

Safety & Efficacy of Supplement Drug Interactions

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Meaning of words used

- **Safety**: Freedom from danger, risk, or injury.
- **Efficacy**: Evidence based effective results.
- **Supplement**: *Food for special dietary use.*
- **Drugs**: Therapeutic substances approved by the drugs & devices sections of FDA

DSHEA 1994 **supplement**

- **product** that contains substances like vitamins, minerals, foods, botanicals, amino acids & is intended to supplement the usual intake of these substances. Dietary supplements are found in pill, tablet, capsule, powder or liquid form and are meant to be taken by mouth.

Natural Products: Cradle to Cradle

- Inherently or intrinsically no waste
- End product used as feedstock
- Inherently high efficiency
- Wholism 'obvious'
- Interdependence
- Physiology
- Quality and sustainability high values
- Was hard to standardize natural products

Extra-natural: Cradle-to-Grave

- Waste disposed, assumed inherent, NIMBY
- End product discarded or abandoned
- Inherently low efficiency
- Reductionism a given
- Autonomy, independence
- Chemical engineering
- Quantity and ROI are high values
- Standardized doses & delivery of drugs

Adverse Events (AE)

What data says
comparing AE events
from dietary supplements
compared to all AE
reports (2006)

Dietary supplements AE 2006

- **275 of 450,000** total AE reported. 2/3 rated as probably or possibly related to supplement use (N=183); coincidental, unrelated (N=92).



41% cases symptomatic self-limited (N=113): caffeine (47%; N=53) & yohimbe (18%; N=20) & 70 TBD. Suspected drug-herb interactions occurred in 6 cases, including *yohimbe* co-ingested with bupropion (1), methamphetamine (3), **additive anticoagulant/anti-platelet effects of NSAIDs taken with fish oils** (1) & ginkgo (1).

8 AE required hospital admission [2,200,000/100,000].


Lab tests confirmed adulteration with pharmacologically active substances in 4 cases & negative in 5 cases.

- [Haller](#) C A, [Kearney](#) T, [Bent](#) S, [Ko](#) R, [Benowitz](#) N L, [Olson](#) K, Dietary supplement adverse events: Report of a one-year poison center surveillance project, [J Medical Toxicology](#), 2008; [4\(2\)](#): 84-92.

ASA or NSAID + Omega 3 EFA

- Fish oil did *not* affect bleeding time or plasma levels of beta-thromboglobulin; an  in platelet count after operation was slightly *less* pronounced in fish-oil group. Apart from a small  in PAI-1 antigen *borderline* sig., no long-term effects by fish oil on parameters of coagulation & fibrinolysis were seen.
- Eritsland J, Arnesen H, Seljeflot I, Kierulf P. Long-term effects of n-3 polyunsaturated fatty acids on haemostatic variables and bleeding episodes in patients with coronary artery disease. *Blood Coagul Fibrinolysis*. 1995 Feb;6(1):17-22.

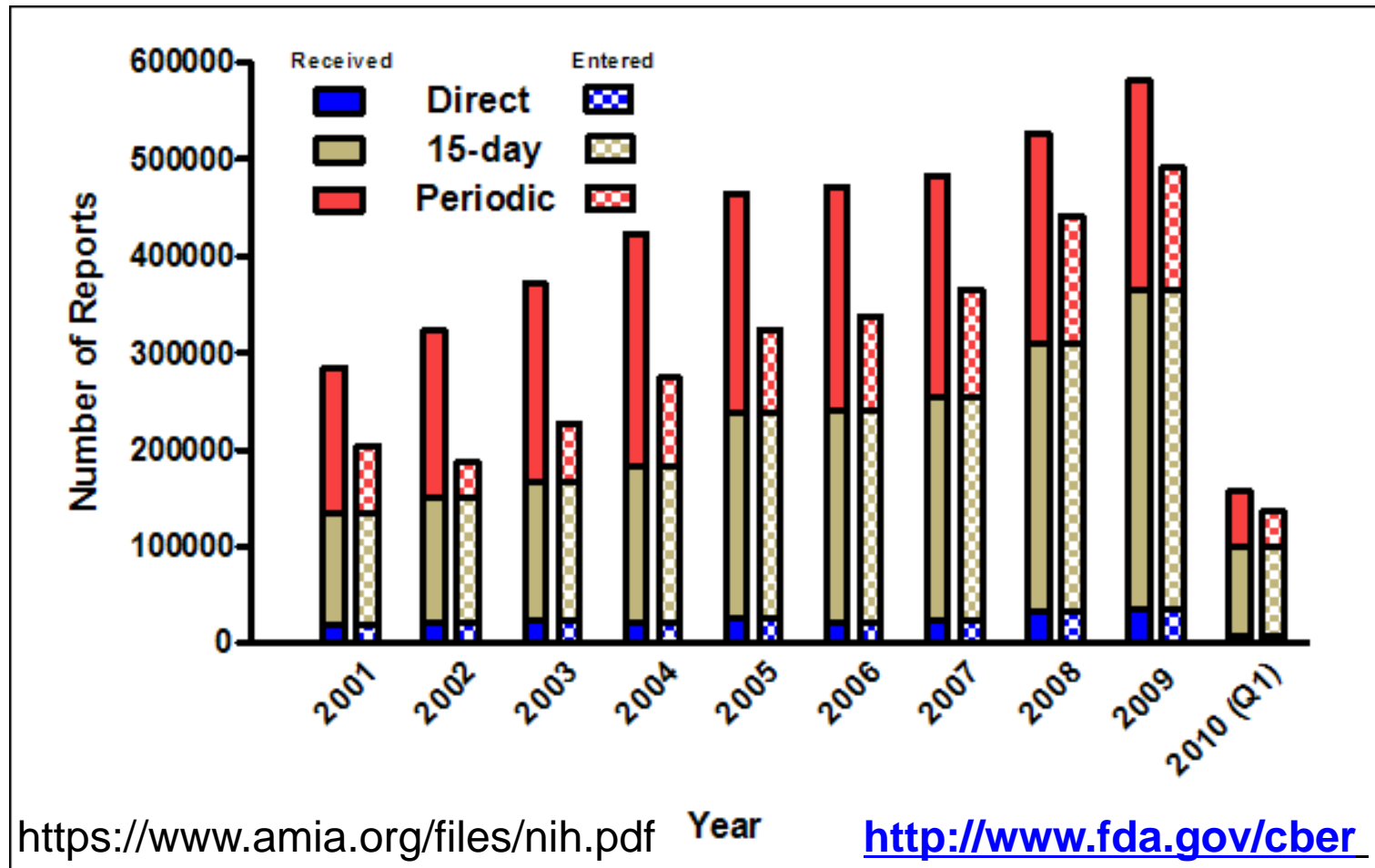
ASA or NSAID + Omega 3 EFA

- Bleeding time & mesenteric vascular reactivity to noradrenaline were  2-4 weeks after receiving a moderate intake of EPA & effects persisted 5-21 d after switching to control diet...

in male Wistar rats under stress... *not* found for people in either PubMed or Google Scholar [myths linger on... Linus Pauling]

Mark G, Sanders TA. The influence of different amounts of n-3 polyunsaturated fatty acids on bleeding time and in vivo vascular reactivity. *Br J Nutr.* 1994 Jan;71(1):43-52.

