRA I PIU' POTENTI VELENI E TOSSINE CONOSCIUTI SONO NATURALISSIMI!!!

IL PARADOSSO DELLA FITOTERAPIA

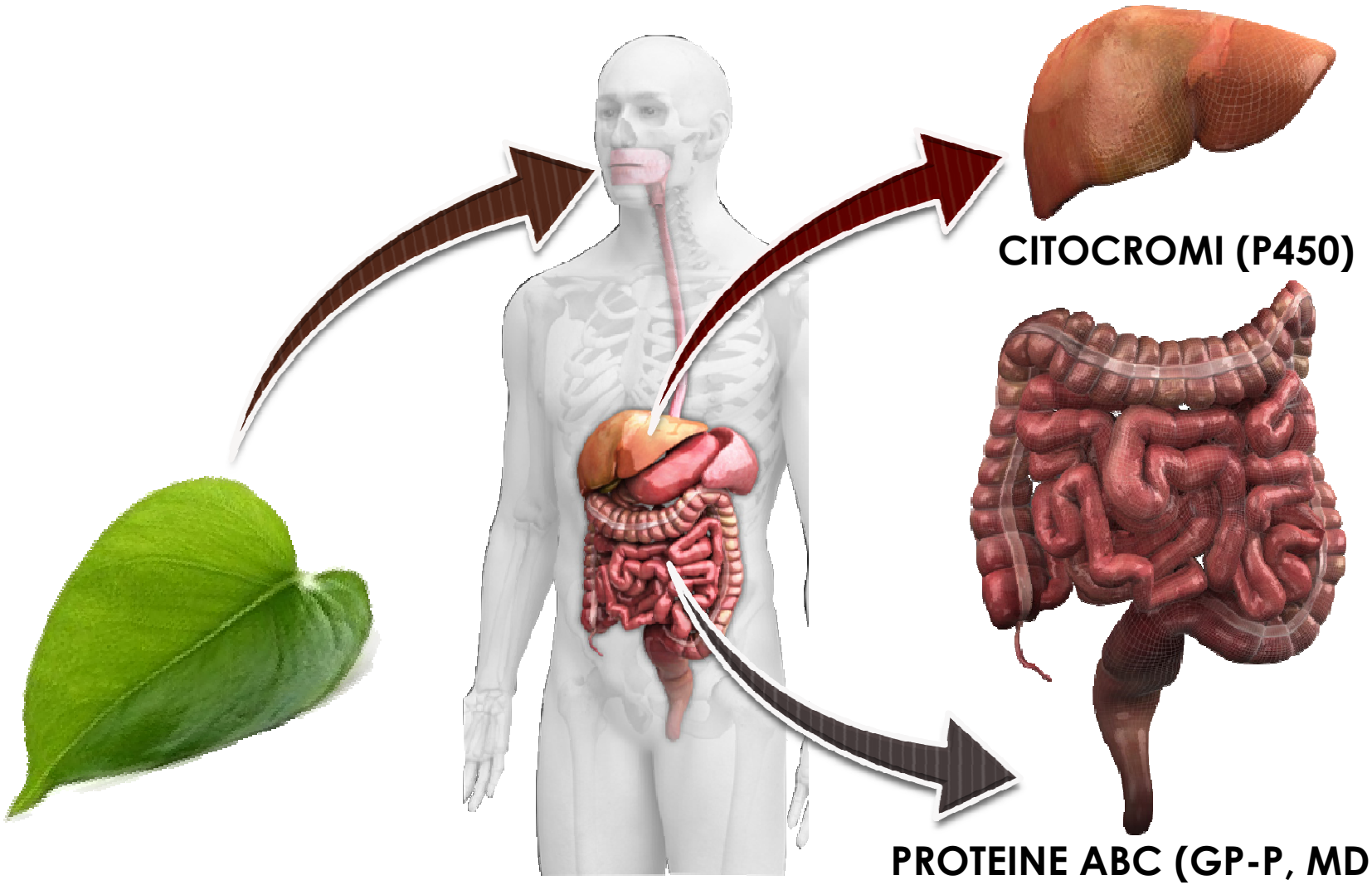
CONCENTRARE NELL'ORGANISMO DERIVATI MOLECOLARI CHE SONO STATI LA PRINCIPALE SPINTA ADATTATIVO/EVOLUTIVA AI SISTEMI DI DETOSSIFICAZIONE:

CITOCROMI (P450)

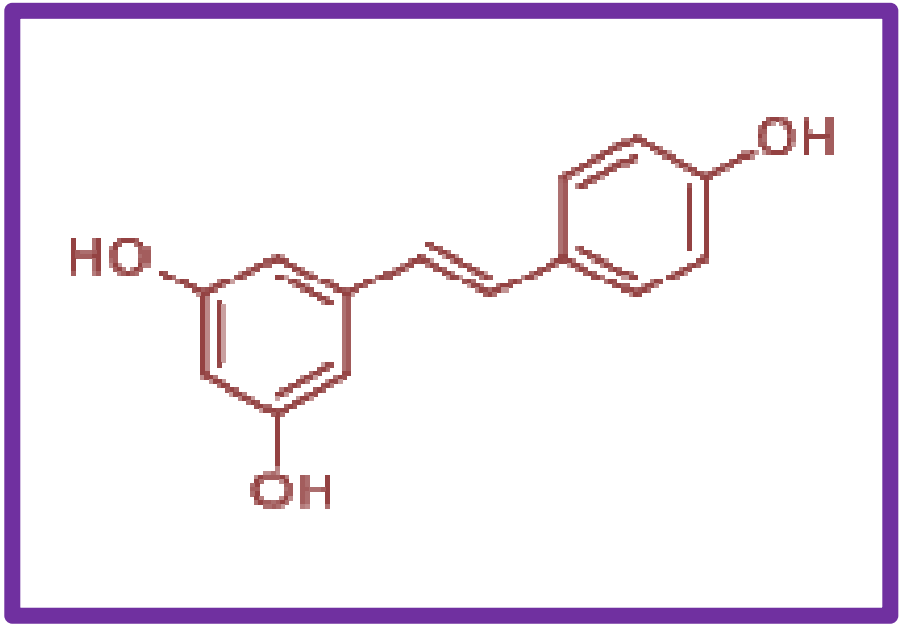
PROTEINE ABC (GP-P, MDR, ETC.)

F. DI PIERRO

IL PARADOSSO DELLA FITOTERAPIA



Il resveratrolo (3,5,4'-triidrossi-trans-stilbene) è una **fitoalessina (fenolo non flavonoide)** prodotta naturalmente da numerose piante come difesa da agenti patogeni o in risposta ad un evento lesivo



Uva (solo buccia)
Vino
Succo d'uva
Arachidi
More
Mirtilli neri
Mirtilli rossi
Lamponi
Polygonum cuspidatum

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

E QUINDI???

MEZZO BICCHIERE DI VINO A PASTO???

Br J Clin Pharmacol. 2011 Mar 16

Resveratrol - pills to replace a healthy diet?

Chachay VS, Kirkpatrick CM, Hickman IJ, Ferguson M, Prins JB, Martin JH.
The University of Queensland

Nutrapharmacology, or the use of bioactive food compounds at pharmacological dose is emerging as a therapeutic approach to target the complex metabolic dysregulations in ageing and obesity-related chronic disease. Resveratrol, a polyphenol found in the skin of grapes, and other edible plants and related food products, has received extensive attention through the link with the French paradox, and later with its chemo-preventive activity demonstrated in-vitro and in animal cancer models. A plethora of laboratory investigations has provided evidence for the multi-faceted properties of resveratrol and suggests that resveratrol may target ageing and obesity related chronic disease by regulating inflammation and oxidative stress. A number of obstacles stand in the path to clinical usage however, not least **the total lack of clinical evidence** to date, and the myriad of doses and formulations available. Further, data on the effects of resveratrol consumption in a capsule versus food form is conflicting, and there are uncertain effects of long-term dosing. The review will summarize the human pharmacokinetic and pharmacodynamic published data, and the topics for research if resveratrol is to become a multi-target therapeutic agent addressing chronic disease.

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Ann N Y Acad Sci. 2011

Bioavailability of resveratrol.

Walle T.
Department of Pharmacology, Medical University of South Carolina, USA.

This paper reviews our current understanding of the absorption, bioavailability, and metabolism of resveratrol, with an emphasis on humans. **The oral absorption of resveratrol in humans is about 75% and is thought to occur mainly by transepithelial diffusion. Extensive metabolism in the intestine and liver results in an oral bioavailability considerably less than 1%.** Dose escalation and repeated dose administration of resveratrol does not appear to alter this significantly. Metabolic studies, both in plasma and in urine, have revealed major metabolites to be glucuronides and sulfates of resveratrol. However, reduced dihydroresveratrol conjugates, in addition to highly polar unknown products, may account for as much as 50% of an oral resveratrol dose. Although major sites of metabolism include the intestine and liver (as expected), colonic bacterial metabolism may be more important than previously thought. Deconjugation enzymes such as β-glucuronidase and sulfatase, as well as specific tissue accumulation of resveratrol, may enhance resveratrol efficacy at target sites. Resveratrol analogs, such as methylated derivatives with improved bioavailability, may be important in future research.

Eur J Nutr. 2011 Mar 4.

Lack of effect of oral administration of resveratrol in LPS-induced systemic inflammation.

Larrosa M, Azorín-Ortuño M, Yañez-Gascón MJ, García-Conesa MT, Tomás-Barberán F, Espín JC.
Department of Food Science and Technology, Spain,

PURPOSE: The high mortality index due to sepsis and the lack of an effective treatment requires the search for new compounds that can serve as therapy for this disease. Resveratrol, a well-known anti-inflammatory natural compound, might be a good candidate for the treatment of sepsis. The aim of this work was to study the effects of oral administration of resveratrol, before and after sepsis initiation, on inflammation markers in a murine model of endotoxin-induced sepsis.
METHODS: Sprague-Dawley male rats were treated with resveratrol the 3 days prior to LPS administration and 45 min later. Hematological parameters, TNF-a, IL-1β and CINC-1, FRAP and TBARS levels were determined. Resveratrol and resveratrol-derived metabolites profile in plasma was compared after oral and intraperitoneal administration.
RESULTS: **Oral treatment with resveratrol had no systemic protective effects. However, resveratrol reduced the levels of lipid peroxidation in the small intestine and colon.** Importantly, the administration of LPS caused a decrease in resveratrol absorption. When resveratrol bioavailability after i.p. administration was compared to that observed after oral administration, a different profile of resveratrol metabolites was found in plasma.
CONCLUSION: These results highlight the importance of studying the bioavailability of the assayed compounds in the experimental models used to be able to choose the best route of administration depending on the target organ and to determine which compounds or derived metabolites are effective treating the studied disease.

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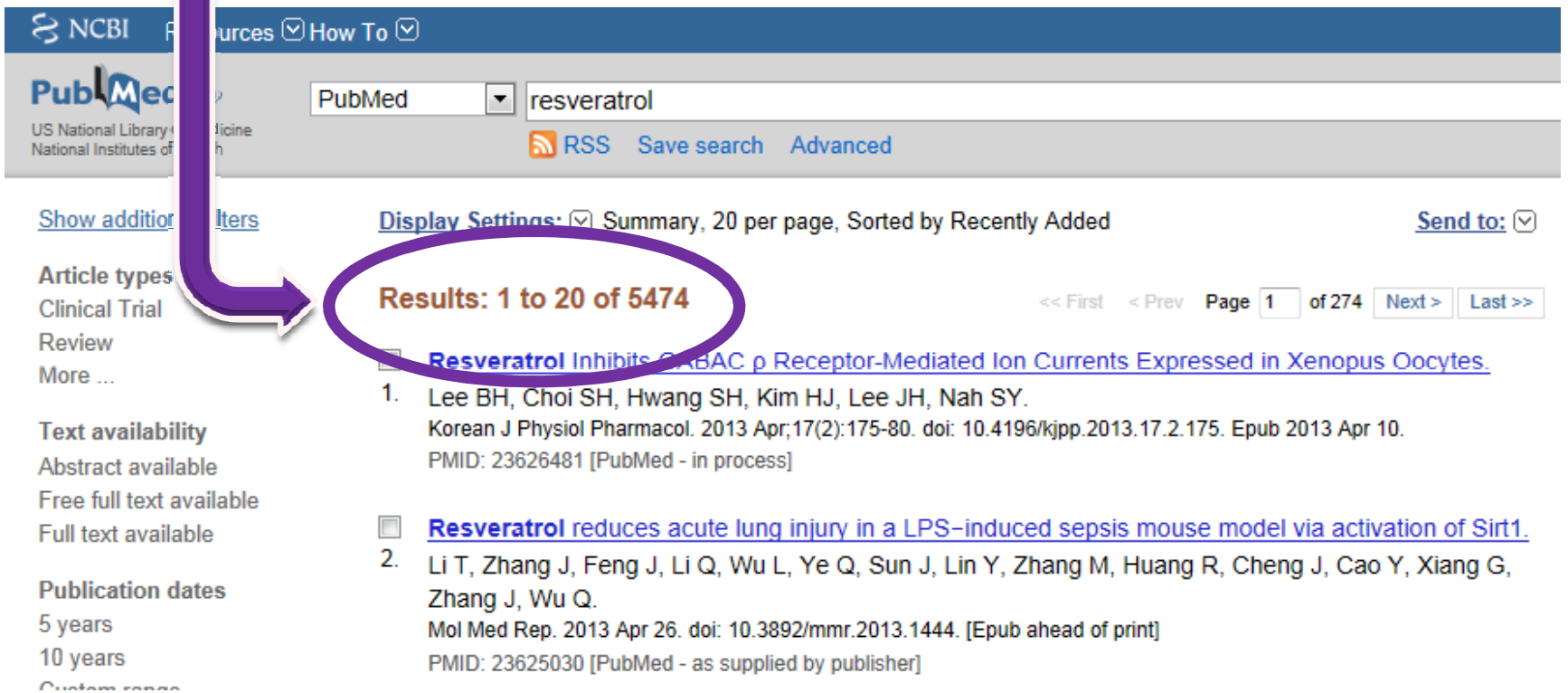


Ma allora perché questo FORTISSIMO interesse per il resveratrolo?

