Ο ρόλος βιοδραστικών ενώσεων στην προστασία έναντι ασθενειών και στην θεραπεία

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- Διατροφή –απαραίτητα στοιχεία για τη δομή και ομοιοστασία του οργανισμού
- Δομικά συστατικά (λιπίδια, αμινοξέα)
- Βιταμίνες
- Ιχνοστοιχεία

Σημασία των βιοδραστικών ενώσεων

- Πρόδρομα μόρια για σύνθεση φαρμακευτικών ουσιών
- Διατροφικά συμπληρώματα

Δράσεις βιοδραστικών ενώσεων

- Αντιφλεγμονώδεις δράσεις
- Αντι-νευροεκφυλιστική
- Αντι- διαβητική δράση
- Αντι- καρκινική δράση

Βιοδραστικές ενώσεις σε φυτικούς οργανισμούς: πρωτογενείς μεταβολίτες

- λιπαρά οξέα
- πρωτεΐνες
- υδατάνθρακες
- νουκλεϊκά οξέα

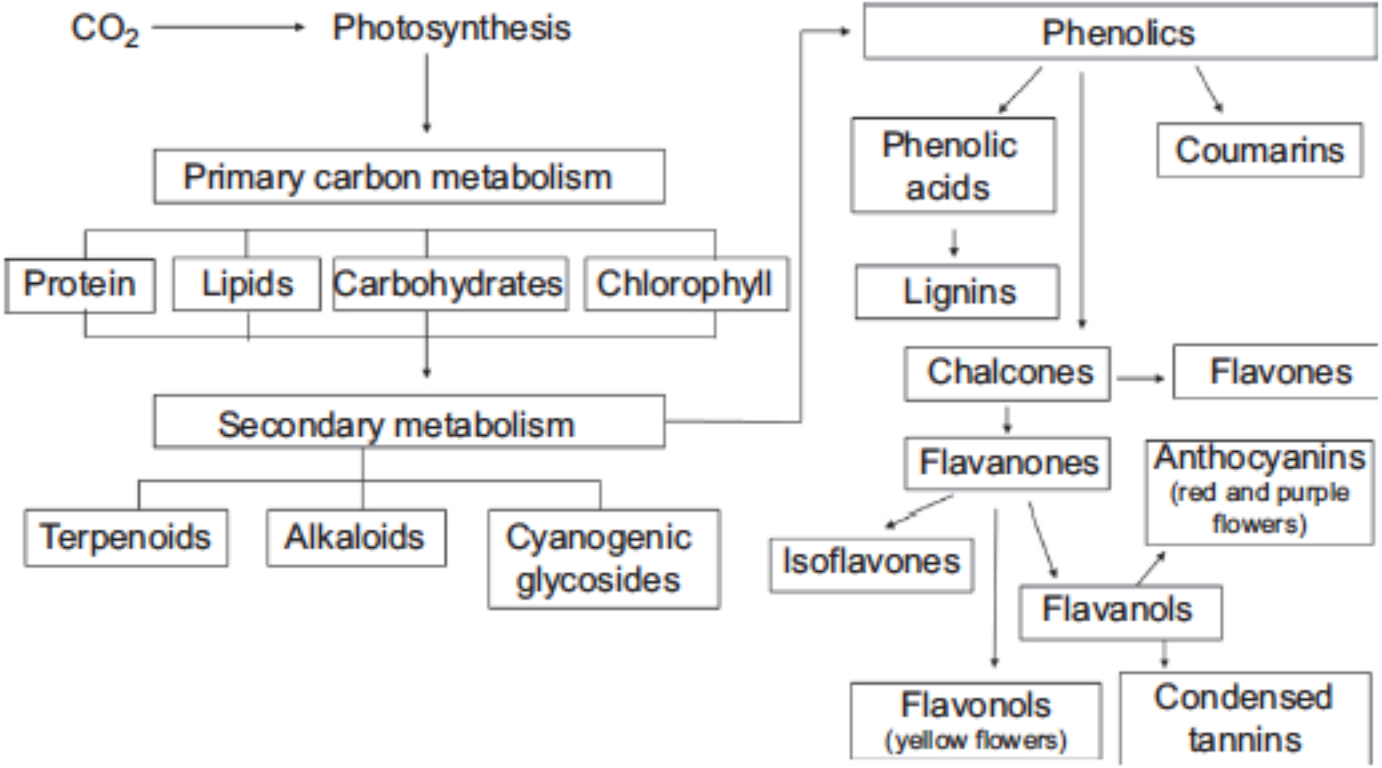
Είναι όλα απαραίτητα για την επιβίωση του φυτού

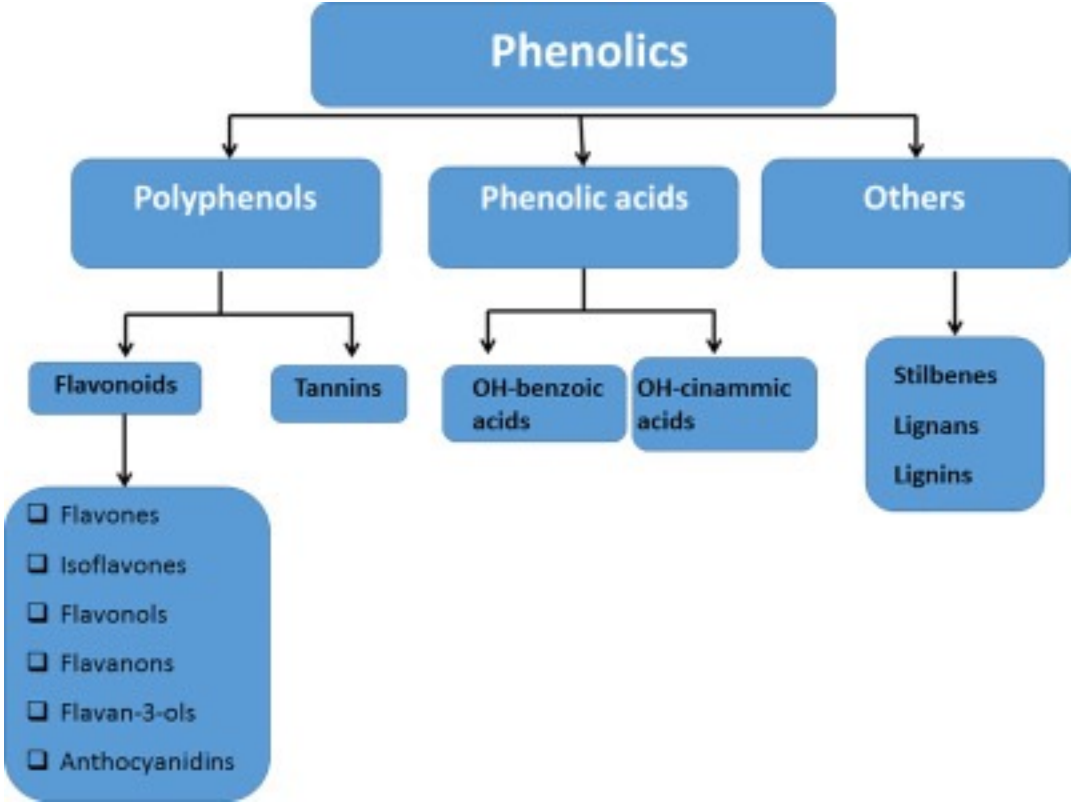
Βιοδραστικές ενώσεις: δευτερογενείς μεταβολίτες

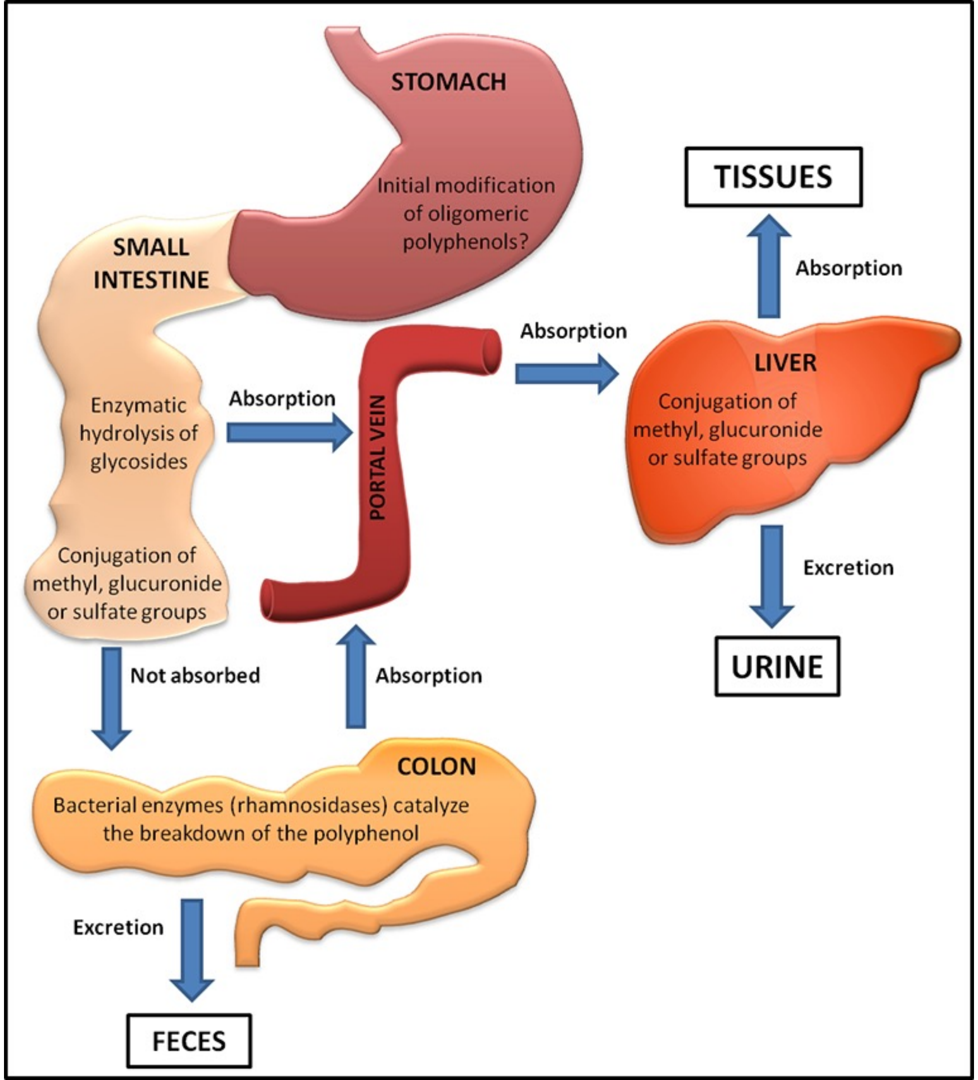
- phenolic and polyphenolic compounds
- flavonoids
- terpenoids
- nitrogen-containing alkaloids
- sulfur-containing compounds

