La fitoterapia biofarmaceutica nella *supportive care* oncologica

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).

FEDER SALUS

Il mercato degli integratori: dinamiche aggiornate a Marzo 2014

I. Evoluzione del mercato degli integratori: focus canali di vendita

Nel periodo aprile 2013 – marzo 2014 il mercato degli integratori ha realizzato un valore di 1.995,6 milioni di euro per un totale di quasi 143 milioni di confezioni vendute. Le variazioni registrate rispetto allo stesso periodo dell'anno precedente rilevano un incremento dei pezzi venduti pari al +3,1% che corrisponde ad una variazione positiva del fatturato del 4,2%.

Terapie convenzionali	**Terapie complementari**
Funzionano	Non funzionano (oltre effetto placebo)
Vasta documentazione	Documentazione scarsa
Side effects	Non hanno *side effects*
«Chimiche»	«Naturali»

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

PLANT DERIVED ACTIVE AGENTS

Plant	Agent	Activity	
Papaver somniferum L.	Morphine	Narcotic analgesic	1806
	Noscapine	Antitussive	1817
	Codeine	Antitussive, narcotic analgesic	1832
	Papaverine		1848
Strychnos nux - vomica L.	Strychnine	CNS stimulant	1817
Cephaelis ipecacuanha (Brot.) Tussac	Emetine	Amebicide	1817
Cinchona ledgeriana Bern. Moens ex Trimen	Quinine	Antimalarial	1819
	Quinidine	Antiarrhytmic	1833
Coffea arabica L.	Caffeine	CNS stimulant	1819
Colchicum autumnale L.	Colchicine	Antinflammatory (gout)	1820
Filipendula ulmaria (L.) Maxim.	Salicin	Analgesic	1829
Atropa belladonna L.	Atropine	Anticholinergic, mydriatic	1831
Theobroma cacao L.	Theobromine	Smooth muscle relaxant	1842
Erythroxylum coca Lam.	Cocaine	Topical anesthetic	1860
Physostigma venenosum Bal.	Physostigmine	Cholinergic	1864
Pilocarpus jaborandi Holmes	Pilocarpine	Antiglaucoma, miotic	1875
Datura metel L.	Scopolamine	Anticholinergic	1881
Hyoscyamus niger L.	Hyoscyamine	Anticholinergic	1881
Ephedra sinica Stapf.	L-Ephedrine	Sympathomimetic	1897
Digitalis purpurea L.	Digoxin	Cardiotonic	1930
Rauwolfia serpentina L.	Ajmaline	Antiarrhytmic	1931
	Reserpine	Antihypertensive	1952
	Rescinnamine	Antihypertensive	1954
Chondrodendron tomentosum Ruitz et	Tubocurarine	Skeletal muscle relaxant	1935
Catharantus roseus (L.) G. Don	Vinblastine	Antitumor	1952
	Vincristine	Antitumor	1958
Ammi visnaga (L.) Lam.	Visnadine	Coronary vasodilator	1961
Silybum marianum (L.) Gartn.	Silybin	Antitoxic, liver protectant	1968
Coleus forskohlii Brig.	Forskolin	Adenylate cyclase stimulator	1977
Taxus baccata L.	Paclitaxel	Antitumor	1991
Camptotheca acuminata L.	Camptothecin	Antitumor	1993

STANDARDIZED EXTRACTS FROM PLANTS

***Centella asiatica* (L.) Urban**

***Silybum marianum* (L.) Gaertn.**

***Vaccinium myrtillus* L.**

***Ginkgo biloba* L.**

***Panax ginseng* C.A. Meyer**

***Vitis vinifera* L.**

***Senna alexandrina* Miller**

***Serenoa repens* (Bartr.) Small**

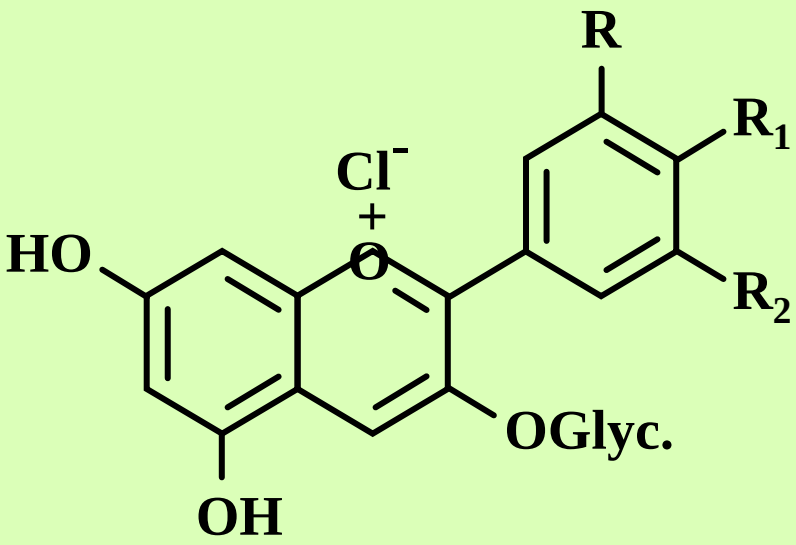
***Hypericum perforatum* L.**

***Crataegus oxyacantha* L.**

***Cynara scolymus* L.**

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*

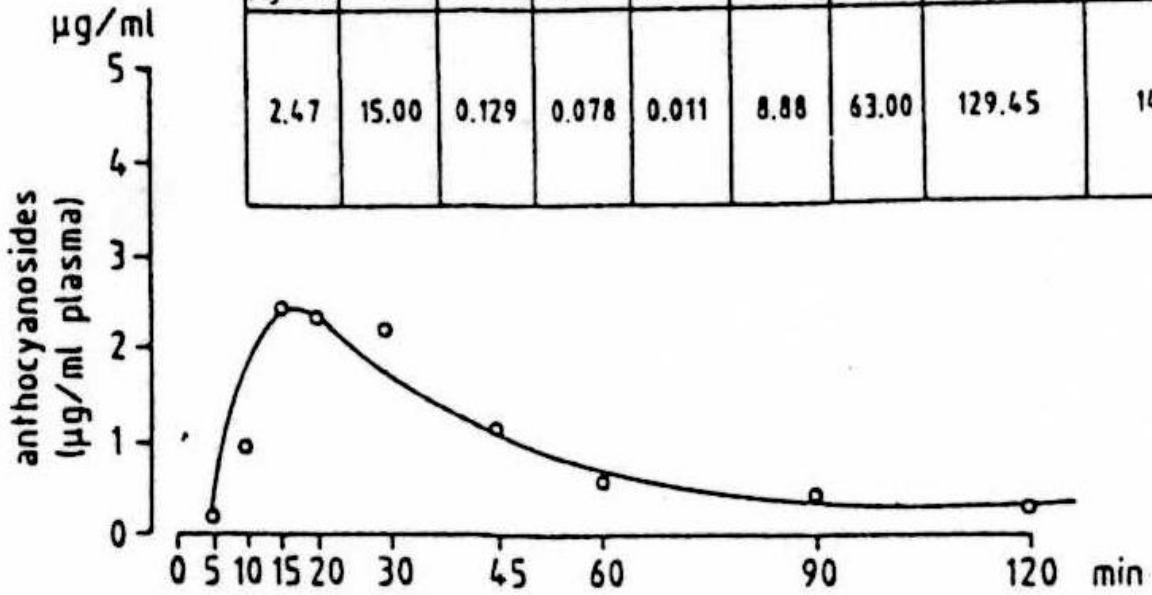


Fig. 4: Plasma levels and pharmacokinetic data after oral VMA (400 mg/kg). * Value calculated in relation to intravenous VMA.

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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,*]

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[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

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**
- **Flora intestinale** } intestinale

- **Ruolo della detossificazione epatica** } epatico

Glucidi
Lipidi
Protidi
Vitamine

Polifenoli

Rimasuglio degradazione tannini

Colori vegetali per attrarre insetti/animali

Nessuna valenza nutrizionale

Attivi (*in vitro*)

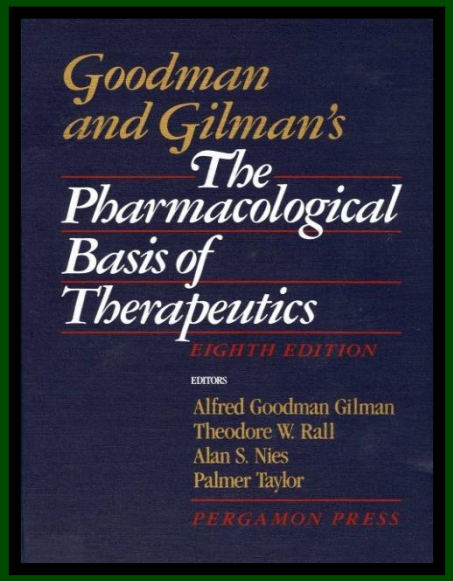
L’organismo tenta di bloccarli

Trends Genet. 1990 Jun;6(6):182-6.

Evolution of the P450 gene superfamily: animal-plant 'warfare', molecular drive and human genetic differences in drug oxidation.

Gonzalez FJ, Nebert DW.

Drug-metabolizing enzymes, such as those encoded by the cytochrome P450 genes, are noted for their high degree of interspecies and intraspecies variability.
We believe that much of this diversity is the result of **continuous molecularly driven coevolution of plants producing secondary metabolites and animals responding with new enzymes to detoxify these chemicals.** One consequence of human P450 gene evolution is polymorphism in drug metabolism, leading to marked differences in the response of individuals to the effects of drugs and other environmental chemicals.



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.)

The American Journal of Clinical Nutrition

Evaluation of botanicals for improving human health[1–4]

David M Ribnicky, Alexander Poulev, Barbara Schmidt, William T Cefalu, and Ilya Raskin

ABSTRACT

Botanical preparations have been used medicinally for thousands of years. Many commercially available botanical products are being marketed in the United States with little or no publicly available scientific validation of efficacy or consistency. For botanicals to be reliable for research purposes and consumer products, they must be standardized with sufficient quality controls to ensure consistent composition, safety, and potency. This includes uniform cultivation of source plants with controls to monitor for contamination from other species, pesticides, and environmental toxins. The active components of botanicals must be identified by activity-guided fractionation with the use of in vitro assays that require little test material followed by validation in vivo. Concentrations of active compounds within the botanicals can then be accurately measured to ensure the delivery of a dependable dose in the final product. The use of bioenhancing agents may be considered for compounds with poor bioavailability. Standardization of botanical therapeutics can only be achieved when the active compounds are identified and biological activity is confirmed, thus ensuring a consistent product. *Am J Clin Nutr* 2008;87(suppl):472S–5S.

KEY WORDS Botanicals, standardization, bioactivity, bioassay-guided fractionation, LC-MS analysis, bioenhancers

same quality as drugs but contain multiple compounds, many of which may not be identified.

Botanical products that are encapsulated dried plant material are generally regarded as being low quality because they are typically standardized on the basis of the dry weight of the plant material. Most botanical extracts are produced from a defined part of a plant and represent a large collection of compounds. Ideally, compounds within the extract that are responsible for the overall activity have been identified. The extract can then be standardized on the basis of the content of these compounds. Hypericin, for example, is thought to be the active compound in extracts from St John's Wort (*Hypericum perforatum*), which is used to prevent and treat some forms of depression (5). St John's Wort extracts can be standardized for hypercin content, and consistent doses can be obtained from different batches of plant material. Despite the apparent simplicity of this botanical, a study comparing 10 products showed variations from the label claim for hypericin ranging from 22% to 140% (6; GH Constantine, Y Karchesy, unpublished observations, 1999), which could account for variations in study results. In contrast, Ginseng products contain 2 families of active compounds—ginsenosides and eleutherosides—and are generally standardized for the total content of each class of compound. Although this form of standard-

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Volume 2012, Article ID 637953, 33 pages
doi:10.1100/2012/637953

The ScientificWorldJOURNAL

Review Article

A Comprehensive Review on Pharmacotherapeutics of Herbal Bioenhancers

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Received 24 June 2012; Accepted 9 August 2012