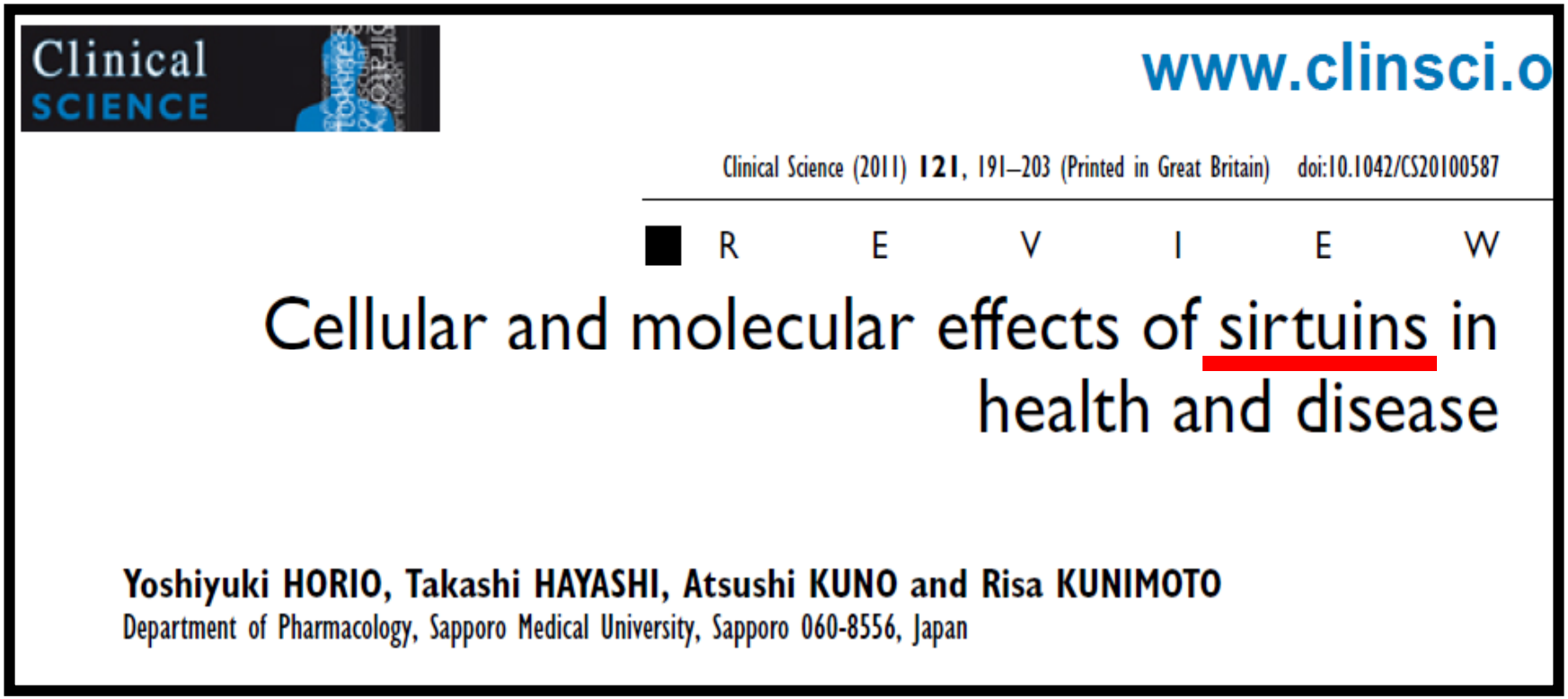
SIRTUINE

FORME PURE DI RESVERATROLO

1) **Resveratrolo sintetico: ResVida™ – Purezza DSM > 99% Novel food in EU – GRAS in USA**

2) **Resveratrolo estratto da *Polygonum cuspidatum* Purezza > 99% GRAS in USA**

SIRTUINE



Clinical SCIENCE

www.clinsci.o

Clinical Science (2011) **121**, 191–203 (Printed in Great Britain) doi:10.1042/CS20100587

REVIEW

Cellular and molecular effects of sirtuins in health and disease

Yoshiyuki HORIO, Takashi HAYASHI, Atsushi KUNO and Risa KUNIMOTO
Department of Pharmacology, Sapporo Medical University, Sapporo 060-8556, Japan

SIRTUINE

Le sirtuine sono proteine presenti lungo tutta la scala evolutiva (dai batteri all'uomo)

Svolgono la funzione di de-acetilare altre proteine (attivandole e disattivandole) contribuendo quindi a regolare vari aspetti della vita cellulare

Molto studiate sono quelle dei lieviti: SIR2 (Silent Information Regulator)

Mutazioni che inattivano SIR2 producono sterilità e accorciamento della vita
(lieviti, vermi, insetti)

Over-espressione di SIR2 produce allungamento della vita di circa il 30% (lieviti, vermi, insetti)

SIRTUINE

Nell'uomo l'acronimo è SIRT (da 1 a 7).

SIRT(1/2/ 3) si comportano nelle cellule umane quasi esattamente come SIR2

Differentemente da SIR2 però:
1) non determinano allungamento della sopravvivenza
2) riducono infiammazione
3) Regolano differenziamento

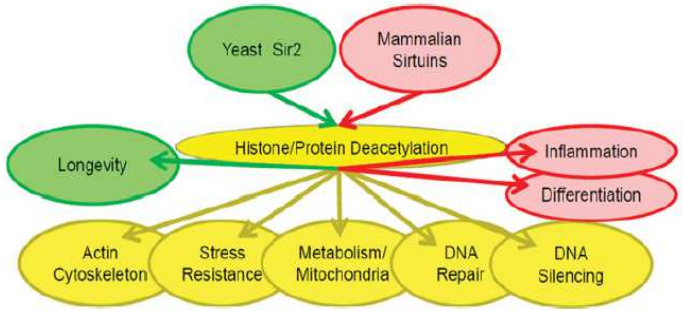


Figure 1 Common functions of yeast Sir2 and mammalian sirtuins
Sir2 and mammalian sirtuins deacetylate histones and various other proteins and affect physiological functions, many of which are common to both yeast and mammalian cells (yellow arrows). Green and red arrows indicate Sir2-specific and sirtuin-specific functions respectively.

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SIRTUINE

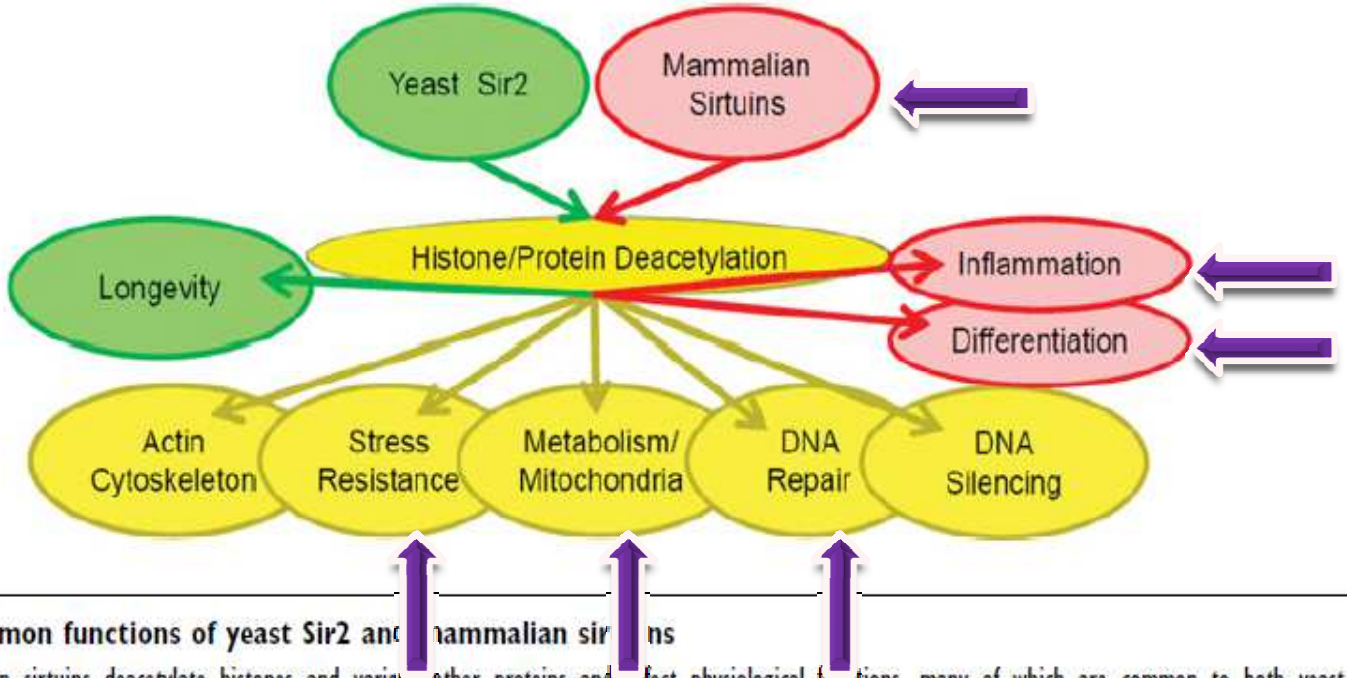


Figure 1 **Common functions of yeast Sir2 and mammalian sirtuins**

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.

RELAZIONE SIRTUINE PROTEZIONE DNA

Nature. 2003 Sep 11;425(6954):191-6.

Small molecule activators of sirtuins extend Saccharomyces cerevisiae lifespan.

Howitz KT et al. (BIOMOL Research Laboratories, Pennsylvania, USA)

In diverse organisms, calorie restriction slows the pace of ageing and increases maximum lifespan. In the budding yeast Saccharomyces cerevisiae, calorie restriction extends lifespan by increasing the activity of Sir2 (ref. 1), a member of the conserved sirtuin family of NAD(+)-dependent protein deacetylases. Included in this family are SIR-2.1, a Caenorhabditis elegans enzyme that regulates lifespan, and SIRT1, a human deacetylase that promotes cell survival by negatively regulating the p53 tumour suppressor.
Here we report **the discovery of small molecules that activate sirtuins**. We show that the **potent activator resveratrol**, a polyphenol found in red wine, lowers the Michaelis constant of SIRT1 for both the acetylated substrate and NAD(+), and increases cell survival by stimulating SIRT1-dependent deacetylation of p53. In yeast, resveratrol mimics calorie restriction by stimulating Sir2, increasing DNA stability and extending lifespan by 70%. We discuss possible evolutionary origins of this phenomenon and suggest new lines of research into the therapeutic use of sirtuin activators.

RELAZIONE SIRTUINE RESTRIZIONE CALORICA

La restrizione calorica, dai lieviti ai roditori, allunga la vita anche del 50%

La restrizione calorica in queste forme animali è SIR-dipendente

La restrizione calorica, nell'uomo non allunga la vita, ma riduce l'incidenza di molte patologie cronico-degenerative

La restrizione calorica nell'uomo **è anch'essa probabilmente SIRT-dipendente**

HEALTH & WELLNESS
Updated August 30, 2012, 10:21 a.m. ET

Big Calorie Cuts Don't Equal Longer Life, Study Suggests Monkeys on Severe Diets Get Health Benefits But, Unlike Rodents, No More Years

Severe Diet Doesn’t Prolong Life,at Least in Monkeys

Kolata, Gina (2012-09-29). "Severe Diet Doesn’t Prolong Life, at Least in Monkeys". The New York Times.

MONKEY MENU

Daily calories

445 **885**

Monkeys also receive an apple each day.

NORMAL DIET

Owen, 26

He gets more food, but Owen, above, isn't aging as well. His posture has been affected by arthritis. His skin is wrinkled and his hair is falling out. Owen is frail and moves slowly. His bloodwork shows unhealthy levels of glucose and triglycerides.

Diet of an average, active human male of 36

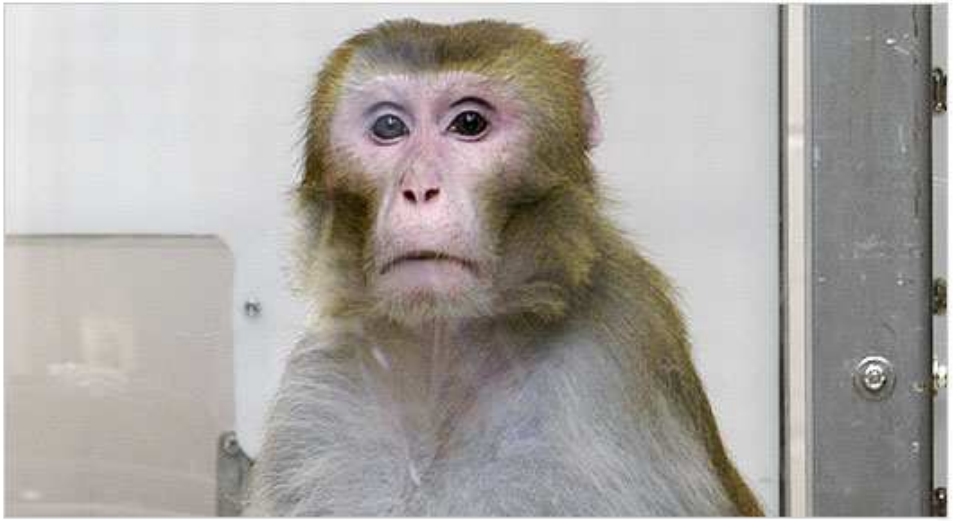
HUMAN MENU

Daily calories

2,000 **3,000**

Beverages, snacks and desserts not shown. Diet varies according to body type, sex and activity level.

Photos by Jim Wilson and Tony Cenicola/The New York Times and Lars Klove for The New York Times



CALORIE RESTRICTION DIET

Canto, 25

Although a senior citizen — the average rhesus monkey lifespan in captivity is 27 — Canto, above, is aging fairly well. Outwardly, he has a nice coat, elastic skin, a smooth gait, upright posture and an energetic demeanor. His bloodwork shows he is as healthy as he looks.

MONKEY MENU

Daily calories

445 **885**

Monkeys also receive an apple each day.