Λειτουργούν σαν σηματοδοτικά μόρια, για προσέλκυση εντόμων ή ζώων, προστατεύουν απο οξείδωση και υπεριώδη ακτινοβολία, προστατεύουν απο παθογόνα

Βιογενεση και μεταβολισμος φαινολών




Phenolics
Polyphenols
Phenolic acids
Others
Flavonoids
Tannins
OH-benzoic acids
OH-cinammic acids
Stilbenes
Lignans
Lignins
Flavones
Isoflavones
Flavonols
Flavanons
Flavan-3-ols
Anthocyanidins


STOMACH
Initial modification of oligomeric polyphenols?
SMALL INTESTINE
Enzymatic hydrolysis of glycosides
Conjugation of methyl, glucuronide or sulfate groups
Absorption
PORTAL VEIN
Absorption
LIVER
Conjugation of methyl, glucuronide or sulfate groups
Absorption
TISSUES
Excretion
URINE
Not absorbed
Absorption
COLON
Bacterial enzymes (rhamnosidases) catalyze the breakdown of the polyphenol
Excretion
FECES

Βιοδραστικές ενώσεις: flavonoids

- Η μεγαλύτερη ομάδα φαινολικών μεταβολιτών
- Βασική τους δράση ειναι η αναστολή οξείδωσης.
- Εχουν:
  - αντι-ιική
  - Αντι-διαβητική
  - Αντι-καρκινική δράση

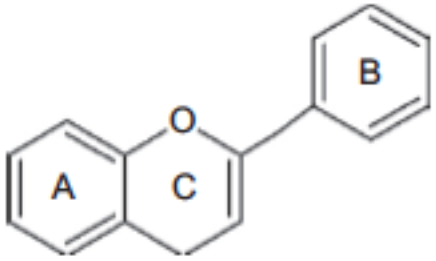


Figure 2.3
Structure of a flavonoid molecule.

Βιοδραστικές ενώσεις: terpenes

Αντι- οξειδωτική δράση

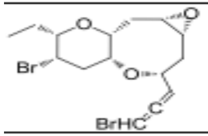
Αντι-φλεγμονώδη δράση

κυτταροστατική δράση

Activity of algae-derived terpenes

Compound NKUAMAR	IC50 (µM)
156	23.03 +/- 3.731
157	12.4 +/- 1.094
158	37.39 +/- 2.514
159	No action <62.5µM
160	0.004387 +/- 0.008
161	0.002263 +/- 0.002
162	4.181 +/- 0.481
163	3.98 +/- 0.6016
164	13.23 +/- 0.5687

156



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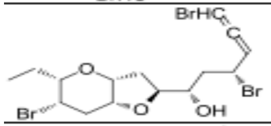

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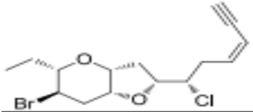

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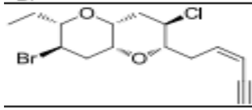

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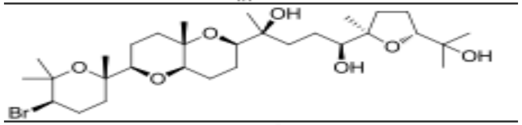

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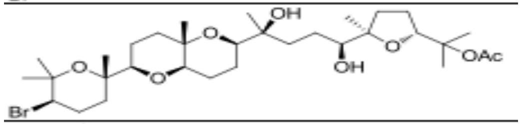

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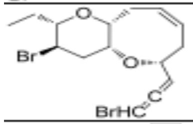

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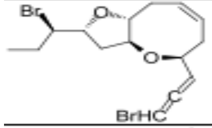

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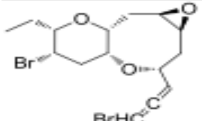
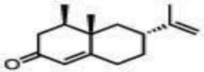
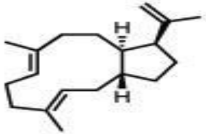
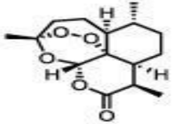
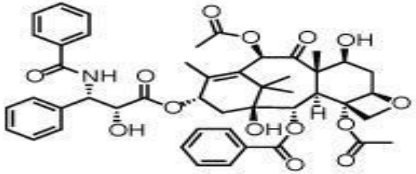
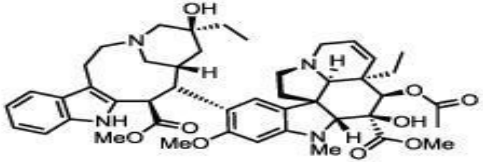
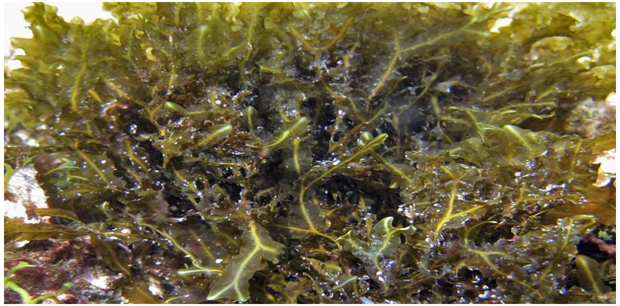


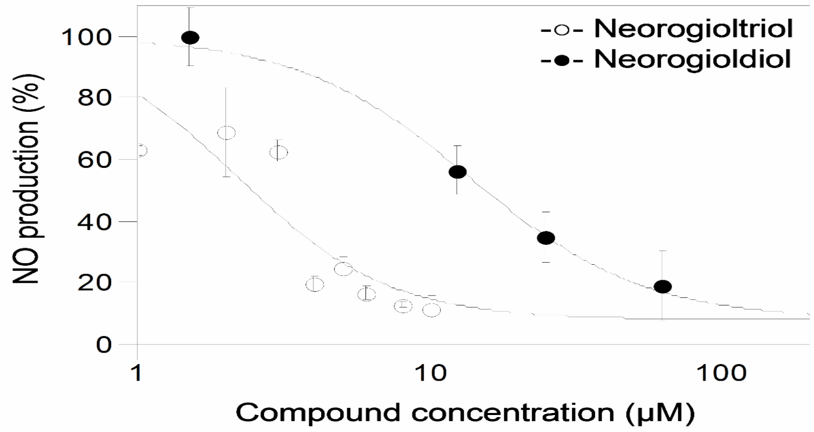
Natural source	Terpene	Structure	New method of production	
 Grapefruit	Nootkatone		Bioconversion of valencene using P450 in yeast	anti-insect aromatic
 Brown algae	Dolabellatriene		CotB2 derivative in *E. coli*	αντιμικροβιακό (πολυανθεκτικά)
 Sweet wormwood	Artemisinin		Yeast cells to make precursor artemisinic acid	κατα της φυματιωσης βαση για αρώματα
 Pacific yew tree	Paclitaxel		*E. coli* to make oxygenated taxane precursors	αντικαρκινικό
 Madagascar periwinkle	Vinblastine		Addition/removal of genes from yeast to give intermediate strictosidine	αντικαρκινικό

Cell cycle arrest	Apoptosis	Autophagy	Differentiation	Anti-angiogenesis	Anti-metastasis	Anti-MDR	Chemoprevention	Terpenoids	Mechanisms
●	●			●	●		●	D-limonene	Inhibition of HMG-CoA reductase and CoA synthesis, etc.
●	●				●	●		Cantharidin	Inhibition of serine/threonine PP1 and PP2A, etc.
●	●		●	●	●	●		Artemisinin and its derivatives	Cleavage of iron- or heme-mediated peroxide bridge, etc.
●	●		●	●	●	●		Tanshinone IIA	DNA minor groove binder, etc.
●	●	●		●	●	●		Triptolide	Inhibition of XPB ATPase and transcription factors, etc.
●	●	●		●		●		Pseudolaric acid B	Blockage of microtubule and degradation of HIF-1α, etc.
●	●	●	●	●	●			Andrographolide	Inhibition of NF-κB, JAK-STAT, PI3K, HSP90 and MMPs, etc.
●	●	●	●	●				Oridonin	Downregulation of AP-1 and inhibition of NF-κB signaling, etc.
●	●	●		●	●			Celastrol	Inhibition of the IKK α, β kinases and proteasomes, etc.
●	●	●	●	●	●	●		Cucurbitacins	Interfere with F-actin and inhibition of STAT3, etc.
●	●	●				●		Alisol	Inhibition of sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase, etc.
	●				●			Pachymic acid	Inhibition of DNA topoisomerase I and II, MMP9 and NF-κB, etc.
●	●		●	●	●	●	●	Lycopene	Scavengers of ROS, inhibition of MMP2 and u-PA, etc.