Adverse Event (AE) US



Natural v Extra-Natural Products

Category Condition	Natural Product	Extra-Natural Product	Safety ratio	Efficacy ratio	Lives/year (Est.)	\$/year \$100K/
Malaria Prophylaxis	Chincona Bark	Quinine	100	1	20	NA
Malaria Treatment	Artemesia Annu	Artemisinin	75	0.2	20	NA
Food Preserve Anti-oxidant	Vitamins E Tocopherols/ Tocotrienols	BHA/BHA	>500	0.5	1,500	\$0.3 Bn
Balance Calcium	Magnesium	Calcium channel blockers	>500	0.5	5,000	\$0.5 Bn
Digestion	Probiotics/ Prebiotics	Antibiotics/ Biocides	>500	0.4	20,000	\$2 Bn
Comfort	Polyphenolics	Cox-2 modulators	>500	0.5	50,000	\$5 Bn
Pain	Poppies	Morphine/Heroin	50	0.25	15,000	\$1.5 Bn
Cancer risk	Sulforophane/ ECGC	Preventive chemo	>500	??	??	
Gut repair Energy	Glutamine/ PAK	Cross-link enhancers	>500	0.4	5,000	\$0.5 Bn

Malaria Prophylaxis

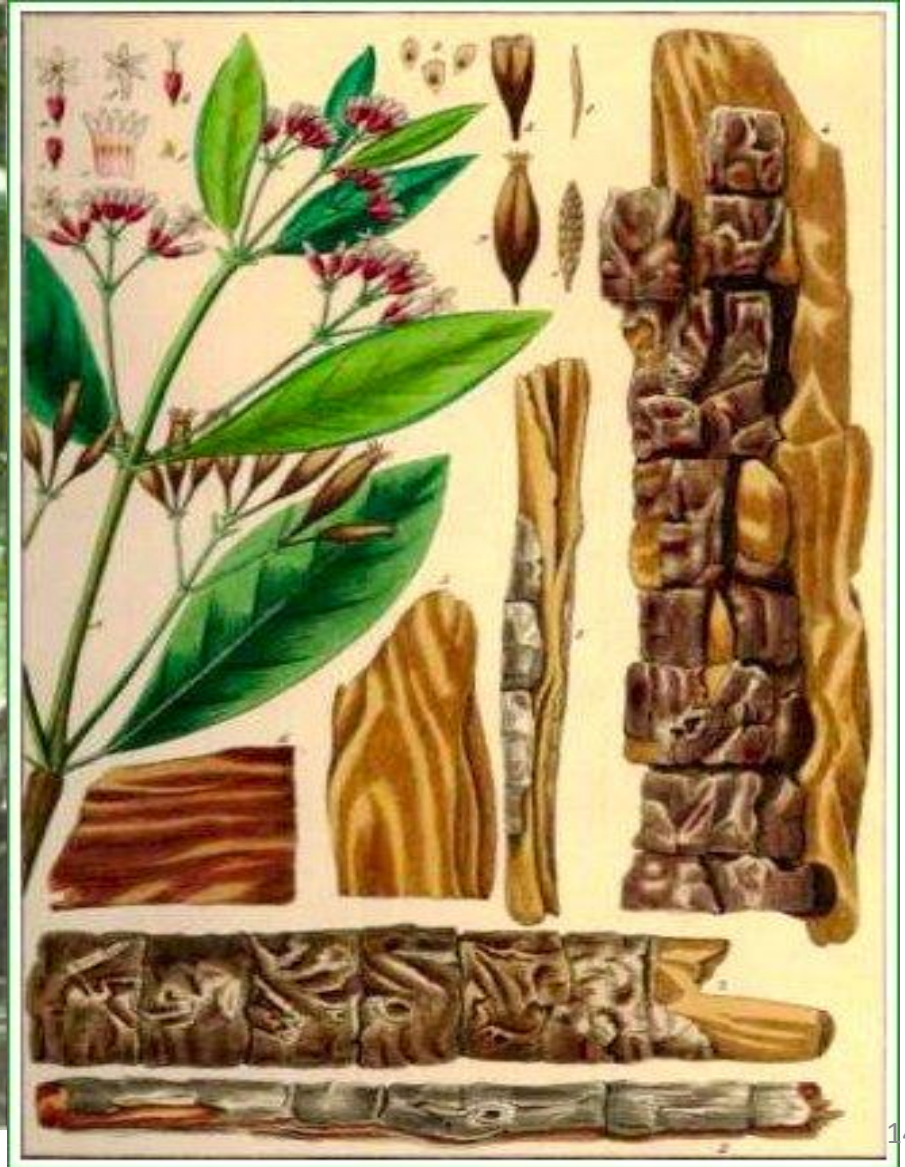
- Traditional tree bark
or isolated ingredient:
Safety, efficacy, risk

Chincona Bark Medicinals

- Chincona, Jesuit's or Peruvian bark: Active alkaloids including anti-malarial quinine interferes w/ reproduction of malaria-causing protozoa, & quinidine antiarrhythmic.
- Quinine causes liver scars; chincona has protective antioxidants; both effective.

Rice, Benjamin Lewis (1897). [Mysore: A gazetteer compiled for Government Vol. 1](http://www.archive.org/stream/mysoregazetteerc01rice#page/n199/mode/2up/search/cinchona+biligiri). Westminster: A Constable. pp. 892

Chincona Bark Tree



Malaria Treatment

- Artemesia Annua v
Artemesinin: Safety,
efficacy, risk,
outcomes

Malaria treatment

- Artemesia Annua & synthetic Artimesinin work
- Artemesia Vulgaris or Sweet Annie; mugwort do **not** work [*workalikes* often don't work]

