14:40 **Biofarmaceutica in neurologia: razionali per corrette formulazioni**

F. Di Pierro

QUALE RUOLO DELLA MEDICINA COMPLEMENTARE NELLA NEUROLOGIA DI OGGI

mercoledì 5 febbraio 2014

ore 14:00 - 21:30

Il mercato degli Integratori
Gennaio 2013

La performance sull'anno terminante a Gennaio 2013 vede il mercato degli Integratori sviluppare in **Farmacia** 1.670,1 milioni di Euro circa (+2,8% rispetto all'anno precedente) per un totale di quasi 111,2 milioni di confezioni (+1,5% rispetto all'anno precedente).

Nel canale degli **Ipermercati+Supermercati** gli Integratori movimentano 133,9 milioni di Euro (+10,7%) e circa 22,5 milioni di confezioni (+14,7%).

La **Parafarmacia** sviluppa nel mercato degli Integratori 111,5 milioni di Euro registrando una **flessione a valore del 3,5%.** Passando all'analisi dei **volumi** sono state immesse sul mercato circa 7,5 milioni di confezioni **in calo del 4%** (rispetto all'anno precedente).

Efficacia (percepita)

BJCP British Journal of Clinical Pharmacology

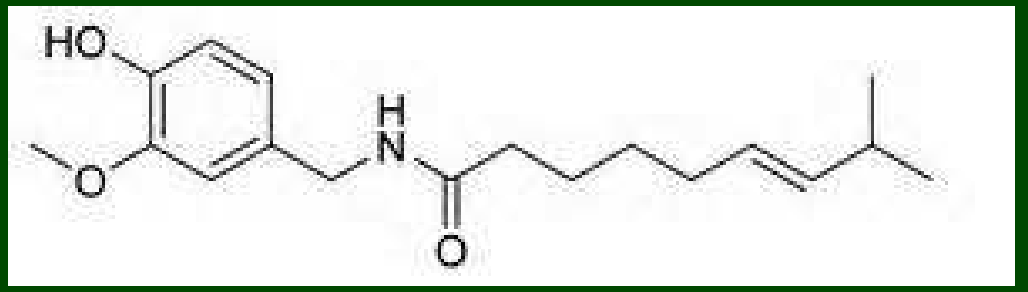
DOI:10.1111/j.1365-2125.2009.03365.x

Letter to the Editors

Too much effectiveness from a herbal drug

Alfredo Vannacci,[1,2] Francesco Lapi,[1,2,3] Roberto Baronti,[4] Eugenia Gallo,[2,5] Luigi Gori,[5] Alessandro Mugelli[1,2] & Fabio Firenzuoli[5]

[1]Tuscan Regional Centre of Pharmacovigilance, [2]Department of Preclinical and Clinical Pharmacology, University of Florence, [3]Regional Agency for Healthcare Services of Tuscany, Epidemiology Unit and [4]Public Health Laboratory, Department of Prevention, Local Health Service, Florence, and [5]Centre of Natural Medicine, S. Giuseppe Hospital, Empoli, Italy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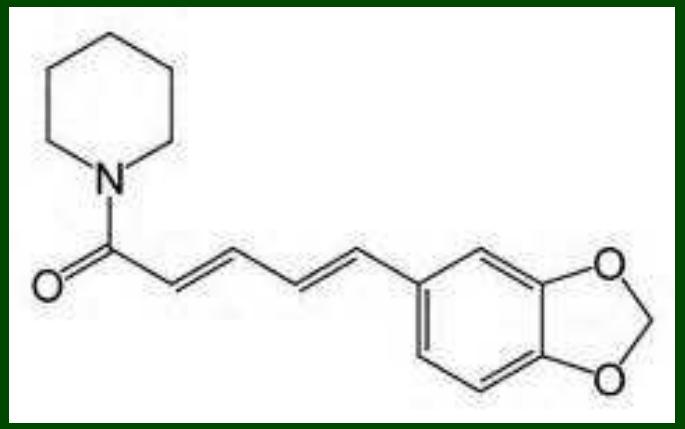
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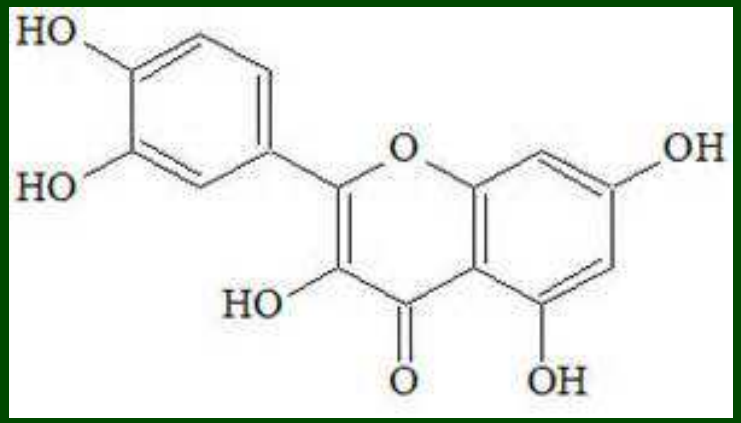
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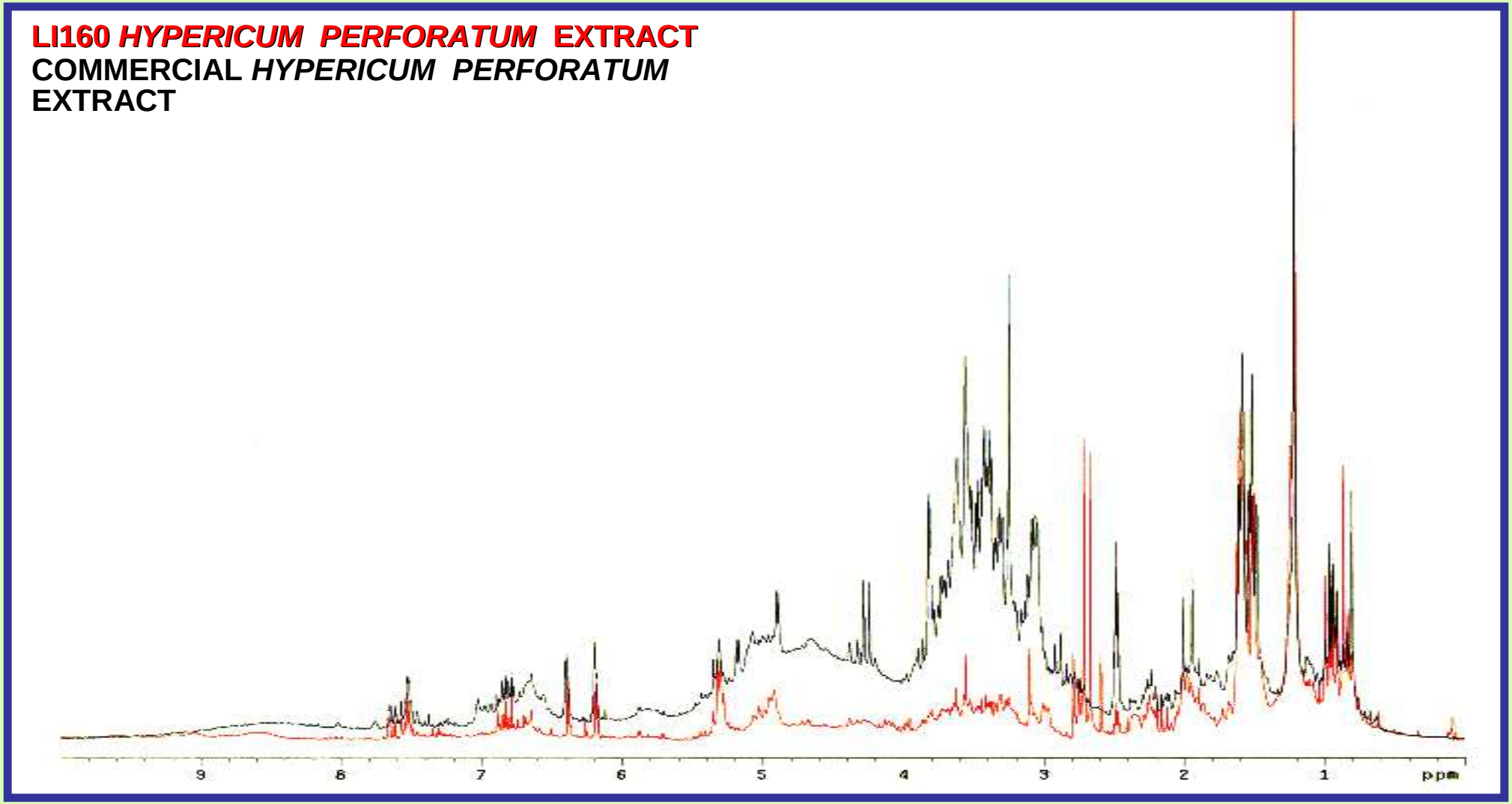
COMPARATIVE ^{1}H-NMR OF TWO *HYPERICUM PERFORATUM* EXTRACTS

LI160 *HYPERICUM PERFORATUM* EXTRACT

COMMERCIAL *HYPERICUM PERFORATUM* EXTRACT



EFFECT OF *HYPERICUM PERFORATUM* EXTRACTS ON ESCAPE DEFICIT DEVELOPMENT IN RATS

Substance	No. of animals	Dose mg/kg p.o.	ESCAPE NUMBERS (mean ± s.e.)
CONTROL (NAIVE)	16	---	21.1 ± 1.6
CONTROL (ED)	16	---	2.6 ± 0.7
Hypericum perforatum COMMERCIAL EXTRACT	8	25	2.4 ± 0.6
	8	50	2.9 ± 0.7
	8	100	4.3 ± 0.6
	8	300	10.2 ± 0.9★
	8	1000	16.8 ± 1.7★★
Hypericum perforatum LI130	8	25	9.4 ± 1.3★
	8	50	16.5 ± 5.3★★
	8	100	20.8 ± 1.8★★
	8	300	21.3 ± 1.3★★
	8	1000	21.6 ± 1.6★★

★p <0.05 ★★ p <0.01 Dunnett *t* test

Neuropsychiatr Dis Treat. 2011;7:441-7.

Ginkgo biloba extract in the treatment of tinnitus: a systematic review.

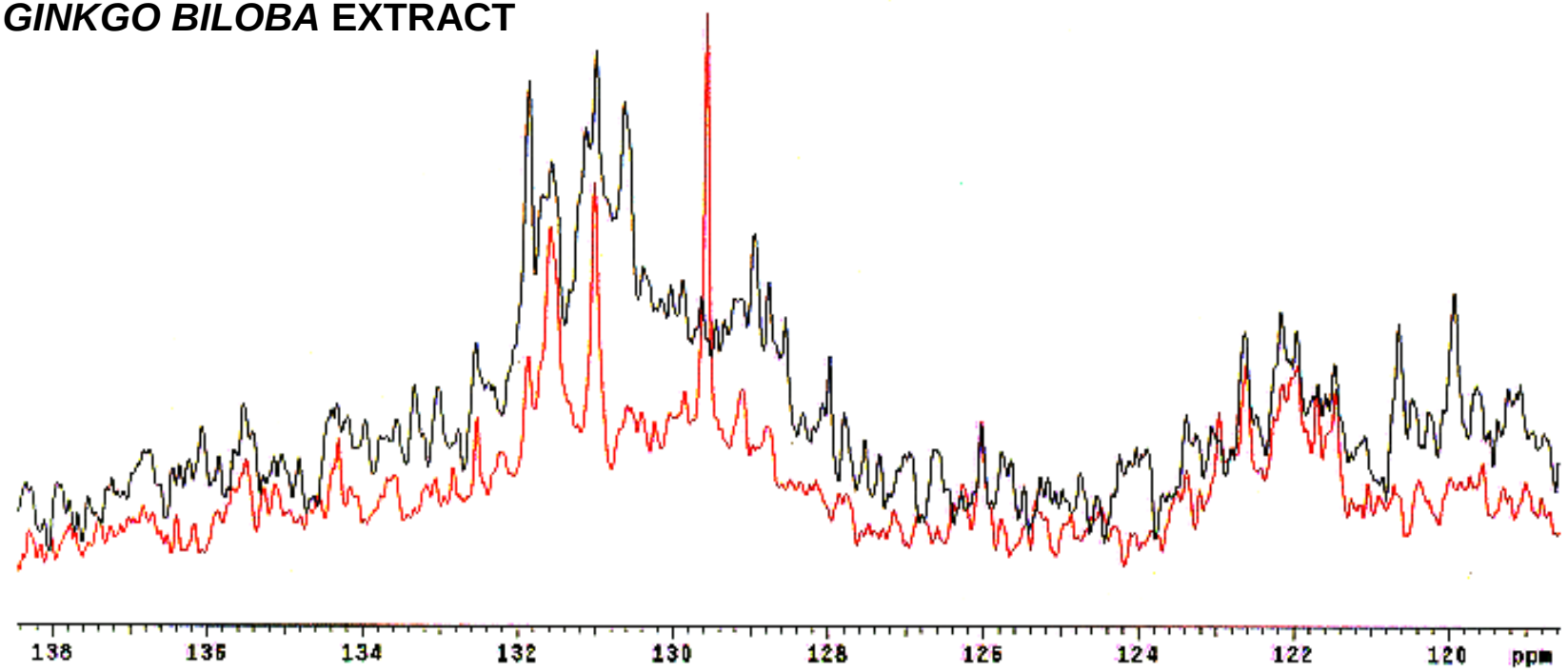
von Boetticher A
Ear, Nose and Throat Surgery, Lueneburg, Germany.