Example: anti-inflammatory actions of terpenes from algae



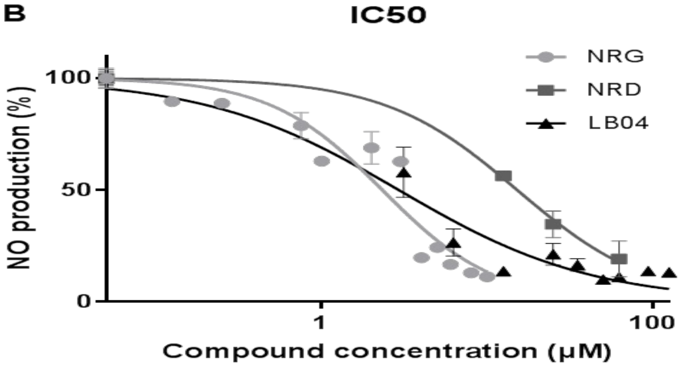
Dictyopteris membranacea

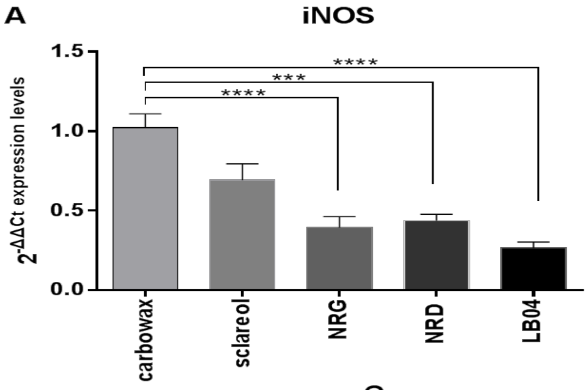


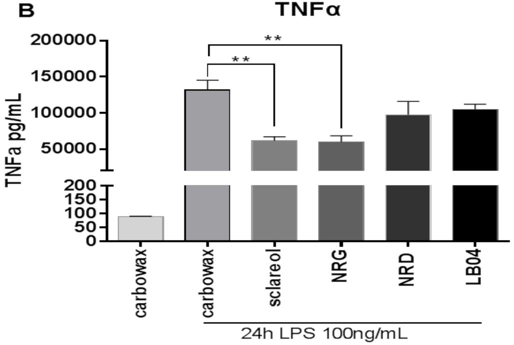
Compound	IC50
NRG	2.24 ± 2.29 uM
NRD	13.77 ± 2.81 uM

Daskalaki et al, Supported by EU and Greek National funds

Βιοδραστικότητα τερπενίων σαν αντιφλεγμονώδεις παράγοντες

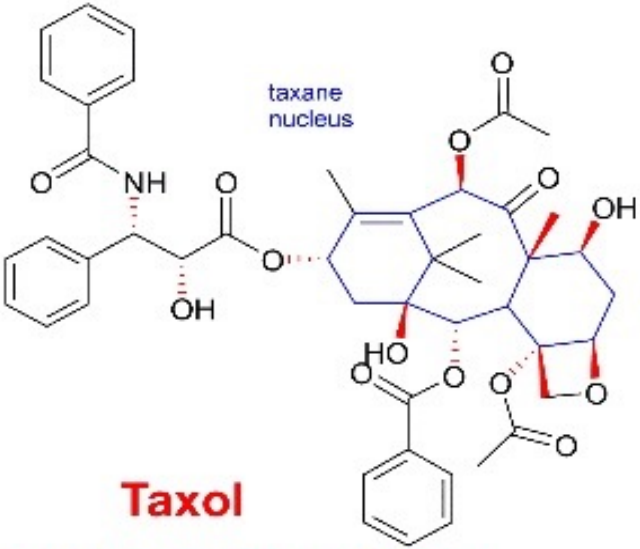






Daskalaki et al, Mar Drugs

Anticancer drugs: Taxol (Paclitaxel)

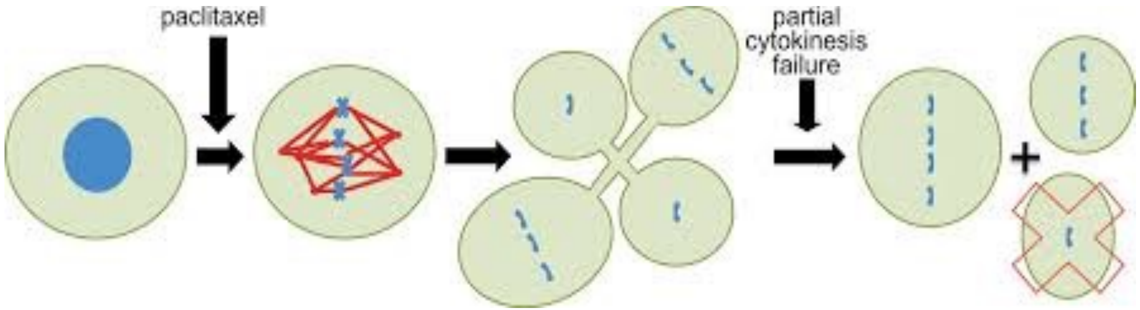


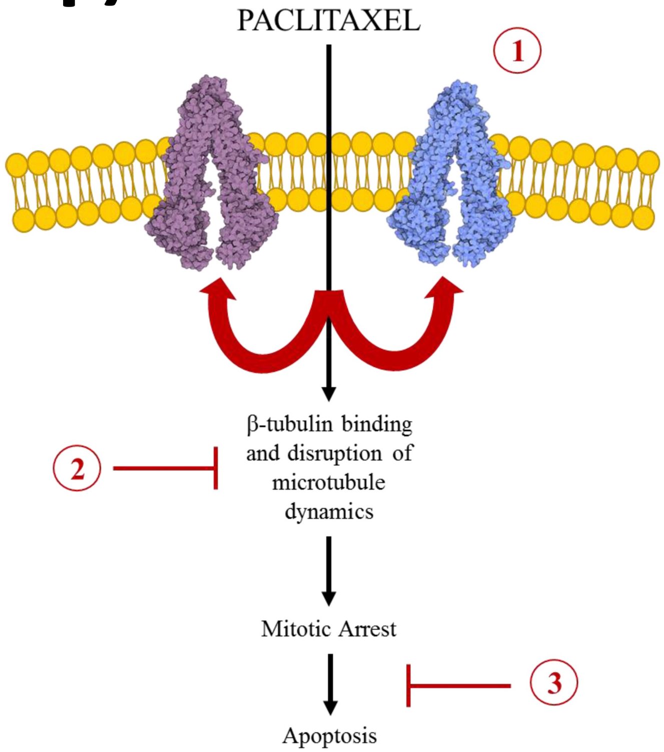
Taxol

(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12b*S*)-9-(((2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-3,4,4a,5,6,9,10,11,12,12a-decahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]oxete-6,12b(2a*H*)-diyl diacetate

- **Taxol**, a complex diterpene amide, was first isolated from the bark of *Taxus brevifolia* (pacific yew tree) after initial studies at 1962, and its structure was elucidated at **1971**. *Taxus brevifolia* contains low amounts of toxic alkaloids (**taxine A and B**) and reasonable levels of taxol compared to other *Taxus* species.
- Taxol and taxol analogues are the most important drugs for treatment of **drug-refractory ovarian cancer** as well as **lung and breast cancers**.

Δράση της ταξόλης





Stages of natural product-derived drug development within a year

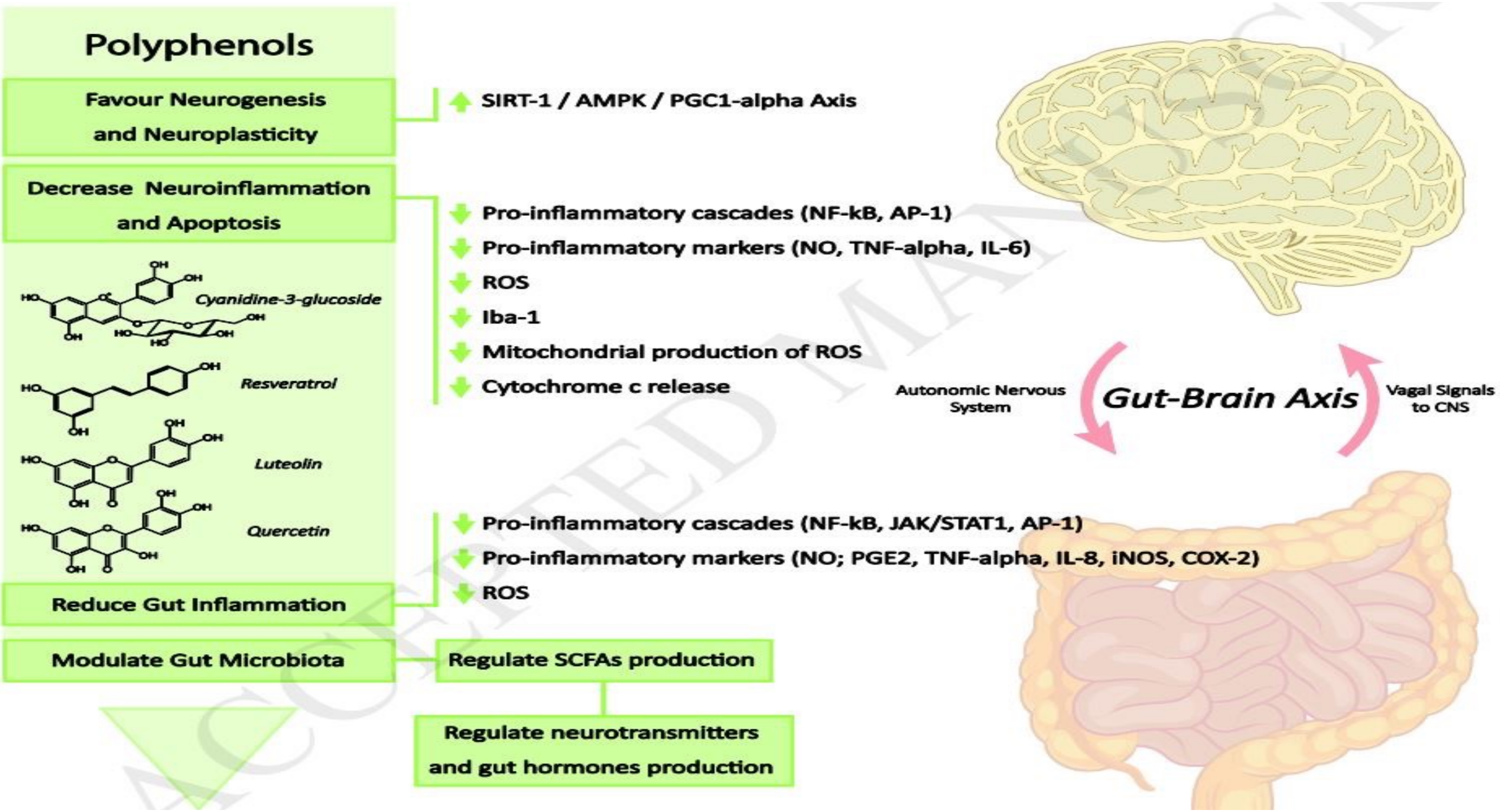
Drugs based on natural products at different stages of development