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

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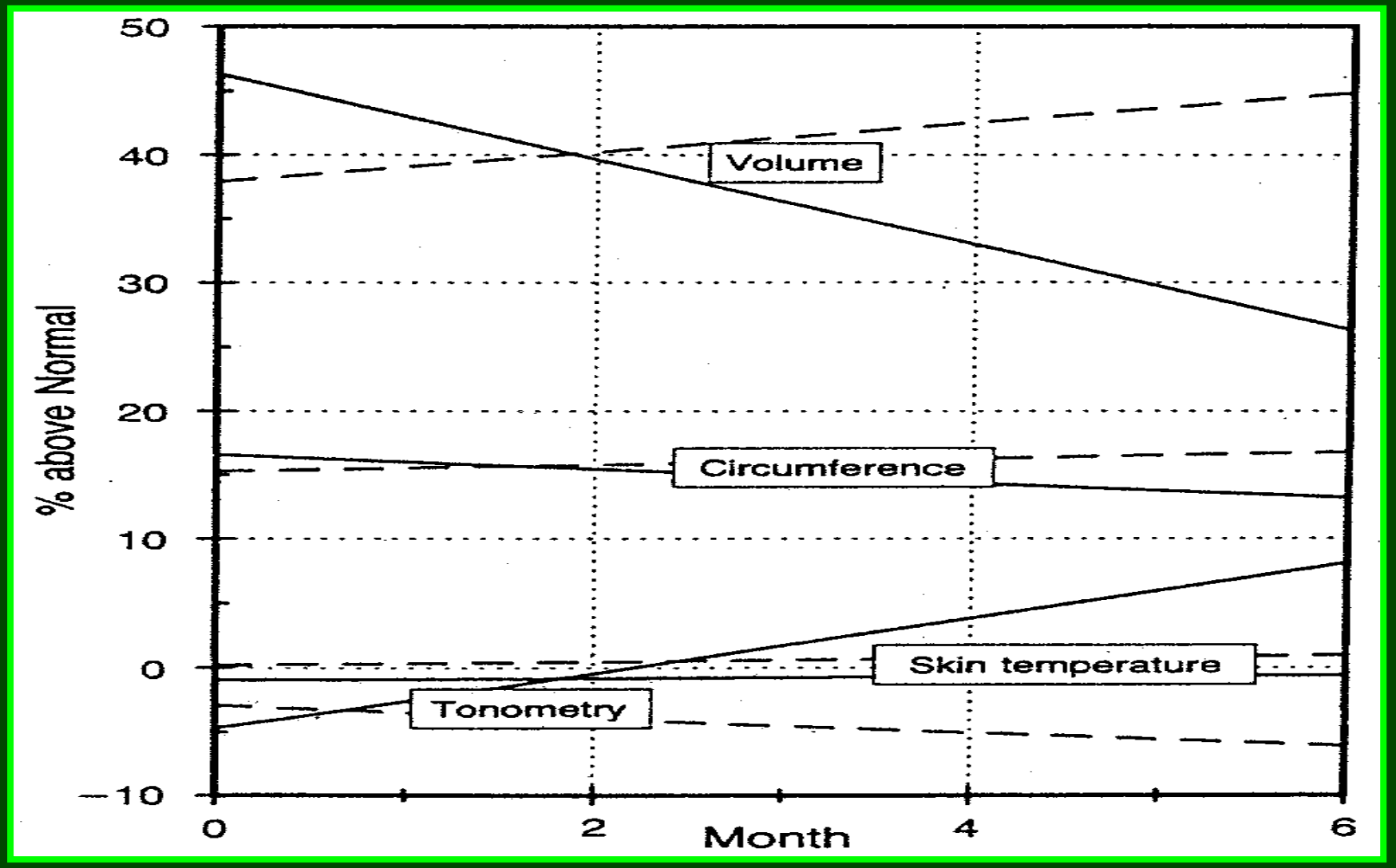
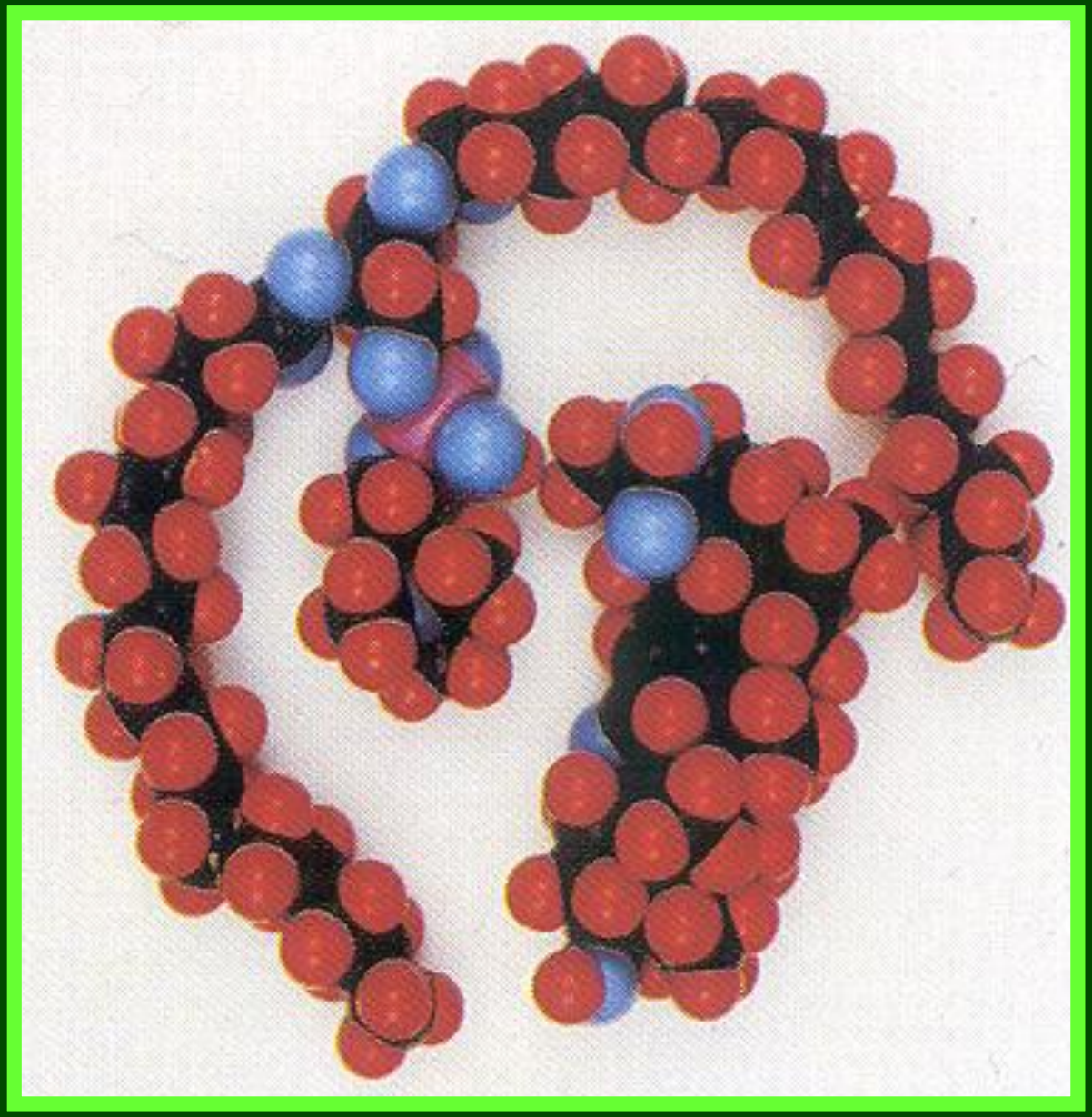
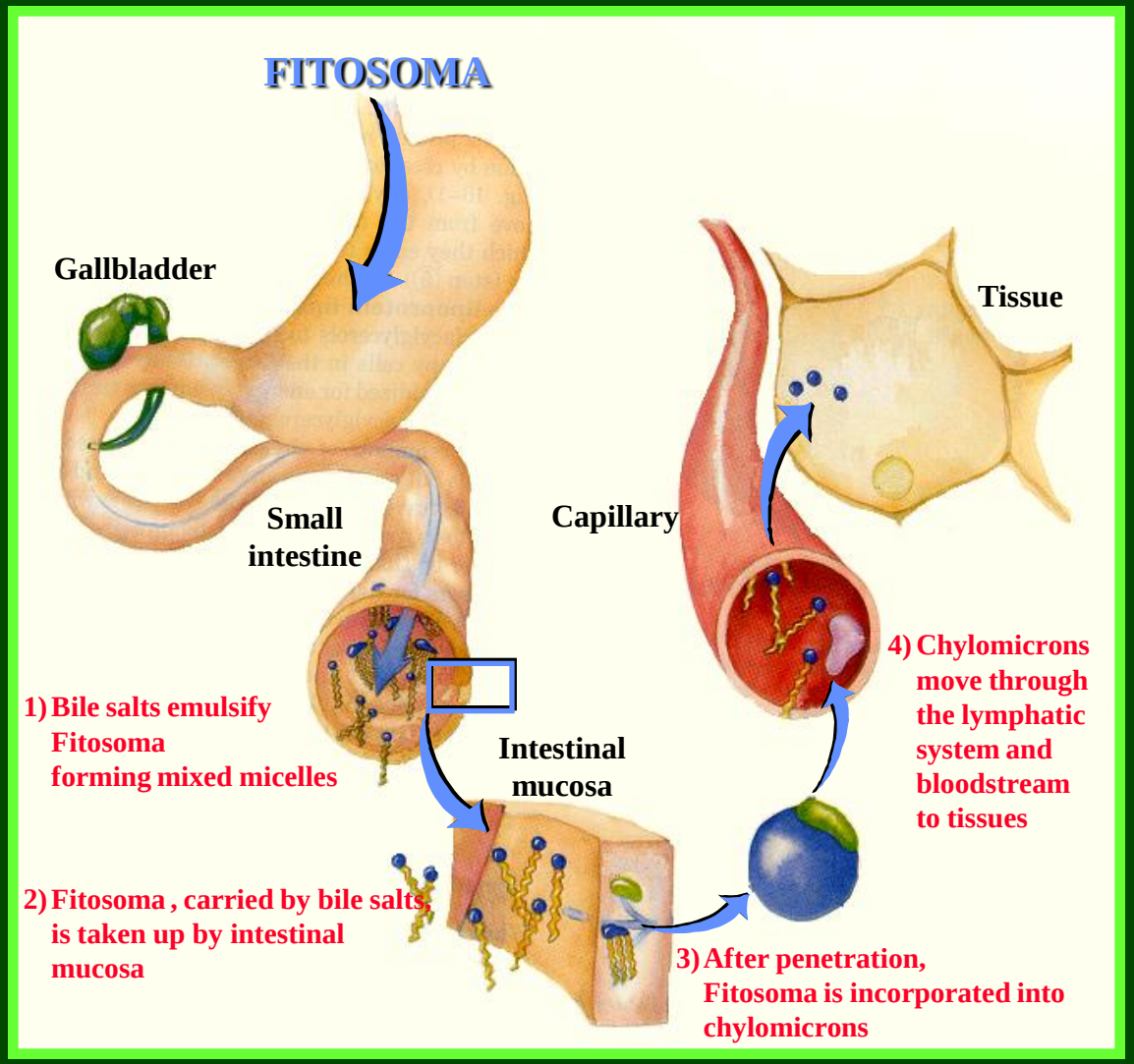
Abstract: Prolonged-release tablets containing coumarin were compared to intravenous and peroral administration of coumarin solution in man. Unchanged coumarin, the Phase I metabolite 7-hydroxycoumarin, and the Phase II metabolite 7-hydroxycoumarin glucuronide were determined in whole blood. Upon peroral 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



INTESTINAL ABSORPTION OF PHYTOSOME



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

Figura 2 *Rilevazione plasmatica su volontari sani dopo somministrazione orale di Gbe o GsF*