Tinnitus is a symptom frequently encountered by ear, nose, and throat practitioners. A causal treatment is rarely possible, and drug and nondrug treatment options are limited. One of the frequently prescribed treatments is Ginkgo biloba extract. Therefore, randomized, placebo-controlled clinical trials of Ginkgo biloba extract preparations were searched for and reviewed systematically. **There is evidence of efficacy for the standardized extract, EGb 761(®)** (Dr Willmar Schwabe GmbH & Co KG Pharmaceuticals, Karlsruhe, Germany), in the treatment of tinnitus from three trials in patients in whom tinnitus was the primary complaint. Supportive evidence comes from a further five trials in patients with age-associated cognitive impairment or dementia in whom tinnitus was present as a concomitant symptom. As yet, the efficacy of other ginkgo preparations has not been proven, which does not necessarily indicate ineffectiveness, but may be due to flawed clinical trials. In conclusion, EGb 761(®), a **standardized Ginkgo biloba extract, is an evidence-based treatment option in tinnitus.**

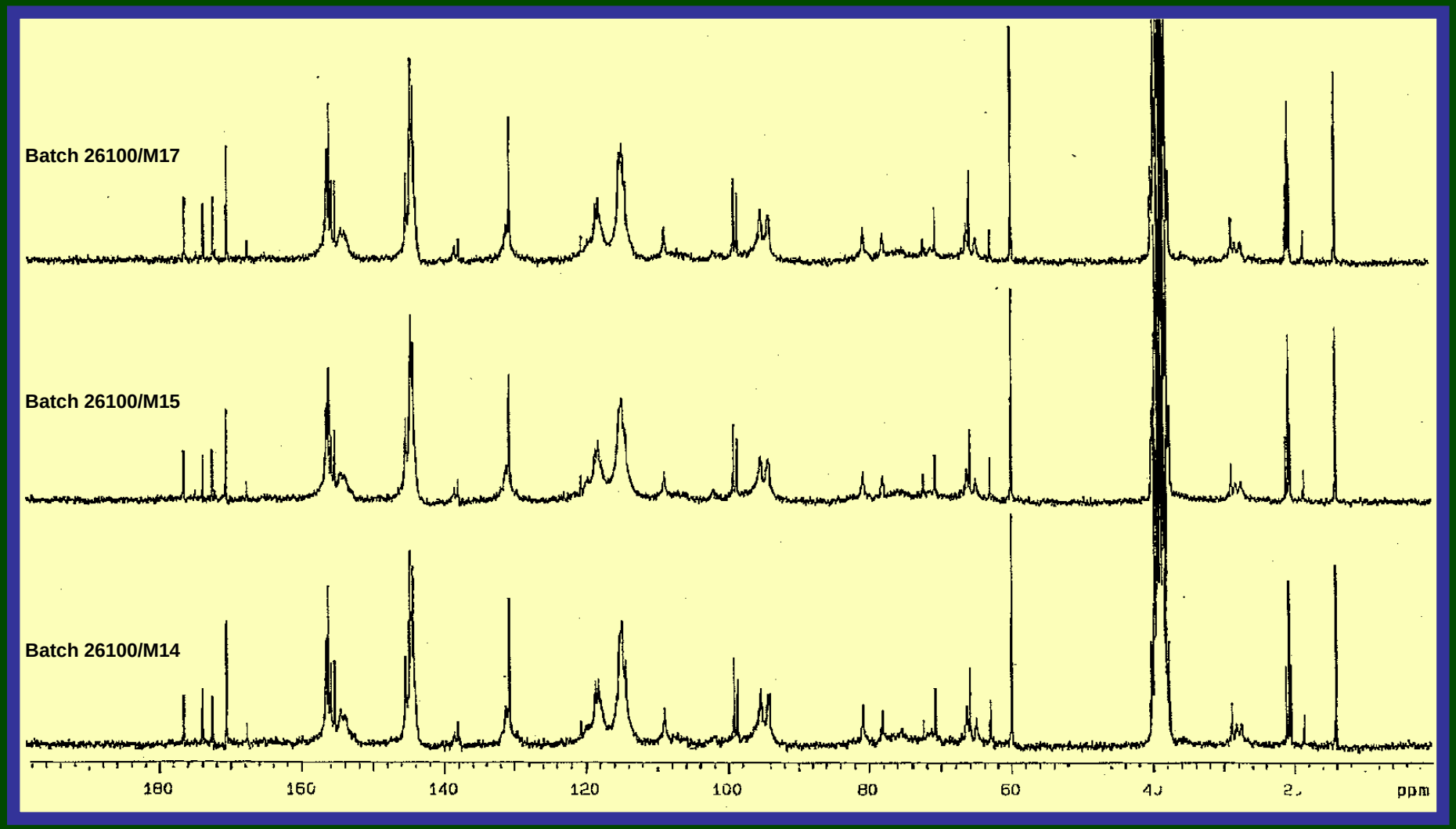
COMPARATIVE ^{1}H-NMR OF TWO *GINKGO BILOBA* EXTRACTS

EGB 761

***GINKGO BILOBA* EXTRACT**



^{13}C-NMR OF SEVERAL BATCHES OF ENDOTHELON (SANOFI)



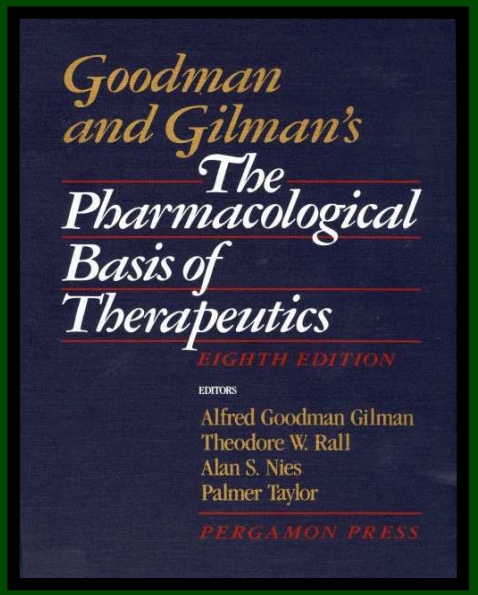
L’azione biologica di un composto è legato alla quota di composto che raggiunge la circolazione plasmatica

Intoppi?

- Ruolo dell’acidità gastrica } gastrico

-Assorbimento seguito da estrusione
-Composti idrofili non assorbiti
(o viceversa) } intestinale

- Ruolo della detossificazione epatica } epatico



BIOTRANSFORMATION OF DRUGS

The physicochemical properties of drug molecules that permit rapid passage across cellular membranes during absorption and distribution also impair subsequent excretion. For example, after filtration at the renal glomerulus most lipid-soluble drugs largely escape excretion from the body because they are readily reabsorbed from the filtrate by diffusion through the renal tubular cells. Thus, the enzymatic biotransformation of drugs to more polar and less lipid-soluble metabolites enhances their excretion and reduces their volume of distribution. Such biotransformation relieves the burden of foreign chemicals and is critical for the survival of the organism. Studies of the genes that encode the enzymes of biotransformation have led to the view that they evolved millions of years ago as a mechanism for removal of natural constituents of foods, such as flavones, terpenes, steroids, and alkaloids. (For excellent summaries of drug biotransformation, *see* Goldstein *et al.*, 1974; Lee *et al.*, 1977; Jacqz *et al.*, 1986; Nebert and Gonzalez, 1987.)

Il paradosso della fitoterapia:

Concentrare derivati molecolari che sono stati
la principale spinta evolutiva
alla genesi dei sistemi di detossificazione
“citocromi” (P450)

Fitoterapia *nemica*:

Competizione coi farmaci e
Inibizione della loro attività

Clin Pharmacol Ther. 2003 Dec;74(6):525-35.

The interaction between St John's wort and an oral contraceptive.

Hall SD et al.

OBJECTIVES: The popular herbal remedy St John's wort is an inducer of cytochrome P450 (CYP) 3A enzymes and **may reduce the efficacy of oral contraceptives**. Therefore we evaluated the effect of St John's wort on the disposition and efficacy of Ortho-Novum 1/35 (Ortho-McNeil Pharmaceutical, Inc, Raritan, NJ), a popular combination oral contraceptive pill containing ethinyl estradiol (INN, ethinylestradiol) and norethindrone (INN, norethisterone). RESULTS: Concomitant use of St John's wort was associated with a significant (P <.05) increase in the oral clearance of norethindrone (8.2 +/- 2.7 L/h to 9.5 +/- 3.4 L/h, P =.042) and a significant reduction in the half-life of ethinyl estradiol (23.4 +/- 19.5 hours to 12.2 +/- 7.1 hours, P =.023). The oral clearance of midazolam was significantly increased (109.2 +/- 47.9 L/h to 166.7 +/- 81.3 L/h, P =.007) during St John's wort administration, but the systemic clearance of midazolam was unchanged (37.7 +/- 11.3 L/h to 39.0 +/- 10.3 L/h, P =.567). Serum concentrations of follicle-stimulating hormone, luteinizing hormone, and progesterone were not significantly affected by St John's wort dosing (P >.05). Breakthrough bleeding occurred in 2 of 12 women in the control phase compared with 7 of 12 women in the St John's wort phase. The oral clearance of midazolam after St John's wort dosing was greater in women who had breakthrough bleeding (215.9 +/- 66.5 L/h) than in those who did not (97.5 +/- 37.2 L/h) (P =.005). CONCLUSION: St John's wort causes an induction of ethinyl estradiol-norethindrone metabolism consistent with increased CYP3A activity. Women taking oral contraceptive pills should be counseled to expect breakthrough bleeding and should consider adding a barrier method of contraception when consuming St Johns wort.

*A*TP *B*inding *C*assette

(ABC)

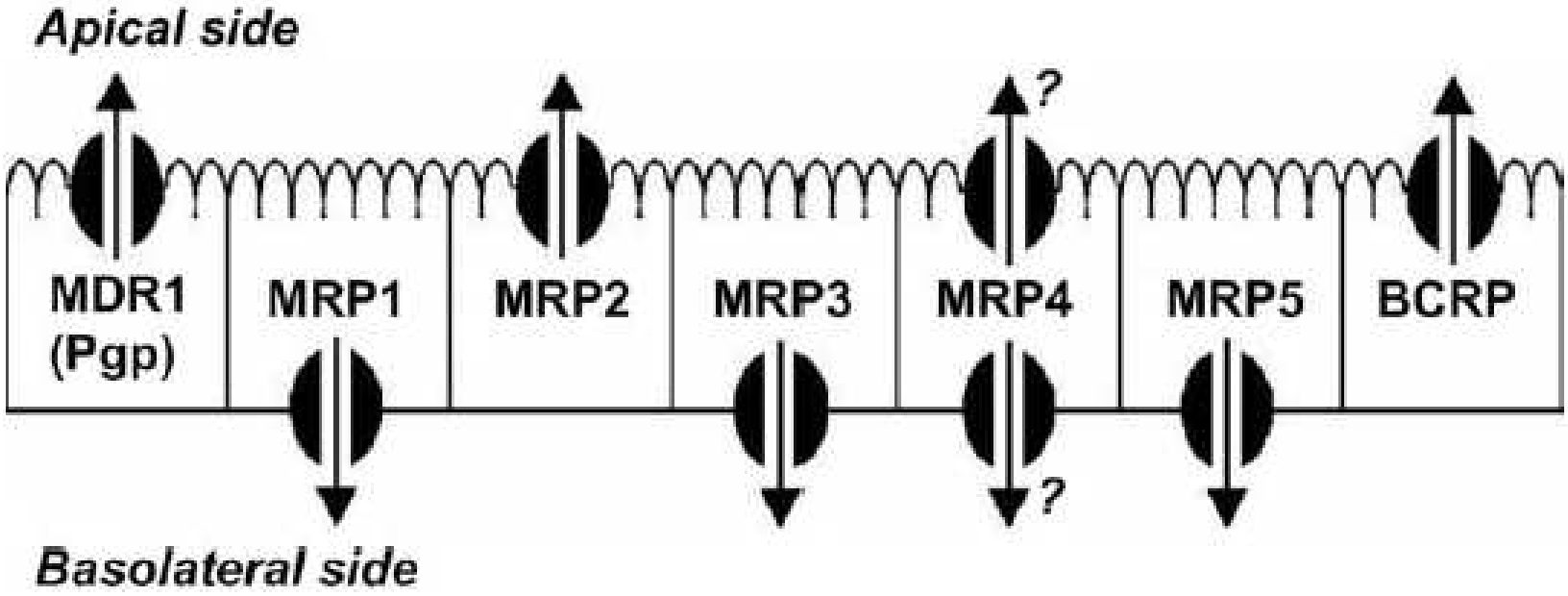


Fig. 1. Cellular localization of intestinal ABC transporters. P-glycoprotein (Pgp/MDR1/ABCB1), MRP2 (ABCC2) and breast cancer resistance protein (BCRP/ABCG2/ABCP) are localized in apical membranes [4,6,8]. MRP1 (ABCC1), MRP3 (ABCC3) and MRP5 (ABCC5) are localized in basolateral membranes of enterocytes [5,9–11]. MRP4 (ABCC4) has been suggested to be located in the apical as well as in the basolateral membrane of the intestine [4, 12,13].