Development stage	Plant	Bacterial	Fungal	Animal	Semi-synthetic	Total[a]
Preclinical	46	12	7	7	27	99
Phase I	14	5	0	3	8	30
Phase II	41	4	0	10	11	66
Phase III	5	4	0	4	13	26
Pre-registration	2	0	0	0	2	4
Total	108	25	7	24	61	225

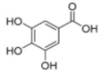
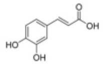
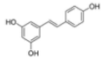
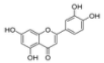
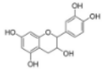
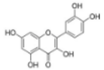
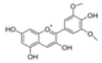
Therapeutic categories of natural product-derived drug development

Therapeutic categories of natural product-derived drugs at different stages of development						
Therapeutic area	Preclincal	Phase I	Phase II	Phase III	Pre-registration	Total
Cancer	34	15	26	9	2	86
Anti-infective	25	4	7	2	2	40
Neuropharmacological	6	3	9	4	0	22
Cardiovascular/gastrointestinal	9	0	5	6	0	20
Inflammation	6	2	9	1	0	18
Metabolic	7	3	6	1	0	17
Skin	7	1	2	0	0	10
Hormonal	3	0	2	1	0	6
Immunosuppressant	2	2	0	2	0	6
Total	99	30	66	26	4	225

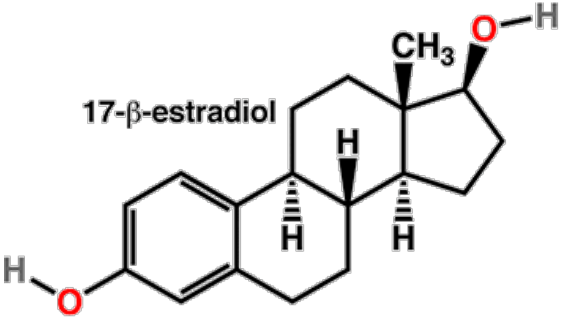
Polyphenolic compounds



Polyphenols present in red wine

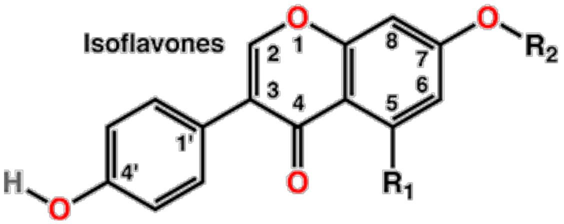
Group	Subclass	Main Representatives	Range in mg/L	Characteristic Structure
Non-flavonoid				
	Hydroxybenzoic acids	Gallic, ellagic, parahydroxybenzoic, protocatechuic, vanillicand syringic acids	0–218.0	 Gallic acid
	Hydroxycinnamic acids	Coutaric, caftaric, and fertaric acids	60.0–334.0	 Caffeic acid
	Stilbenes	Resveratrol	0.1–7.0	 Resveratrol
Flavonoids				
	Flavones	Luteolin	0.2–1.0	 Luteolin
	Flavan-3-ols	Catechin and epicatechin	50.0–120.0	 Catechin
	Flavonols	Myricetin, quercetin, kaempferol, and rutin	12.7–130.0	 Quercetin
	Anthocyanins	Malvidin, cyanidin, peonidin, delphinidin, pelargonidin, petunidin	90.0–400.0	 Malvidin

Phytoestrogenes



What human estrogen looks like

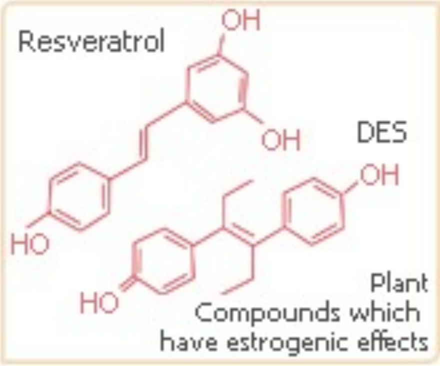
This is estradiol, one of the three forms of estrogen found in women (the other two are estrone and estriol)



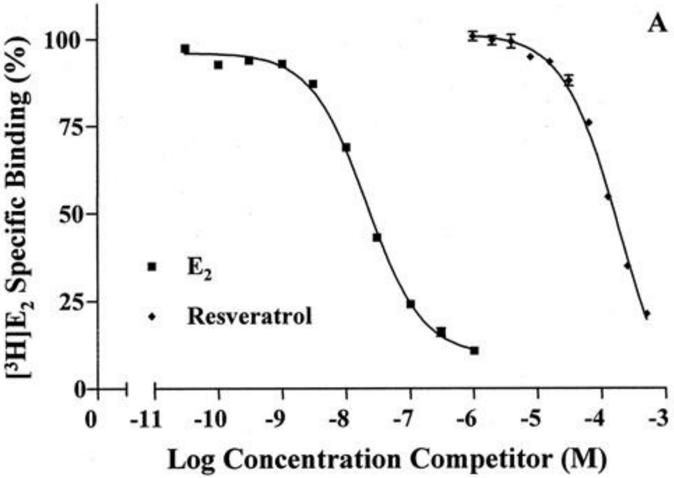
What plant estrogen looks like

Isoflavones are the most common type found in plants

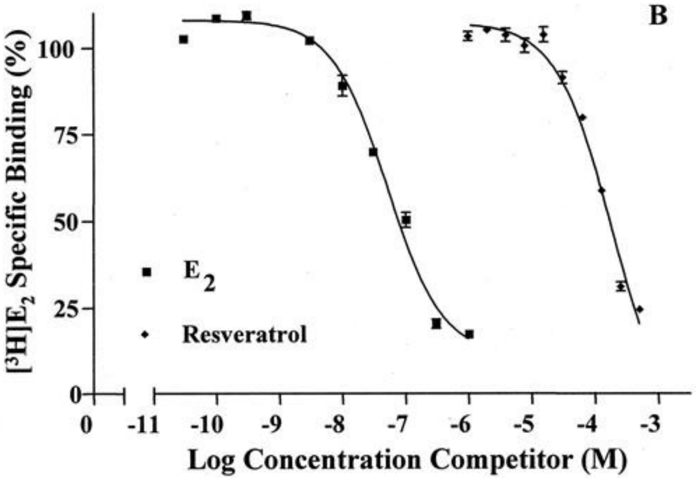
	R_1	R_2
daidzein	H	H
formononetin	H	CH_3
genistein	OH	H
biochanin A	OH	CH_3



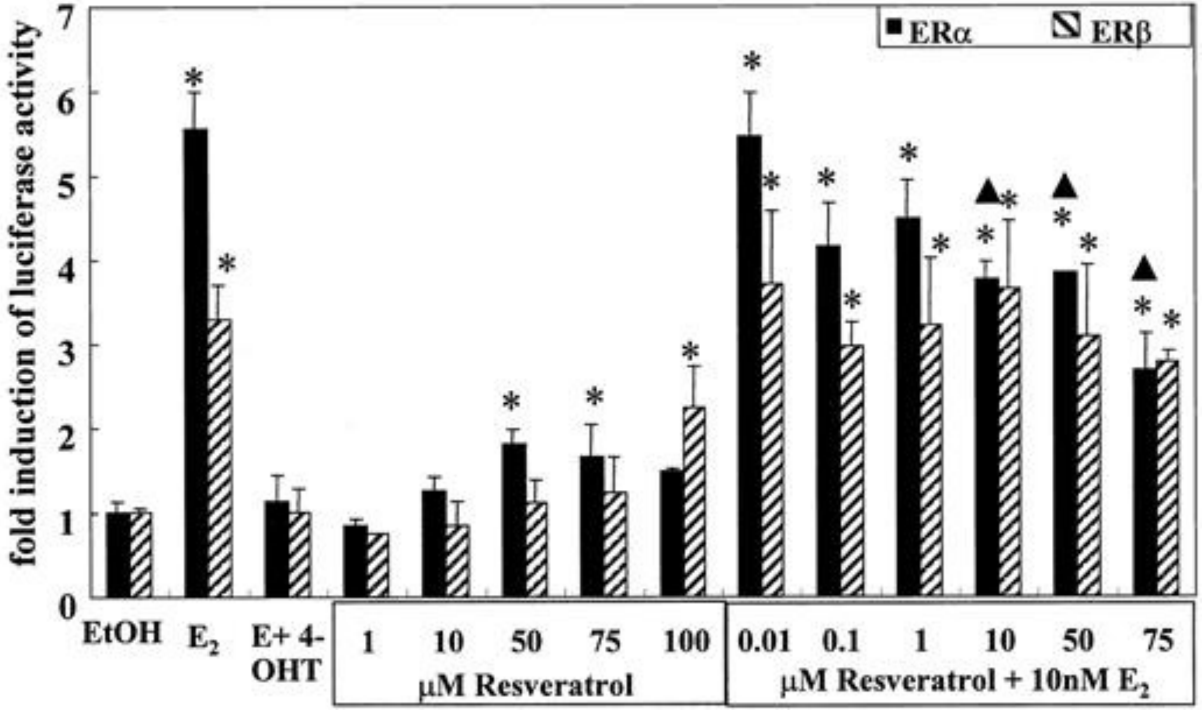
ERα


A
100
75
50
25
0
[3H]E2 Specific Binding (%)
E2
Resveratrol
0
-11
-10
-9
-8
-7
-6
-5
-4
-3
Log Concentration Competitor (M)