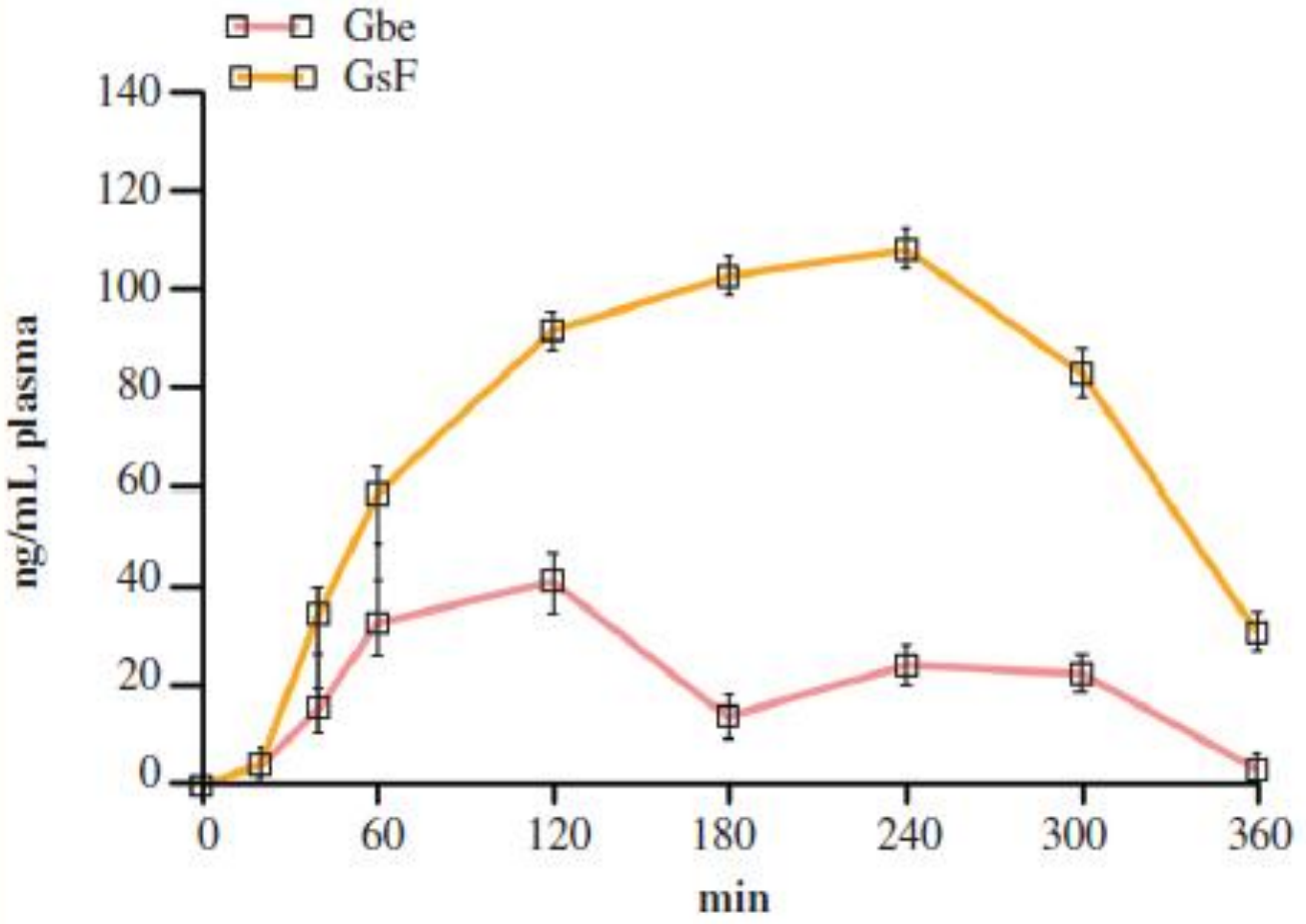
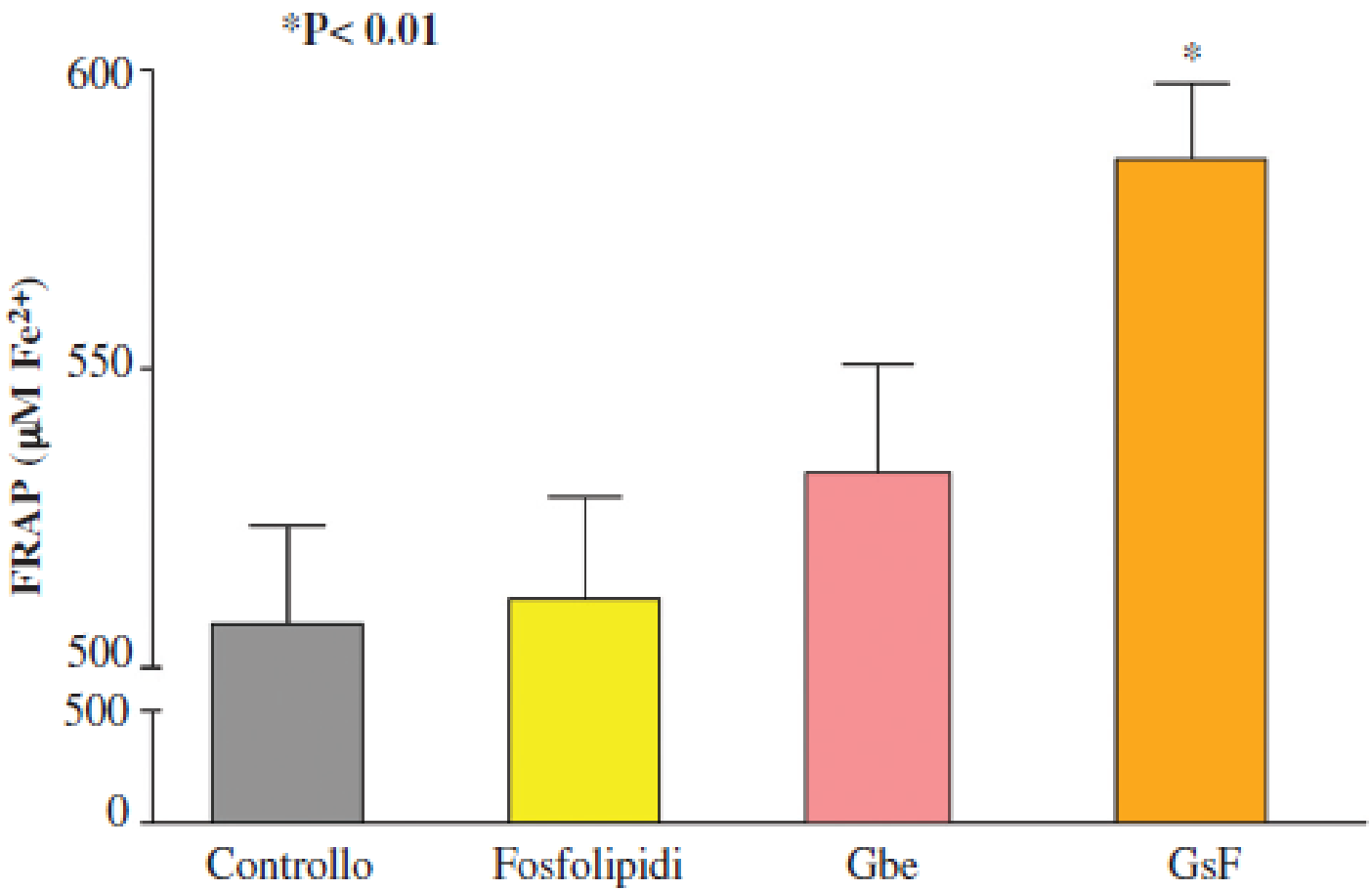


Figura 3 *Variazione antiossidante neuronale* (FRAP) *dopo somministrazione di Gbe o GsF*



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

Bioavailability of curcumin: problems and promises.

Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB.

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.

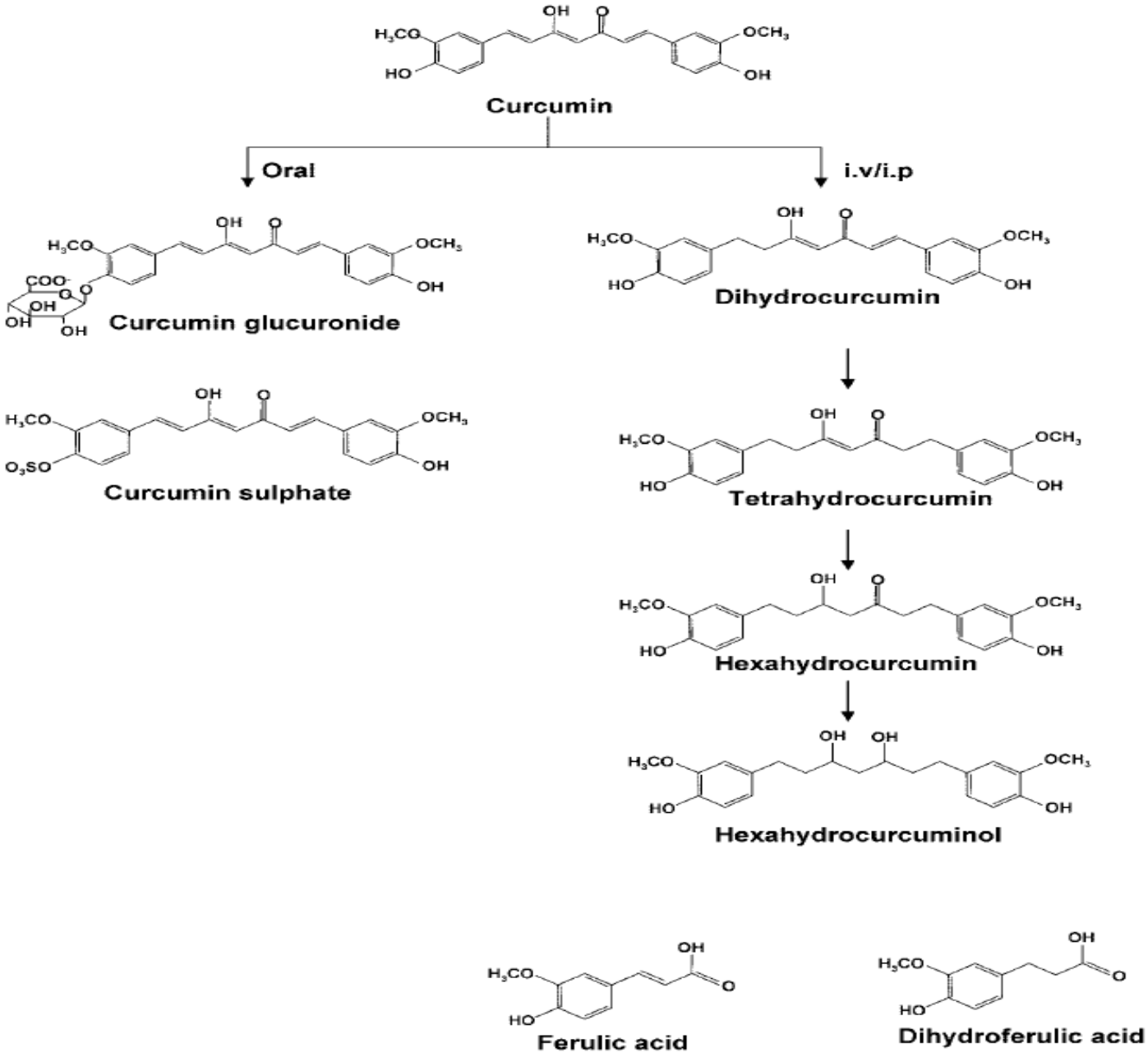
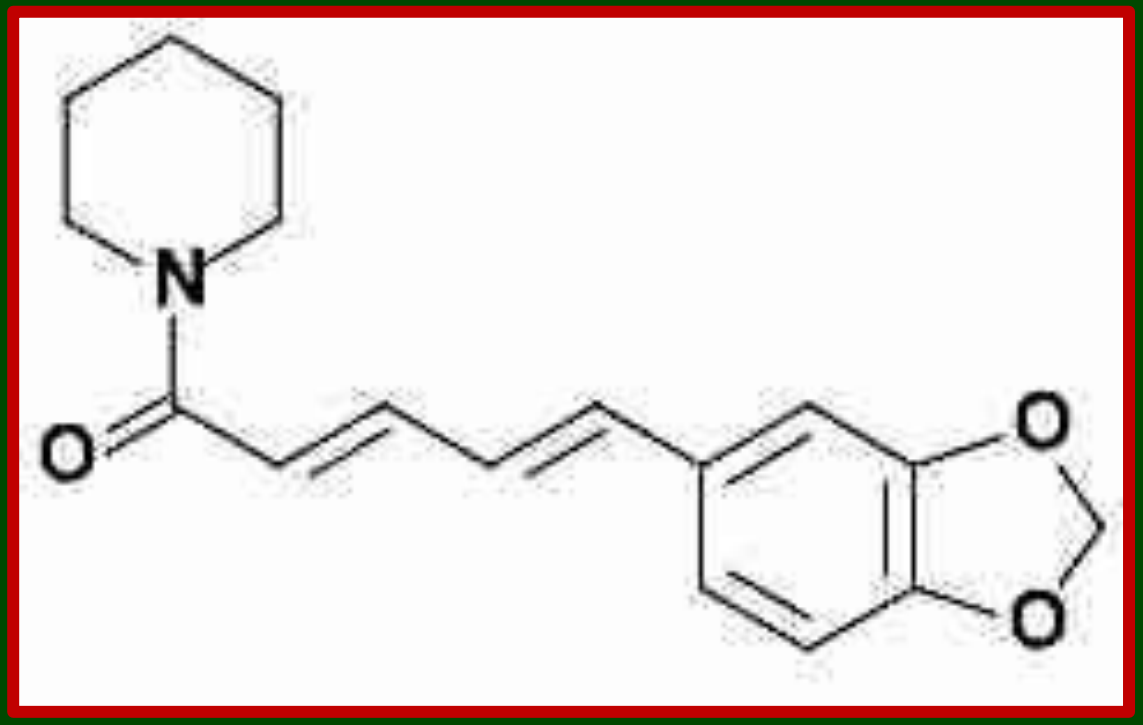


Figure 1. Structure of curcumin and its metabolites.

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]

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.