Transplant Proc. 2005 Jun;37(5):2051-3.

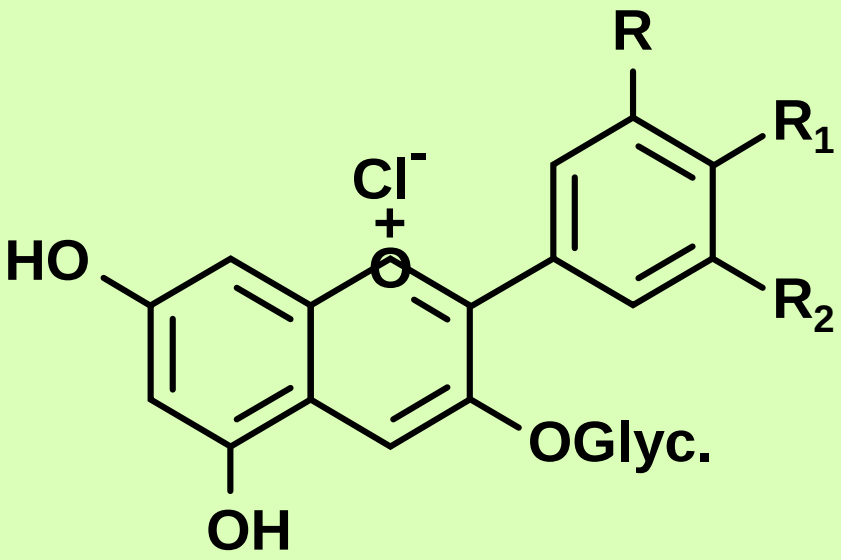
Different evolution of trough and dose levels during the first year after transplantation for tacrolimus versus cyclosporine.

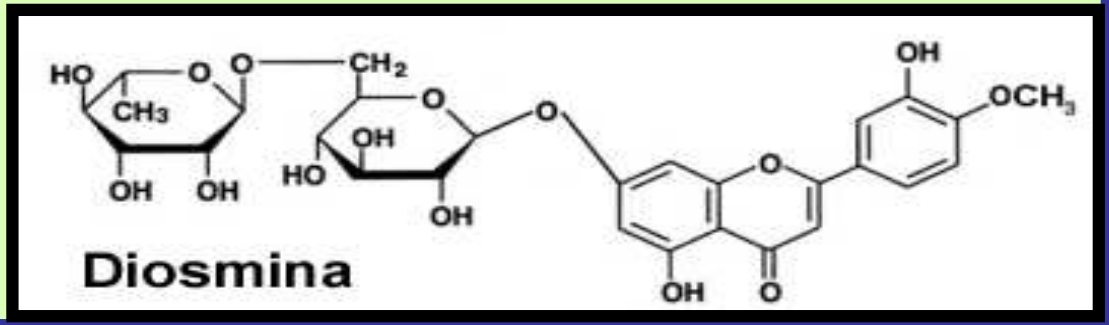
Lemahieu WP, Maes BD, Vanrenterghem Y.

At present, the two calcineurin inhibitors-cyclosporine (CsA) and tacrolimus (FK506)-are among the most frequently used immunosuppressants in clinical transplantation. **Both drugs share variable oral bioavailability, which necessitates intense drug monitoring. This variability is attributed to large drug efflux by P-glycoprotein (PGP).** In addition, the activity of both CYP3A4 and PGP can vary substantially within the same individual due to environmental factors such as concomitant intake of inducing/inhibiting medications (eg, rifampicin/sporanox) or **food substances (eg, grapefruit juice).** More recently, an inducing effect of methylprednisolone on intestinal and hepatic CYP3A4 has been shown. Also, an influence of gender on CYP3A4 activity (being higher in women) has been reported. Once CsA and FK506 are absorbed and reach the bloodstream, both drugs are avidly bound to erythrocytes (up to 95% for FK506 and 50% for CsA) and plasma proteins, leaving only a small fraction of circulating active drug. This phenomenon also limits further hepatic catabolism and hence clearance of drug, which is influenced by hematocrit and levels of plasma proteins such as albumin. The aim of the present study was to compare the influence of changing steroid doses, hematocrit, and albumin on trough and dose levels of FK506 versus CsA during the first year after transplantation. In addition, the evolution of trough and dose levels of FK506 versus CsA was stratified according to gender.

Scarsa biodisponibilità orale

Antocianosidi del mirtillo





BILBERRY: PHARMACOKINETICS

C_{max} µg/ml	T_{max} min	K_{ab} min^{-1}	α min^{-1}	β min^{-1}	$t_{1/2}\alpha$ min	$t_{1/2}\beta$ min	AUC $0 \rightarrow \infty$ min µg ml^{-1}	Cl_p ml $min^{-1} kg^{-1}$	Bioav. %
2.47	15.00	0.129	0.078	0.011	8.88	63.00	129.45	14.10	1.2*

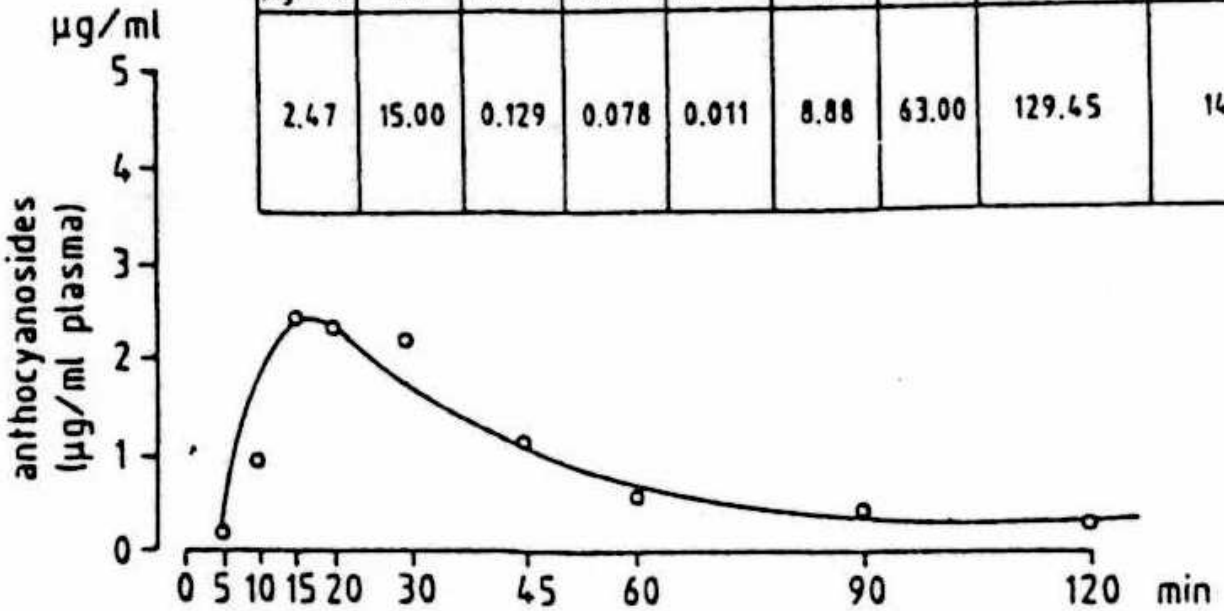


Fig. 4: Plasma levels and pharmacokinetic data after oral VMA (400 mg/kg). * Value calculated in relation to intravenous VMA.

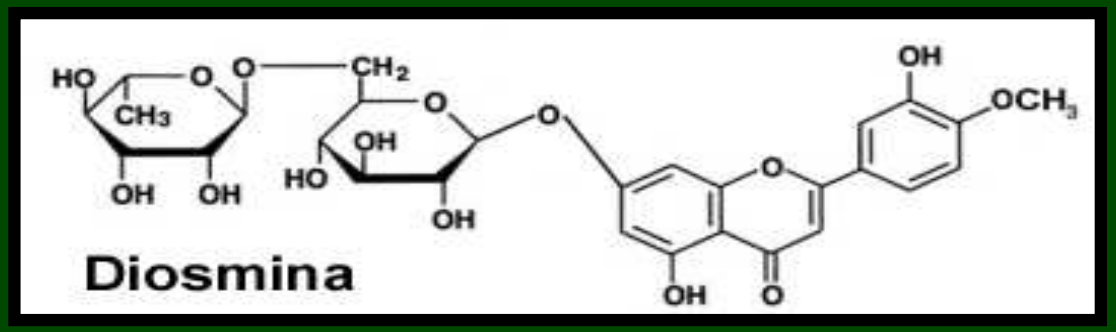
Mol Pharm. 2007 Nov-Dec;4(6):807-18

Bioavailability of curcumin: problems and promises.

Anand P et al.

Curcumin, a polyphenolic compound derived from dietary spice turmeric, possesses diverse pharmacologic effects including anti-inflammatory, antioxidant, antiproliferative and antiangiogenic activities. Phase I clinical trials have shown **that curcumin is safe even at high doses (12 g/day) in humans but exhibit poor bioavailability.**

Major reasons contributing to the low plasma and tissue levels of curcumin appear to be due to poor absorption (os), rapid metabolism (iv), and rapid systemic elimination (os). To improve the bioavailability of curcumin, numerous approaches have been undertaken. These approaches involve, first, the use of adjuvant like piperine that interferes with glucuronidation; second, the use of liposomal curcumin; third, curcumin nanoparticles; fourth, the use of curcumin phospholipid complex; and fifth, the use of structural analogues of curcumin (e.g., EF-24). The latter has been reported to have a rapid absorption with a peak plasma half-life. Despite the lower bioavailability, therapeutic efficacy of curcumin against various human diseases, including cancer, cardiovascular diseases, diabetes, arthritis, neurological diseases and Crohn's disease, has been documented. Enhanced bioavailability of curcumin in the near future is likely to bring this promising natural product to the forefront of therapeutic agents for treatment of human disease.



6 X 500 mg = 3000 mg/die

Compliance

Costi

Regolatorio

2. Sostanze per le quali sono stati definiti livelli massimi di apporto giornaliero

Betaina mg 250
Effetti: metabolismo dell'omocisteina

Bioflavonoidi (come complesso) mg 1000
Effetti: azione antiossidante; trofismo del microcircolo.
Avvertenza supplementare:
Non assumere in gravidanza
Quercetina, diosmina, esperidina non superiori,
singolarmente, a mg 300

Epigallocatechinagallato (ECG) da tè verde mg 300
Donne gravidanza e durante l'allattamento mg 120
Gli apporti sopra indicati vanno frazionati in almeno due assunzioni,
dopo i pasti.
Effetti: antiossidante; trofismo della pelle; equilibrio del peso corporeo;
metabolismo dei carboidrati; regolare funzionalità dell'apparato cardiovascolare