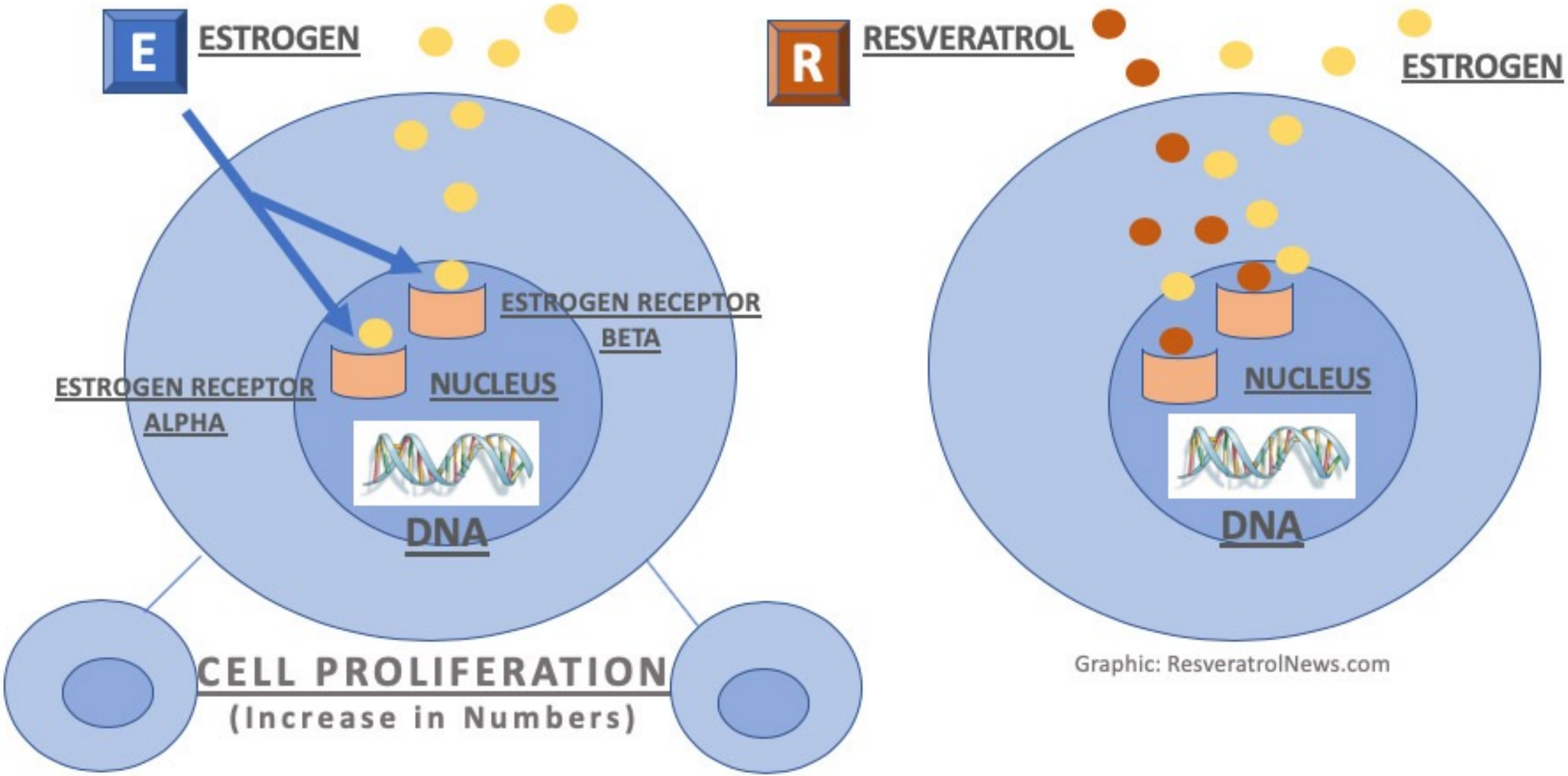
ERβ


B
100
75
50
25
0
[3H]E2 Specific Binding (%)
E2
Resveratrol
0
-11
-10
-9
-8
-7
-6
-5
-4
-3
Log Concentration Competitor (M)