Artemisia Annua or Artemisinin

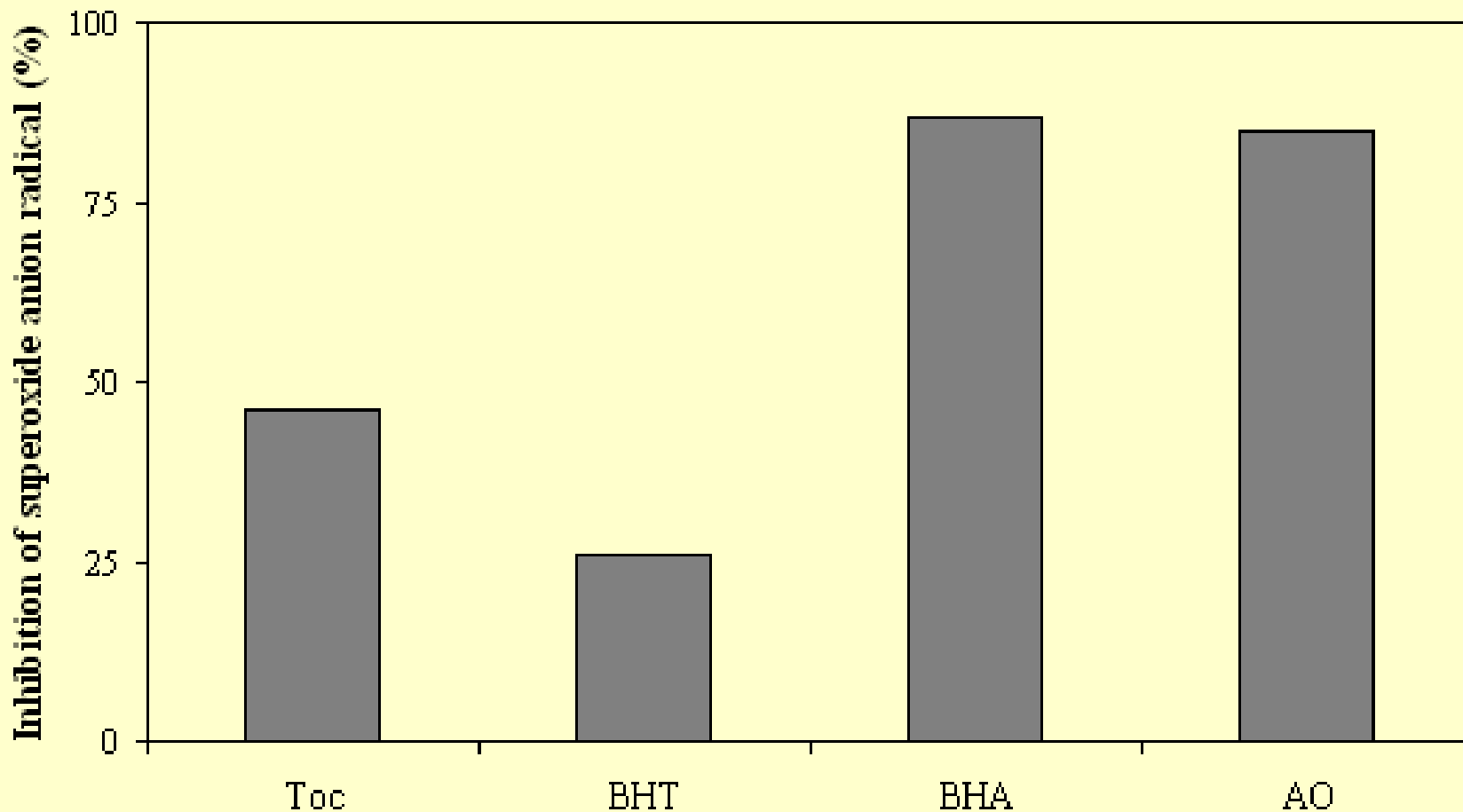
- **Artemisia annua L., Asteraceae; quinghao**
Asian annual herb is Artemisinin source.
Grows in Argentina, Bulgaria, France, Hungary, Romania, Italy, Spain, U.S. & Yougosalavia. Leaf secretory cells 89% total artemisinin in plant w/uppermost foliar portion of plant (top 1/3 of growth at maturity) containing almost 2X that of lower leaves.
Natural product not provoke resistance;
synthetic artemisinin has resistance & >AE.
- **Klayman D L.** (1993) *Artemisia annua*: From weed to respectable antimalarial plant. In: Kinghom A D, Balandrin M F. (eds.), Human Medicinal Agents from Plants. Am. Chem. Soc. Symp. Series. Washington, DC.
- **Ferreira J F S, Laughlin J C, Delabays N, Magalhães P M, de Magalhães P M.** Cultivation and genetics of *Artemisia annua* L. for increased production of the antimalarial artemisinin. Plant Genetic Res 2005; **3**: 206-229.

Antioxidant Food Protectors

Natural Vitamins E v

Synthetic BHA / BHT

Compare antioxidant activity



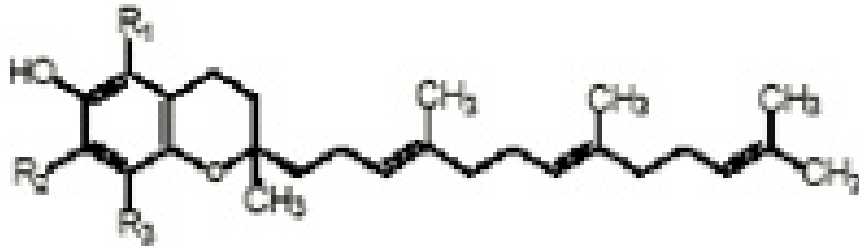
7th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-7), <http://www.mdpi.net/ecsoc-7>, 1-30 November 2003

Synthetic Antioxidants

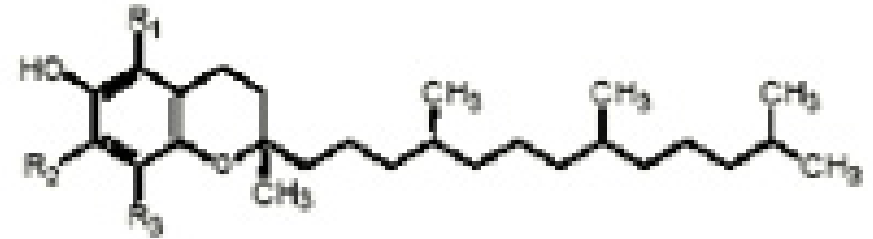
- **BHA** is mixture of isomers 3-*tert*-butyl-4-hydroxyanisole and 2-*tert*-butyl-4-hydroxyanisole. A/K/A BOA, *tert*-butyl-4-hydroxyanisole, (1,1-dimethylethyl)-4-methoxyphenol, *tert*-butyl-4-methoxyphenol, antioxyne B; Molecular formula $C_{11}H_{16}O_2$
- **BHT** (3,5-di-*tert*-butyl-4-hydroxytoluene; methyl-di-*tert*-butylphenol; 2,6-di-*tert*-butyl-*para*-cresol)
Molecular formula $C_{15}H_{24}O$

Williams GM, Iatropoulos MJ, Whysner J. [Safety assessment of butylated hydroxyanisole and butylated hydroxytoluene as antioxidant food additives](#). Food Chem Toxicol. 1999 Sep-Oct;37(9-10):1027-1038