1° soluzione: tecnica galenica

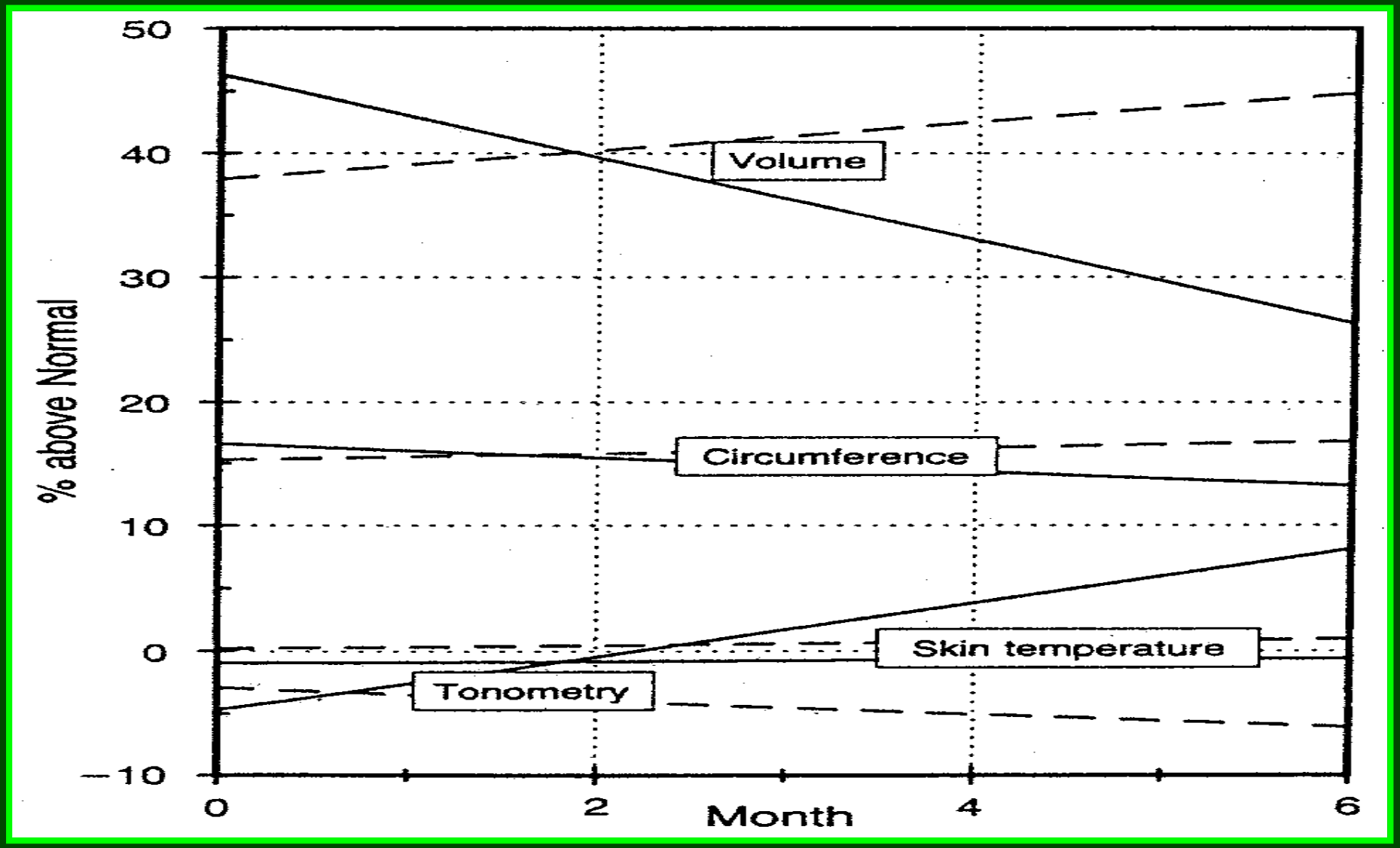
Cessioni programmate
Gastro-protezioni
Colon-specificità
Nano-emulsioni

J Clin Pharmacol. 1981; **21**:294–300.

Pilot Study on Bioavailability of Coumarin and 7-Hydroxycoumarin upon Peroral Administration of Coumarin in a Sustained-Release Dosage Form

W. A. RITSCHEL, Ph.D., Dr.Univ. and K. A. HOFFMANN, M.D. Cincinnati, Ohio

Abstract: Prolonged-release tablets containing coumarin were compared to intravenous and peroral administration of coumarin solution in man. Unchanged coumarin, the Phase I metabolite 7-hydroxycoumarin, and the Phase II metabolite 7-hydroxycoumarin glucuronide were determined in whole blood. Upon peroral administration, only approximately 1 per cent coumarin was found unchanged in the systemic circulation. However, the amount of the glucuronide found indicates complete absorption with extensive first-pass effect. When the prolonged-release dosage form was compared to the peroral solution, the extent of bioavailability of coumarin was 35 per cent, whereas the 7-hydroxycoumarin glucuronide was totally available. This supports the hypothesis that coumarin might be a prodrug and 7-hydroxycoumarin the active moiety. The drug liberation of coumarin from the sustained-release tablets follows first-order kinetics. A linear correlation was found between per cent of drug released in vitro and the area under the concentration–time curve, *AUC* (0–t), of total 7-hydroxycoumarin (7HC + 7HCG).



From: N. Engl. J. Med., Oct. 14 (1993), p 1162

2° soluzione: uso di bio-enhancer

Vettorizzazioni con lipidi (fitosomi)
Uso di antagonisti MDR
Uso di inibitori enzimatici (epatici)

The Scientific World Journal
Volume 2012, Article ID 637953, 33 pages
doi:10.1100/2012/637953

The ScientificWorldJOURNAL

Review Article

A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers

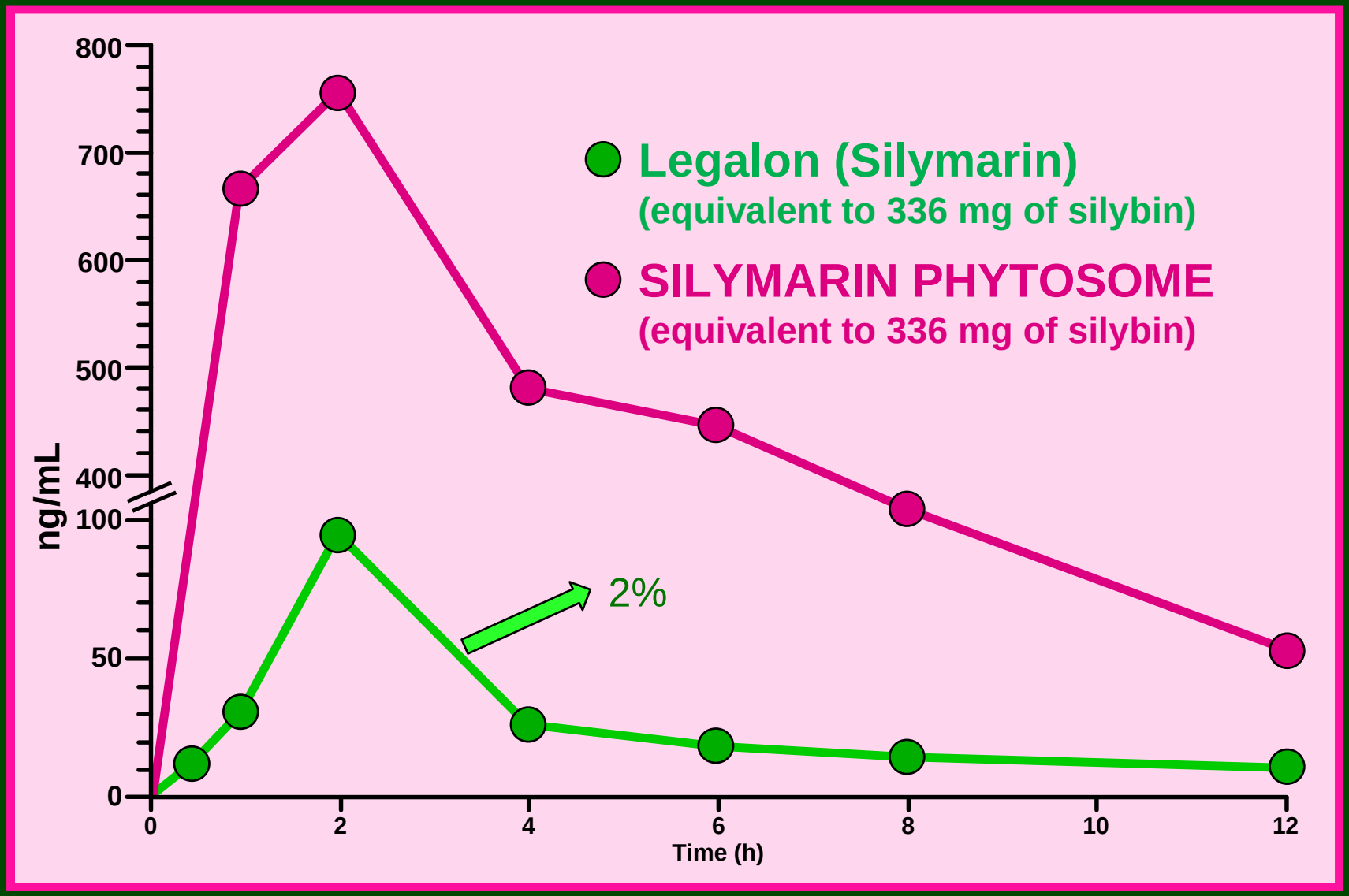
Ghanshyam B. Dudhatra, Shailesh K. Mody, Madhavi M. Awale, Hitesh B. Patel, Chirag M. Modi, Avinash Kumar, Divyesh R. Kamani, and Bhavesh N. Chauhan

Department of Pharmacology & Toxicology, College of Veterinary Science & Animal Husbandry, Sardarkrushinagar Dantiwada Agricultural University, Sardarkrushinagar 385506, Gujarat, India

Correspondence should be addressed to Ghanshyam B. Dudhatra, drgvets@gmail.com

Received 24 June 2012; Accepted 9 August 2012

SILYMARIN, SILYMARIN-PHYTOSOME: DIFFERENT ABILITY TO CONCENTRATE IN PLASMA



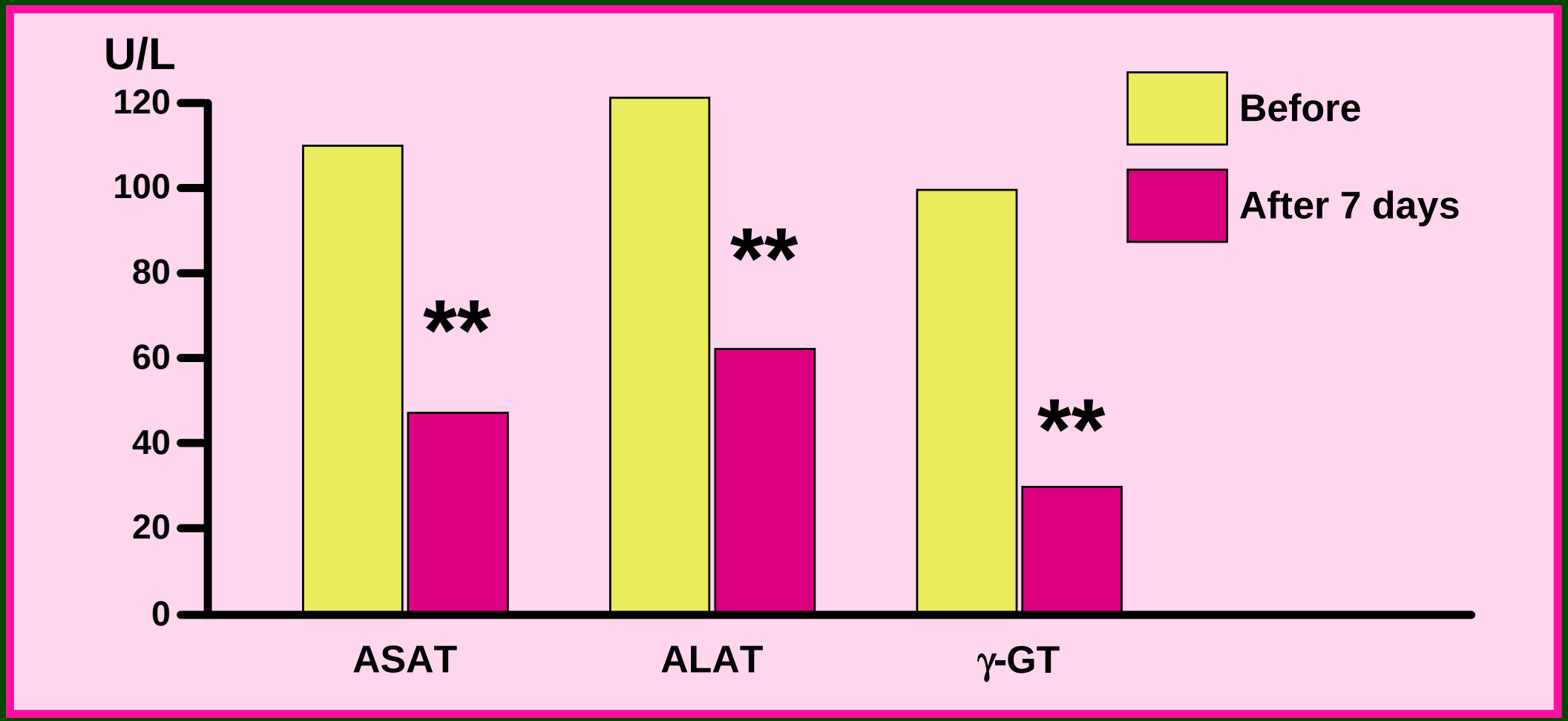
Int J Clin Pharmacol Ther Toxicol. 1993 Sep;31(9):456-60.

A pilot study on the liver protective effect of silybin-phosphatidylcholine complex (IdB1016) in chronic active hepatitis.

Buzzelli G, Moscarella S, Giusti A, Duchini A, Marena C, Lampertico M.