…come

Prevenzione danno iatrogeno
Terapia danno iatrogeno
Chemio-sensibilizzante
Immunostimolante
Chemio-prevenzione

Vaccinium macrocarpon

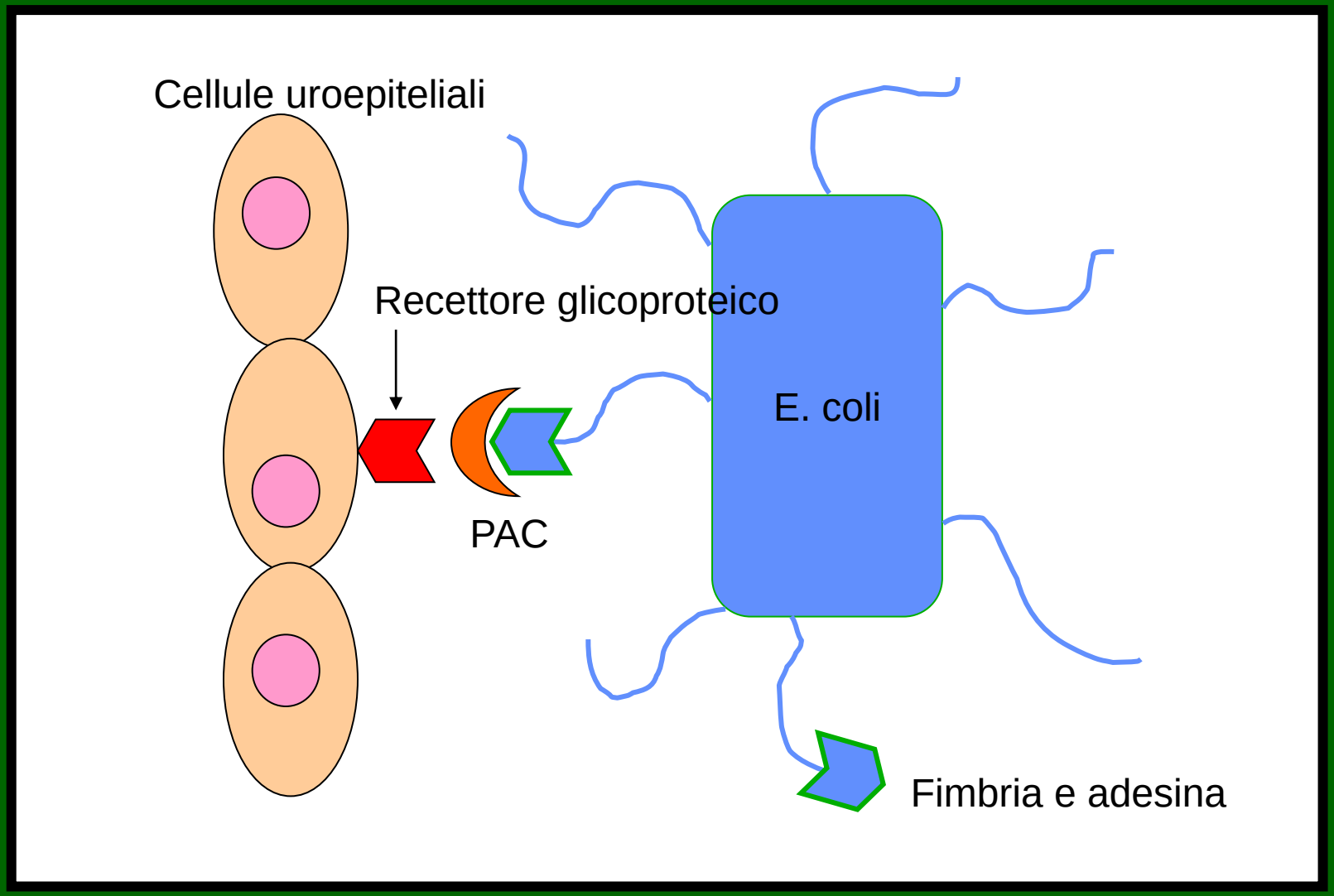


Fig. 3 Ruolo delle PAC nell'impedire l'aggancio di E. coli alle cellule uroepiteliali

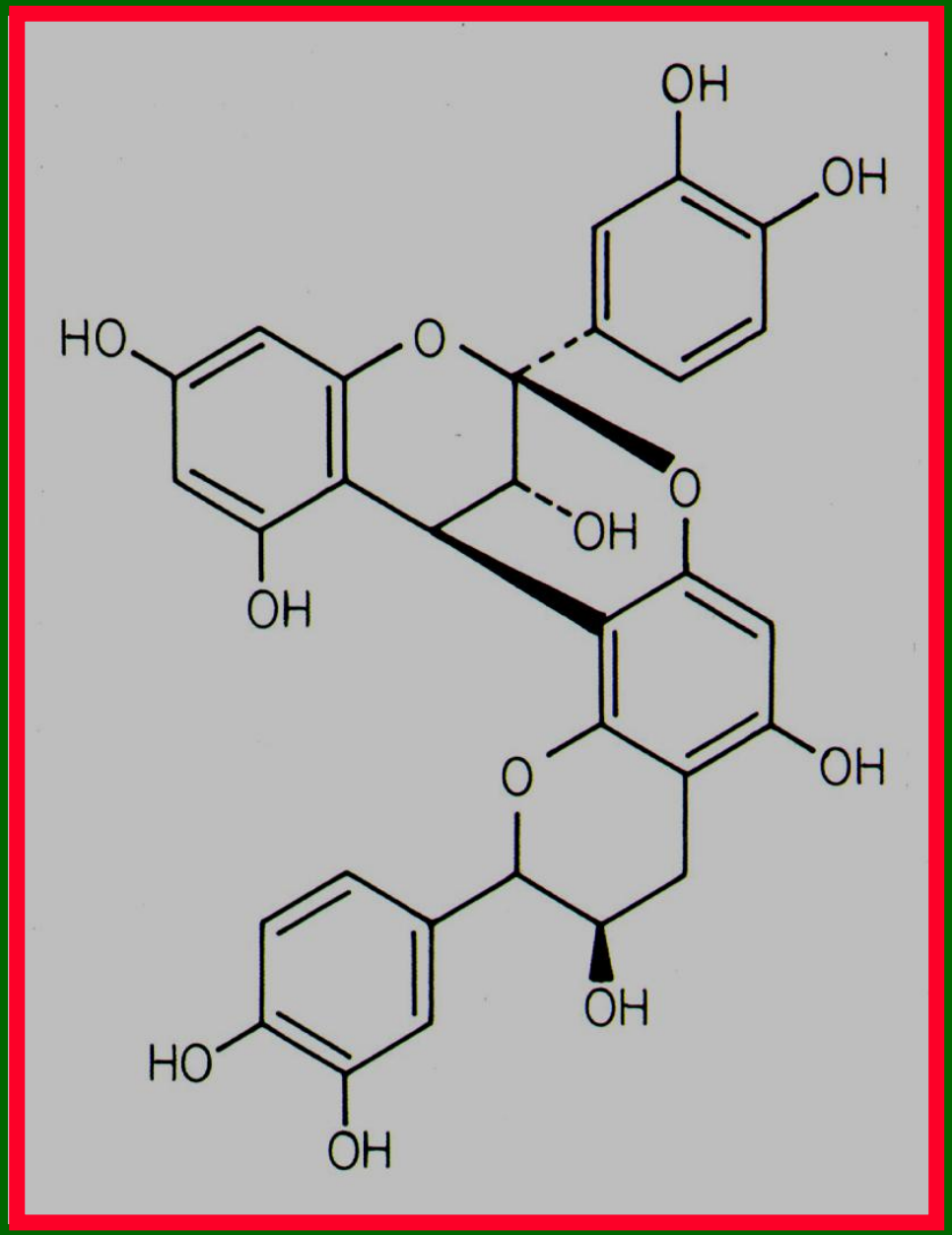

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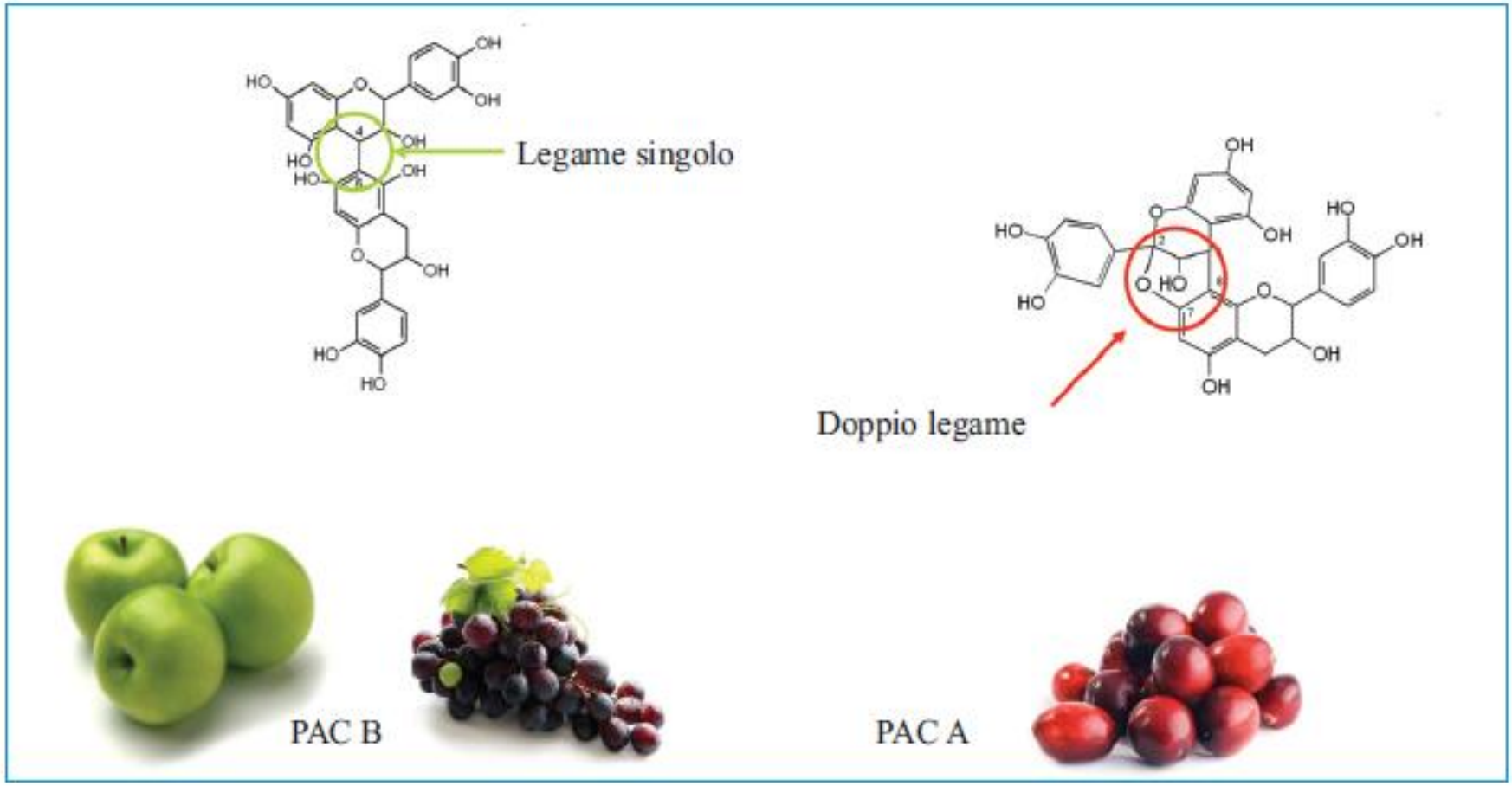
Figura 1 *Struttura chimica delle proantocianidine di tipo A (presenti nel frutto di macrocarpon) e di tipo B (normalmente presenti nella frutta)*



PAC

instabilità ambientale

instabilità a basso pH

interazione con batteri gastrici

Cancer Management and Research

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Enteric-coated, highly standardized cranberry extract reduces risk of UTIs and urinary symptoms during radiotherapy for prostate carcinoma

This article was published in the following Dove Press journal:
Cancer Management and Research
1 August 2012
Number of times this article has been viewed

Alberto Bonetta[1]
Francesco Di Pierro[2]

[1]Unità Operativa Radioterapia Oncologica, Istituti Ospedalieri di Cremona, Cremona; [2]Velleja Research, Milan, Italy