Tocopherol & Tocotrienol AO



Tocotrienol



Tocopherol

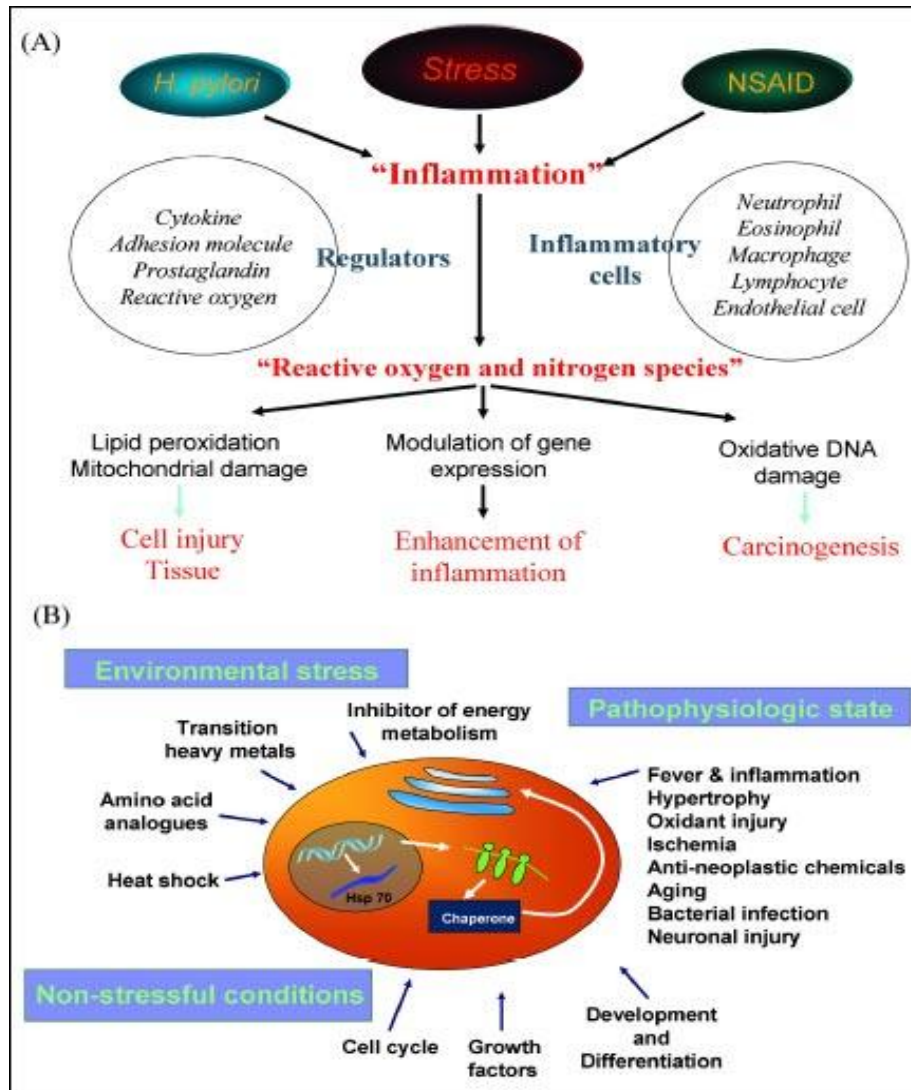
R ₁	R ₂	R ₃	Tocopherol	Tocotrienol
CH ₃	CH ₃	CH ₃	α -Tocopherol	α -Tocotrienol
CH ₃	H	CH ₃	β -Tocopherol	β -Tocotrienol
H	CH ₃	CH ₃	γ -Tocopherol	γ -Tocotrienol
H	H	CH ₃	δ -Tocopherol	δ -Tocotrienol

**Bendich A, Machlin LJ, Safety of oral intake of vitamin E,
Am J Clinical Nutrition, 1988; 48: 612-619**

**Induce Repair 1st Responders
or Suppress Inflammation
for comfort, safety, risk**

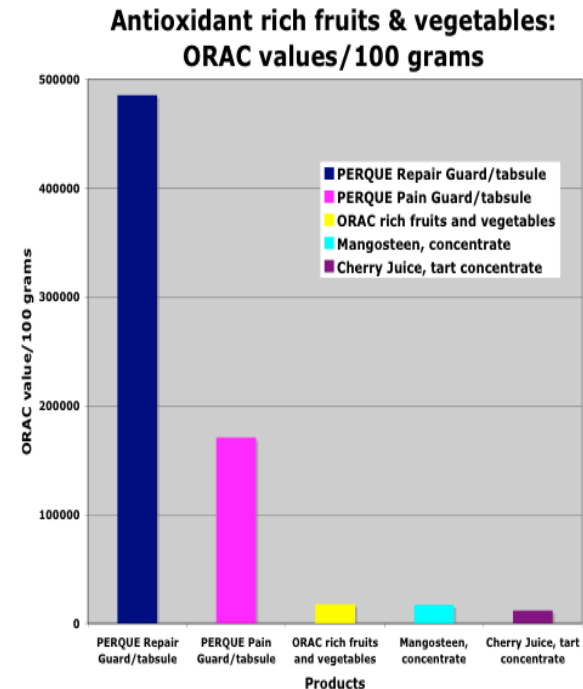
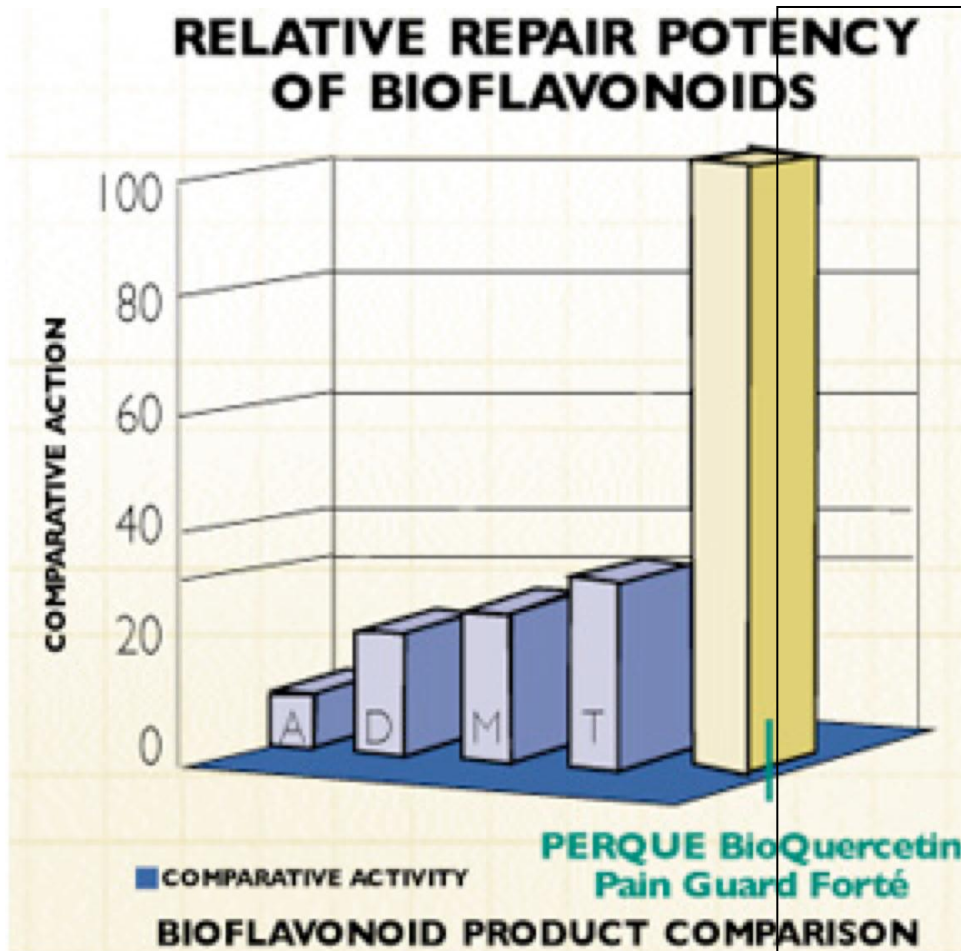
- **Polyphenolics v ASA,
NSAIDs,
Acetaminophen**