In order to assess the liver protective activity and the antioxidant properties of a new silybin complex (IdB1016), we carried out a short-term pilot study on 20 patients with chronic active hepatitis (CAH), randomly assigned to 240 mg of silybin b.i.d. (10 patients, 4 m/6 f, mean age: 50 years) or placebo (10 patients, 2 m/8 f, mean age: 55 years). Blood samples were collected before and **after 7 days** of treatment for liver function tests (LFTs), malonaldehyde (MDA) as an index of lipid peroxidation, and copper (Cu) and zinc (Zn), two trace elements involved in protecting cells against free radical-mediated lipid peroxidation. In the treated group, there was a statistically significant reduction of mean (+/- SEM) serum concentrations of aspartate aminotransferase (AST) from 88.0 (+/- 13.3) to 65.9 (+/- 7.5) u/l, ($p < 0.01$), of alanine aminotransferase (ALT) from 115.9 (+/- 12.9) to 82.5 (+/- 10.6) u/l ($p < 0.01$), of gamma-glutamyltranspeptidase (gamma-GT) from 51.4 (+/- 9.3) to 41.3 (+/- 4.2) u/l ($p < 0.02$) and of total bilirubin (TB) from 0.76 (+/- 0.08) to 0.53 (+/- 0.04) mg/dl ($p < 0.05$). Alkaline phosphatase (AP) fell slightly from 143.4 (+/- 6.4) to 137.5 (+/- 7.8) u/l. There were no significant changes in MDA, Cu or Zn serum concentrations. These results show that IdB1016 may improve LFTs related to hepatocellular necrosis and/or increases membrane permeability in patients affected by CAH.

Effect of SILIPIDE
on hepatocellular damage measured as serum enzymes activity in patients with chronic active hepatitis



Phytomedicine. 2009 May;16(5):391-400.

A randomized controlled trial to assess the safety and efficacy of silymarin on symptoms, signs and biomarkers of acute hepatitis.

El-Kamary SS, et al.

PURPOSE: Milk thistle or its purified extract, silymarin (Silybum marianum), is widely used in treating acute or chronic hepatitis. Although silymarin is hepatoprotective in animal experiments and some human hepatotoxic exposures, its efficacy in ameliorating the symptoms of acute clinical hepatitis remains inconclusive. In this study, our purpose was to determine whether silymarin improves symptoms, signs and laboratory test results in patients with acute clinical hepatitis, regardless of etiology. METHODS: This is a randomized, placebo-controlled trial in which participants, treating physicians and data management staff were blinded to treatment group. The study was conducted at two fever hospitals in Tanta and Banha, Egypt where patients with symptoms compatible with acute clinical hepatitis and serum alanine aminotransferase (ALT) levels >2.5 times the upper limit of normal were enrolled. The intervention consisted of three times daily ingestion of either a standard recommended dose of 140 mg of silymarin (Legalon, MADAUS GmbH, Cologne, Germany), or a vitamin placebo for four weeks with an additional four-week follow-up. **The primary outcomes were signs of acute hepatitis and results of liver function tests on weeks 4 and 8**. Side-effects and adverse events were ascertained by self-report. RESULTS: From July 2003 through October 2005, 105 eligible patients were enrolled after providing informed consent. No adverse events were noted and both silymarin and placebo were well tolerated. Patients randomized to the silymarin group had quicker resolution of symptoms related to biliary retention: dark urine (p=0.013), jaundice (p=0.02) and scleral icterus (p=0.043). There was a reduction in indirect bilirubin among those assigned to silymarin (p=0.012), but other variables including direct bilirubin, ALT and aspartate aminotransferase (AST) were not significantly reduced. CONCLUSIONS: Patients receiving silymarin had earlier improvement in subjective and clinical markers of biliary excretion. Despite a modest sample size and multiple etiologies for acute clinical hepatitis, our results suggest that standard recommended doses of silymarin are safe and may be potentially effective in improving symptoms of acute clinical hepatitis despite lack of a detectable effect on biomarkers of the underlying hepatocellular inflammatory process.

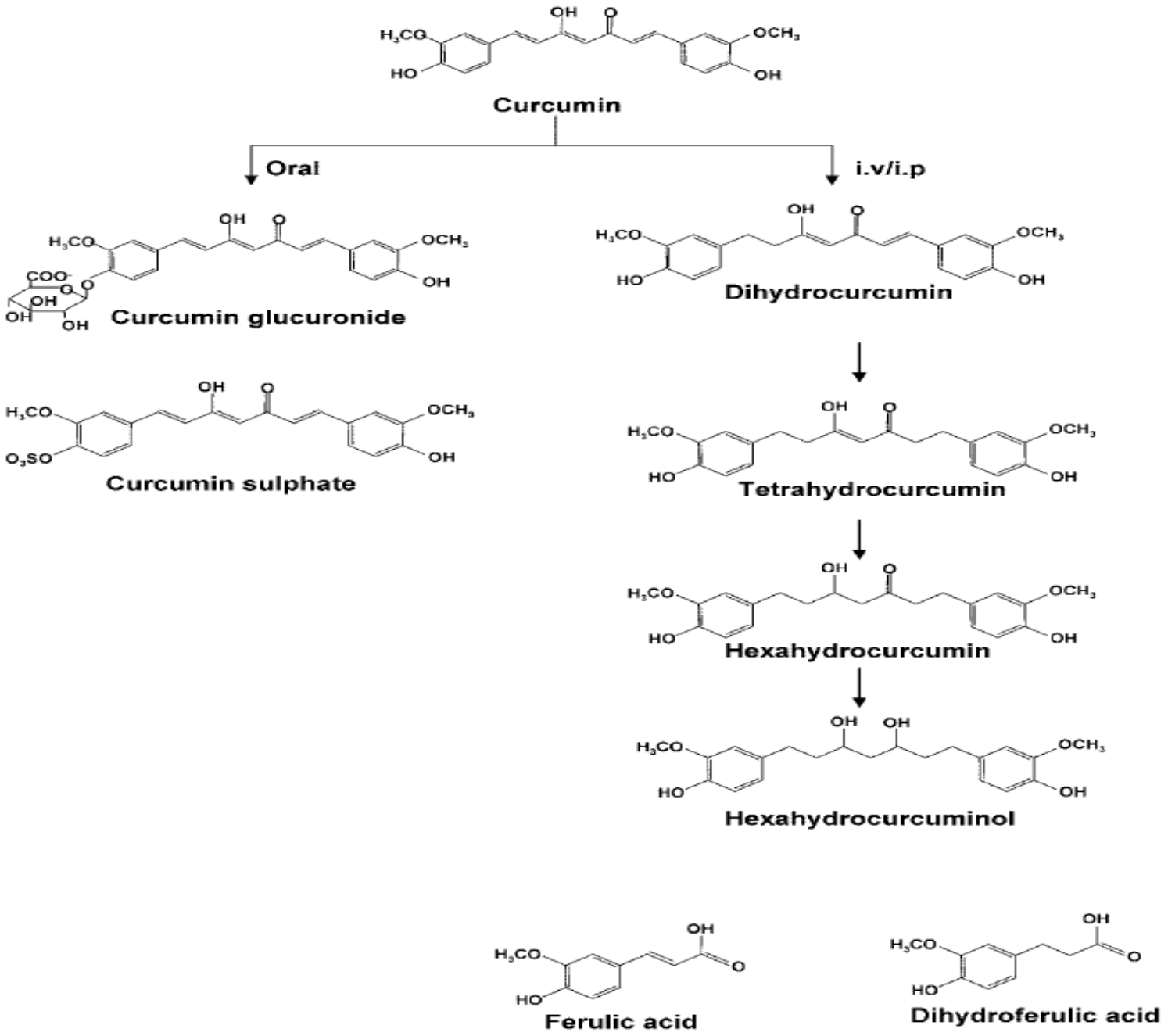
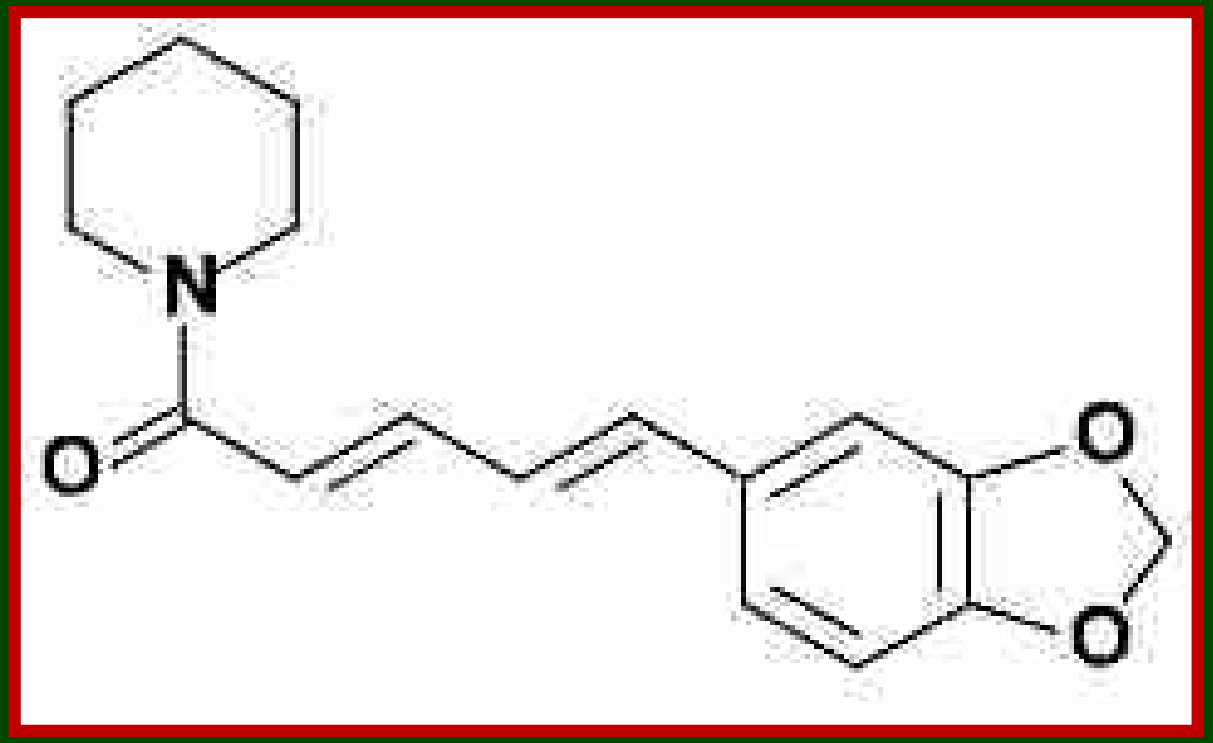
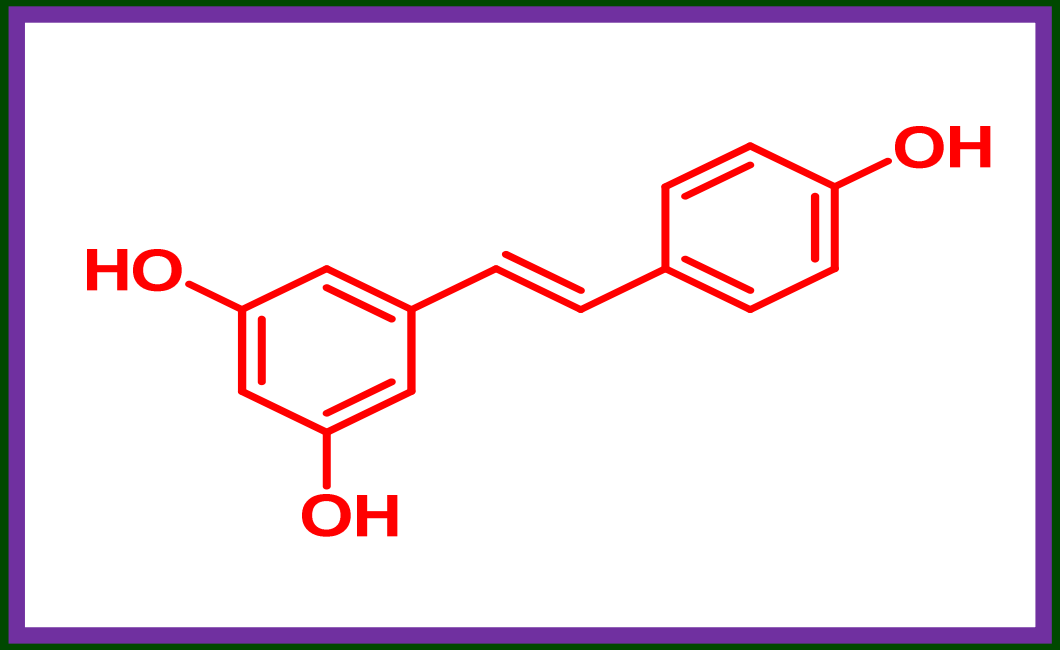


Figure 1. Structure of curcumin and its metabolites.

Piperina



Because of curcumin's rapid plasma clearance and conjugation, its therapeutic usefulness has been somewhat limited, leading researchers to investigate the benefits of complexing curcumin with other substances to increase systemic bioavaility. One substance that has been studied is the alkaloid piperine, a constituent from black pepper and long pepper (*Piper nigrum* and *Piper longum*, respectively). In humans 20 mg piperine given concomitantly with 2 g curcumin increased serum curcumin bioavailability 20-fold, which was attributed to piperine's inhibition of hepatic glucuronidation and intestinal metabolism.[13]



Resveratrol (**3, 4, 5-tri-hydroxy-trans-stilbene**) is a plant **phytoalexin** (compound produced after physical, chemical or biological insult) widespread in plants, and accumulated, in various amounts, in grape skin and leaves.

Resveratrol has a vague and pleiotropic biological profile and has been at the center of recent polemics bound to its activity on **sirtuins** (extension of life span).