Human equivalent Meals prepared by Mike Linksvayer, 36

Breakfast fermented soybeans and garlic

Lunch tofu, konyakku and carrots

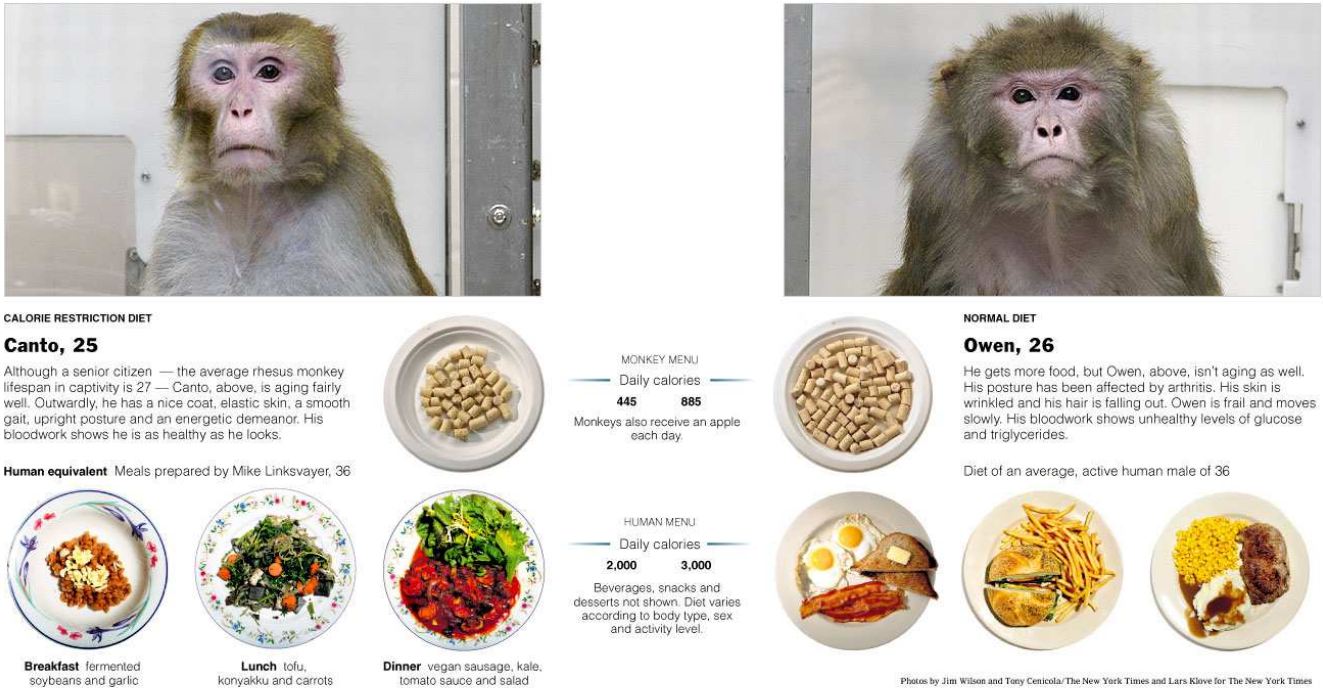
Dinner vegan sausage, kale, tomato sauce and salad

HUMAN MENU

Daily calories

2,000 **3,000**

Beverages, snacks and desserts not shown. Diet varies according to body type, sex and activity level.

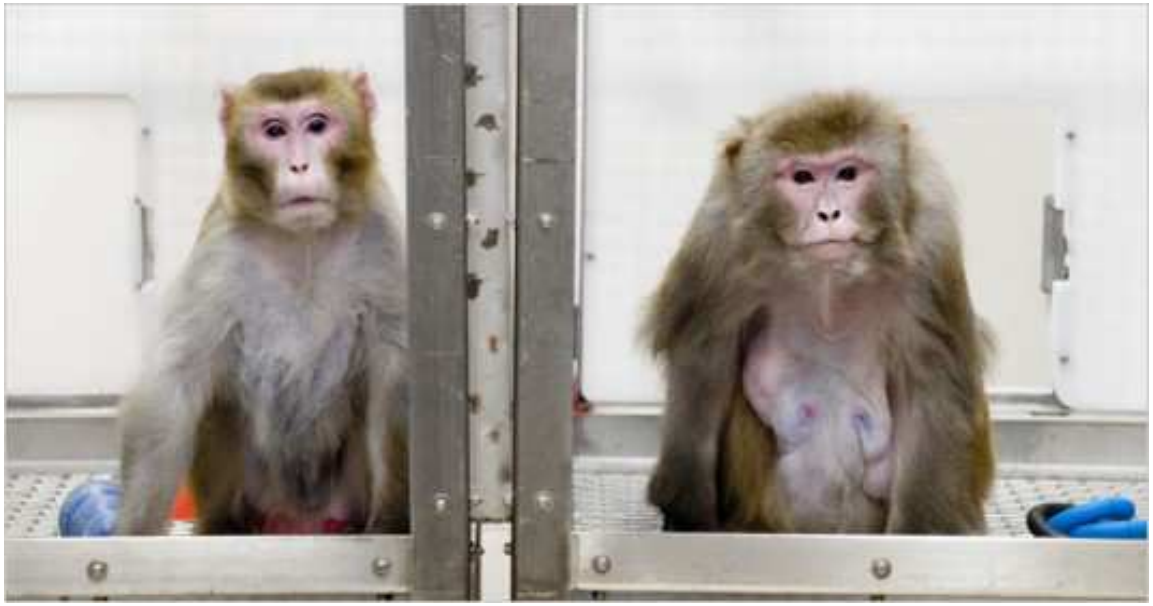


I risultati di questo importante studio a lungo atteso, che ha avuto inizio nel 1987, sono finalmente arrivati.

Essi **non hanno portato alla rivendicazione che gli appassionati di restrizione calorica avevano anticipato**.

Si scopre **le scimmie magre non vivono più a lungo rispetto a quelle mantenute a pesi più normali**.

Alcuni parametri di laboratorio sono migliorati, ma solo nelle scimmie messe a dieta da vecchie. **Le cause di morte** - cancro e malattie cardiache - **sono state le stesse** in entrambi i gruppi, scimmie denutrite e normalmente nutrite.



Anderson, R. M.; Shanmuganayagam, D.; Weindruch, R. (2009). "Caloric Restriction and Aging: Studies in Mice and Monkeys". *Toxicologic Pathology* **37** (1): 47–51. doi:10.1177/0192623308329476. PMID 19075044.

Colman RJ, Anderson RM, Johnson SC, *et al. (2009)*. "Caloric restriction delays disease onset and mortality in rhesus monkeys.". Science ***325*** *(5937): 201–4*. Bibcode:2009Sci...325..201C. doi:10.1126/science.1173635. PMC 2812811. PMID 19590001.

Colman RJ, Anderson RM, Johnson SC, *et al. (2009)*. "Caloric restriction delays disease onset and mortality in rhesus monkeys.". Science ***325*** *(5937): 201–4*. Bibcode:2009Sci...325..201C. doi:10.1126/science.1173635. PMC 2812811. PMID 19590001.

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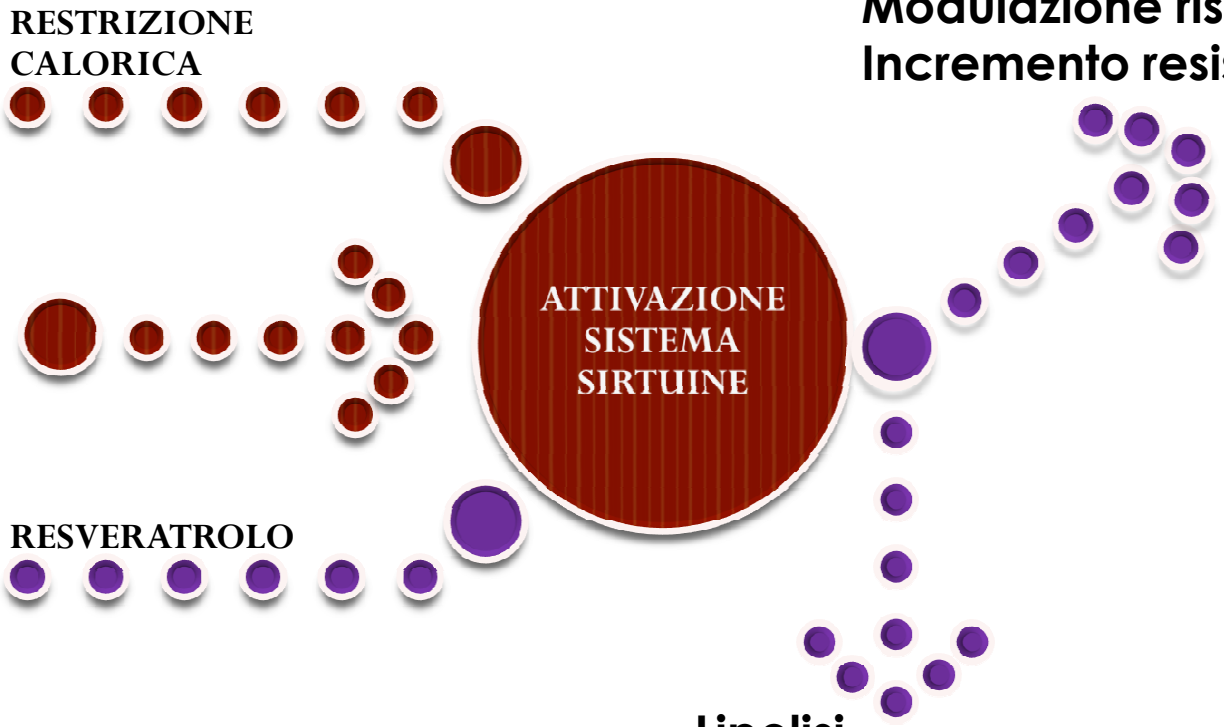
Protezione DNA
Riduzione fenomeni infiammatori
Differenziamento cellulare
Protezione citoscheletro cellulare
Riduzione cortisolemia
Modulazione risposta immunitaria
Incremento resistenza



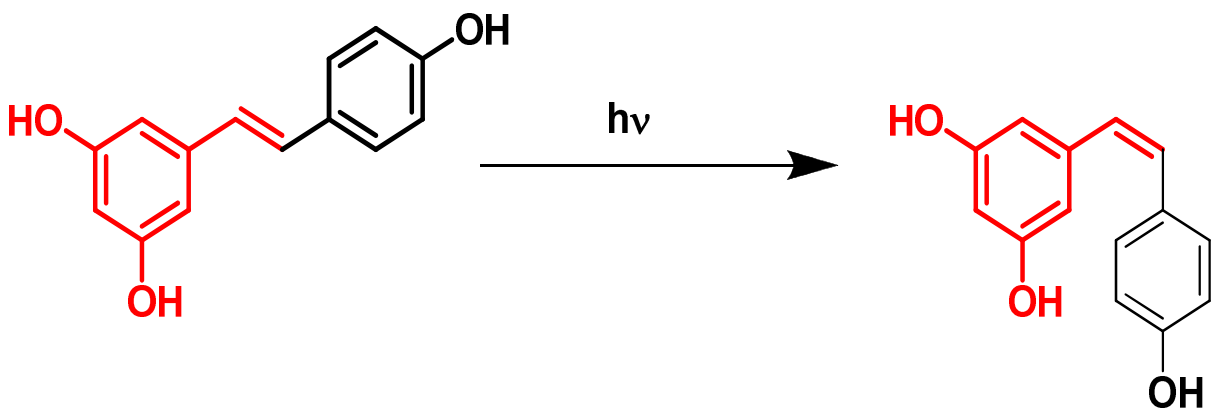
Lipolisi
Gluconeogenesi
Efficienza mitocondriale

BIODISPONIBILITA' DEL RESVERATROLO: ASPETTI FARMACOCINETICI

Il Resveratrolo viene facilmente isomerizzato dalla luce nella sua forma CIS **biologicamente inattiva**.

Tale processo è irreversibile e dipendente dal tempo di esposizione

La tecnica di formulazione nella lavorazione della materia prima diviene fondamentale per il mantenimento di una corretta attività biologica



BIODISPONIBILITA' DEL RESVERATROLO: ASPETTI FARMACOCINETICI

Comparato con gli altri polifenoli il resveratrolo mostra una buona biodisponibilità orale nell'uomo (70 % di assorbimento circa)

La maggior parte del resveratrolo assorbito è presente nel plasma in forma coniugata per l'azione degli enzimi di fase 2

Il rapporto tra resveratrolo libero e coniugato è mediamente di 1:20

I metaboliti di fase 2 vengono escreti molto più facilmente rispetto al resveratrolo libero

La maggior sfida farmacocinetica per l'utilizzo del resveratrolo non risiede quindi nell'aumentarne la biodisponibilità, ma nel migliorare il rapporto a livello plasmatico tra resveratrolo libero e resveratrolo coniugato dagli enzimi di fase 2

2) RESVERATROLO FITOSOMA: UTILITA?

Il resveratrolo generalmente mostra una buona biodisponibilità orale: è realmente utile formularlo in forma fitosomiale? **RISULTATI:**

Aumento della biodisponibilità:
(circa 4 volte sia per quanto riguarda AUC che Cmax).