Polyphenolics v NSAIDs, ASA



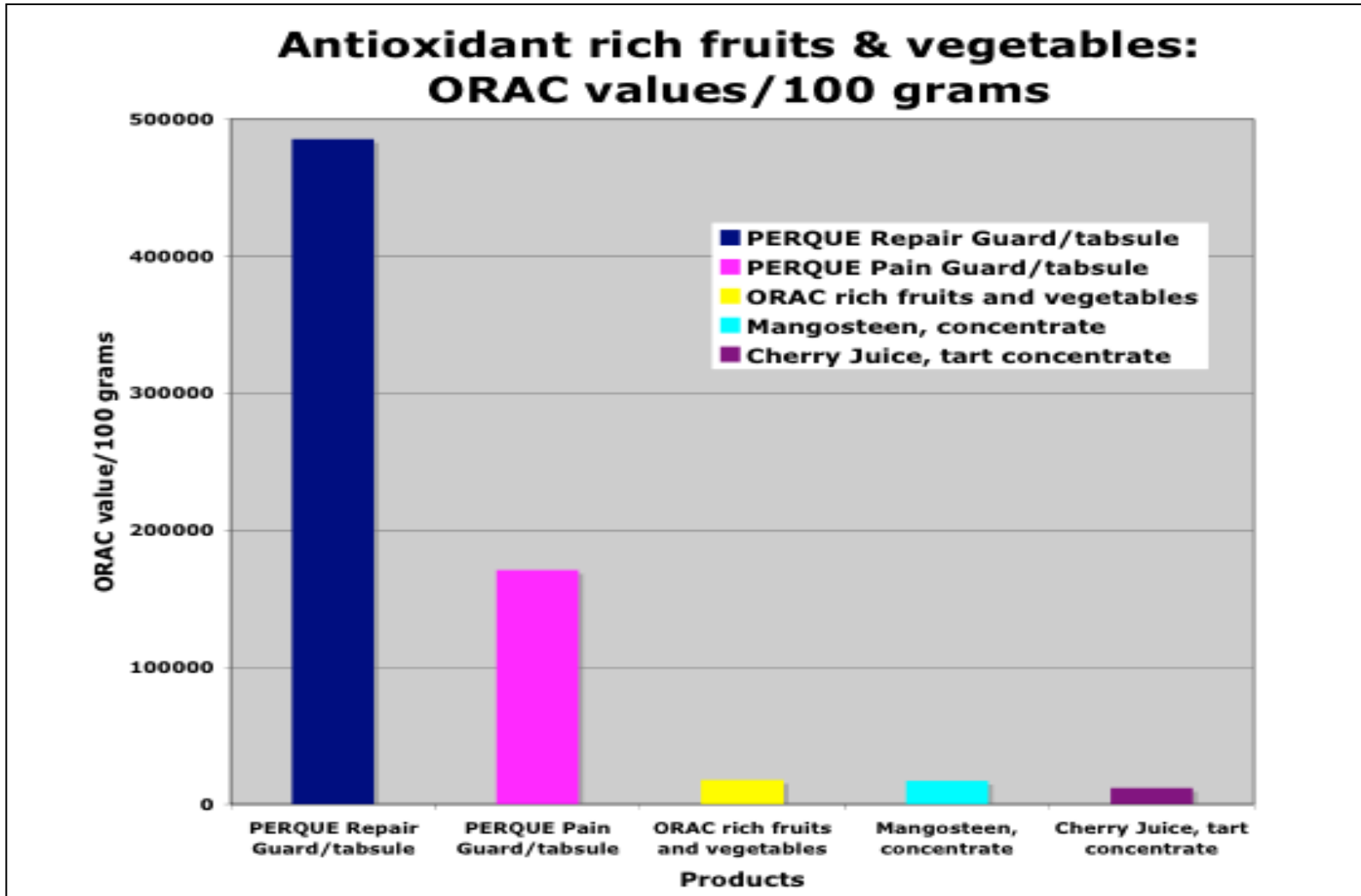
- Polyphenolic flavanoids & flavanols activate 1st responder repair cells.
- NSAIDs, ASA, & acetaminophen inhibit COX-1&2 enzymes; 50±25,000 deaths/yr; toxicities *multiply* in concurrent use.

Quercetin Dihydrate & OPC: Safer Repair Stimulation



Middleton E Jr. Effect of plant flavonoids on immune and inflammatory cell function. *Adv Exp Med Biol* 1998; 439: 175-182.

Repair Guard delivers highest, safer antioxidant protection



Pain: Opium, Morphine, Heroin

- Compare options for serious pain management:
Safety, Efficacy, Risk

Natural Pain Killers from Poppy

- Latex alkaloids from immature seed capsules 1 - 3 weeks > flowering. Incisions made in walls of green seedpods, & milky exudation is collected & dried. Opium & isoquinoline alkaloids morphine, codeine, noscapine, papaverine, & thebaine isolated from dried material.

Poppy seeds & pressed oil are not narcotic; they develop after capsule has lost opium-yielding potential. Total yield of alkaloids depends on light, temperature, plant species, & time of harvest.

Angelo HR, Kaa E. *Ugeskr Laeger* 1993 Dec 6; 155(49): 4011-4013

Poppy Juice v. Morphine, etc



Spiro T, Jaffe R, Holland P, Alter H. A Study of Street Heroin Lots for the presence of the Hepatitis-B surface antigen. Drug and Alcohol Dependence 1978; 6: 393-397.

Biosis: Microbial Interdependence

- Prebiotics & Probiotics v Antibiotics & Biocides

Probiotic v Antibiotic

- Probiotic viable microbial dietary supplement beneficially affects host through its effects on intestinal tract... Several health-related effects associated with intake of probiotics include alleviation of lactose intolerance & immune enhancement. Some evidence probiotics reduce risk of rotavirus-induced diarrhea & colon cancer.

Roberfroid M B, Prebiotics and probiotics: are they functional foods? American Journal of Clinical Nutrition, 2000; 71, No. 6: 1682s-1687s.

Prebiotic fibers

- Prebiotics are nondigestible food ingredients that benefit host by selectively stimulating growth or activity of...beneficial bacteria in colon. Inulin-type fructan prebiotics generate sufficient data for thorough evaluation regarding their possible use as functional food ingredients.

When Antibiotics Fail: Restoring the Ecology of the Body by [Marc Lappe](#), Trade Paperback, 1995, 296 p.

Prebiotics & Probiotics

- **Benefits:** Constipation relief, suppression of diarrhea, & reduction of osteoporosis, atherosclerotic cardiovascular disease associated with dyslipidemia & insulin resistance, obesity, & type 2 diabetes risk. Synergy of probiotics & prebiotics deserves study. This combo might improve survival of bacteria crossing upper part of GI tract, enhancing their effects in large bowel. Effects might be additive or even synergistic.