Resveratrol activates ER but antagonizes E2 action

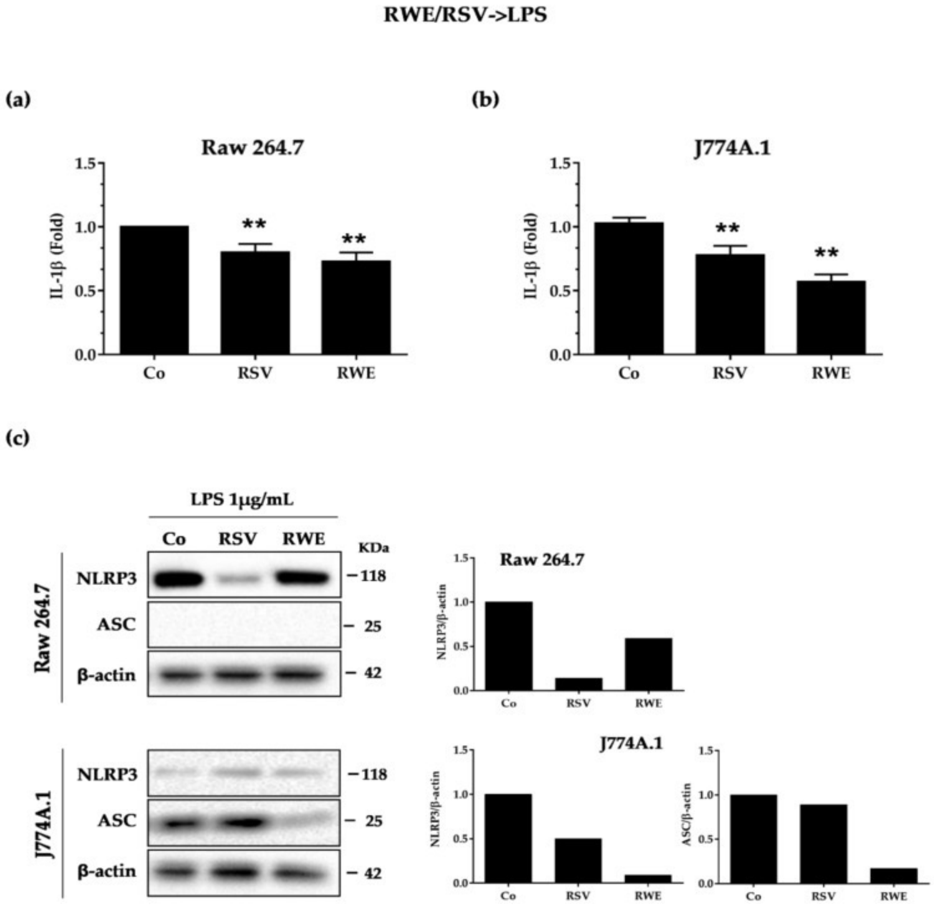


Endocrinology, 141, 2000:3657



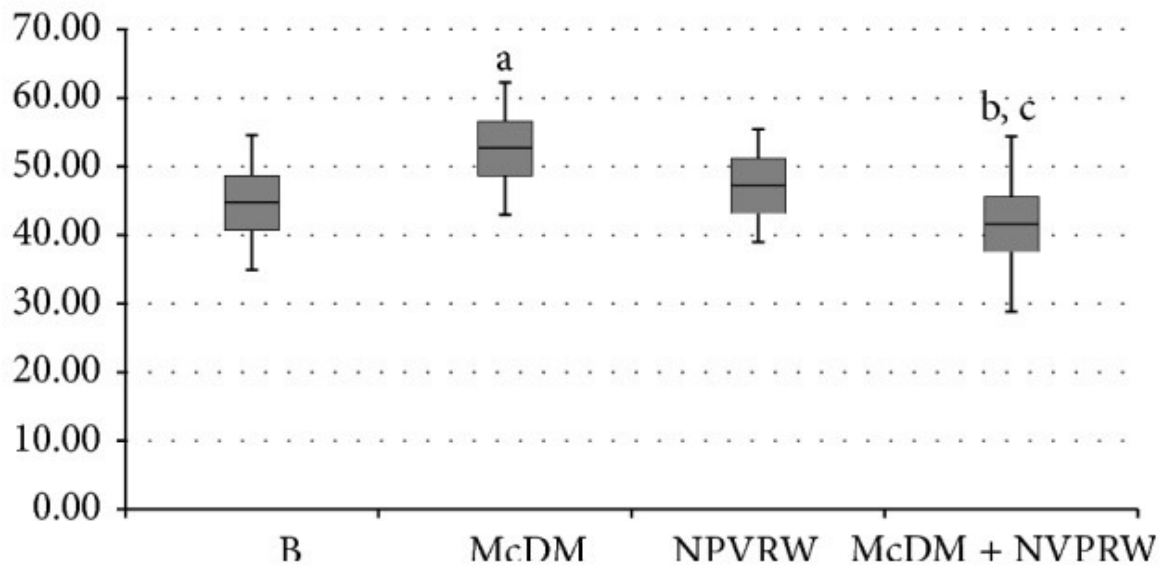
ESTROGEN RECEPTORS AND RESVERATROL

Effect of resveratrol on IL-1 secretion



Nutrients, 2018

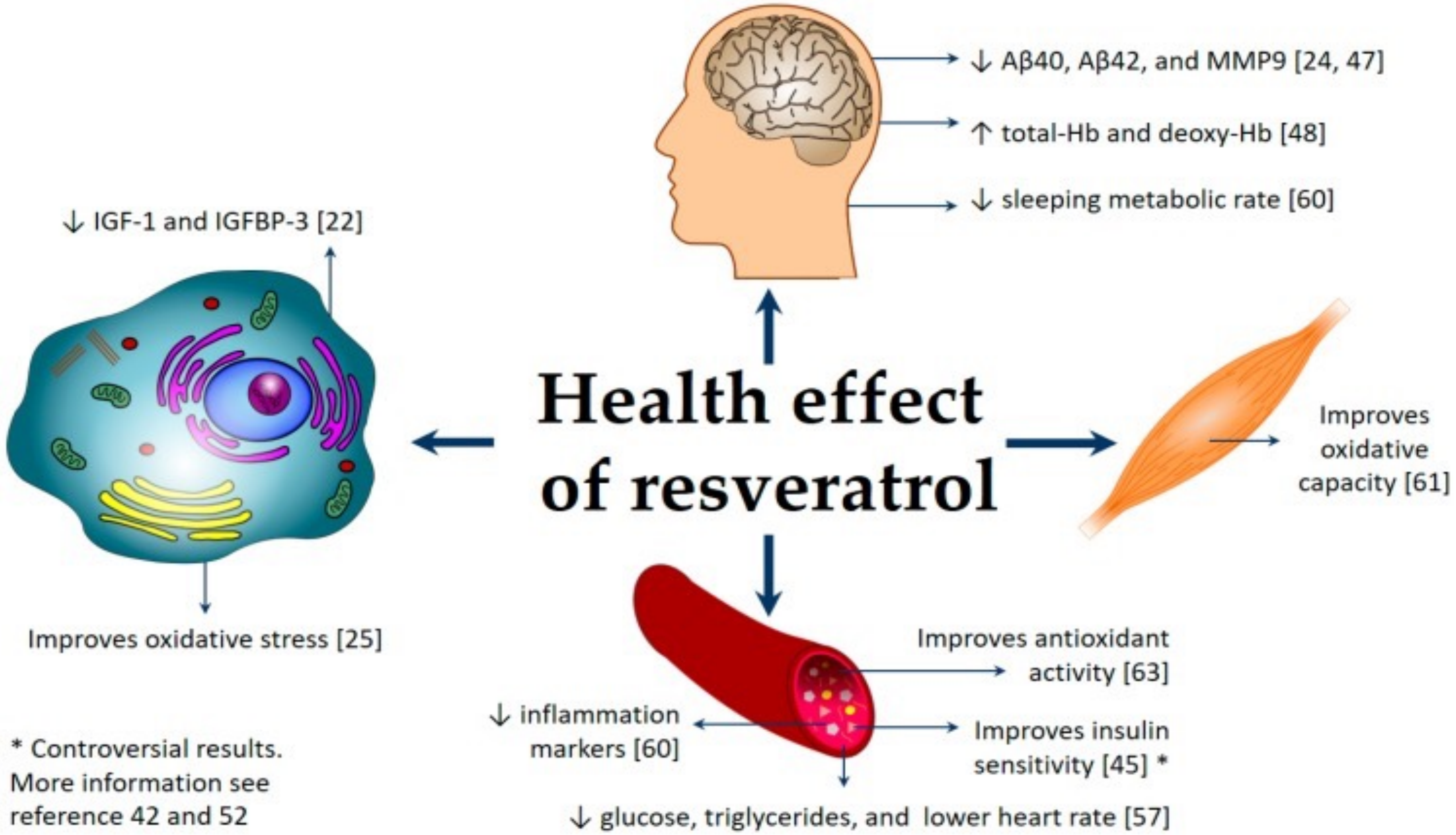
Changes in LDL Oxidative Status and Oxidative and Inflammatory Gene Expression After Red Wine Intake in Healthy People: A Randomized Trial



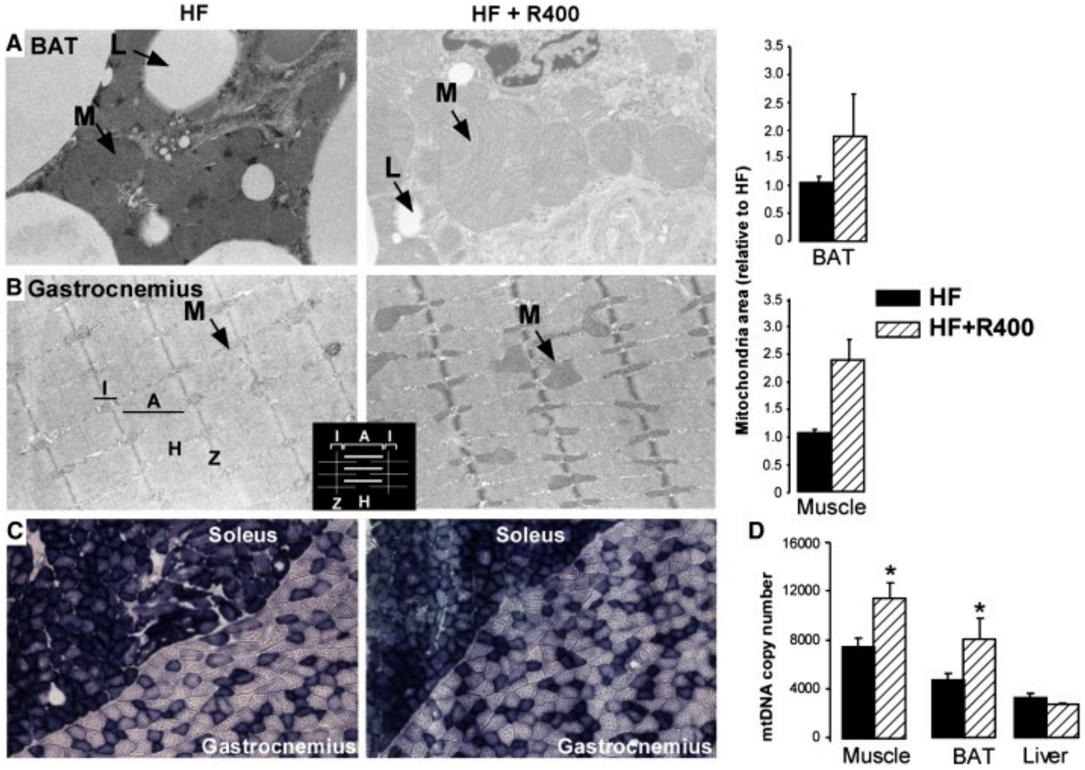
Comparative values of ox-LDL level for each treatment intervention. The significant values are expressed as (a) baseline versus McDonald's meal ($P \leq 0.05$); (b) McDonald's meal versus McDonald's meal + not pruned vineyard red wine ($P \leq 0.05$); (c) baseline versus not pruned vineyard red wine ($P > 0.05$); baseline versus McDonald's meal + not pruned vineyard red wine ($P > 0.05$).

Total of 30 participants

Mediators Inflamm, 2015, 317348

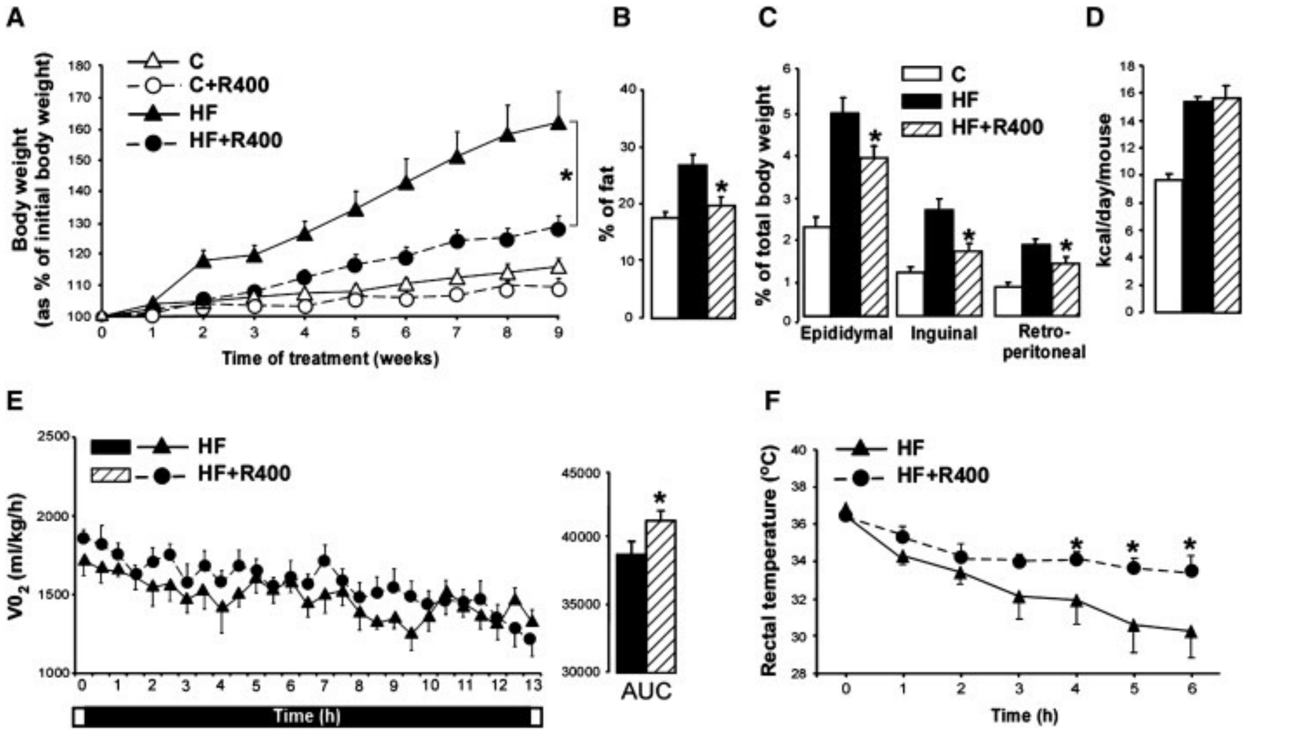

Health effect of resveratrol
↓ Aβ40, Aβ42, and MMP9 [24, 47]
↑ total-Hb and deoxy-Hb [48]
↓ sleeping metabolic rate [60]
↓ IGF-1 and IGFBP-3 [22]
Improves oxidative stress [25]
Improves oxidative capacity [61]
Improves antioxidant activity [63]
↓ inflammation markers [60]
Improves insulin sensitivity [45] *
↓ glucose, triglycerides, and lower heart rate [57]
* Controversial results. More information see reference 42 and 52