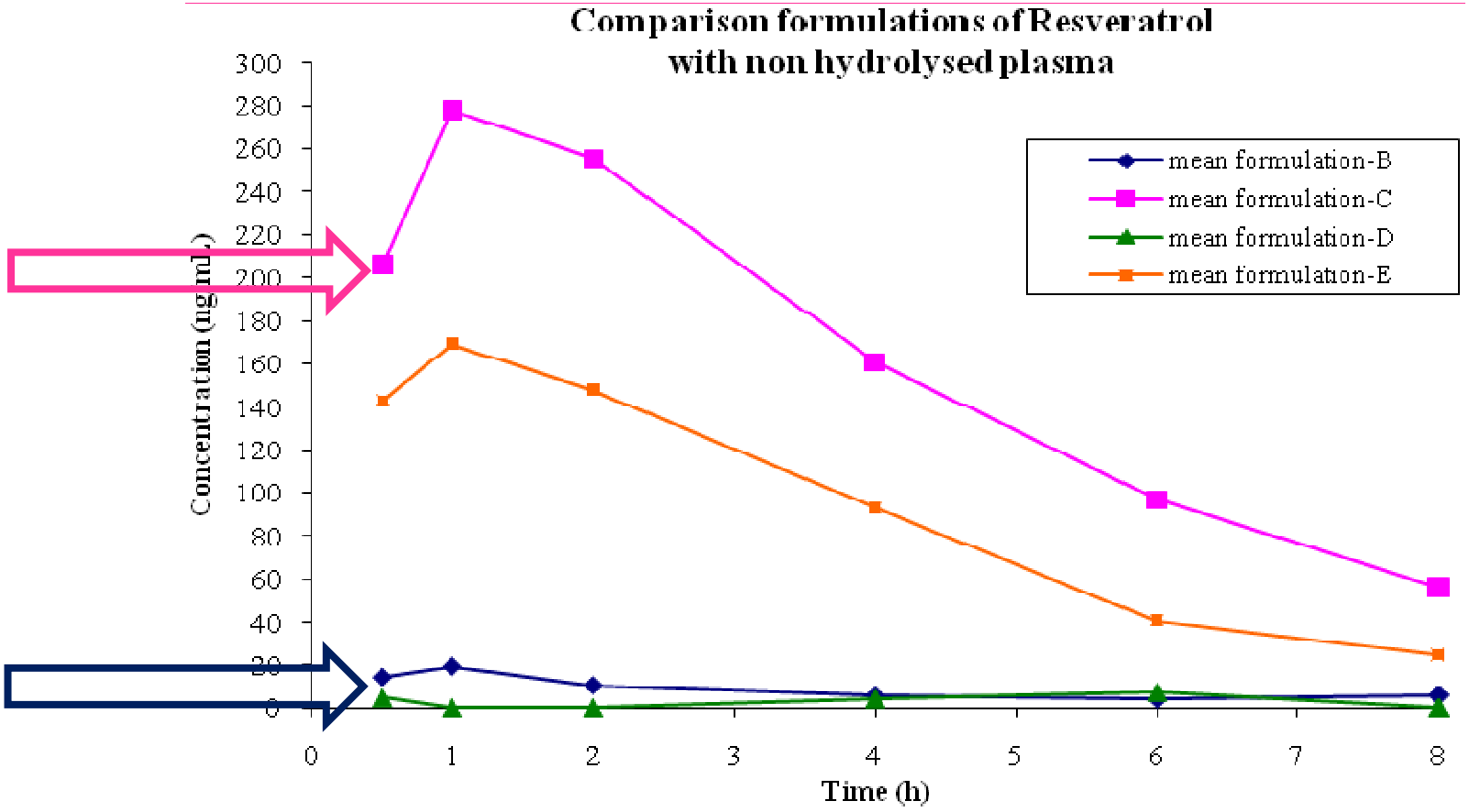
Rallenta e prolunga l'assorbimento del resveratrolo con una Cmax aumentata di nei 30 min successivi all'assunzione rispetto al non formulato

Promuove l'assorbimento del resveratrolo libero (x14 volte Cmax), e migliora il rapporto tra resveratrolo libero e resvetralo coniugato (**da 80:1 a 16:1**).

… Resveratrolo + piperina (da 80:1 a 40:1)

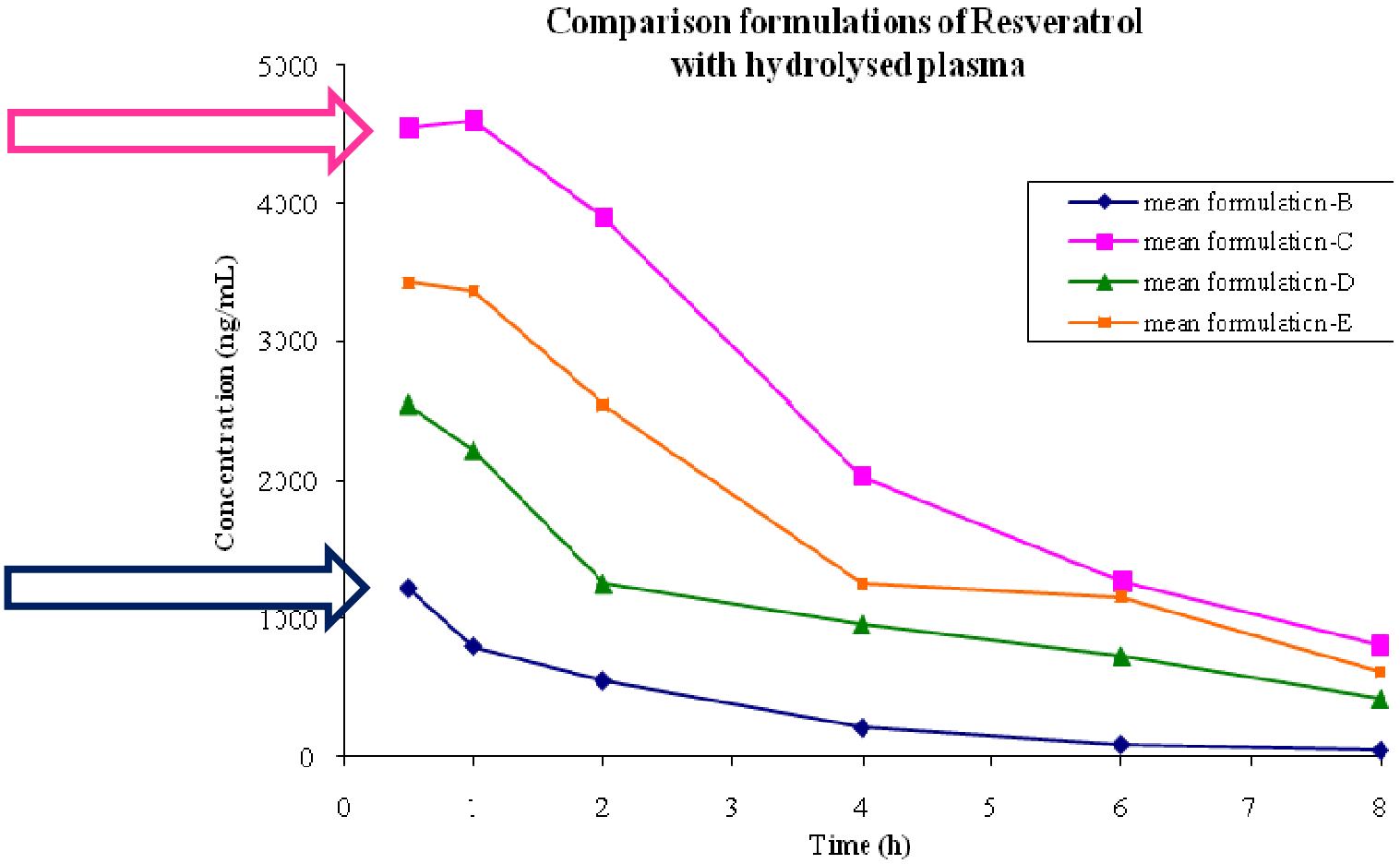
2) RESVERATROLO FITOSOMA: UTILITA?

Cmax (x14) e AUC sono marcatamente incrementate dalla complessazione con fosfolipidi



2) RESVERATROLO FITOSOMA: UTILITA?

Marcato incremento nell'assorbimento orale di resveratrolo anche in termini di somma tra resveratrolo libero e coniugato



2) RESVERATROLO FITOSOMA: UTILITA?

Formulato	Resveratrolo			Resveratrolo+ metaboliti
	Tmax	Cmax	AUC	AUC
Resveratrolo + Piperina	-30 ‘	X 15,5	X 2,2	X 0,9
Resveratrolo Fitosoma	+ 30’	X 14	X 5	X 4

COME SI SPIEGANO QUESTI DATI?

2) RESVERATROLO FITOSOMA: UTILITA?

La piperina aumenta solo di 2 volte il resveratrolo perché gran parte della coniugazione avviene nell'intestino dove la piperina è meno efficace

Il fitosoma scavalca la coniugazione intestinale e parte del prodotto non arriva al fegato ma in altri tessuti portato dai chilomicroni

3) TOSSICITA' RESVERATROLO

Phase I Dose Escalation Pharmacokinetic Study in Healthy Volunteers of Resveratrol, a Potential Cancer Chemopreventive Agent

The red grape constituent resveratrol possesses cancer chemopreventive properties in rodents. The hypothesis was tested that, in healthy humans, p.o. administration of resveratrol is safe and results in measurable plasma levels of resveratrol. A phase I study of oral resveratrol (**doses of 0.5, 1, 2.5, or 5 g**) was conducted in 10 healthy volunteers per dose level. Resveratrol and its metabolites were identified in plasma and urine by high-performance liquid chromatography-tandem mass spectrometry and quantitated by high-performance liquid chromatography-UV. **Consumption of resveratrol did not cause serious adverse events**.

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Review Article

Oxidative Medicine and Cellular Longevity
Volume 2012, Article ID 386527, 11 pages

Pleiotropic Protective Effects of Phytochemicals in Alzheimer's Disease

60 lavori

Sergio Davinelli,[1] Nadia Sapere,[1] Davide Zella,[2] Renata Bracale,[1] Mariano Intrieri,[1] and Giovanni Scapagnini[1]

[1] *Clinical Biochemistry and Clinical Molecular Biology Laboratory, Department of Health Sciences, University of Molise, 86100 Campobasso, Italy*
[2] *Department of Biochemistry and Molecular Biology, Institute of Human Virology, University of Maryland-School of Medicine, Baltimore MD 21201, USA*

Alzheimer's disease (AD) is a severe chronic neurodegenerative disorder of the brain characterised by progressive impairment in memory and cognition. In the past years an intense research has aimed at dissecting the molecular events of AD. However, there is not an exhaustive knowledge about AD pathogenesis and a limited number of therapeutic options are available to treat this neurodegenerative disease. Consequently, considering the heterogeneity of AD, therapeutic agents acting on multiple levels of the pathology are needed. Recent findings suggest that phytochemicals compounds with neuroprotective features may be an important resources in the discovery of drug candidates against AD. In this paper we will describe some polyphenols and we will discuss their potential role as neuroprotective agents. Specifically, curcumin, catechins, and resveratrol beyond their antioxidant activity are also involved in antiamyloidogenic and anti-inflammatory mechanisms. We will focus on specific molecular targets of these selected phytochemical compounds highlighting the correlations between their neuroprotective functions and their potential therapeutic value in AD.

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Oral Resveratrol Reduces Neuronal Damage in a Model of Multiple Sclerosis

12 lavori

Kenneth S. Shindler, MD, PhD[*,1], **Elvira Ventura, MS**[2], **Mahasweta Dutt, MS**[1], **Peter Elliott, PhD**[3], **Denise C. Fitzgerald, PhD**[2], and **Abdolmohamad Rostami, MD, PhD**[2]

Background—Neuronal loss in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), correlates with permanent neurological dysfunction. Current MS therapies have limited ability to prevent neuronal damage.

Methods—We examined whether oral therapy with SRT501, a pharmaceutical-grade formulation of resveratrol, reduces neuronal loss during relapsing/remitting EAE. Resveratrol activates SIRT1, an NAD^+-dependent deacetylase that promotes mitochondrial function.

Results—Oral SRT501 prevented neuronal loss during optic neuritis, an inflammatory optic nerve lesion in MS and EAE. SRT501 also suppressed neurological dysfunction during EAE remission, and spinal cords from SRT501-treated mice had significantly higher axonal density than vehicle-treated mice. Similar neuroprotection was mediated by SRT1720, another SIRT1-activating compound; and sirtinol, a SIRT1 inhibitor, attenuated SRT501 neuroprotective effects. SIRT1 activators did not prevent inflammation.

Conclusions—These studies demonstrate SRT501 attenuates neuronal damage and neurological dysfunction in EAE by a mechanism involving SIRT1 activation. SIRT1 activators are a potential oral therapy in MS.

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frontiers in
PHARMACOLOGY

REVIEW ARTICLE
published: 17 July 2012
doi: 10.3389/fphar.2012.00141

Resveratrol: French paradox revisited

768 lavori

Betul Catalgol, Saime Batirel, Yavuz Taga and Nesrin Kartal Ozer*

Department of Biochemistry, Faculty of Medicine, Genetic and Metabolic Diseases Research Center, Marmara University, Istanbul, Turkey

Edited by:
Issy Laher, University of British Columbia, Canada

Reviewed by:
Ramaroson Andriantsitoaina, Université d'Angers, France
Huige Li, Johannes Gutenberg University Mainz, Germany
Valérie Schini-Kerth, University of Strasbourg, France

***Correspondence:**
Nesrin Kartal Ozer, Department of Biochemistry, Faculty of Medicine, Genetic and Metabolic Diseases Research Center, Marmara University, 34668 Haydarpasa, Istanbul, Turkey.
e-mail: nkozer@marmara.edu.tr

Resveratrol is a polyphenol that plays a potentially important role in many disorders and has been studied in different diseases. The research on this chemical started through the "French paradox," which describes improved cardiovascular outcomes despite a high-fat diet in French people. Since then, resveratrol has been broadly studied and shown to have antioxidant, anti-inflammatory, anti-proliferative, and anti-angiogenic effects, with those on oxidative stress possibly being most important and underlying some of the others, but many signaling pathways are among the molecular targets of resveratrol. In concert they may be beneficial in many disorders, particularly in diseases where oxidative stress plays an important role. The main focus of this review will be the pathways affected by resveratrol. Based on these mechanistic considerations, the involvement of resveratrol especially in cardiovascular diseases, cancer, neurodegenerative diseases, and possibly in longevity will be is addressed.

Keywords: cancer, cardiovascular diseases, resveratrol, signal transduction

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Epigenetics 6:7, 870-874; July 2011; © 2011 Landes Bioscience

407 lavori

The effects of the dietary polyphenol resveratrol on human healthy aging and lifespan

Agustín F. Fernández[1] and Mario F. Fraga[1,2,*]

[1]Cancer Epigenetics Laboratory; Instituto Universitario de Oncología del Principado de Asturias (IUOPA); HUCA; Universidad de Oviedo; Oviedo, Spain;

[2]Department of Immunology and Oncology; National Center for Biotechnology; CNB-CSIC; Cantoblanco, Madrid, Spain

The physiological effects of the dietary polyphenol resveratrol are being extensively studied. Resveratrol has been proposed to promote healthy aging and to increase lifespan, primarily through the activation of the class III histone deacetylases (sirtuins). Although its positive effects are evident in yeast and mice, they still have to be confirmed in humans. The molecular mechanisms involved in the processes are not fully understood because resveratrol may have other targets than sirtuins and the direct activation of sirtuins by resveratrol is under debate.

receiving considerable attention in recent years.[2] The study of diseases associated with premature aging[7,8] and experiments in different model organisms[9] have demonstrated the relevance of genetic alterations in these processes. However, the role of epigenetics has not been clearly established yet.[2,10]

Many studies have highlighted the importance the environment may have on the epigenome.[1,11] It has been proposed that specific environmental exposures during early ontogenic development may have long-term effects in adulthood.[1,11] These studies support the idea that maternal influences (dietary and

Anticancer Agents Med Chem. 2012 Dec 11.