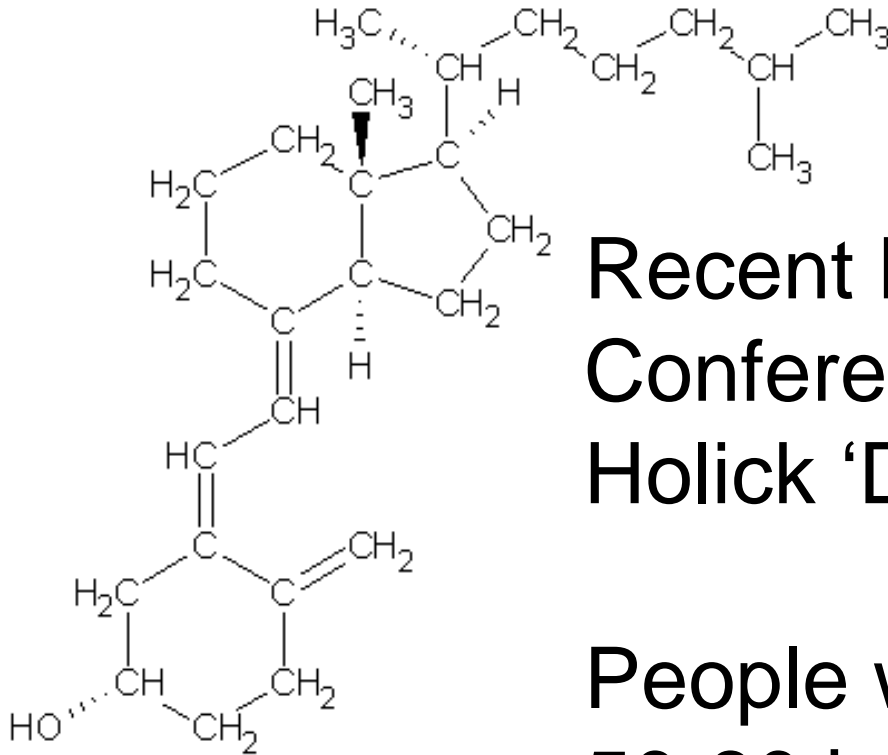
Bosscher D, Breyngaert A, Pieters L, Hermans N. [Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects.](#) J Physiol Pharmacol. 2009 Dec;60 Suppl 6:5-11

Natural Cancer Risk Reduction

- Vitamin D3 hormone vitamin
- EGCG
- Sulforaphane

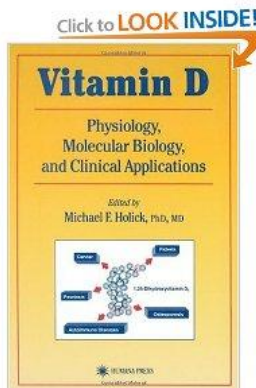
As possible enhancers of
innate anti-cancer mechanisms

D3 hormone vitamin & v Chemo

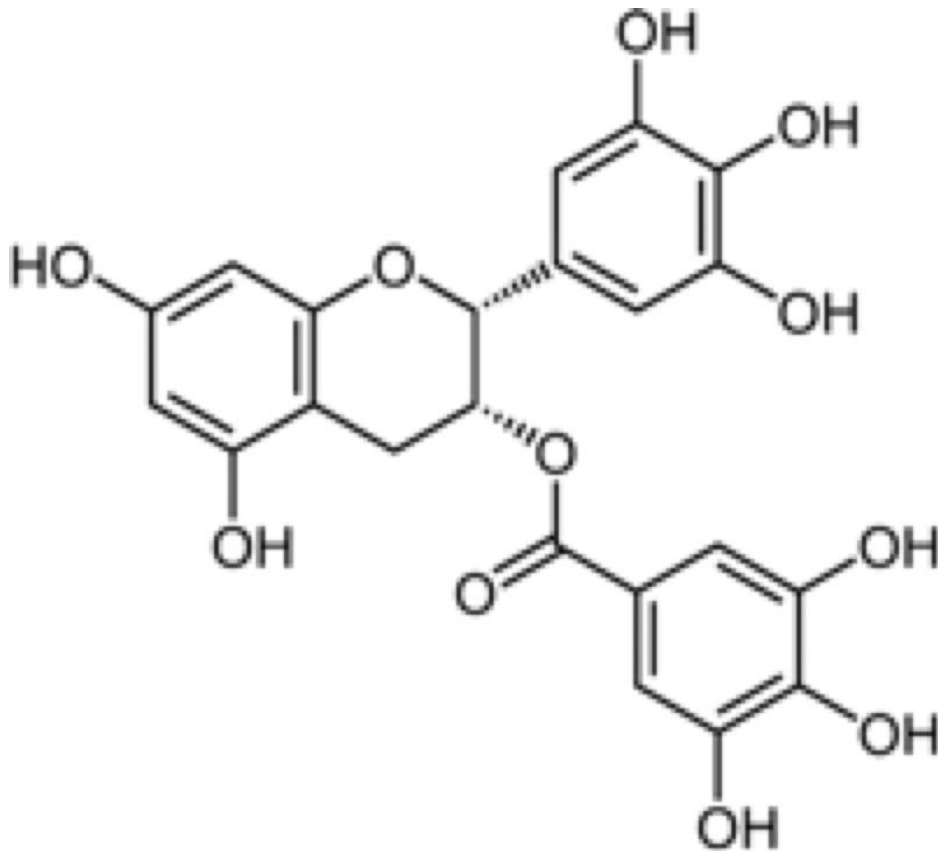


Recent NCI Consensus Conference & Dr Michael Holick 'Dr Sunshine'

People with D3 blood levels of 50-80 have < **half** cancer compared to people with < 25 ng/dl.