Resveratrol induces mitochondrial activity in BAT and muscle



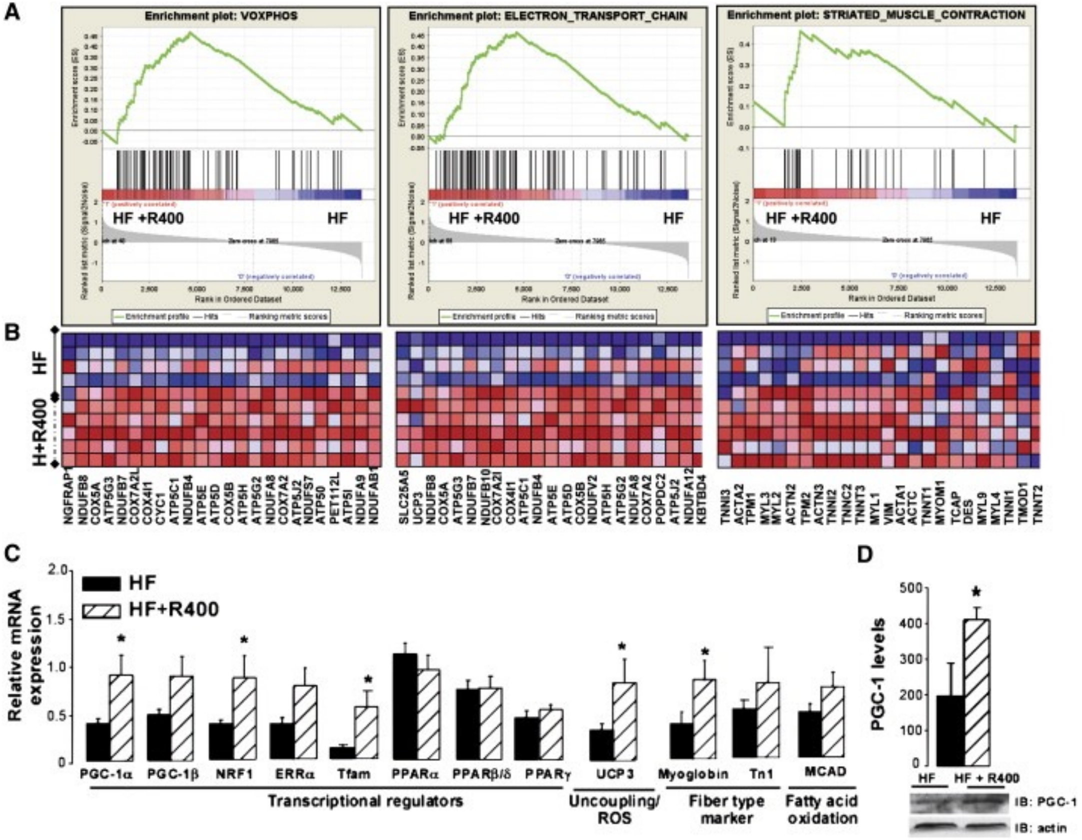
Cell, 2006, 167:1109

Resveratrol prevents diet-induced obesity in mice



Cell, 2006, 167:1109

Resveratrol Improves Mitochondrial Function and Protects Against Metabolic Disease by Activating SIRT1 and PGC-1alpha in mice



Cell, 2006, 167:1109

Resveratrol levels and all cause mortality in older community adults in Chianti

In older community-dwelling adults, total urinary resveratrol metabolite concentration was not associated with inflammatory markers, cardiovascular disease, or cancer or predictive of all-cause mortality. Resveratrol levels achieved with a Western diet **did not have a substantial influence on health status and mortality ris**k of the population in this study.

JAMA Int. Med, 2014

The therapeutic potential of resveratrol: a review of clinical trials

npj Precision Oncology **volume 1**, Article number: 35 (2017)

Disease type	Study conditions	Length of trial	Resveratrol dosage	Biomarker changes	Effect	Reference
Cancer						
Prostate cancer	14 patients, phase 1 trial	2–31 months (depending on patient)	500, 1000, 2000, 3000, or 4000 mg of MPX. Every 500 mg MPX has 4.4 μg resveratrol	Increase in PSADT	Beneficial	33
Prostate cancer	66 patients, randomized, placebo-controlled, single-site clinical trial	4 months	150 mg or 1000 mg daily	Decrease in androstenedione, DHEA, and DHEAS. No effect on prostate size and PSA levels	None	34
Colorectal cancer	9 patients randomized, placebo- controlled, double blind, phase 1 trial	14 days prior to surgery	5.0 g SRT501	Increase in cleaved Caspase-3 (apoptosis)	Beneficial	26
Colorectal cancer	20 patients	8 days prior to surgery	500 or 1000 mg	Reduction in tumor cell proliferation, indicated by reduction in Ki-67 staining	Beneficial	37
Multiple myeloma	24 patients, phase 2 trial	~4 months	5.0 g SRT501	NA	Severe adverse events	27
Breast cancer	39 patients, randomized, double-blind, placebo-controlled clinical trial	3 months	5 or 50 mg twice daily	Decrease in *RASSF-1α*methylation	Beneficial	39
Neurological disorders						
AD	119 patients, randomized, placebo- controlled, double blind, multi-site, phase 2 trial	12 months	500 mg once daily, with 500 mg dose escalation every 13 weeks, ending with 1000 mg twice daily	Reduced CSF MMP9, increase IL-4, attenuated decline in Aβ42 and Aβ40	Beneficial	43
AD	119 patients, randomized, placebo-controlled, double-blind, multicenter, phase 2 trial	12 months	500 mg once daily, with 500 mg dose escalation every 13 weeks, ending with 1000 mg twice daily	Attenuated decline in Aβ42 and Aβ40 increased brain volume loss	Beneficial	44
Ischemic stroke	312 patients, randomized,	60 min after 0–2 h of stroke onset	2.5 mg resveratrol/kg of body weight	Reduced MMP-9 and MMP-2	Beneficial	48

The therapeutic potential of resveratrol: a review of clinical trials

Diabetes						
Type 2 diabetes	14 patients, double-blind, randomized, placebo-controlled, crossover design	25-week intervention periods with 5-week washout period in between	500 mg twice daily	No effect on GLP-1 secretion	None	62
Type 2 diabetes, glycemia	62 patients, prospective, open-label, randomized, controlled trial	3 months	250 mg daily	Improved glycemic control: decreased HbA1c, systolic BP, total cholesterol, and total protein	Beneficial	63
Type 2 diabetes	19 patients, double-blind, randomized, placebo-controlled study	1 month	5 mg twice daily	Decreased insulin resistance, decreased blood glucose, delayed glucose peaks after meals, urinary ortho-tyrosine excretion	Beneficial	64
IGT	10 patients with mean age 72 ± 3 years, open-label study	1 month	1000, 1500, or 2000 mg daily	Decrease in peak postmeal glucose and 3-h glucose, increased insulin sensitivity	Beneficial	65
NAFLD						
NAFLD	28 patients, randomized, placebo- controlled	6 months	1500 mg daily	No change in ALT No improvement in lipid profile or insulin sensitivity	None	67
NAFLD	20 patients, randomized, placebo- controlled	2 months	3000 mg	No change in insulin resistance or steatosis. Increase in ALT and AST	None	69
NAFLD	60 patients, randomized, placebo- controlled, double blind	3 months	300 mg twice daily	Reduced AST, ALT, cholesterol, glucose, TNF-α	Beneficial	70
NAFLD	50 patients, randomized, double-blind, placebo-controlled	3 months	500 mg (in addition to exercise and healthy diet)	Reduction in ALT, IL-6, NF-κB activity improved lipid profiles	Beneficial	71

npj Precision Oncology **volume 1**, Article number: 35 (2017)

Resveratrol: where we stand in therapy

- Limited bioavailability
- Gastrointestinal side effects (over 1g/day)
- Toxicity, particularly nephrotoxicity

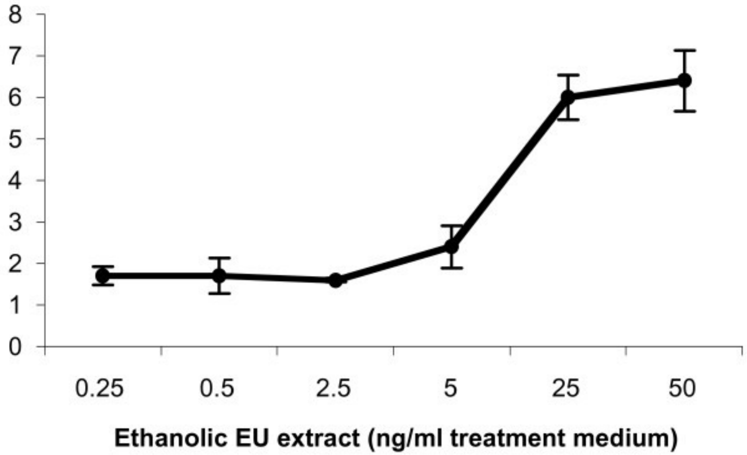
Improve bioavaliablity: Derivatives (Pterostilbene); Metabolites (resveratrol-3-O-sulfate)