1606 lavori

Targeting mTOR: Evaluating the Therapeutic Potential of Resveratrol for Cancer Treatment.

Wu Y, Liu F.
Institute of Aging and Geriatric Diseases, Central South University, Hunan, China.

Resveratrol (3,4',5-trihydroxystilbene; RSV), a natural polyphenol found in a variety of daily food including grapes and red wine, has long been suspected to have multifaceted health beneficial properties, including anti-inflammation, anti-oxidant, and anti-cancer activities. Over the past few years, numerous studies have suggested that suppressing the activity of mammalian target of rapamycin (mTOR), a critical regulator of cell metabolism, growth, and proliferation, may provide a key mechanism underlying the anti-carcinogenic properties of resveratrol. It has been found that resveratrol targets multiple components of the phosphatidylinositol 3-kinase(PI3K)/Akt and mTOR signaling pathways, including PI3K, Akt, PTEN, and DEPTOR, suggesting that this natural compound and its derivatives may offer a promising new cancer treatment. In the current review, we discuss recent findings on the molecular mechanisms regulating mTOR signaling and the therapeutic potential of resveratrol for cancer treatment by targeting mTOR.

PRINCIPALI APPLICAZIONI

1) Come co-adiuvante nei regimi dietetici finalizzati al calo ponderale

2) Alla sospensione del regime dietetico per minimizzare l'effetto REBUOND

3) Nella terapia della sindrome metabolica caratterizzata da iperlipemia, IFG o IGT, aumento di peso e modesta ipertensione

4) Nella profilassi e nella terapie anti-invecchiamento

5) Nella terapia complementare del morbo di Alzheimer

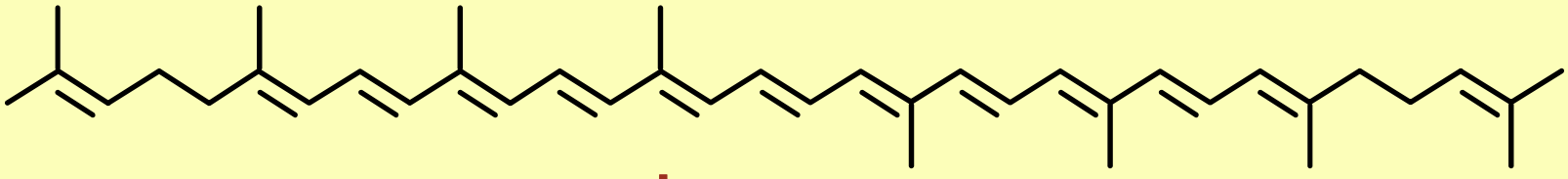
6) Nella terapia complementare della sclerosi multipla

7) Nella chemo-prevenzione oncologica

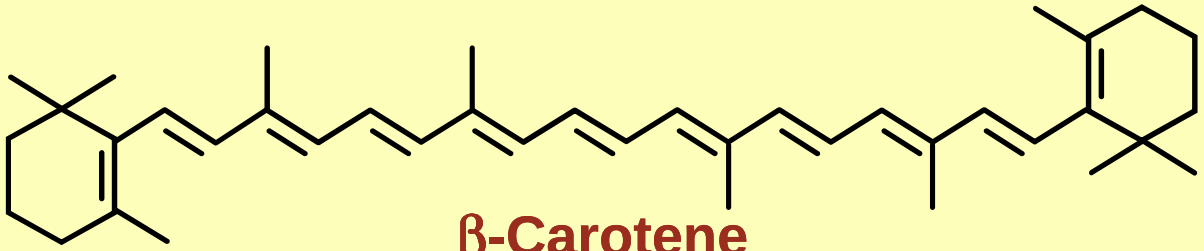
8) Nella chemio-sensibilizzazione oncologica

Lycopersicum aesculentum

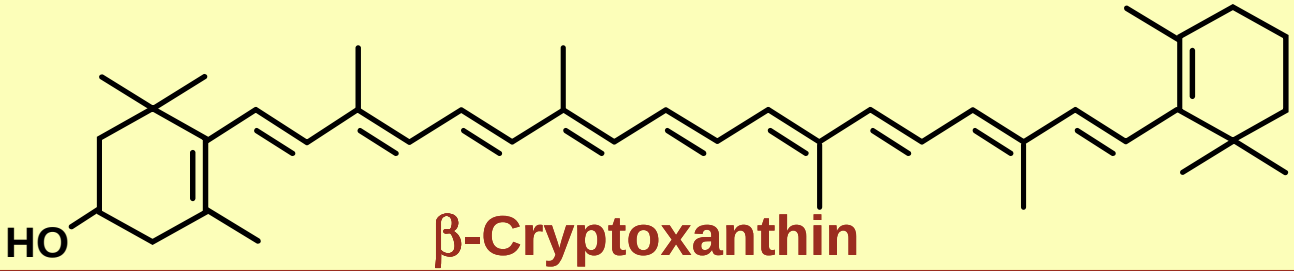
STRUCTURES OF THE FOUR CHIEF CAROTENOIDS FOUND IN HUMAN PLASMA



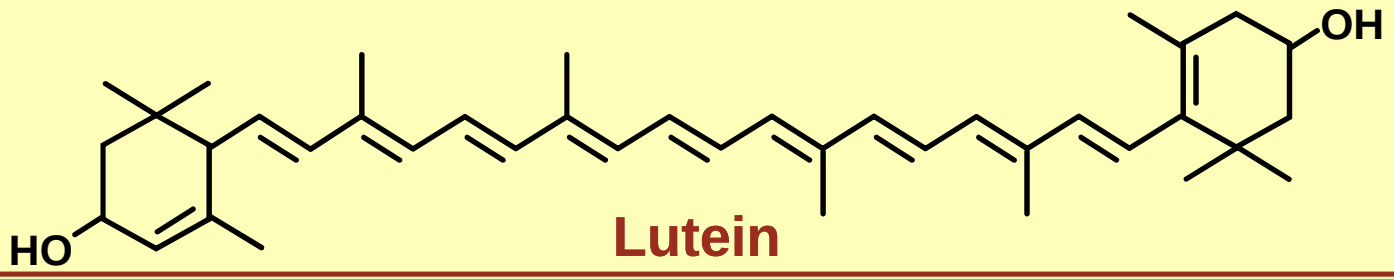
Lycopene



β-Carotene



β-Cryptoxanthin



Lutein

Lycopene is more bioavailable from tomato paste than from fresh tomatoes.

Gärtner C, Stahl W, Sies H. Institut für Physiologische Chemie I, Heinrich-Heine-Universität Düsseldorf, Germany.

Lycopene bioavailability from a single dose of fresh tomatoes or tomato paste (23 mg lycopene) ingested together with 15 g corn oil was compared by analyzing carotenoid concentrations in the chylomicron fraction. The lycopene isomer pattern was the same in both fresh tomatoes and tomato paste. The triacylglycerol response in chylomicrons was not significantly different after both treatments. Ingestion of tomato paste was found to yield 2.5-fold higher total and all-trans-lycopene peak concentrations ($P < 0.05$ and $P < 0.005$, respectively) and 3.8-fold higher area under the curve (AUC) responses ($P < 0.001$) than ingestion of fresh tomatoes. The same was calculated for lycopene cis-isomers, but only the AUC response for the cis-isomers was significantly higher after ingestion of tomato paste ($P < 0.005$). No difference was observed in the alpha- and beta-carotene response.

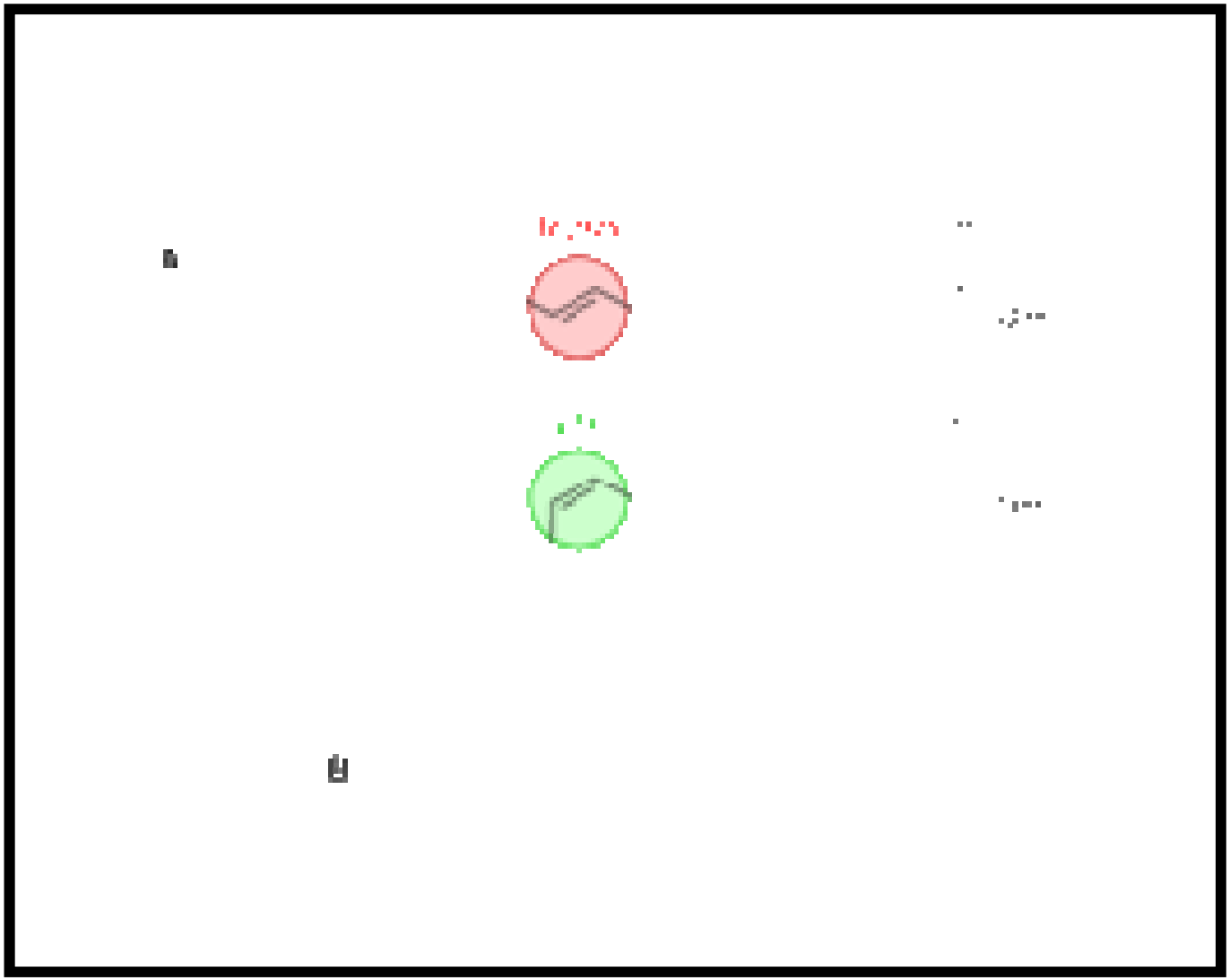
Thus, in humans, the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes.

Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans.

Stahl W, Sies H. Institut für Physiologische Chemie I, Universität Düsseldorf, Germany

Lycopene and beta-carotene are the most abundant carotenoids in human blood and tissues. Although lacking provitamin A activity, lycopene may be biologically active by contributing to the antioxidative defense system of the organism. We studied the uptake of lycopene from processed (boiled with 1% corn oil for 1 h) and unprocessed tomato juice in humans. Lycopene concentrations in human serum increased only when processed tomato juice was consumed. Lycopene uptake varied with individuals, but peak serum concentrations were always reached between 24 and 48 h. The carotenoid was eliminated from serum with a half-life of 2-3 d. The increase in peak serum concentrations was dose-dependent but not linear with the dose. Repeated doses led to a continual rise of lycopene in human serum.

Of the different geometrical isomers (all-trans, 9-cis and 13-cis), the cis isomers seemed to be somewhat better absorbed than the all-trans form.



Exp Biol Med (Maywood). 2002 Nov;227(10):914-9.

Bioavailability of all-trans and cis-isomers of lycopene.

Boileau TW, Boileau AC, Erdman JW Jr. Department of Human Nutrition and Food Management, The Ohio State University, Columbus, OH 43210, USA.

Lycopene, the predominant carotenoid in tomatoes, is among the major carotenoids in serum and tissues of Americans. Although about 90% of the lycopene in dietary sources is found in the linear, all-trans conformation, **human tissues contain mainly cis-isomers. Several research groups have suggested that cis-isomers of lycopene are better absorbed than the all-trans form because of the shorter length of the cis-isomer, the greater solubility of cis-isomers in mixed micelles, and/or as a result of the lower tendency of cis-isomers to aggregate**. Work with ferrets, a species that absorbs carotenoids intact, has demonstrated that whereas a lycopene dose, stomach, and intestinal contents contained 6-18% cis-lycopene, the mesenteric lymph secretions contained 77%-cis isomers. **The ferret studies support the hypotheses that cis-isomers are substantially more bioavailable then all-trans lycopene. In vitro studies suggest that cis-isomers are more soluble in bile acid micelles and may be preferentially incorporated into chylomicrons**. The implications of these findings are not yet clear. Rats appear to accumulate lycopene in tissues within the ranges reported for humans, suggesting that they can be used to study effects of lycopene isomers on disease processes. Investigations are underway to determine whether there are biological differences between all-trans and various cis-isomers of lycopene regarding its antioxidant properties or other biological functions.

Overview of mechanisms of action of lycopene.

Heber D, Lu QY.