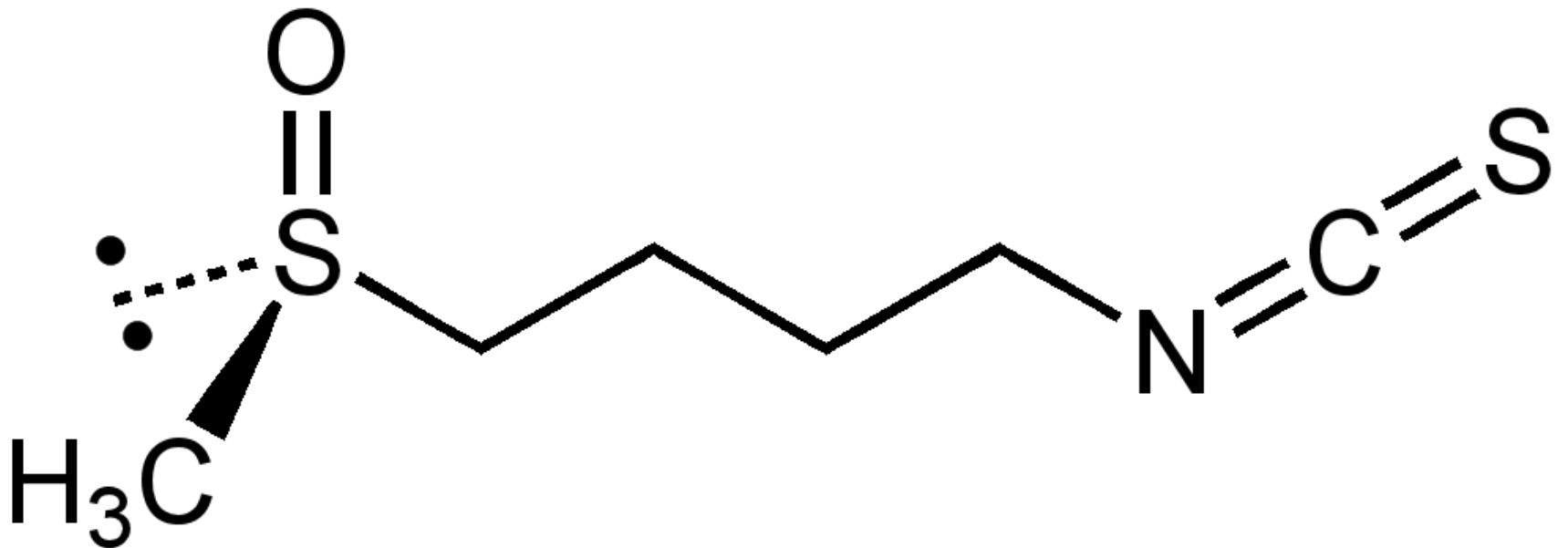
EGCG: Green tea benefit



en.wikipedia.org/wiki/Health_effects_of_tea

- Green tea is EGCG rich & drunk by low cancer people
- EGCG 'sits' at cell multiplication site.
- Weinberg @ Whitehead

Sulforaphane: Brassica sprouts



www.brassica.com/press/pr0012.htm

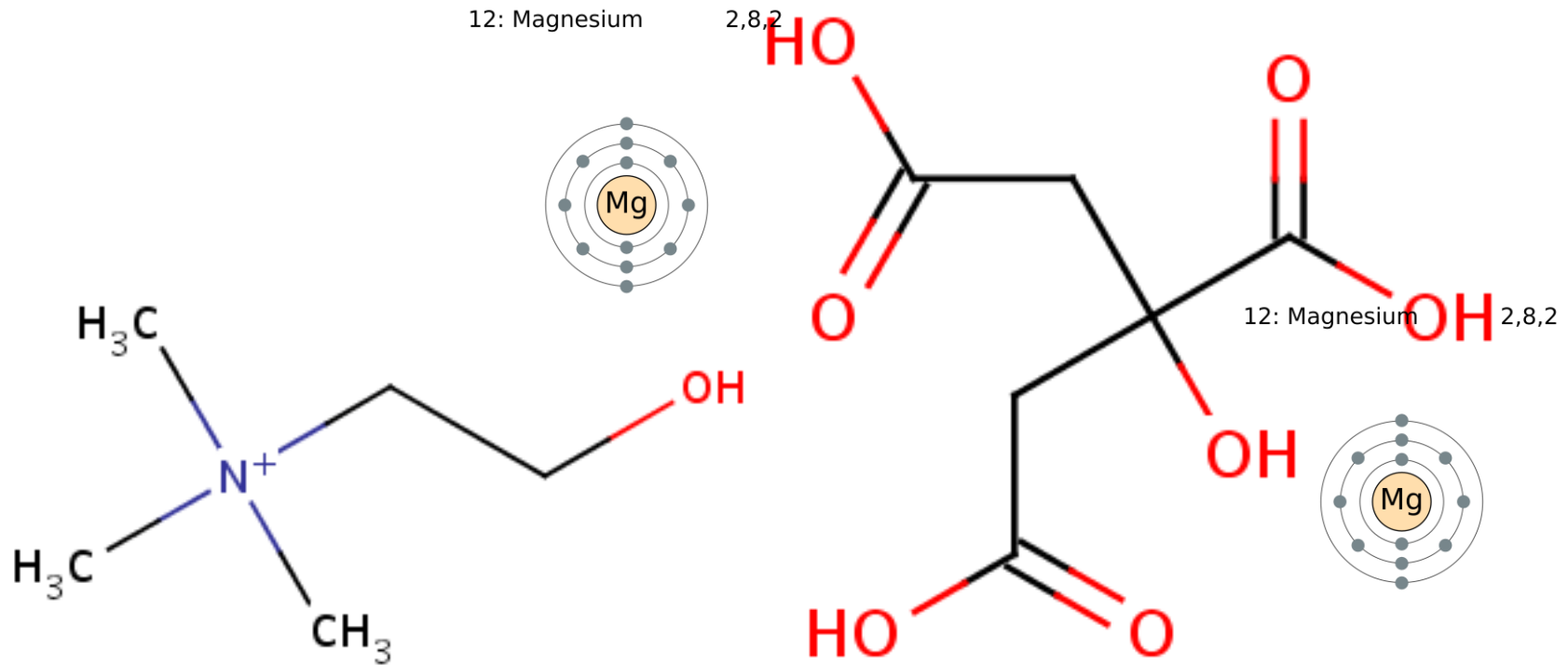
Calcium Channel

- Magnesium: Uptake enhanced through choline citrate; nature's balance to calcium

or

- Calcium Channel Blockers

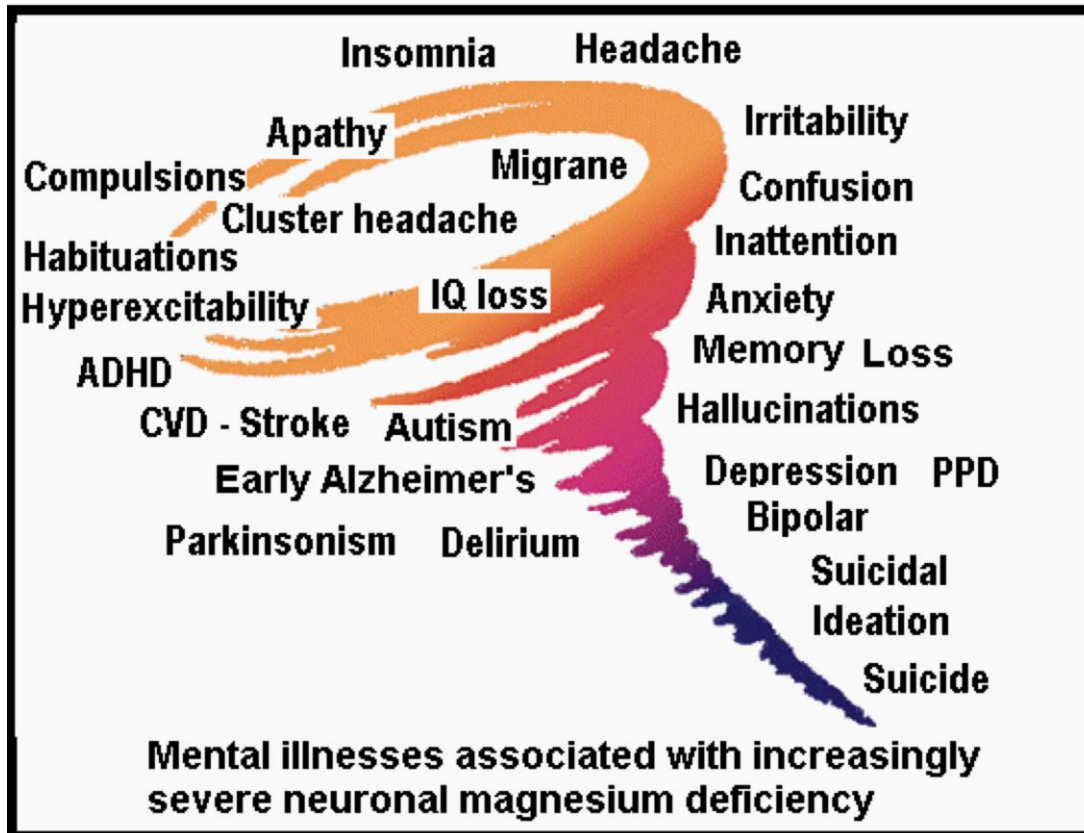
Magnesium & Choline Citrate: Nature's Calcium Channel Blocker