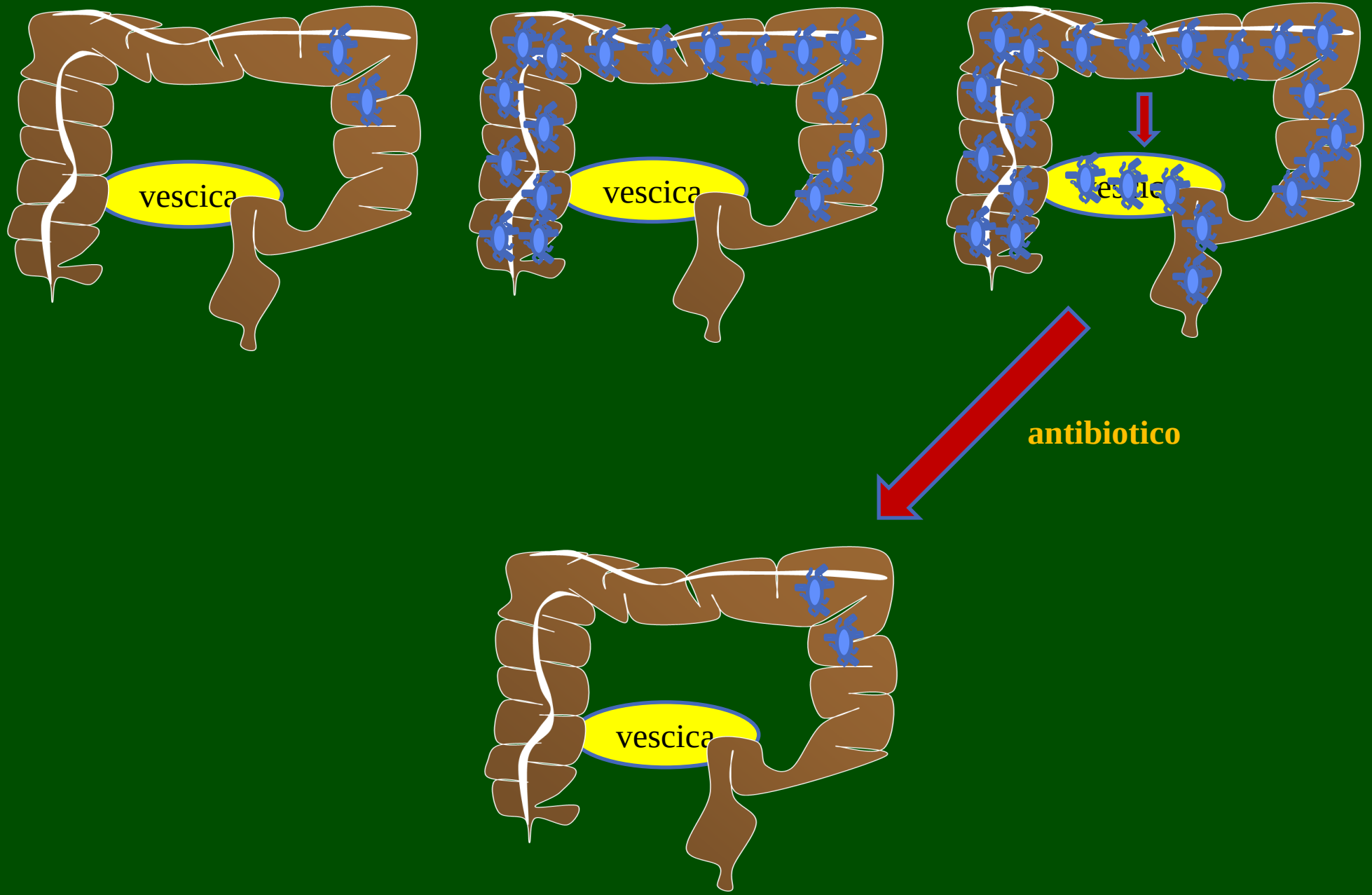
Background: Cranberry (*Vaccinium macrocarpon*) proanthocyanidins can interfere with adhesion of bacteria to uroepithelial cells, potentially preventing lower urinary tract infections (LUTIs). Because LUTIs are a common side effect of external beam radiotherapy (EBRT) for prostate cancer, we evaluated the clinical efficacy of enteric-coated tablets containing highly standardized *V. msacrocarpon* (ecVM) in this condition.

Methods: A total of 370 consecutive patients were entered into this study. All patients received

Table 1 Frequency and type of urinary infections in the treatment and control groups

Bacterium	Treatment group		Control group	
	Absolute NR	Percentage with infections	Absolute NR	Percentage with infections
Escherichia coli	5	30%	21	60%
Enterococcus faecalis	6	40%	10	8%
Enterobacter cloacae + *E. coli*	0		1	0
Enterobacter cloacae	2	10%	2	4%
Pseudomonas aeruginosa	1	10%	2	8%
Streptococcus agalactiae	2	10%	–	–
Staphylococcus epidermidis	–	–	1	4%
Staphylococcus emolitico	–	–	1	4%
Klebsiella pneumoniae	–	–	1	4%
Proteus mirabilis	–	–	3	4%
Not known/mixed	–	–	3	4%
Total	16	100%	45	100%

Dove agiscono le PAC nella cistite ricorrente o nella cistite da radioterapia?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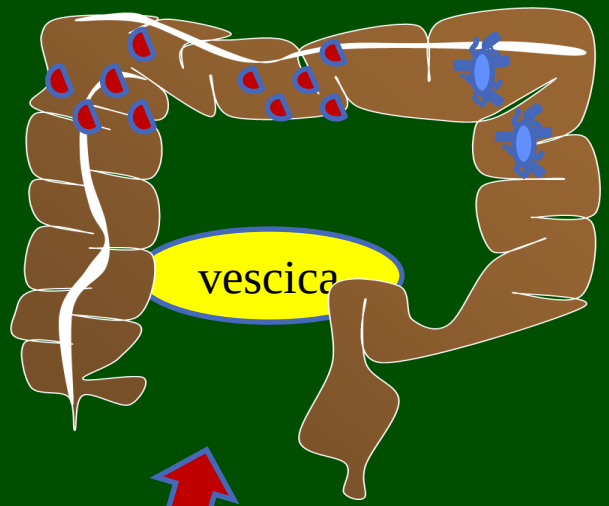
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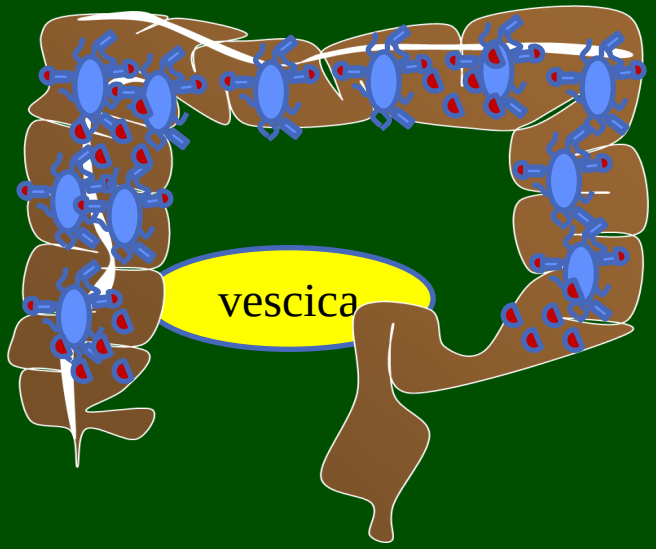
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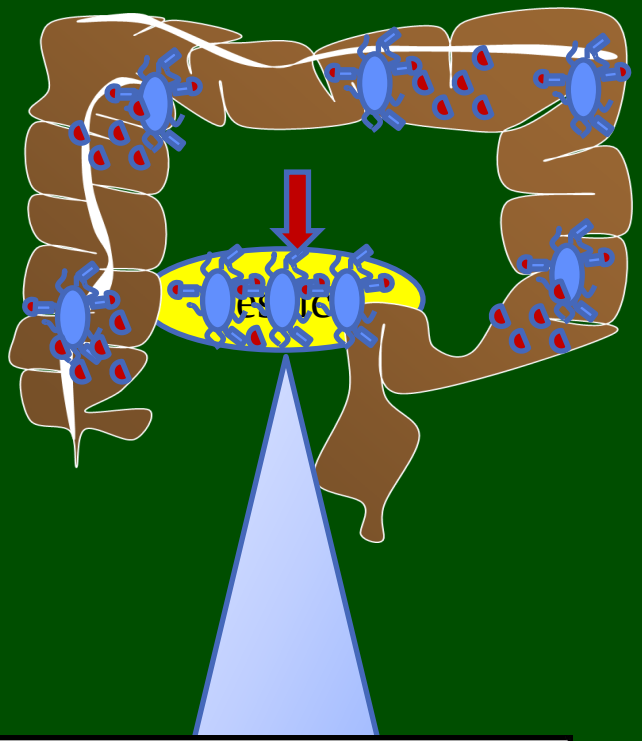
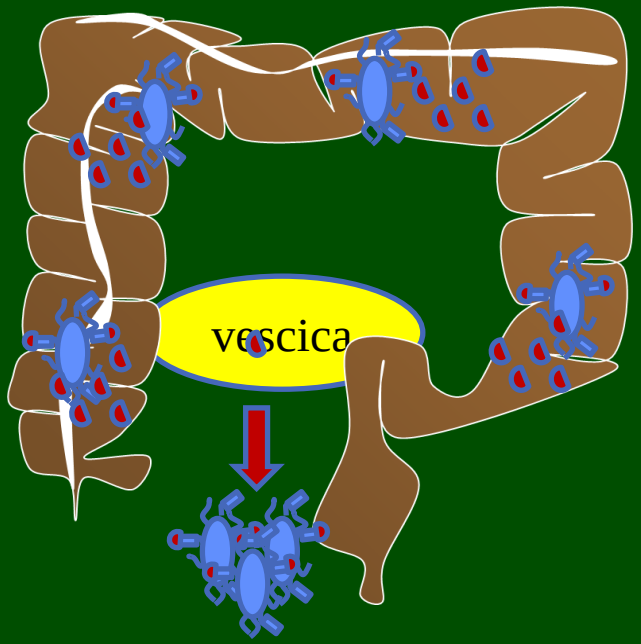


cranberry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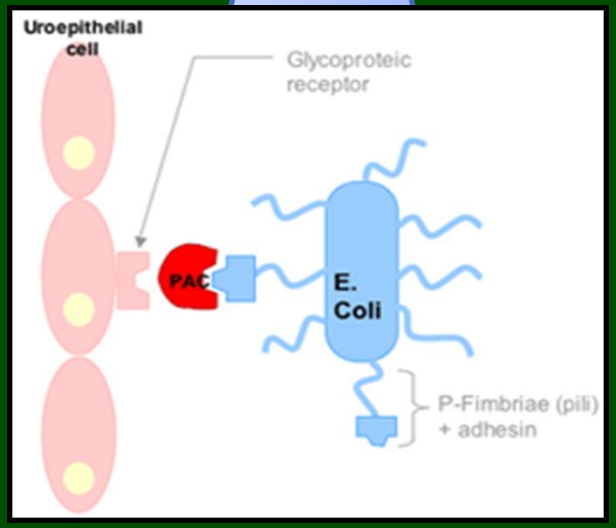
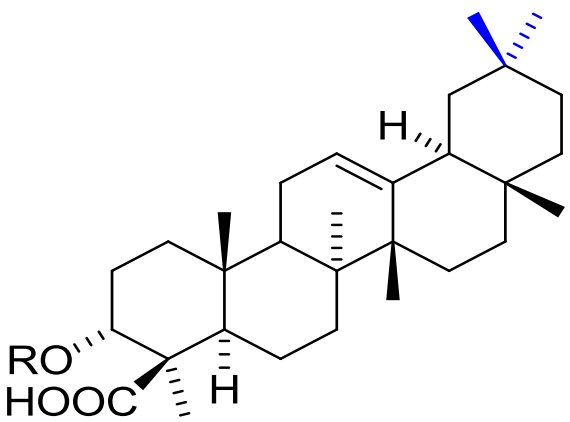

Uroepithelial cell
Glycoproteic receptor
PAC
E. Coli
P-Fimbriae (pili) + adhesin

Boswellia serrata R. resina
e.s. titolato al 65% in ac. boswellici

The boswellic acid alphabet



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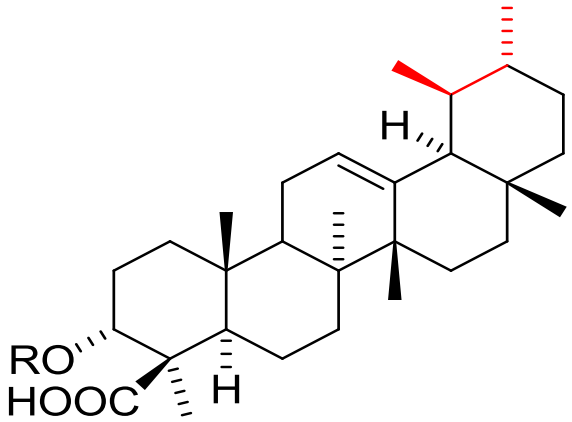
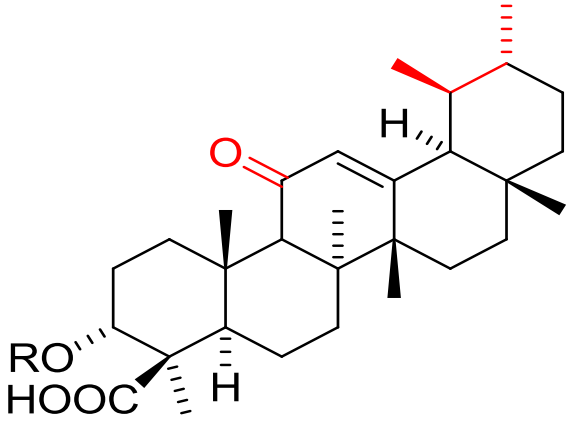
αBA	H
AαBA	Ac