Resveratrol is found in

Grapes (only in skin)
Wine
Grape Juice
Peanuts
Blueberries
Bilberries
Cranberries

Polygonum cuspidatum

Chemical synthesis (SRT-501)

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

NIH-PA Author Manuscript

NIH Public Access
Author Manuscript
J Neuroophthalmol. Author manuscript; available in PMC 2012 March 26.

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Oral Resveratrol Reduces Neuronal Damage in a Model of Multiple Sclerosis

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ORIGINAL RESEARCH ARTICLE
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Resveratrol neuroprotection in a chronic mouse model of multiple sclerosis

*Zoe Fonseca-Kelly†, Mayssa Nassrallah†, Jorge Uribe, Reas S. Khan, Kimberly Dine, Mahasweta Dutt and Kenneth S. Shindler **

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Resveratrol is a naturally occurring polyphenol that activates SIRT1, an NAD-dependent deacetylase. SRT501, a pharmaceutical formulation of resveratrol with enhanced systemic absorption, prevents neuronal loss without suppressing inflammation in mice with relapsing experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS). In contrast, resveratrol has been reported to suppress inflammation in chronic EAE, although neuroprotective effects were not evaluated. The current studies examine potential neuroprotective and immunomodulatory effects of resveratrol in chronic EAE induced by immunization with myelin oligodendroglial glycoprotein peptide in C57/Bl6 mice. Effects of two distinct formulations of resveratrol administered daily orally were compared. Resveratrol delayed the onset of EAE compared to vehicle-treated EAE mice, but did not prevent or alter the phenotype of inflammation in spinal cords or optic nerves. Significant neuroprotective effects were observed, with higher numbers of retinal ganglion cells found in eyes of resveratrol-treated EAE mice with optic nerve inflammation. Results demonstrate that resveratrol prevents neuronal loss in this chronic demyelinating disease model, similar to its effects in relapsing EAE. Differences in immunosuppression compared with prior studies suggest that immunomodulatory effects may be limited and may depend on specific immunization parameters or timing of treatment. Importantly, neuroprotective effects can occur without immunosuppression, suggesting a potential additive benefit of resveratrol in combination with anti-inflammatory therapies for MS.

Keywords: optic neuritis, multiple sclerosis, EAE, resveratrol, SIRT1, neuroprotection

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.

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

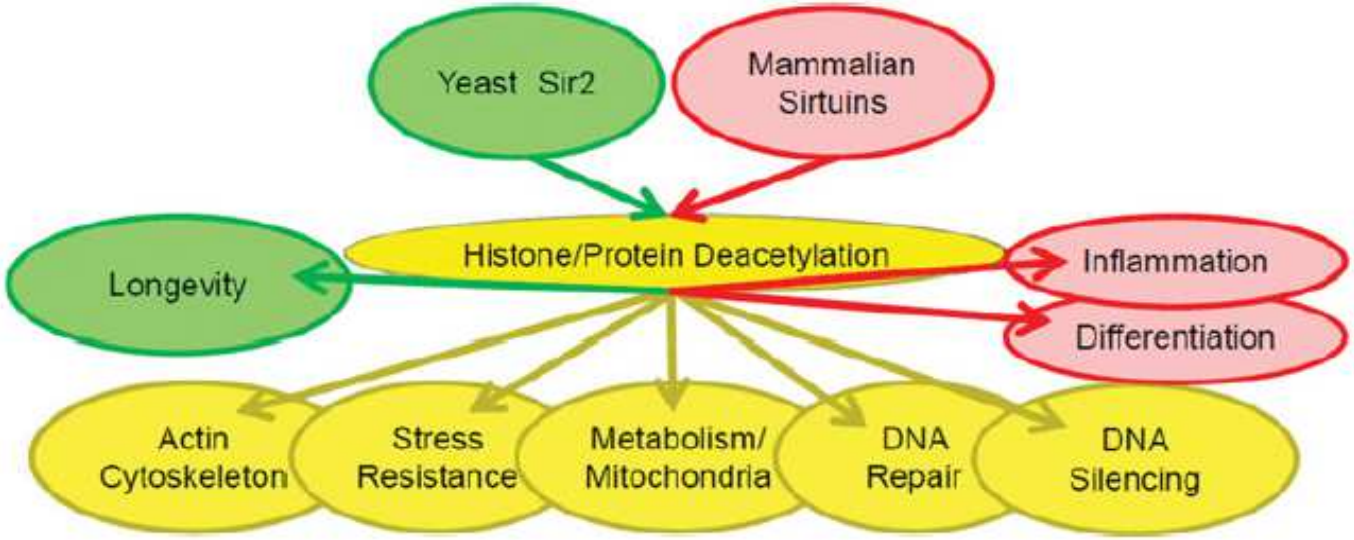
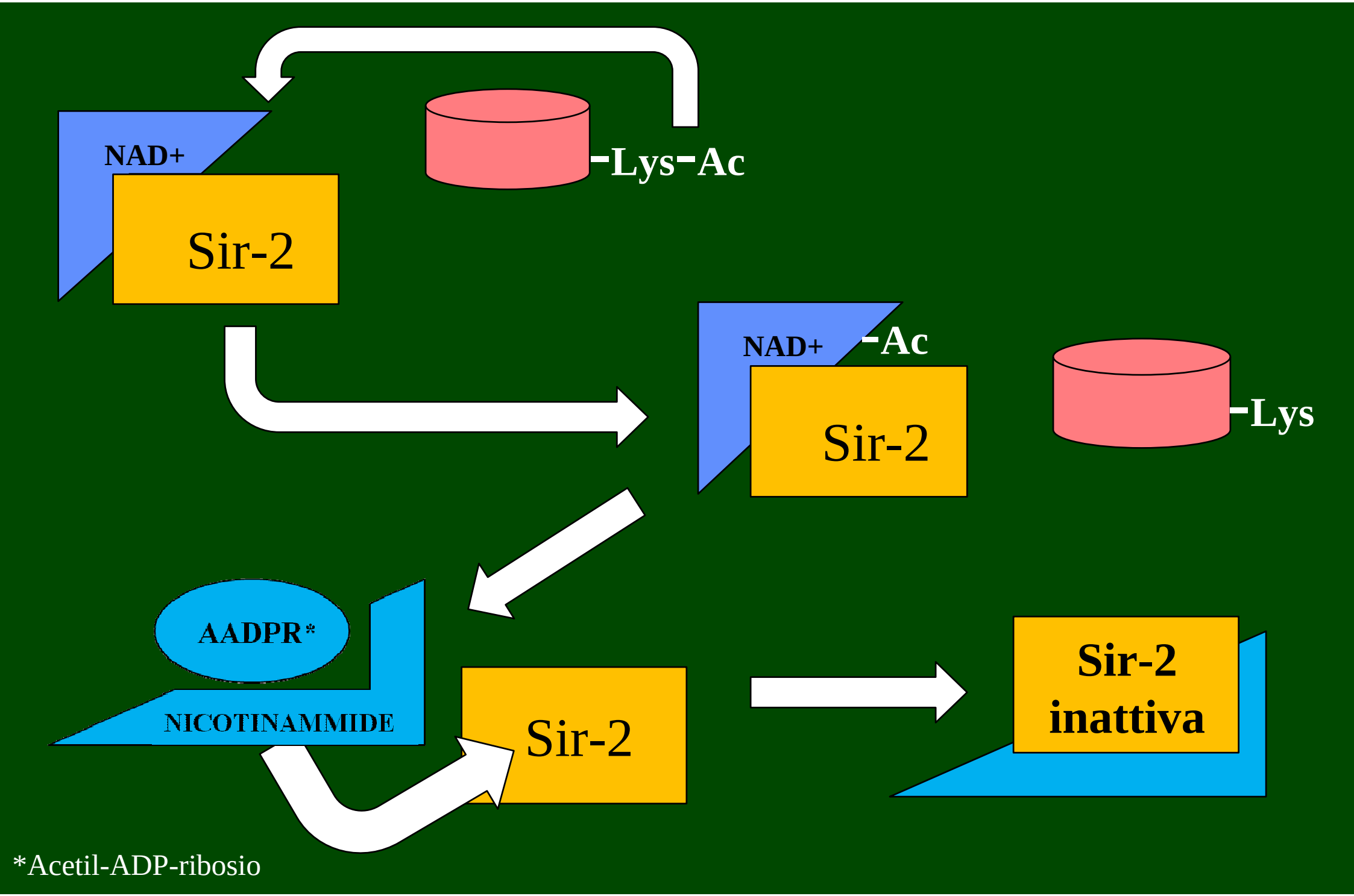


Figure 1 Common functions of yeast Sir2 and mammalian sirtuins

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.



*Acetil-ADP-ribosio

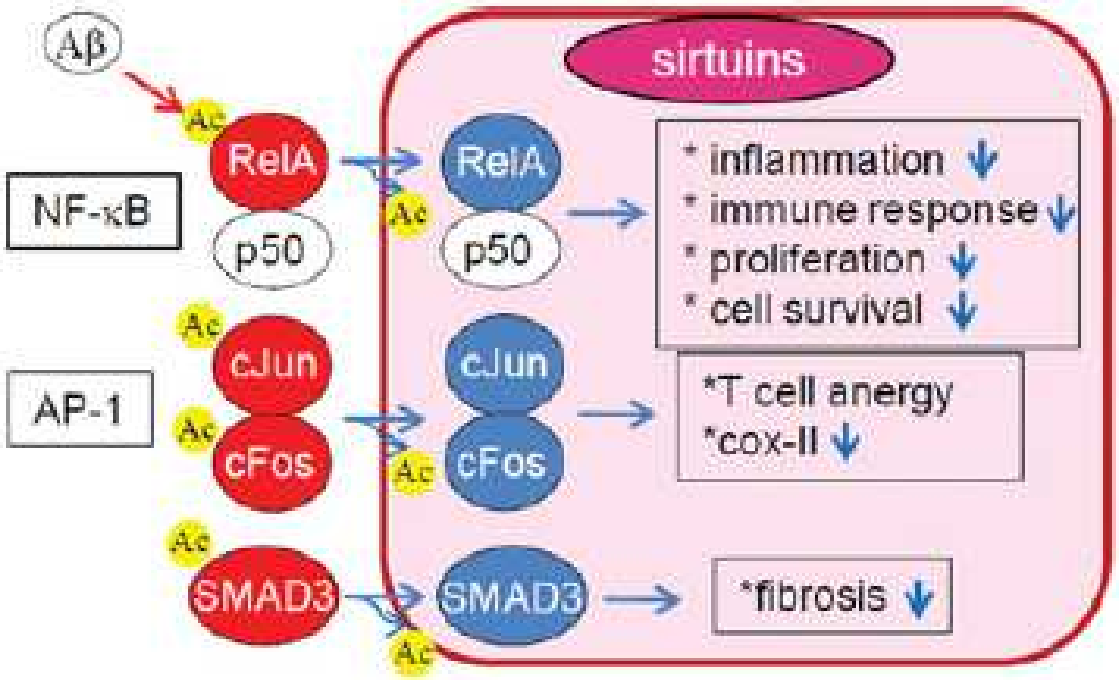


Figure 3 Inhibition of inflammation by sirtuins

Sirtuins inhibit inflammation. SIRT1 inhibits NF-κB, AP-1 and Smad3, whereas SIRT6 inhibits NF-κB target-gene transcription. Aβ promotes the acetylation of RelA and activates NF-κB. Red, active state; blue, inactive state; Ac, an acetyl-lysine residue.

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SIRT1 Activation Confers Neuroprotection in Experimental Optic Neuritis

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2 Department of Neurology, Thomas Jefferson University, Philadelphia, Pennsylvania

3 Sirtris Pharmaceuticals, Cambridge, Massachusetts

Abstract

Purpose—Axonal damage and loss of neurons correlate with permanent vision loss and neurologic disability in patients with optic neuritis and multiple sclerosis (MS). Current therapies involve immunomodulation, with limited effects on neuronal damage. The authors examined potential neuroprotective effects in optic neuritis by SRT647 and SRT501, two structurally and mechanistically distinct activators of SIRT1, an enzyme involved in cellular stress resistance and survival.

Methods—Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, was induced by immunization with proteolipid protein peptide in SJL/J mice. Optic neuritis developed in two thirds of eyes with significant retinal ganglion cell (RGC) loss detected 14 days after immunization. RGCs were labeled in a retrograde fashion with fluorogold by injection into superior colliculi. Optic neuritis was detected by inflammatory cell infiltration of the optic nerve.

Results—Intravitreal injection of SIRT1 activators 0, 3, 7, and 11 days after immunization significantly attenuated RGC loss in a dose-dependent manner. This neuroprotective effect was blocked by sirtinol, a SIRT1 inhibitor. Treatment with either SIRT1 activator did not prevent EAE or optic nerve inflammation. A single dose of SRT501 on day 11 was sufficient to limit RGC loss and to preserve axon function.

Conclusions—SIRT1 activators provide an important potential therapy to prevent the neuronal damage that leads to permanent neurologic disability in optic neuritis and MS patients. Intravitreal administration of SIRT1 activators does not suppress inflammation in this model, suggesting that their neuroprotective effects will be additive or synergistic with current immunomodulatory therapies.