RMJH PQ EAB Cycles Healing territory09_v2.pdf

1.800.525.7372 or www.PERQUE.com or clientservices@PERQUE.com

1st Do No Harm; 2nd Think Mg⁺⁺



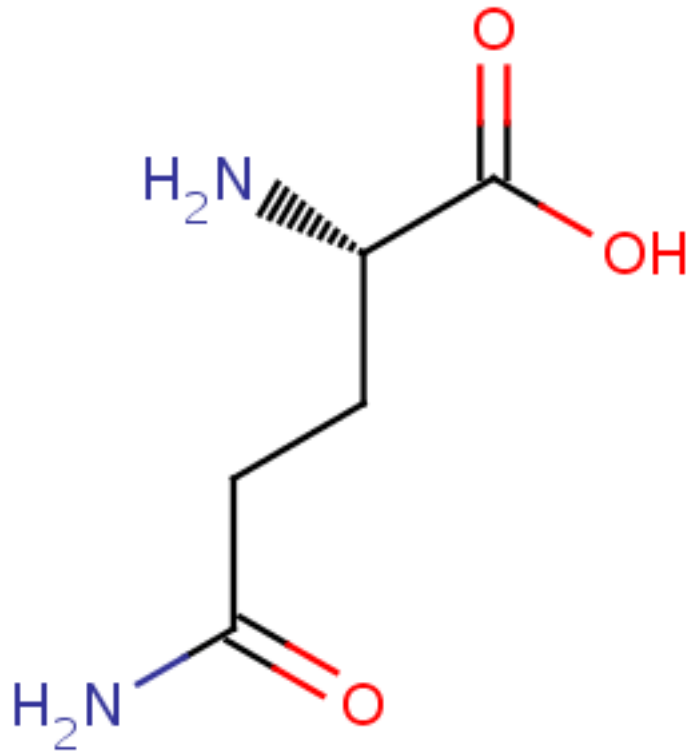
- Enhanced uptake forms available, use Mg⁺⁺ as cell function balancer

MAGNESIUM DEFICIENCY IN THE PATHOGENESIS OF DISEASE
Early Roots of Cardiovascular, Skeletal and Renal Abnormalities by
Mildred S. Seelig, M.D., M.P.H., F.A.C.N, 1980.

Repair: Connective Tissue

- Glutamine recycled by PAK
- Better basement membrane, collagen & elastin cross-linking

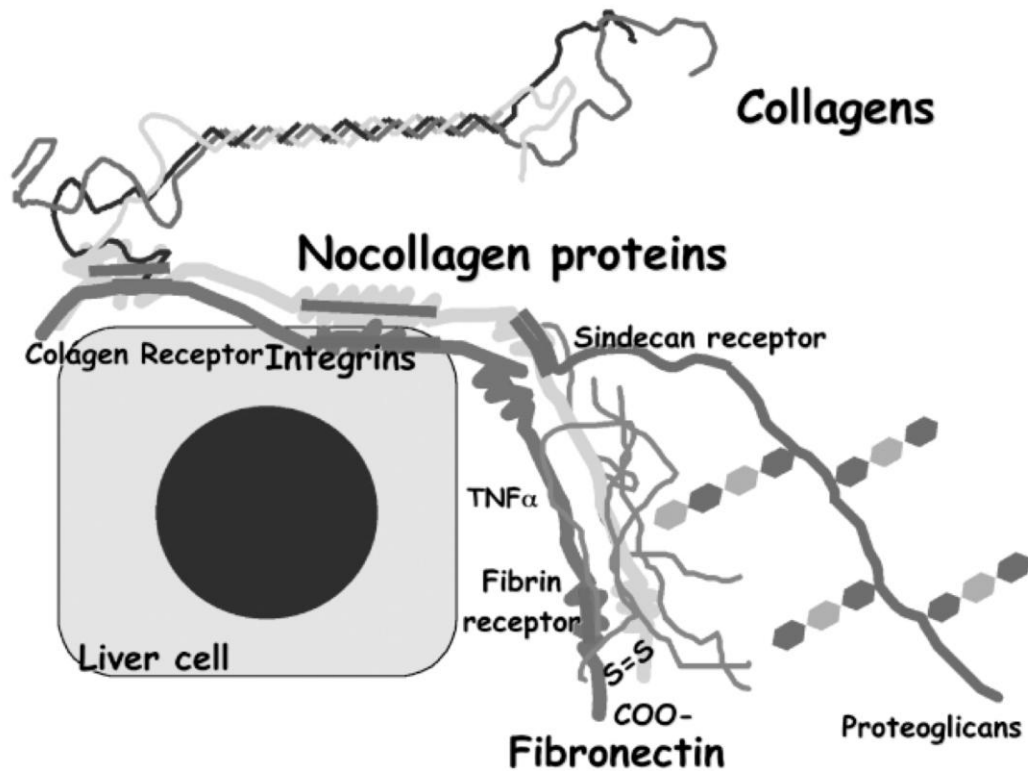
Glutamine Recycled 10x by PAK



Glutamine \longleftrightarrow Energy+
Glutamate + NH₃ + PAK
 \longrightarrow Glutamine

www.perque.com/pdfs/PERQUE-Endura-Guard.pdf

Recycled Glutamine or Cross-Links



- Photo-induced increased cross-links allow sculpting of surfaces
- Does this accelerate aging? TBD

Fig. 1.- Composition of the extracellular matrix.
Matriz extracelular.

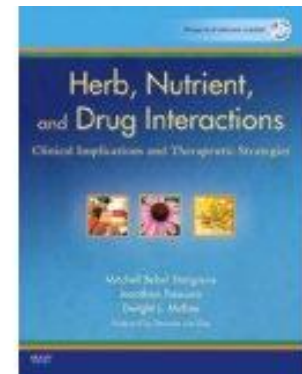
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Cancer risk	Sulforophane/ D3, EGCG	Preventive chemo	>500	??	??	
Gut repair Energy	Glutamine/ PAK	Cross-link enhancers	>500	0.4	5,000	\$0.5 Bn

Natural v. Extra-Natural Products

Result of using Natural rather than Extra-Natural Products on lives and costs:

[Herb, Nutrient, and Drug Interactions: Clinical Implications and Therapeutic Strategies](#) by Mitchell Bebel Stargrove, Jonathan Treasure, Dwight L. McKee



- Save **100,000 lives** per year
- Reduce direct healthcare costs by **\$9.8 Bn/year**
- Reduce **suffering** for affected people
- Use **best of both**: Respect for nature & science
- **ReThink** choices in light of what we now know

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