Dietary intakes of tomatoes and tomato products containing lycopene have been shown to be associated with decreased risk of chronic diseases such as cancer and cardiovascular diseases in numerous studies. Serum and tissue lycopene levels have also been inversely related to the risk of lung and prostate cancers. Lycopene functions as a very potent antioxidant, and this is clearly a major important mechanism of lycopene action. In this regard, lycopene can trap singlet oxygen and reduce mutagenesis in the Ames test. However, evidence is accumulating for other mechanisms as well. Lycopene at physiological concentrations can inhibit human cancer cell growth by interfering with growth factor receptor signaling and cell cycle progression specifically in prostate cancer cells without evidence of toxic effects or apoptosis of cells. Studies using human and animal cells have identified a gene, connexin 43, whose expression is upregulated by lycopene and which allows direct intercellular gap junctional communication (GJC). GJC is deficient in many human tumors and its restoration or upregulation is associated with decreased proliferation. The combination of low concentrations of lycopene with 1,25-dihydroxyvitamin D3 exhibits a synergistic effect on cell proliferation and differentiation and an additive effect on cell cycle progression in the HL-60 promyelocytic leukemia cell line, suggesting some interaction at a nuclear or subcellular level. The combination of lycopene and lutein synergistically interact as antioxidants, and this may relate to specific positioning of different carotenoids in membranes. This review will focus on the growing body of evidence that carotenoids have unexpected biologic effects in experimental systems, some of which may contribute to their cancer preventive properties in models of carcinogenesis. Consideration of solubility in vitro, comparison with doses achieved in humans by dietary means, interactions with other phytochemicals, and other potential mechanisms such as stimulation of xenobiotic metabolism, inhibition of cholesterogenesis, modulation of cyclooxygenase pathways, and inhibition of inflammation will be considered.

Eur J Pharm Biopharm. 2010 Oct;76(2):269-74. Epub 2010 Jun 15.

Bioavailability of natural carotenoids in human skin compared to blood.

Meinke MC, Darvin ME, Vollert H, Lademann J.

Skin functions and structure are significantly influenced by nutrients. Antioxidants protect the supportive layer of the skin against any damaging irradiation effects and the action of free radicals. A lack of suitable methods means that the pharmacokinetic properties of systemically applied carotenoids transferred into the skin remain poorly understood. In this study, a natural kale extract or placebo oil were given orally to 22 healthy volunteers for 4 weeks. Carotenoid bioaccessibility was evaluated using non-invasive resonance Raman spectroscopy on the palm and forehead skin. For the analysis of the blood serum, the standard HPLC method was used. The blood and skin levels of the carotenoids increased significantly during the study but compared to the blood serum values, increases in skin were delayed and depended on the dermal area as well as on the carotenoid. Lycopene, measured as being low in the extract, increases more in the skin compared to the blood indicating that the natural mixture of the extract stabilizes the antioxidative network in the skin. After supplementation had ended, the carotenoids decreased much faster in the blood than in the skin. The delayed decrease in the skin may indicate a peripheral buffer function of the skin for carotenoids.

Photochem Photobiol Sci. 2006 Feb;5(2):238-42. Epub 2005 Aug 12.

Lycopene-rich products and dietary photoprotection.

Stahl W, Heinrich U, Aust O, Tronnier H, Sies H.

Plant constituents such as carotenoids and flavonoids are involved in the light-protecting system in plants and contribute to the prevention of UV damage in humans. As micronutrients they are ingested with the diet and are distributed into light-exposed tissues where they provide systemic photoprotection. beta-Carotene is an endogenous photoprotector, and its efficacy to prevent UV-induced erythema formation has been demonstrated in intervention studies. Lycopene is the major carotenoid of the tomato and is a very efficient singlet oxygen quencher in the group of carotenoids. Following ingestion of lycopene or tomato-derived products rich in lycopene, photoprotective effects have been demonstrated. After 10-12 weeks of intervention a decrease in the sensitivity towards UV-induced erythema was observed in volunteers. Dietary carotenoids may contribute to life-long protection against harmful UV radiation.

Br J Dermatol. 2011 Jan;164(1):154-62. doi: 10.1111/j.1365-2133.2010.10057.x. Epub 2010 Nov 29.

Tomato paste rich in lycopene protects against cutaneous photodamage in humans in vivo: a randomized controlled trial.

Rizwan M, Rodriguez-Blanco I, Harbottle A, Birch-Machin MA, Watson RE, Rhodes LE.

BACKGROUND: Previous epidemiological, animal and human data report that lycopene has a protective effect against ultraviolet radiation (UVR)-induced erythema.

OBJECTIVES: We examined whether tomato paste--rich in lycopene, a powerful antioxidant--can protect human skin against UVR-induced effects partially mediated by oxidative stress, i.e. erythema, matrix changes and mitochondrial DNA (mtDNA) damage.

METHODS: In a randomized controlled study, 20 healthy women (median age 33 years, range 21-47; phototype I/II) ingested 55 g tomato paste (16 mg lycopene) in olive oil, or olive oil alone, daily for 12 weeks. Pre- and postsupplementation, UVR erythemal sensitivity was assessed visually as the minimal erythema dose (MED) and quantified with a reflectance instrument. Biopsies were taken from unexposed and UVR-exposed (3 × MED 24 h earlier) buttock skin pre- and postsupplementation, and analysed immunohistochemically for procollagen (pC) I, fibrillin-1 and matrix metalloproteinase (MMP)-1, and by quantitative polymerase chain reaction for mtDNA 3895-bp deletion.

RESULTS: Mean ± SD erythemal D(30) was significantly higher following tomato paste vs. control (baseline, 26·5 ± 7·5 mJ cm(-2); control, 23 ± 6·6 mJ cm(-2); tomato paste, 36·6 ± 14·7 mJ cm(-2); P = 0·03), while the MED was not significantly different between groups (baseline, 35·1 ± 9·9 mJ cm(-2); control, 32·6 ± 9·6 mJ cm(-2); tomato paste, 42·2 ± 11·3 mJ cm(-2)). Presupplementation, UVR induced an increase in MMP-1 (P = 0·01) and a reduction in fibrillin-1 (P = 0·03). Postsupplementation, UVR-induced MMP-1 was reduced in the tomato paste vs. control group (P = 0·04), while the UVR-induced reduction in fibrillin-1 was similarly abrogated in both groups, and an increase in pCI deposition was seen following tomato paste (P = 0·05). mtDNA 3895-bp deletion following 3 × MED UVR was significantly reduced postsupplementation with tomato paste (P = 0·01).

CONCLUSIONS: Tomato paste containing lycopene provides protection against acute and potentially longer-term aspects of photodamage.

Una composizione di isomeri di licopene

Stabile e biodisponibile

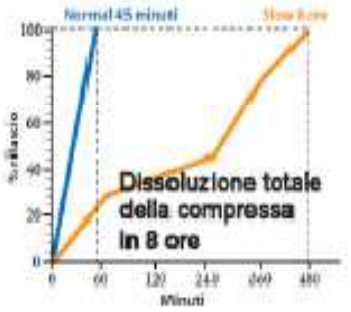
Background scientifico

Il concentrato di pomodoro è la più nota fonte di licopene biodisponibile. Gli estratti di pomodoro contenenti elevate quantità di licopene sono commercialmente disponibili in forma di oleoresina, ma la biodisponibilità del carotenoide contenuto in queste fonti è alquanto limitata. Negli estratti di pomodoro concentrato, il licopene è principalmente presente in forma cristallina, causa principale della bassa biodisponibilità. Il pomodoro contiene circa >90% di licopene nella sua configurazione *all-E*. Le fonti di licopene, commercialmente più disponibili, mostrano un profilo isomerico abbastanza simile a quello del pomodoro di partenza oppure mostrano solo un lieve aumento in isomeri Z, sia che si tratti di derivati (come le salse), sia nel caso degli estratti. Numerosi trattamenti, come ad esempio il trattamento termico, favoriscono l'isomerizzazione del licopene. Di conseguenza, la stabilità dei prodotti a base di licopene dipende dal profilo isomerico e può quindi essere modulata mediante procedure tecnologiche che incidono su questo profilo. Obiettivo della presente invenzione è fornire composizioni primarie con almeno un materiale contenente carotenoide arricchito in isomeri Z.

doro 13-Z ha mostrato una biodisponibilità di poco ma significativamente inferiore ($p<0.03$) rispetto al concentrato di pomodoro. Questi risultati indicano che la configurazione della molecola del licopene influisce marcatamente sul passaggio del licopene nel tratto gastrointestinale e di conseguenza, sulla quantità di licopene che viene assorbito. Questo è il primo studio che ha dimostrato che il miglioramento della biodisponibilità di licopene è correlata alla configurazione isomerica del licopene (5-Z licopene > 9-Z licopene > 13-Z licopene.)

MonoSelect® Licopene

Riduzione rischio carcinoma prostatico
Prevenzione danno da fotoesposizione



BioFarmaceutica vegetale

Ottimizzazione della **resa farmacologica** di **derivati vegetali** altamente **standardizzati**

» **Slow** Release

» **120 mg** *Solanum lycopersicum* L. frutto e.s.s.t. al 5% in licopene pari a 6 mg

Il licopene in natura è presente
quasi esclusivamente come isomero **TRANS**
instabile e **scarsamente biodisponibile**

Il derivato vegetale **utilizzato** grazie ad un particolare
trattamento, subisce un processo di **isomerizzazione**
che eleva significativamente il **tenore** degli isomeri **CIS**
più stabili e assorbiti

Riduzione rischio carcinoma prostatico
Prevenzione danno da fotoesposizione

Elevato tenore di forme isomeriche CIS
a maggior biodisponibilità

ANTIOSSIDANTI NATURALI.....

COSA « CAVOLO » C'ENTRANO?

Brassicaceae: QUANTI DATI?

1) Brassicaceae, cancer:

807 papers di cui 72 clinici su PubMed

2) Isothiocyanate, cancer:

3694 papers di cui 407 clinici su PubMed

J Natl Cancer Inst. 1978 Sep;61(3):709-14.

Diet in the epidemiology of cancer of the colon and rectum.

Graham S, Dayal H, Swanson M, Mittelman A, Wilkinson G.

We examined the diets as reported in interviews of 256 white male patients with cancer of the colon and of 330 white male patients with cancer of the rectum. Controls were 783 patients with non-neoplastic, non-digestive system diseases distributed by age similarly to the colon cancer patients and 628 patients with non-neoplastic, non-digestive diseases distributed by age like those with cancer of the rectum. We found no increase in risk for cancer of the colon or rectum regardless of the amounts of beef or other meats ingested. However, we found an increase in risk of colon cancer with decreases in the frequency with which vegetables were eaten. A study of 214 females with cancer of the colon and 182 females with cancer of the rectum yielded similar results. **The decrease in risk we found associated with frequent ingestion of vegetable**s, and **especially cabbage, Brussels sprouts, and broccoli, is consistent with the decreased numbers of tumors observed in animals challenged with carcinogens and fed compounds found in these same vegetables**.

Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 2399–2403, March 1992
Medical Sciences

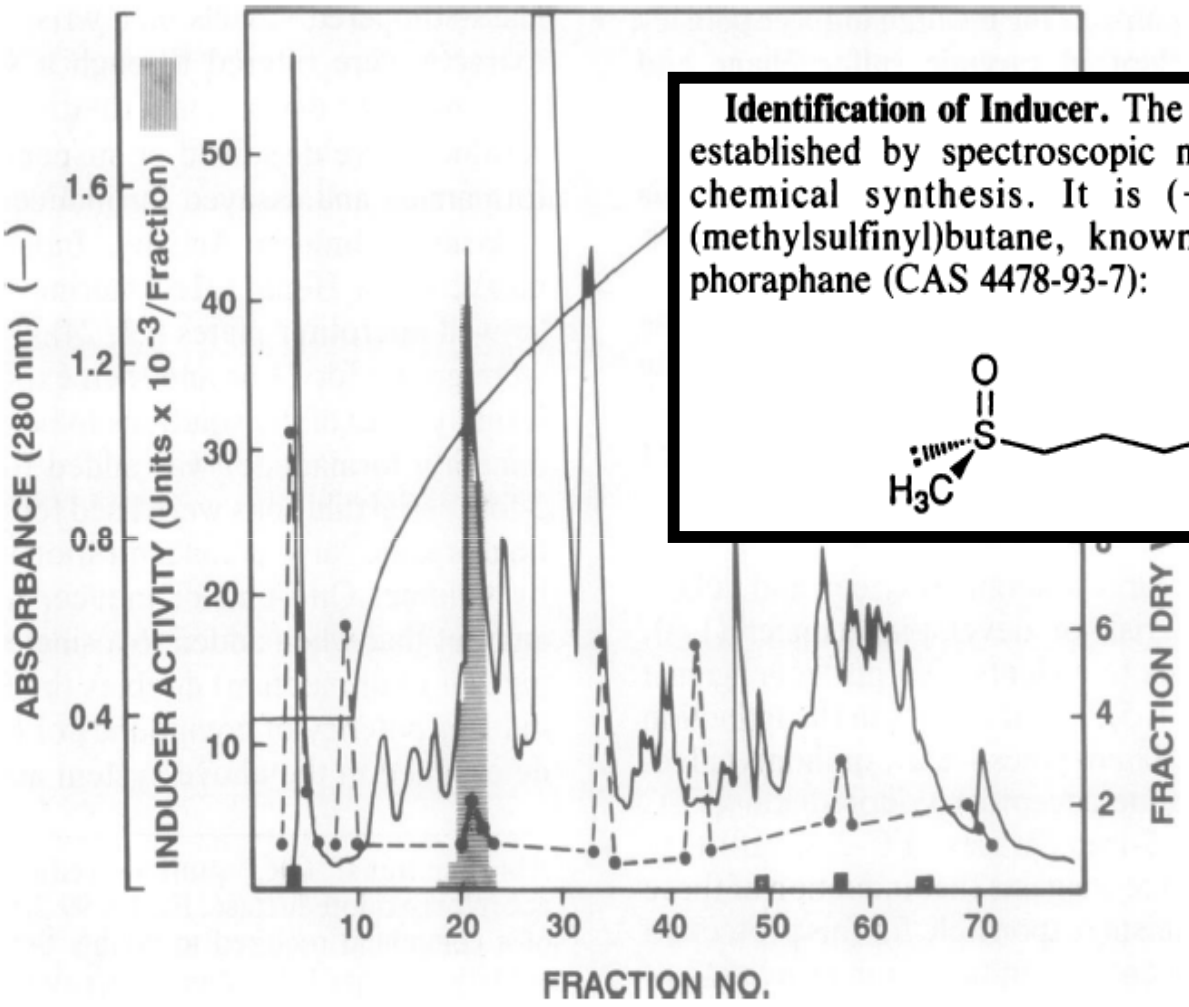
A major inducer of anticarcinogenic protective enzymes from broccoli: Isolation and elucidation of structure

(chemoprotection/enzyme induction/isothiocyanates/sulforaphane/quinone reductase)