Ann N Y Acad Sci. 2013 Jul;1290:107-12. doi: 10.1111/nyas.12130.

Nano- and micro-encapsulated systems for enhancing the delivery of resveratrol.

Augustin MA, Sanguansri L, Lockett T.

There has been interest in the use of trans-resveratrol as a natural preventative agent for improving health and alleviating a range of diseases. However, **resveratrol has low bioavailability**, and this has been associated with its poor water solubility, its low stability against environmental stress, and its inability to reach a target site in the body to exert the desired health effect. Encapsulation offers a potential approach for enhancing the solubility of resveratrol, stabilizing it against trans-to-cis isomerization, and improving its bioavailability. A range of encapsulant materials, formulations, and technologies have been examined for enhancing the delivery of resveratrol. Research on the efficacy of encapsulated resveratrol formulations and relevant doses for specific applications is required before recommendations may be made for the use of these formulations for human health outcomes

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

Review

Administration of resveratrol: What formulation solutions to bioavailability limitations?

A. Amri [a,b], J.C. Chaumeil [a], S. Sfar [b], C. Charrueau [a,*]

[a] Laboratoire de Pharmacie Galénique, EA4466, Université Paris Descartes, Sorbonne Paris Cité, Faculté des Sciences Pharmaceutiques et Biologiques, Paris,
[b] Laboratoire de Pharmacie Galénique, Faculté de Pharmacie, Université de Monastir, Tunisia

However, therapeutic application of these beneficial effects of resveratrol remains very limited due to its short biological half-life, labile properties, and rapid metabolism and elimination [10]. Results from pharmacokinetic studies indicate that the oral bioavailability of resveratrol is almost zero, which casts doubt on the physiological relevance of the high concentrations typically used for in vitro experiments [16,17].

Resveratrol has attracted great interest in the research community, with 4064 publications referenced on the U.S. National Library of Medicine's PubMed service between 1978 and 2011 [18], of which 96% were between 2000 and 2011. Analysis of recent literature reveals an increasing number of formulations under study (Fig. 1), which reflects the major interest in developing pharmaceutical forms able to improve resveratrol bioavailability as a step towards applying its therapeutic potential in vivo. The purpose of this review is

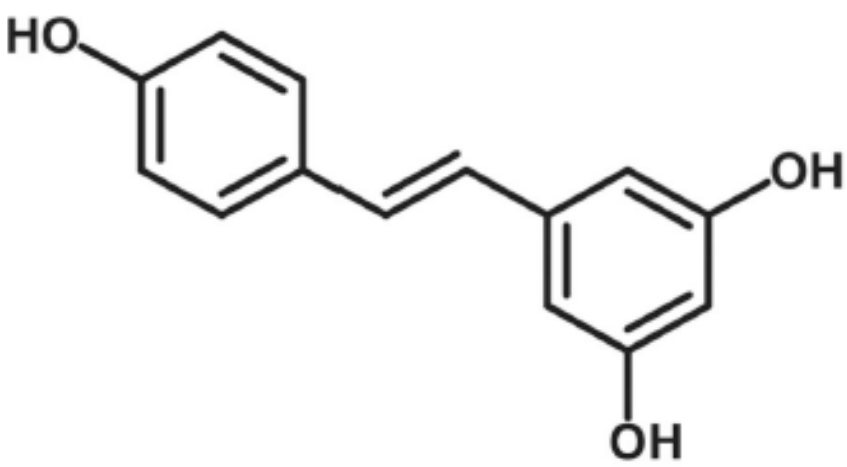
Ann N Y Acad Sci. 2011

Bioavailability of resveratrol.

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

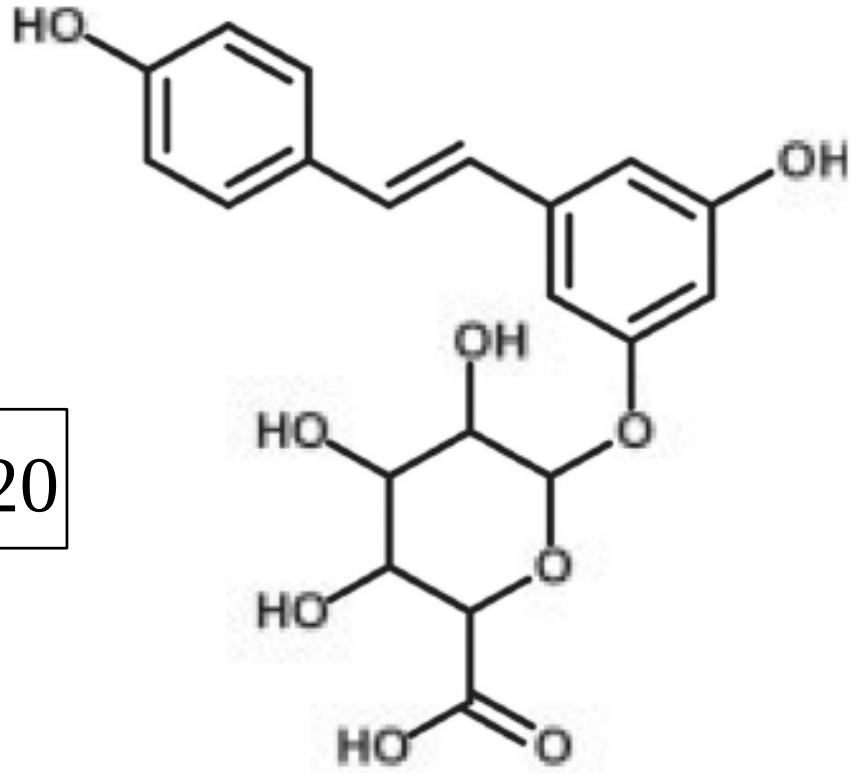
This paper reviews our current understanding of the absorption, bioavailability, and metabolism of resveratrol, with an emphasis on humans. **The oral absorption of resveratrol in humans is about 75% and is thought to occur mainly by transepithelial diffusion. Extensive metabolism in the intestine and 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.

Resveratrol

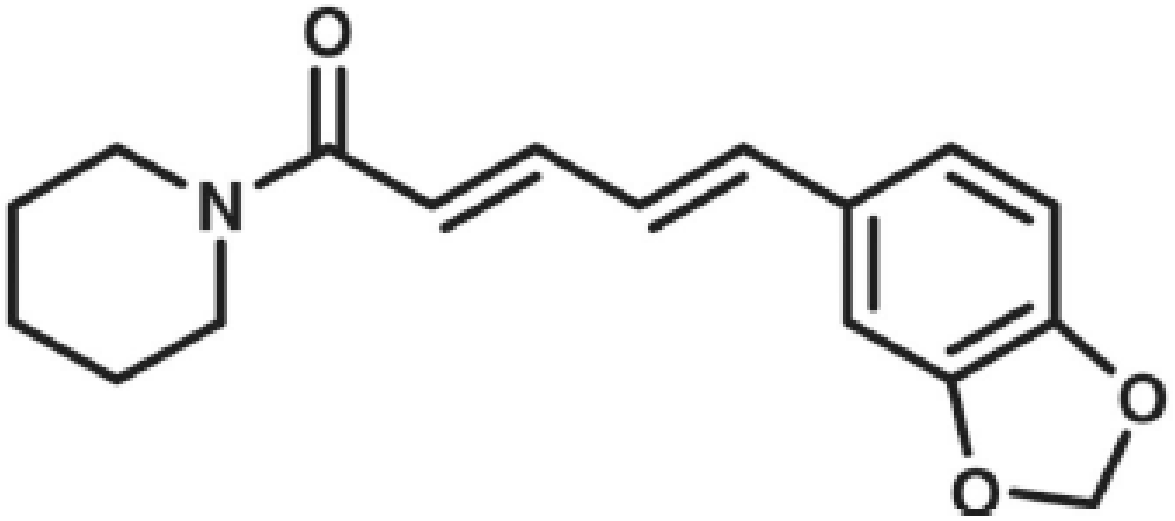


1 : 20

Resveratrol-3-O-β-D-glucuronide



Piperine



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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

Formulato	Resveratrolo			Resveratrolo + metaboliti
	Tmax	Cmax	AUC	AUC
A) Resveratrolo	0	1	1	1
B) Resveratrolo + Piperina	0	x 15.5	x 2.2	x 0.9

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

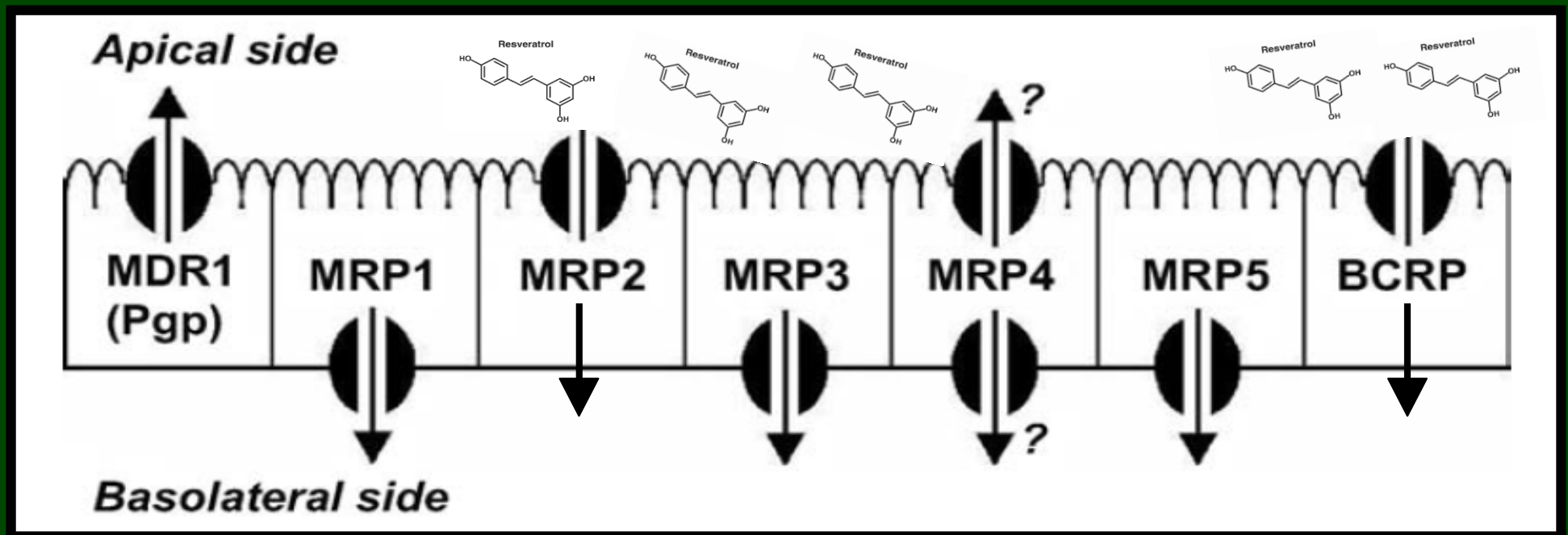
Multidrug Resistance Proteins Restrain the Intestinal Absorption of *trans*-Resveratrol in Rats[1–3]

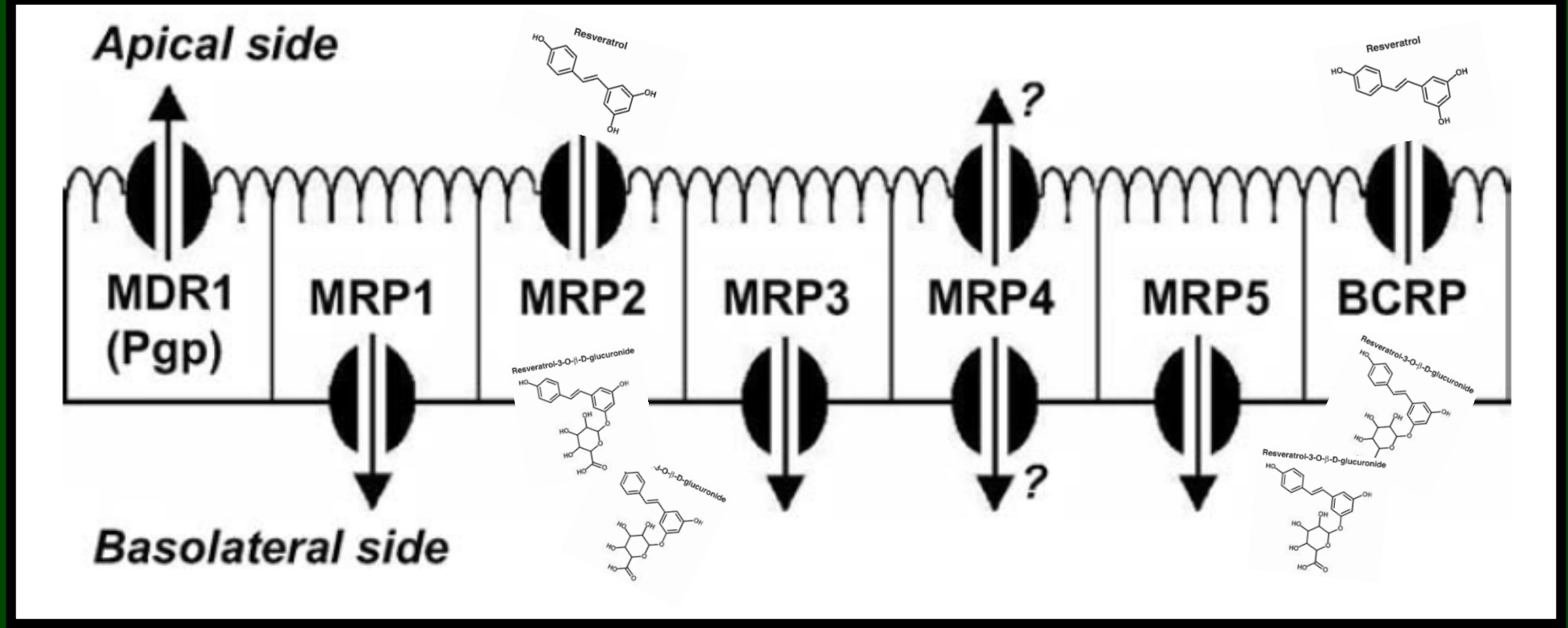
M. Emília Juan,[4]* Eulalia González-Pons,[4] and Joana M. Planas