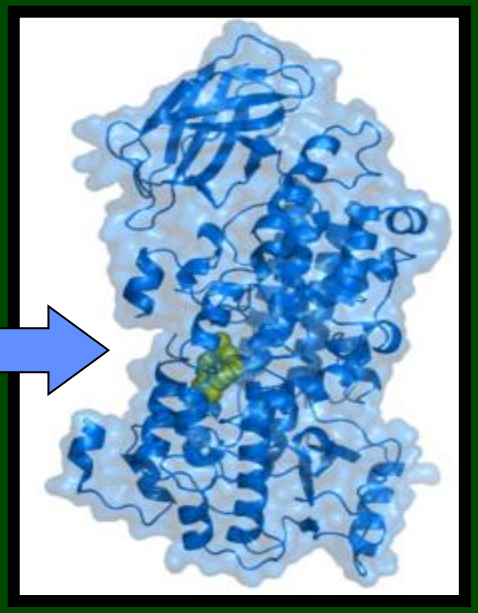


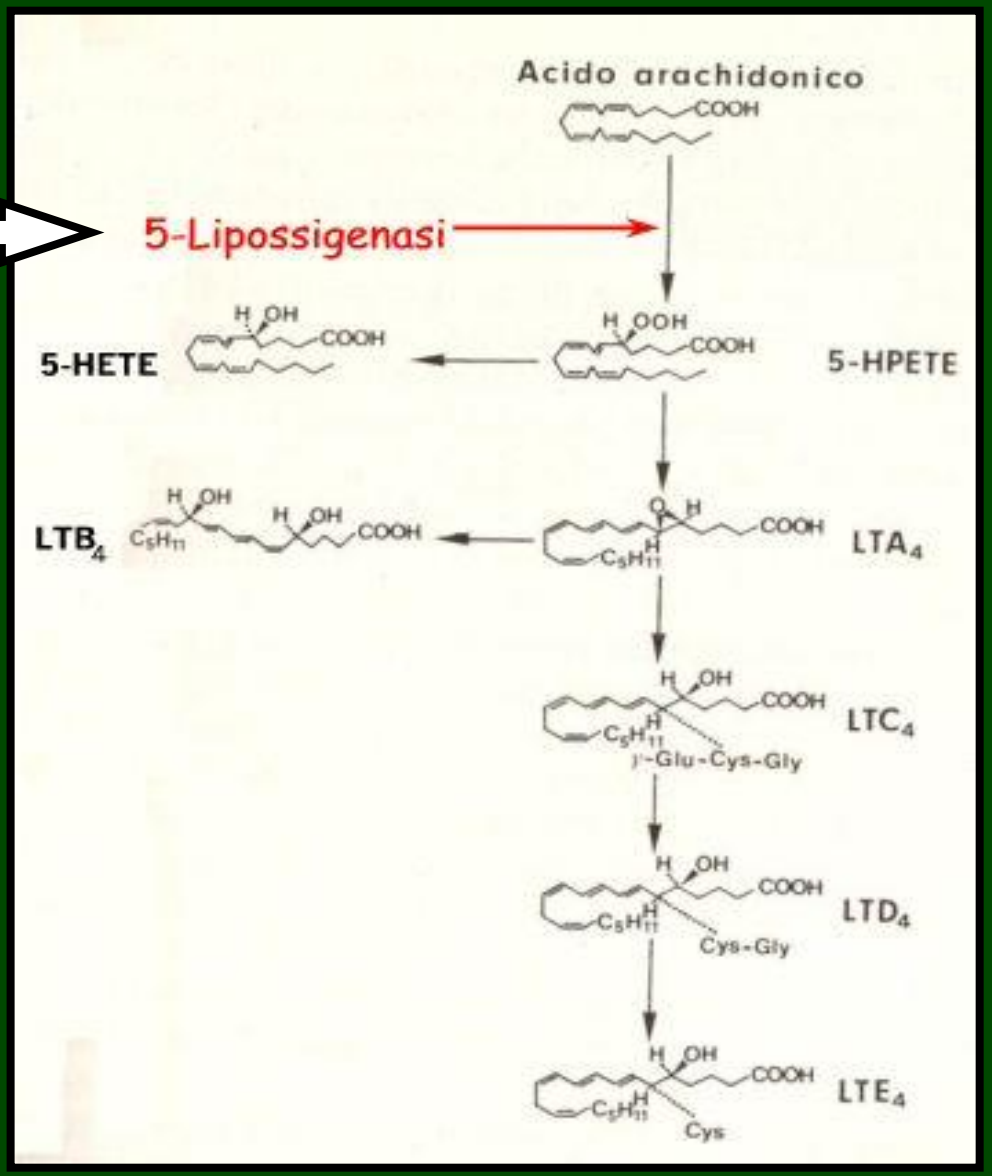
	R
βBA	H
AβBA	Ac



	R
KBA	H
AKBA	Ac

Ac. boswellici





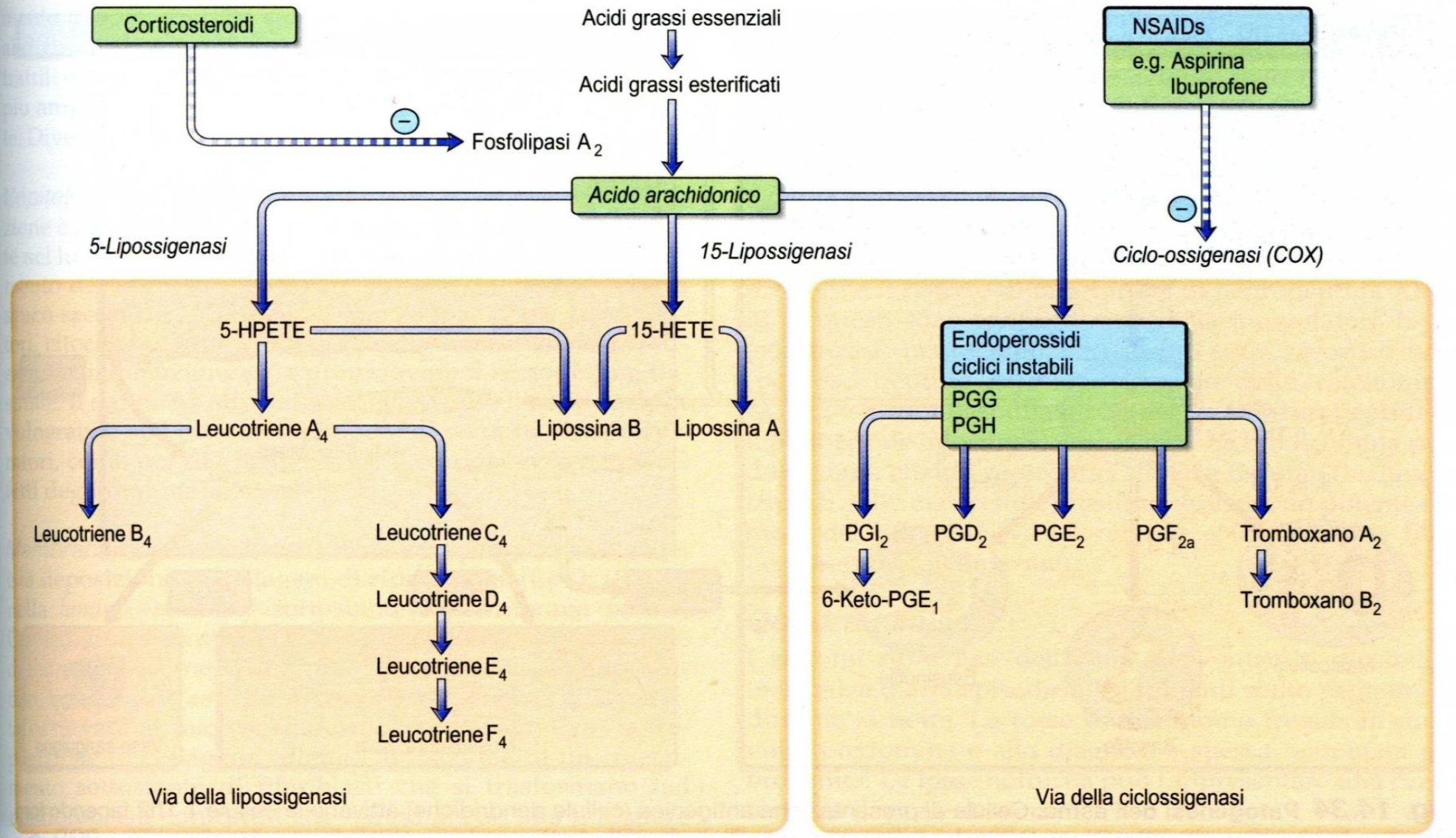


Fig. 14.32 **Metabolismo dell'acido arachidonico ed effetto dei farmaci.** L'enzima ciclo-ossigenasi compare in tre isoforme, COX-1 (costitutiva), COX-2 (inducibile) e COX-3 (nel cervello). PG, prostaglandina.

Valutazioni cliniche

Osteoartrite: riduzione dei sintomi tra il 40 e l'80% dopo 3 mesi di trattamento

Colite (varie forme): riduzione dei sintomi nell' 80% dei casi a 3 mesi

Asma bronchiale: 70% di riduzione sintomatologica già dopo 6 settimane

Edema cerebrale da radioterapia: 25-50% di riduzione

Tollerabilità: abbandoni in studi clinici inferiori all'1%

Tossicità: non evidenziata a 2 g/Kg

Original Article

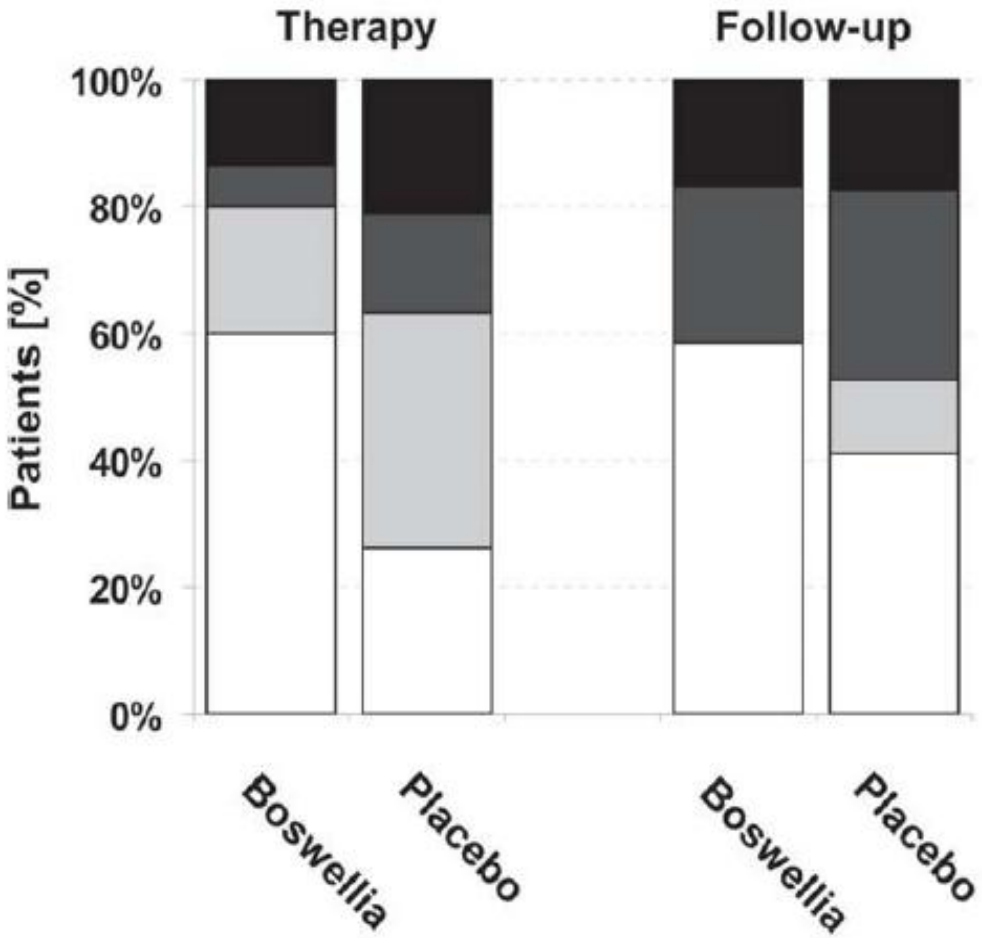
Boswellia serrata Acts on Cerebral Edema in Patients Irradiated for Brain Tumors