YUESHENG ZHANG*, PAUL TALALAY*†, CHEON-GYU CHO‡, AND GARY H. POSNER‡

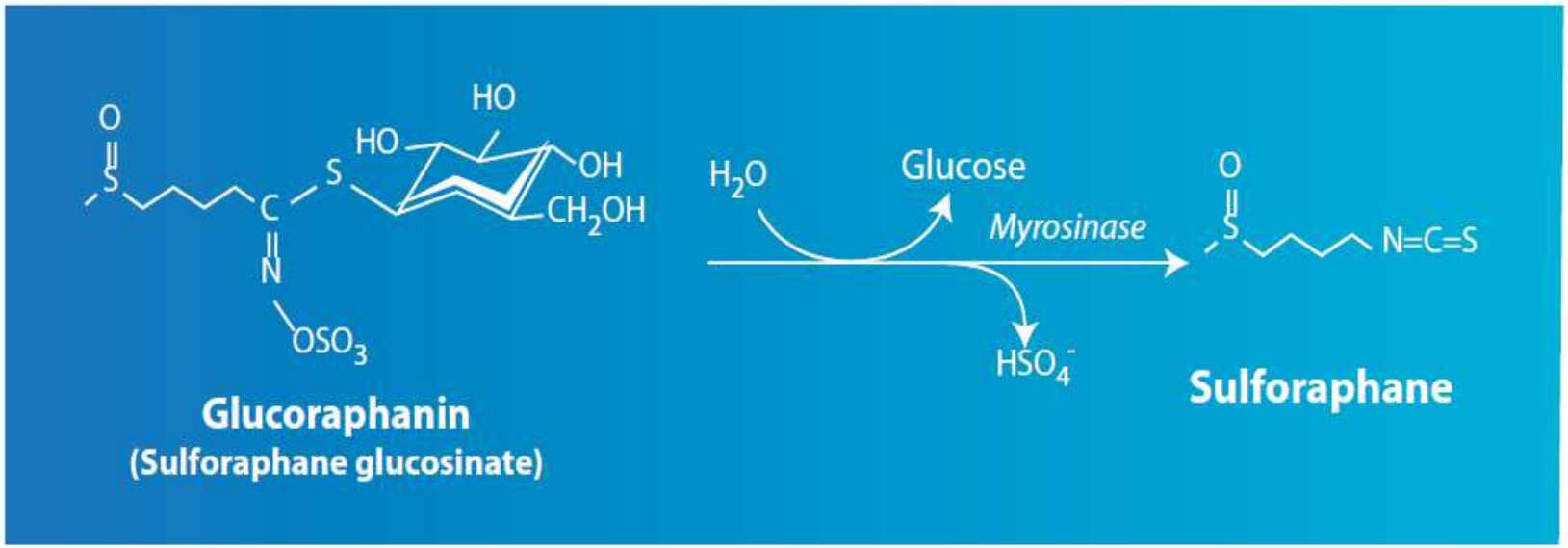
*Department of Pharmacology and Molecular Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD 21205; and ‡Department of Chemistry, The Johns Hopkins University School of Arts and Sciences, Baltimore, MD 21218

Contributed by Paul Talalay, December 19, 1991



Identification of Inducer. The identity of the inducer was established by spectroscopic methods and confirmed by chemical synthesis. It is (−)-1-isothiocyanato-(4*R*)-(methylsulfinyl)butane, known as sulforaphane or sulphoraphane (CAS 4478-93-7):

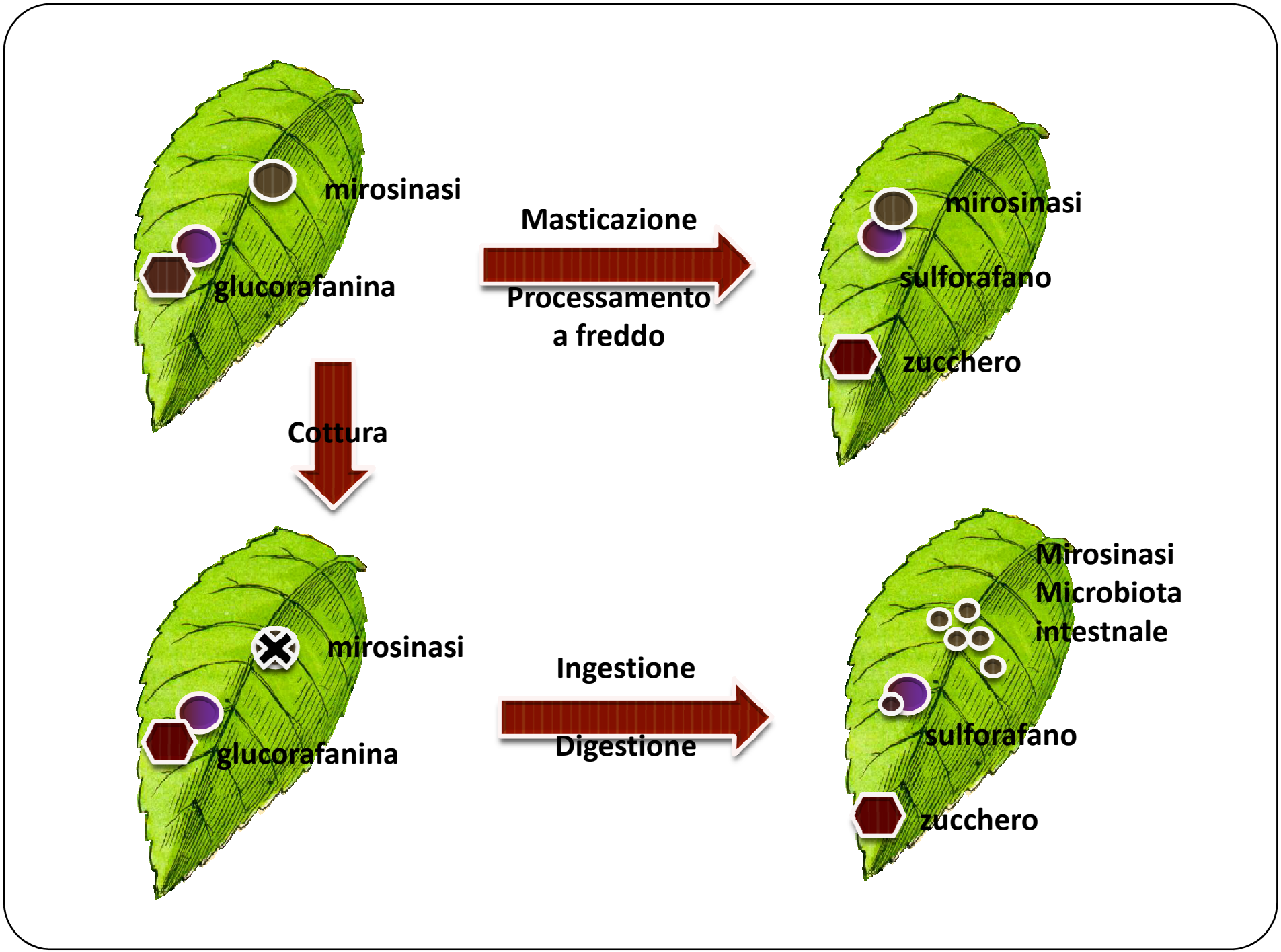
Figure 1. Glucoraphanin Metabolism



glucosinolati (GL)

isotiocianati (ITC)

oltre 120 composti


mirosinasi
glucorafanina
Masticazione
Processamento
a freddo
mirosinasi
sulforafano
zucchero
Cottura
mirosinasi
glucorafanina
Ingestione
Digestione
Mirosinasi
Microbiota
intestnale
sulforafano
zucchero

Farmacocinetica del sulforafano

Assorbimento nell'uomo superiore al 70% della dose somministrata.
Dopo 1 ora è già accumulato nei tessuti.

Nel fegato dà origine a coniugati col glutatione (**Sulforafano-GSH**).

Quest'ultimo raggiunge il rene dove origina:

- Cistinil-glicina-sulforafano
- Cistein-sulforafano
- NAC-sulforafano.

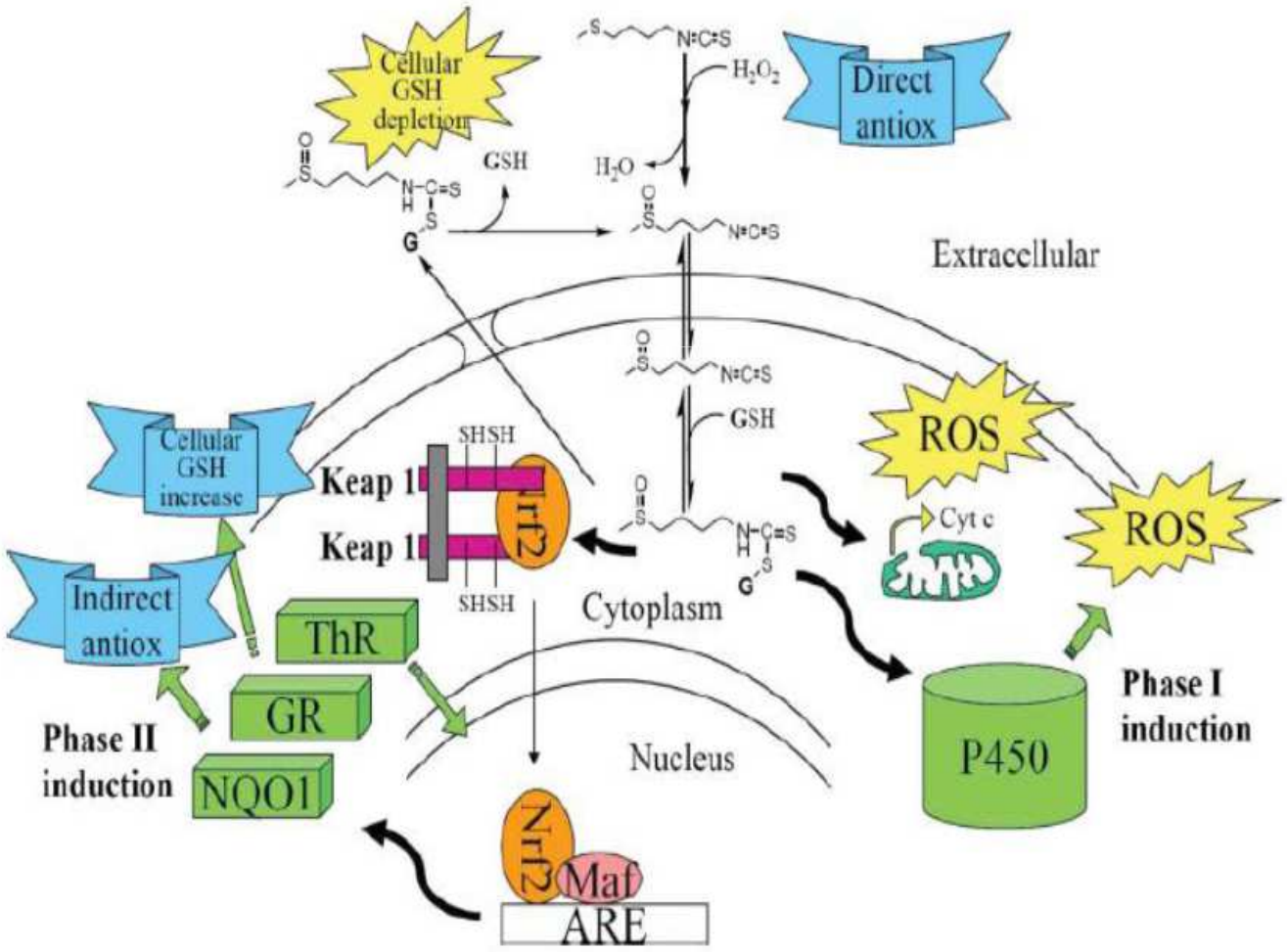
In queste 3 forme torna al fegato dove viene acetilato e re-inviato al rene.

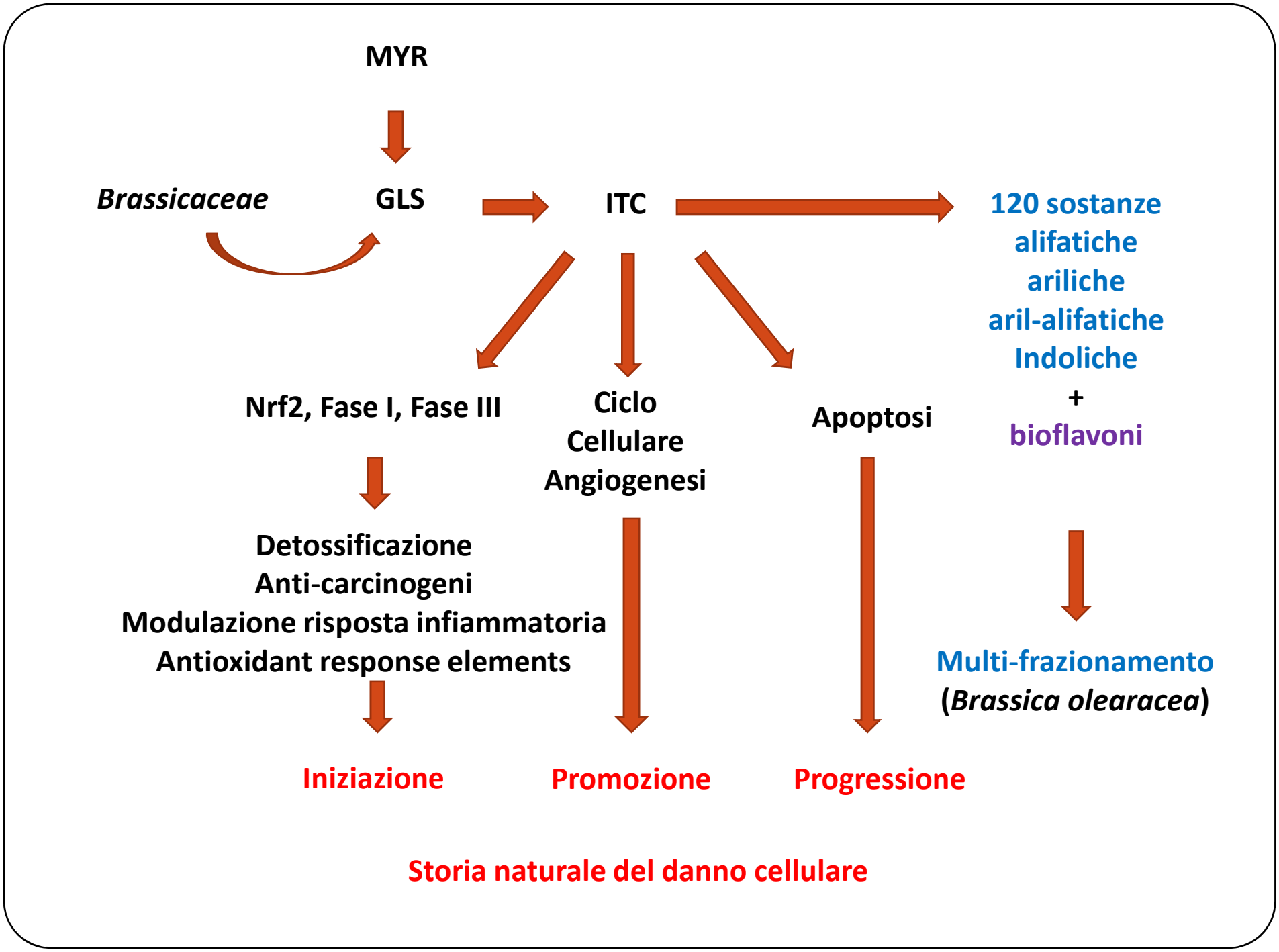
Escrezione renale completa in 72 ore dalla somministrazione.