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

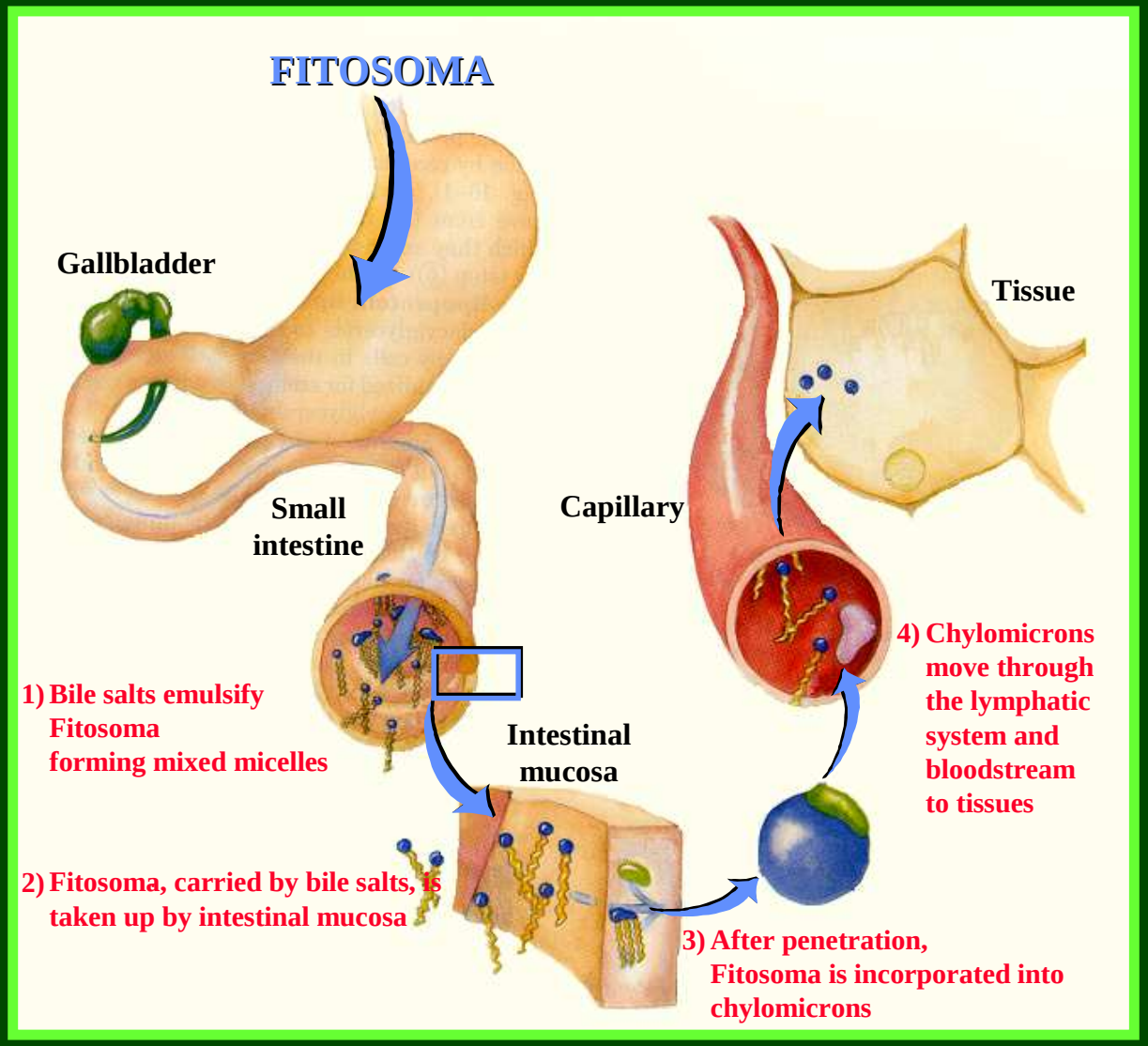
Abstract

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

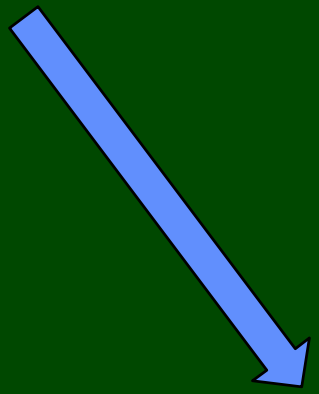

Apical side
Resveratrol
Resveratrol
?
MDR1
(Pgp)
MRP1
MRP2
MRP3
MRP4
MRP5
BCRP
Resveratrol-3-O-β-D-glucuronide
Resveratrol-3-O-β-D-glucuronide
Resveratrol-3-O-β-D-glucuronide
?
Basolateral side

INTESTINAL ABSORPTION OF PHYTOSOME



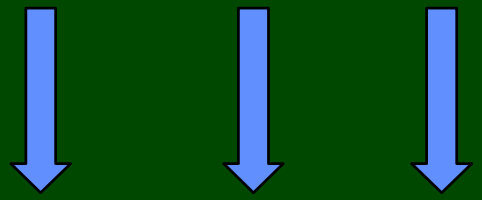
From : Principles of Biochemistry, by A.L. Lehninger (adapted)

Formulato	Resveratrolo		Resveratrolo + metaboliti
	Tmax	Cmax	AUC	AUC
A) Resveratrolo + Piperina	- 30’	x 15.5	x 2.2	x 0.9
B) Resveratrolo Fitosoma	+ 30’	x 14.0	x 10.0	x 4

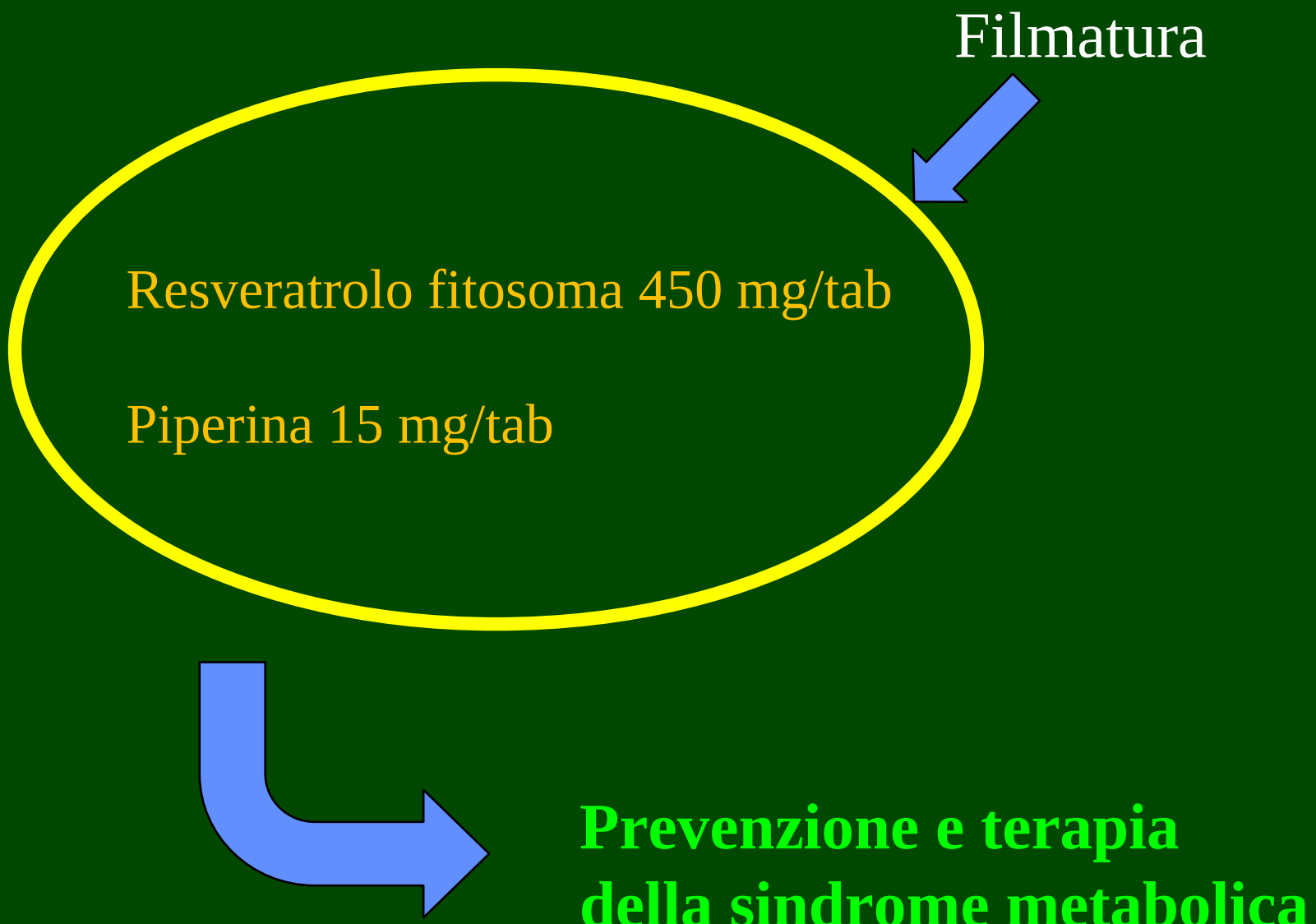


Il fitosoma scavalca la coniugazione intestinale
e parte del prodotto non arriva al fegato ma in altri tessuti
portato dai chilomicroni

Formulato		Resveratrolo			Resveratrolo + metaboliti
		Tmax	Cmax	AUC	AUC
A) Resveratrolo + Piperina	0’	x 15.5	x 2.2	x 0.9	
B) Resveratrolo Fitosoma		+ 30’	x 14.0	x 10.0	x 4
A+ B		?	?	?	?



Il fitosoma scavalca la coniugazione intestinale e la piperina viene utilizzata per antagonizzare la coniugazione in sede epatica


Filmatura
Resveratrolo fitosoma 450 mg/tab
Piperina 15 mg/tab
Prevenzione e terapia
della sindrome metabolica

Prodotto	Dose/cpr	Bioav % teorica	Effetto galenica	Ratio
A	150 mg	1% ➡ 1.5 mg	> X10 ➡ >15 mg	1
B	8.2 mg	1% ➡ 0.08 mg	nessuno ➡ 0.08 mg	1/187

Tossicità 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**. Resveratrol and six metabolites were recovered from plasma and urine. Peak plasma levels of resveratrol at the highest dose were 539 ± 384 ng/mL (2.4 μmol/L, mean ± SD; n = 10), which occurred 1.5 h post-dose. Peak levels of two monoglucuronides and resveratrol-3-sulfate were 3- to 8-fold higher. The area under the plasma concentration curve (AUC) values for resveratrol-3-sulfate and resveratrol monoglucuronides were up to 23 times greater than those of resveratrol. Urinary excretion of resveratrol and its metabolites was rapid, with 77% of all urinary agent-derived species excreted within 4 h after the lowest dose. Cancer chemopreventive effects of resveratrol in cells in vitro require levels of at least 5 μmol/L. The results presented here intimate that consumption of high-dose resveratrol might be insufficient to elicit systemic levels commensurate with cancer chemopreventive efficacy.

Biofarmaceutica

Una metodologia che accompagna l'intero percorso
di un ingrediente vegetale
dai processi estrattivi fino alla sua escrezione
dal corpo umano in forma di catabolita.

Passando attraverso le importanti fasi
1)della **standardizzazione molecolare**
2)della **corretta analisi chimica**
3) degli aspetti di **farmacocinetica e/o farmacodinamica,**
legati all'interazione con i tessuti dell'organismo
4) della **tecnica galenica** e dell'uso di **vettori e antagonisti**
che, entrambi applicati alla formulazione finale,
garantiscono presenze plasmatiche molecolari adeguate.

Grazie per l’attenzione!