A Prospective, Randomized, Placebo-Controlled, Double-Blind Pilot Trial

Simon Kirste, MD[1]; Markus Treier, MD[2]; Sabine Jolie Wehrle, MD[1]; Gerhild Becker, MD[3]; Mona Abdel-Tawab, PhD[4]; Kathleen Gerbeth[4]; Martin Johannes Hug, PhD[5]; Beate Lubrich, PhD[5]; Anca-Ligia Grosu, MD[1]; and Felix Momm, MD[1]

BACKGROUND: Patients irradiated for brain tumors often suffer from cerebral edema and are usually treated with dexamethasone, which has various side effects. To investigate the activity of *Boswellia serrata* (BS) in radiotherapy-related edema, we conducted a prospective, randomized, placebo-controlled, double-blind, pilot trial. **METHODS:** Forty-four patients with primary or secondary malignant cerebral tumors were randomly assigned to radiotherapy plus either BS 4200 mg/day or placebo. The volume of cerebral edema in the T2-weighted magnetic resonance imaging (MRI) sequence was analyzed as a primary endpoint. Secondary endpoints were toxicity, cognitive function, quality of life, and the need for antiedematous (dexamethasone) medication. Blood samples were taken to analyze the serum concentration of boswellic acids (AKBA and KBA). **RESULTS:** Compared with baseline and if measured immediately after the end of radiotherapy and BS/placebo treatment, a reduction of cerebral edema of >75% was found in 60% of patients receiving BS and in 26% of patients receiving placebo ($P = .023$). These findings may be based on an additional antitumor effect. There were no severe adverse events in either group. In the BS group, 6 patients reported minor gastrointestinal discomfort. BS did not have a significant impact on quality of life or cognitive function. The dexamethasone dose during radiotherapy in both groups was not statistically different. Boswellic acids could be detected in patients' serum. **CONCLUSIONS:** BS significantly reduced cerebral edema measured by MRI in the study population. BS could potentially be steroid-sparing for patients receiving brain irradiation. Our findings will need to be further validated in larger studies. ***Cancer* 2011;117:3788–95.** © *2011 American Cancer Society.*

KEYWORDS: brain edema, brain tumor, Boswellia serrata, radiotherapy, supportive care.



Increase of edema (>105% of baseline)

Constant edema (75-105% of baseline)

Slight decrease of edema (25-75% of baseline)

Large decrease of edema (<25% of baseline/no edema)

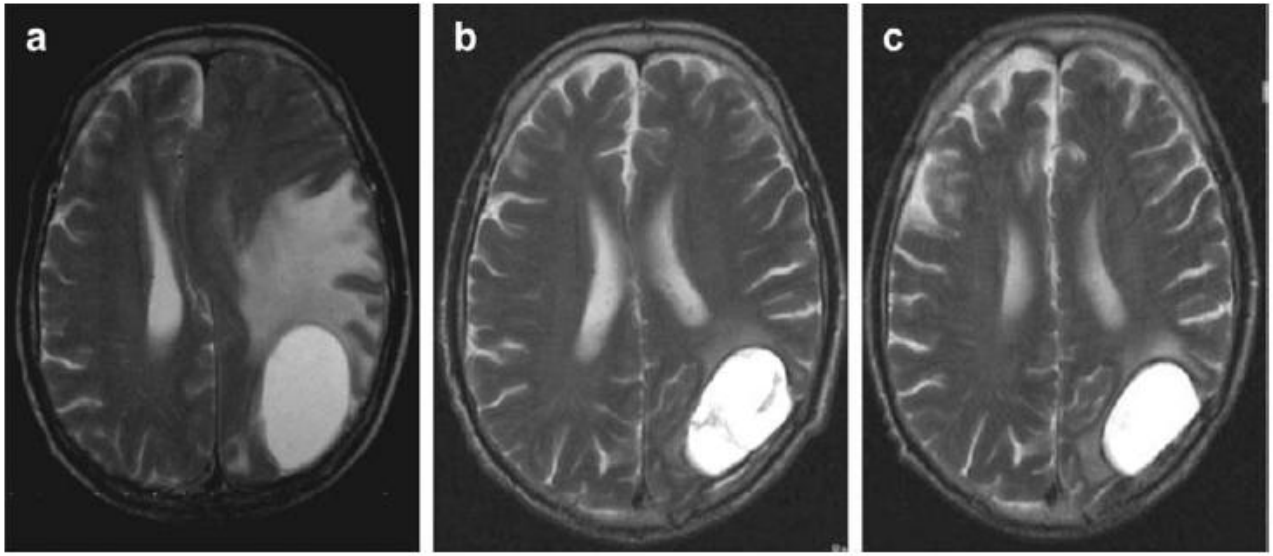


Figure 3. T2-weighted magnetic resonance images of a patient from the *Boswellia serrata* group with metastases from lung cancer (adenocarcinoma) are shown (a) at baseline, (b) after radiotherapy, and (c) at follow-up (4 weeks after radiotherapy).

Pentacyclic triterpenes have gained significant importance because their chemical structures resemble those of steroids. In particular, boswellic acids (BAs), the main active components of the gum resin extract of *Boswellia serrata* (Salai guggal), have received considerable attention. Based on positive data on the treatment of peritumoral brain edema accompanying gliomas (Winking et al., 2000), the European Medicines Agency designated an orphan drug status to *B. serrata* dry resin extract in 2002, thus boosting the status of *B. serrata* extract as an herbal remedy.

Curcuma longa

Figure 1. Structures of Curcumin (Diferuloylmethane), Demethoxycurcumin, and Bisdemethoxycurcumin

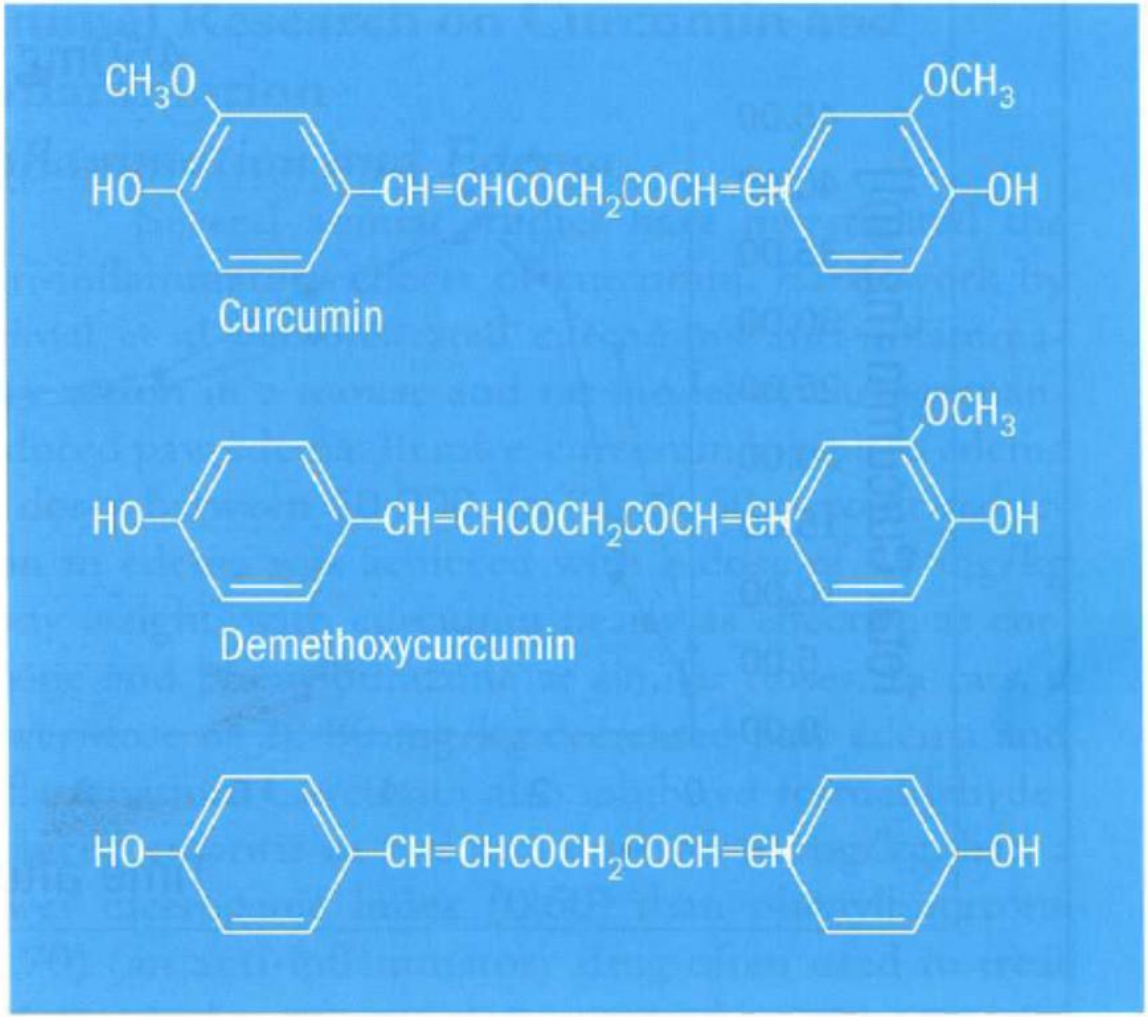


Table 3. Clinical Trials Investigating the Use of Curcumin in Cancer[58]

Clinical Trial Identifier	Condition	Site	Intervention	Trial Phase	Completion Date
NCT00365209	Colon cancer prevention	Chao Family Comprehensive Cancer Center	Curcumin	Phase II	Unknown
NCT00118989	Colon cancer prevention	University of Pennsylvania	Curcuminoid complex, 4 g daily	Phase II	June 2009
NCT00641147	Familial adenomatous polyposis	Johns Hopkins University	Curcumin, 700 mg twice daily	Phase II	March 2013
NCT00745134	Rectal cancer	MD Anderson Cancer Center	Curcumin, 4 g daily, Capecitabine	Phase II	July 2010
NCT00486460	Pancreatic cancer	Tel-Aviv Sourasky Medical Center	Gemcitabine, Curcumin, Celebrex (doses unknown)	Phase III	Unknown
NCT00094445	Pancreatic cancer	MD Anderson Cancer Center	Curcumin, 8 g daily	Phase II	December 2009
NCT00113841	Multiple myeloma	MD Anderson Cancer Center	Curcumin + Bioperine, 2 g twice daily	Pilot Study	December 2008
NCT00689195	Osteosarcoma	Tata Memorial Hospital	Curcumin and Ashwagandha (doses unknown)	Phase I and II	May 2012
NCT00475683	Oral mucositis – children on chemotherapy	Hadassah Medical Organization	Curcumin liquid extract, 10-30 drops 3 times daily	Phase III	December 2009

Adv Exp Med Biol. 2007;595:269-300.

Curcumin as chemosensitizer.

Limtrakul P.

This overview presents curcumin as a significant chemosensitizer in cancer chemotherapy. Although the review focuses on curcumin and its analogues on multidrug resistance (MDR) reversal, the relevance of curcumin as a nuclear factor (NF)-KB blocker and sensitizer of many chemoresistant cancer cell lines to chemotherapeutic agents will also be discussed. One of the major mechanisms of MDR is the enhanced ability of tumor cells to actively efflux drugs, leading to a decrease in cellular drug accumulation below toxic levels. Active drug efflux is mediated by several members of the ATP-binding cassette (ABC) superfamily of membrane transporters, which have now been subdivided into seven families designated A through G. Among these ABC families, the classical MDR is attributed to the elevated expression of **ABCB1 (Pgp),** ABCC1 (MRP1), and ABCG2 (MXR). The clinical importance of Pgp, MRP1, and MXR for MDR and cancer treatment has led to the investigation of the inhibiting properties of several compounds on these transporters. At present, due in part to the disappointing results associated with the many side effects of synthetic modulators that have been used in clinical trials, current research efforts are directed toward the identification of novel compounds, with attention to dietary natural products. The advantage is that they exhibit little or virtually no side effects and do not further increase the patient's medication burden.

Biochem Pharmacol. 2004 Nov 15;68(10):2043-52.

Biochemical mechanism of modulation of human P-glycoprotein (ABCB1) by curcumin I, II, and III purified from Turmeric powder.