PARADOSSO DELLE BRASSICACEE

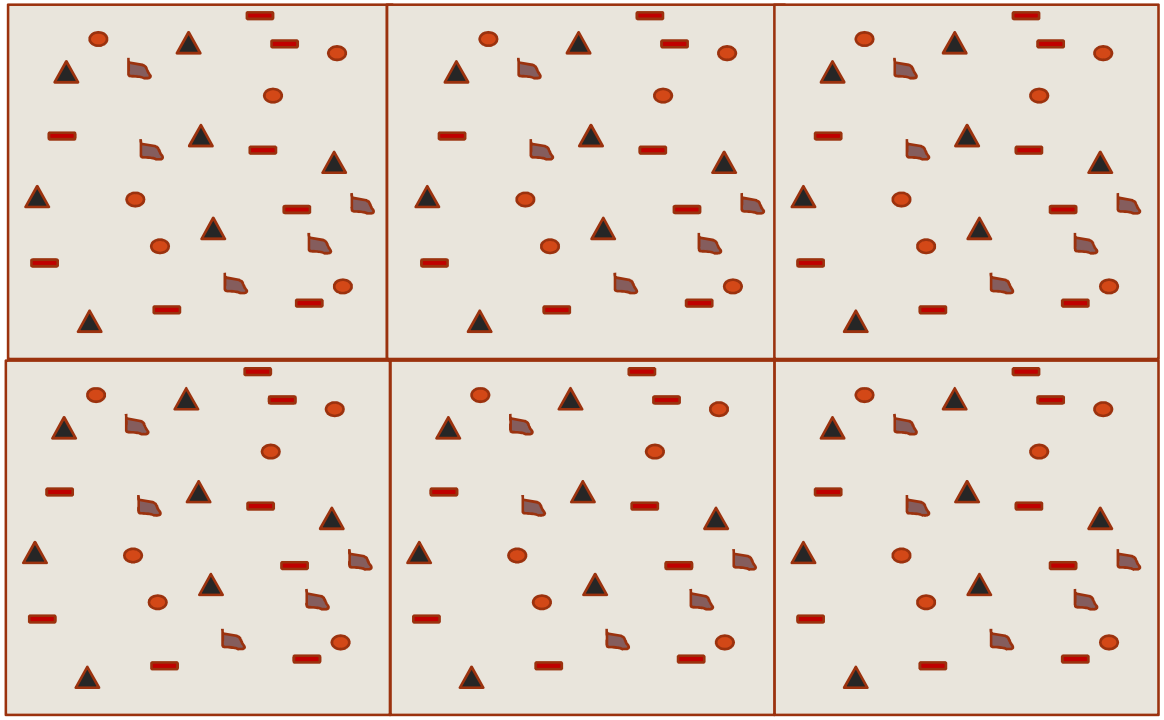
Alla base dell'attività biologica protettiva delle molecole derivate dalla famiglia delle Brassicaceae, come ad esempio gli ITC, proprio la loro capacità proossidante, mediata principalmente dal consumo di GSH intracellulare, rappresenterebbe paradossalmente il fattore principale che provoca l'attivazione di questo sistema di protezione cellulare Nrf2 e ARE dipendente, che controlla le difese antiossidanti e detossificanti (Figura 5.4).

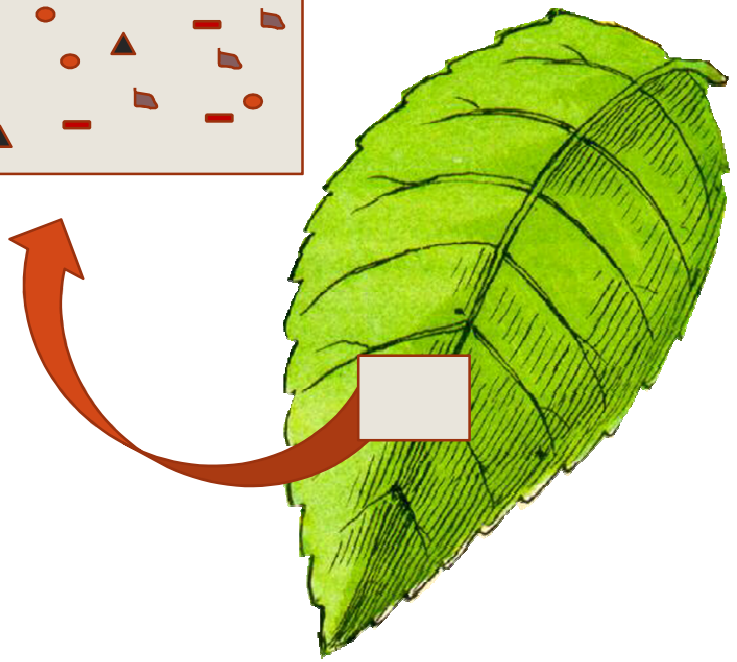
Figura 5.4. Meccanismo di azione antiossidante degli isotiocianati.




MYR
Brassicaceae
GLS
ITC
120 sostanze
alifatiche
ariliche
aril-alifatiche
Indoliche
+
bioflavoni
Nrf2, Fase I, Fase III
Ciclo
Cellulare
Angiogenesi
Apoptosi
Detossificazione
Anti-carcinogeni
Modulazione risposta infiammatoria
Antioxidant response elements
Multi-frazionamento
(Brassica olearacea)
Iniziazione
Promozione
Progressione
Storia naturale del danno cellulare

MULTIFRAZIONAMENTO

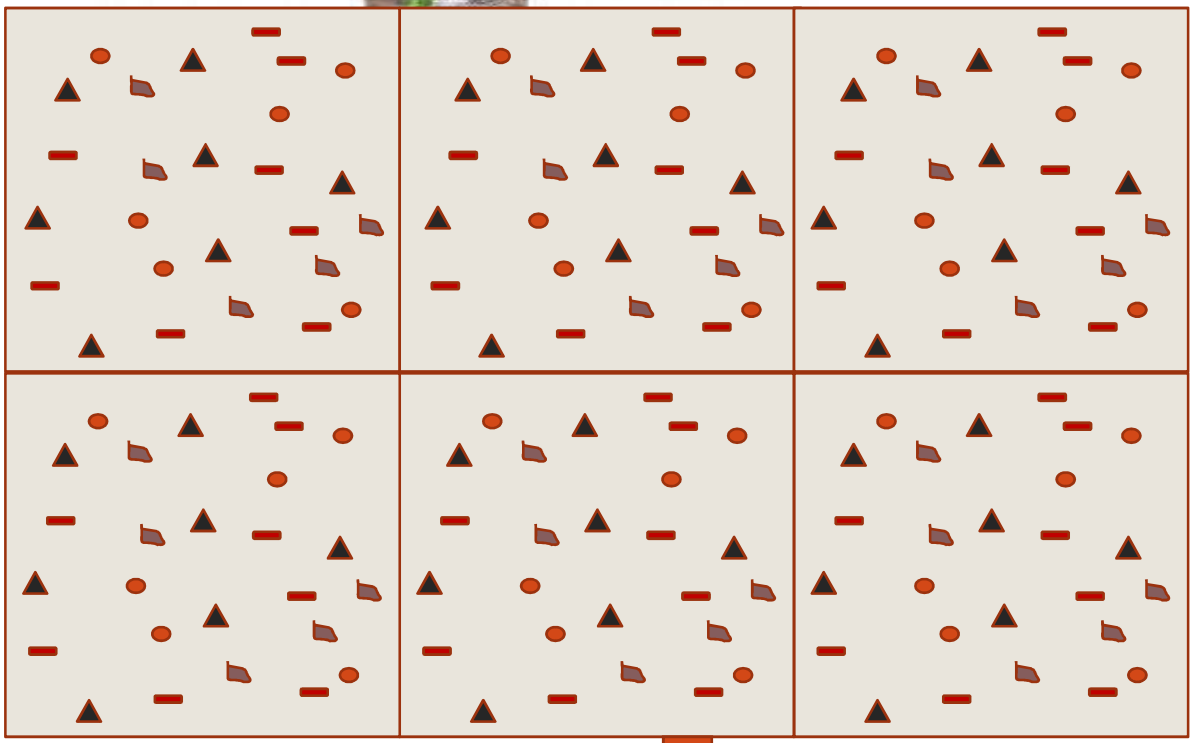




NUOVA TECNICA ESTRATTIVA
PER LE PIANTE DI CUI NON SI
CONOSCONO CON CERTEZZA
GLI ATTIVI O,TRA GLI ATTIVI,
QUELLI CHE FUNZIONANO DI PIU'

QUANDO CONOSCO L'ATTIVO

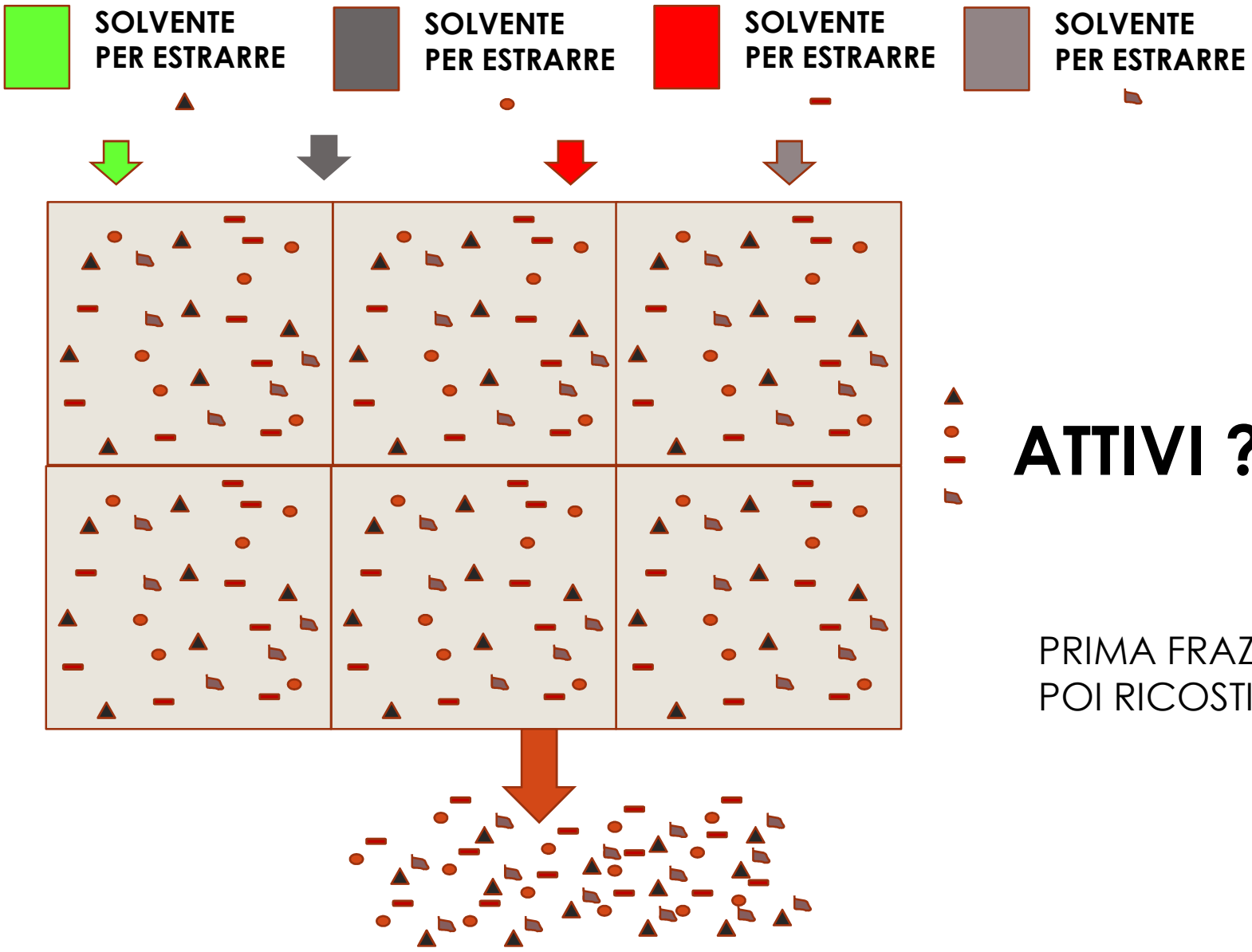
SOLVENTE PER ESTRARRE L'ATTIVO



ATTIVO

NON ATTIVI

QUANDO NON CONOSCO L'ATTIVO



PRIMA FRAZIONO
POI RICOSTITUISCO

ANTIOSSIDANTI NATURALI

- IN CONCLUSIONE….

- QUANDO ASSUMERE INTEGRATORI CONTENENTI ANTIOSSIDANTI NATURALI?

1)IN TUTTE LE SITUAZIONI DI STRESS OSSIDATIVO PRESUNTO O CERTO (MALATTIE CRONICHE,TERAPIE CRONICHE,STRESS ECCESSIVO,FUMO, ALCOOL,SPORT, ESPOSIZIONE SOLARE,ALIMENTAZIONE SCORRETTA)

2)ASSUMERE A CICLI,NON IN MANIERA CONTINUATA (SOPRATTUTTO I LIPOFILI) POSSIBILMENTE VARIANDOLI

3)NON ASSUMERE SENZA REALE BISOGNO, MA SOLO PER SENTITO DIRE…

GRAZIE PER L'ATTENZIONE