Chearwae W et al.

P-glycoprotein (Pgp, ABCB1) is an ATP-dependent drug efflux pump linked to development of multidrug resistance (MDR) in cancer cells. Previously [Biochem Pharmacol 2002;64:573-82], we reported that a curcumin mixture could modulate both function and expression of Pgp. This study focuses on the effect of three major curcuminoids--curcumin I, II and III purified from a curcumin mixture--on modulation of Pgp function in a multidrug resistant human cervical carcinoma cell line (KB-V1). The similar IC(50) values for cytotoxicity of curcuminoids of KB-V1, and KB-3-1 (parental drug sensitive cell line) suggest that these curcuminoids may not be substrates for Pgp. Treating the cells with non-toxic doses of curcuminoids increased their sensitivity to vinblastine only in the Pgp expressing drug resistant cell line, KB-V1, and curcumin I retained the drug in KB-V1 cells more effectively than curcumin II and III, respectively. Effects of each curcuminoid on rhodamine123, calcein-AM, and bodipy-FL-vinblastine accumulation confirmed these findings. Curcumin I, II and III increased the accumulation of fluorescent substrates in a dose-dependent manner, and at 15 microM, curcumin I was the most effective. The inhibitory effect in a concentration-dependent manner of curcuminoids on verapamil-stimulated ATPase activity and photoaffinity labeling of Pgp with the [(125)I]-iodoarylazidoprazosin offered additional support; curcumin I was the most potent modulator. **Taken together, these results indicate that curcumin I is the most effective MDR modulator among curcuminoids, and may be used in combination with conventional chemotherapeutic drugs to reverse MDR in cancer cells.**

Oncol Rep. 2008 Oct;20(4):731-5.

Reversal of P-glycoprotein-mediated multidrug resistance in human sarcoma MES-SA/Dx-5 cells by nonsteroidal anti-inflammatory drugs.

Angelini A, Iezzi M, Di Febbo C, Di Ilio C, Cuccurullo F, Porreca E.

Multidrug resistance (MDR) mediated by P-glycoprotein (P-gp) is one of the major reasons for the failure of cancer therapy. Several chemosensitizers are able to reverse in vitro MDR by inhibiting P-gp, although high toxicity limits their clinical application. In this study, we aimed to investigate the in vitro effectiveness of four common non-steroidal anti-inflammatory drugs (NSAIDs) such as **Curcumin** (Cur), Sulindac (Sul), Ibuprofen (Ibu) and NS-398 (NS) to inhibit P-gp activity at clinically achievable doses and to evaluate their potential use as sensitizers in anti-cancer chemotherapy. The human doxorubicin (doxo) resistant uterine sarcoma cells (MES-SA/Dx-5) expressing high levels of P-gp, were treated with different doxo concentrations in the presence or absence of NSAIDs. Cellular accumulation of doxo, cytotoxicity and apoptosis induction were measured in comparison with Verapamil, a specific P-gp inhibitor, used as a reference molecule. We found that Ibu, Cur and NS-398 enhanced significantly doxo retention, cytotoxicity and apoptosis on resistant MES-SA/Doxo-5 cells when compared with doxo alone. In contrast, no significant changes were found in resistant cells treated with Sul-doxo combinations. **Our results demonstrate that Cur is able to overcome P-gp-mediated MDR in MES-SA/Dx-5 cells. These findings provide the rationale for clinical studies of NSAIDs and/or derivatives as a new potential generation of chemosensitizers to improve effectiveness of the anti-cancer drugs in the treatment of human cancer.**

Nutr Cancer. 2010;62(2):148-53.

Possible benefits of curcumin regimen in combination with taxane chemotherapy for hormone-refractory prostate cancer treatment.

Cabrespine-Faugeras A, Bayet-Robert M, Bay JO, Chollet P, Barthomeuf C.

Complementary and alternative therapies for neoplastic diseases treatment and prevention receive increasing attention from the medical community. Prostate cancer (PC) is the most frequently diagnosed malignancy and the second major cause of male death in industrialized countries. The chemopreventive properties and clinical safety of curcumin, a polyphenolic derivative, have already been established. However, curcumin regimen value in addition to conventional hormone refractory (HR) PC treatment remains largely unknown. This review article summarizes mechanisms by which curcumin may decrease HRPC aggressive proliferation and potentiate activity of taxane therapy. Our analysis suggests that curcumin alone has a therapeutic value in HRPC. **In combination with a taxane agent, this compound may enhance cytotoxicity and retard PC cell resistance to taxane.** As a consequence, a rationale is provided for considering the possible benefits of curcumin regimen in combination with taxane therapy in HRPC patients.

Curr Med Chem. 2009 Nov 24.

Curcumin as an Anti-Cancer Agent: Review of the Gap between Basic and Clinical Applications.

Bar-Sela G, Epelbaum R, Schaffer M.

Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from rhizome (turmeric) of the herb Curcuma longa. Extensive research over the last half century has revealed important functions of curcumin. In vitro and in vivo research has shown various activities, such as anti-inflammatory, cytokines release, antioxidant, immunomodulatory, enhancing of the apoptotic process, and anti-angiogenic properties. **Curcumin has also been shown to be a mediator of chemo-resistance** and radio-resistance. The anti-cancer effect has been seen in a few clinical trials, mainly as a native chemoprevention agent in colon and pancreatic cancer, cervical neoplasia and Barrets metaplasia. **Some clinical studies with healthy volunteers revealed a low bioavailability of curcumin, casting doubt on the use of curcumin.** Our clinical experience with curcumin, along with the anti-metabolite gemcitabine in the treatment of patients with advanced pancreatic carcinoma, produced an objective response in less than 10% of patients, with a minor effect on survival. However, the safety of this combination was proved. Curcumin's potent anti-proliferative activity interacting with several intracellular signal transduction pathways may potentiate the anti-tumor effect of gemcitabine. The preclinical data lead to various, but still scarce, clinical studies (some on-going) that demonstrated the possible efficacy of this treatment as a chemopreventive or chemotherapeutic agent. This review will focus on the clinical evidence, including our experience with curcumin as a chemopreventive and therapeutic agent and the in vitro background results.

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molecular pharmaceutics

reviews

Bioavailability of Curcumin: Problems and Promises

Preetha Anand,[†] Ajaikumar B. Kunnumakkara,[†] Robert A. Newman,[‡] and Bharat B. Aggarwal*[,†]

Cytokine Research Laboratory and Pharmaceutical Development Center, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

Received August 19, 2007; Revised Manuscript Received September 27, 2007; Accepted September 28, 2007

Abstract: Curcumin, a polyphenolic compound derived from dietary spice turmeric, possesses diverse pharmacologic effects including anti-inflammatory, antioxidant, antiproliferative and antian-

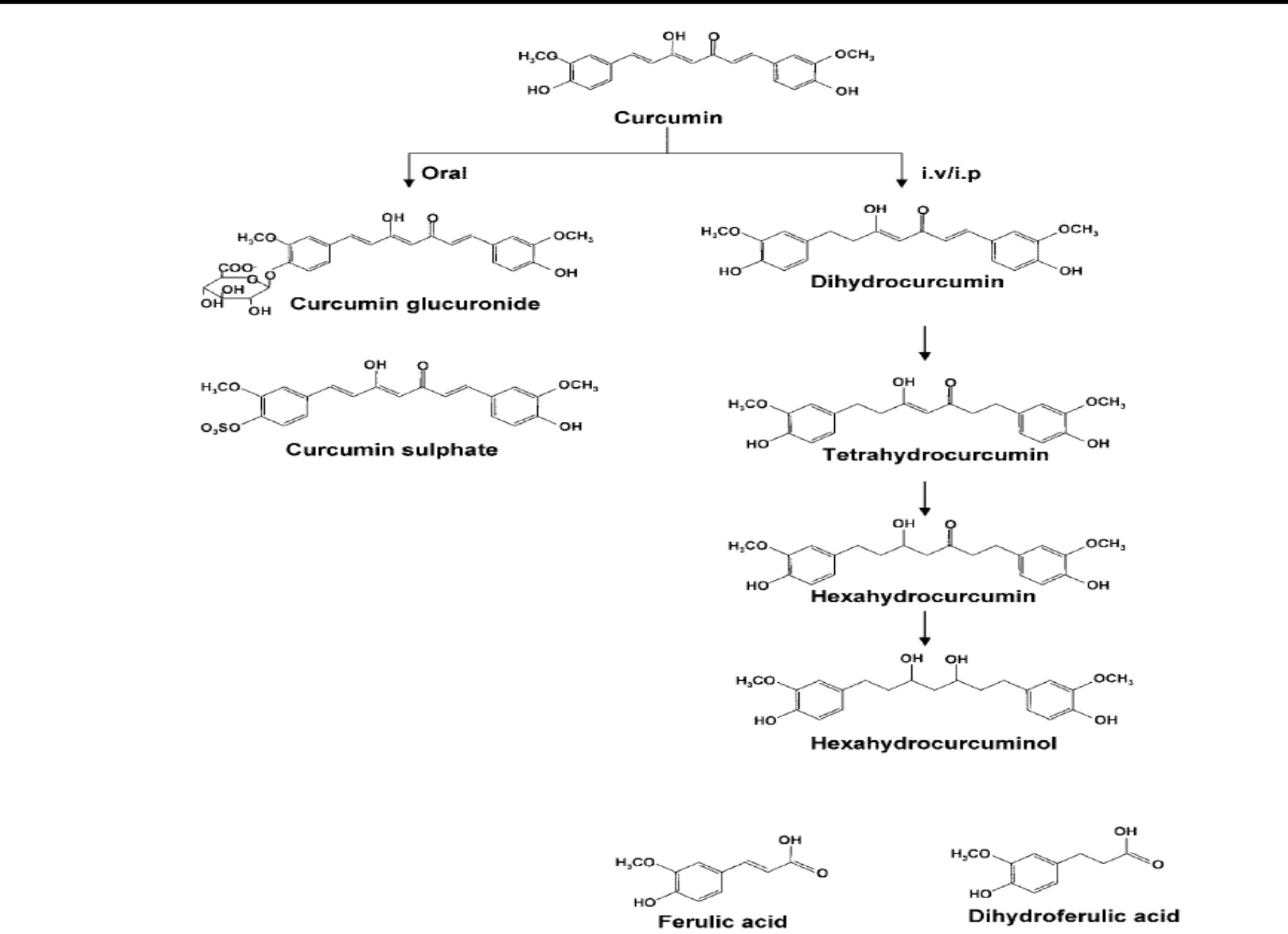

Figure 1. Structure of curcumin and its metabolites.

Biodisponibilità Curcumina nel volontario sano

Trattamento	AUC
1) 400 mg di curcumina pura	2240 197
2) 4000 mg di curcumina pura	23800 1212
3) 400 mg di curcumina fitosoma	24404 1857
4) 400 mg di curcumina fitosoma 4 mg di piperina	596080 29872

Dai dati precedenti risulta evidente che la contemporanea somministrazione di curcumina fitosoma associata a piperina pura incrementa la biodisponibilità orale di curcumina di **circa 260 volte** rispetto alla somministrazione della medesima quantità di curcumina pura non complessata non associata a piperina.

Studio pilota associando curcumina biodisponibile alla chemioterapia con taxotere nel cancro prostatico metastatico

Schema dello studio:

Docetaxel 75 mg/mq giorni 1-21 per 5 cicli.

Alla ripresa della malattia:

Docetaxel con lipicur 1 cp 1 ora prima della CT e 5 compresse successivamente ogni ora (tot 6)

Valutazione del PSA come endpoint surrogato.
Registrazione della tolleranza

n. cartella	psa pre	psa post	varia %	PSA pre t	psa post	varia %	lesioni cliniche	tossicità	risposta
e-419-08	12,07	12,99	**+7,6**	48,28	24,5	**-49,3**	ossee	no	si
e-616-06	48	57,9	**+20,6**	526	317	**-39,7**	ossee	stop 1 ciclo x allergia	si
e-100-04	42,9	86,3	**+ 100**	86,5	50,5	**-41,6**	ossee		si
e-93-05	124	141	+13,7	141	201	+42,6	ossee		no
e-703-02	32,23	11.26	**-65**	28,5	in corso 4 ciclo	**-59**	ossee		Trend si
e-599-09	130	42,77	-67,1	129	in corso 1 ciclo		ossee		
e-421-04	66,9	53,02	-20,7	82	In corso 1 ciclo		ossee		
e-148-05	150	89,5	-40,3	In attesa			ossee		
MN	100	125	+ 125	220	110	- 50%	ossee		si
e-049-06	58,8	129,4	+120,1	129,4			ossee		
e-595-10	124,7	108*	-13,4	108	in corso 5 ciclo				Trend si
e-369-09	252	391	+55.2	Deve iniz lipicur					

Grazie per l’attenzione!