Reduced toxicity: Targeted nanoparticlies (lipid based)

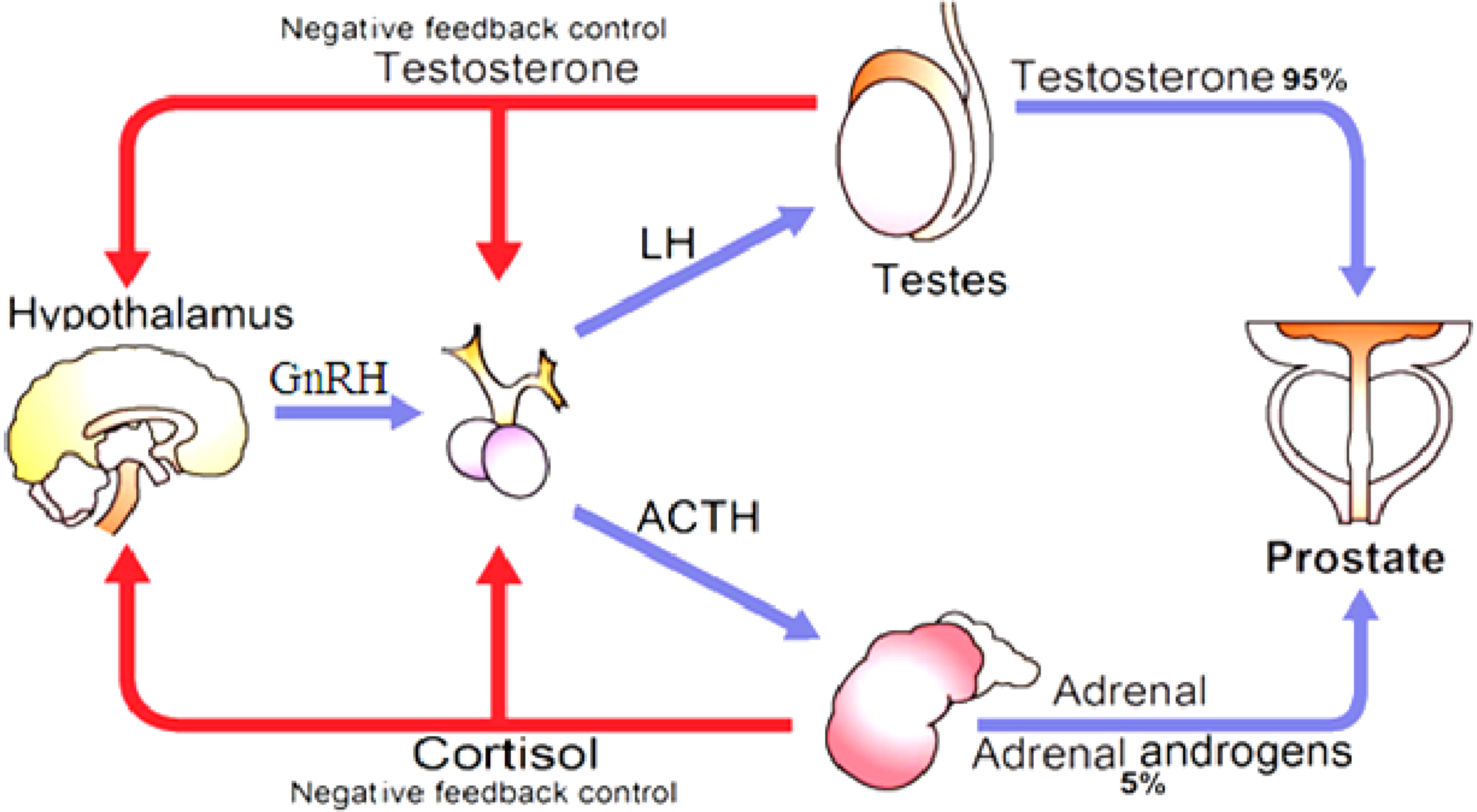
Phytoandrogens

Eucommia ulmoides – Chinese herbs

Binding to AR



Δυνητική αρνητική ανάδραση απο φυτοστερόλες



Βιοδραστικά πεπτίδια

- Συστατικά της τροφής
- Προιόντα υδρόλυσης πρωτεϊνών

Έχουν δράση σε ορμονικούς υποδοχείς αλλά και άλλους υποδοχείς.

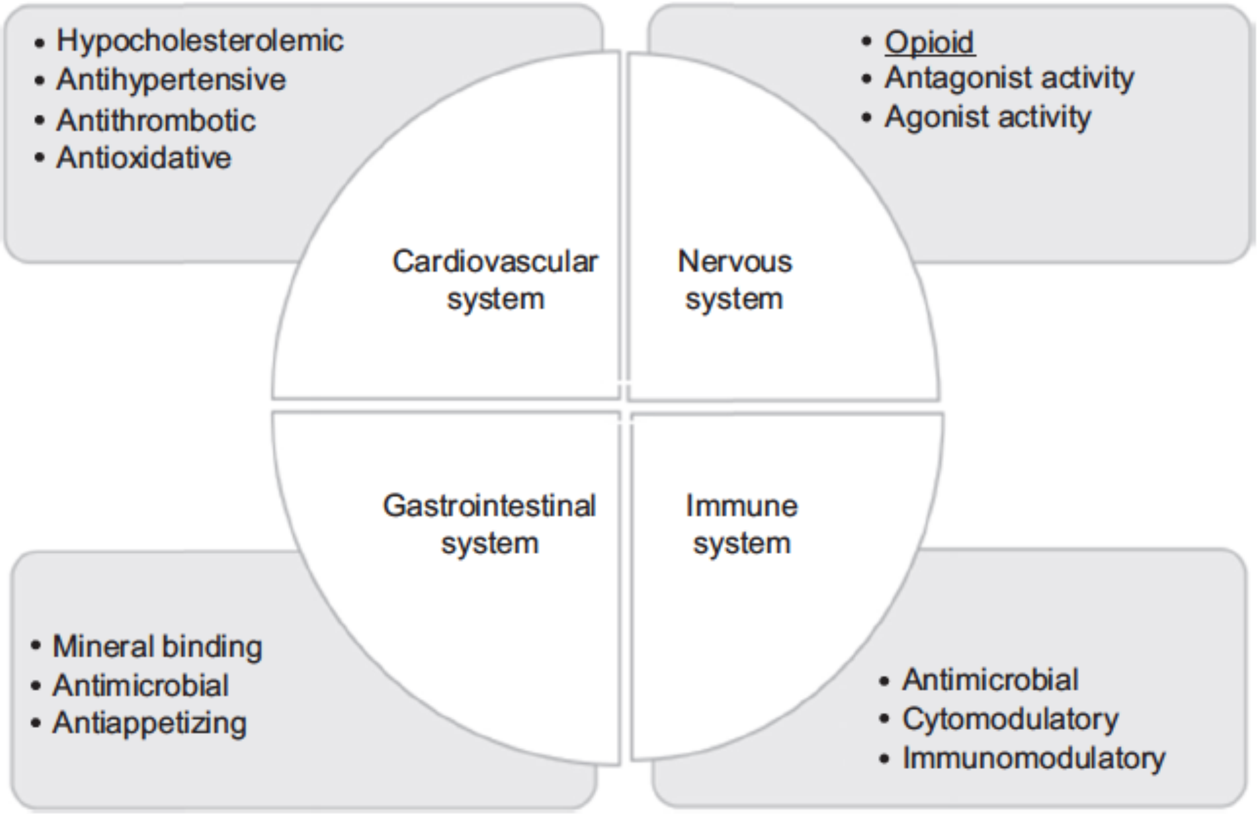
Βιοδραστικά πεπτίδια

- Προκύπτουν απο πεψη πρωτεινών κατα την επεξεργασία τροφών (πχ ζύμωση) ή απο αποδόμηση συστατικών της τροφής απο το εντερικό μικροβίωμα

Δράσεις βιοδραστικών πεπτιδίων

- Αντι-υπερτασικά (ανάλογα δραστικών υπομονάδων φαρμάκων- αναστολή μετατρεπτικού ενζύμου αγγειοτενσίνης- ACE)
- Αντι-φλεγμονώδη δράση (Αναστολή Cox ενζυμων)
- Δράση ανάλογη οπιοειδών
- Αντι-οξειδωτική δράση
- Αντι-θρομβωτική δράση

Δράσεις βιοδραστικών πεπτιδίων



Bioactive peptides against Alzheimer disease

- A fruit peptide (jujube) was introduced as a new peptide and named Snakin-Z, and consists of 31 amino acids with a sequence: CARLNCVPKGTSGNTETCPCYASLHSCRKYG
- Possesses potent Anti Acetylcholinesterase (AChE) activity
- AChE is a serine hydrolase which catalyzes the hydrolysis of neurotransmitter acetylcholine into choline and acetic acid.
- According to cholinergic neurotransmission, AChE inhibition increases the levels of acetylcholine in the brain, thus improving cholinergic synapses in Alzheimer’s disease (AD) patients

Some food protein hydrolysates and their therapeutic application

Protein source	**Microorganism or enzyme used**	**Amino acid sequence**	**Therapeutic application (bioactivity)***	**Reference**
Caprine milk	Pepsin	a_{s2}-casein f(203–208)	Antimicrobial; antihypertensive; antioxidant	Atanasova and Ivanova[19]
Bovine milk	*Lb. helveticus*	Ile-Pro-Pro; Val-Pro-Pro	Antihypertensive*	Jäkälä and Vapaatalo[38]
Bovine milk	Porcine intestinal enzymes	(Tyr-Pro-Phe- Pro-Gly-Pro-Ile- Pro-Asn-Ser-Leu) ß-casein f(60–70)	Immunostimulatory, opioid agonist; ACE-inhibitory	Atanasova and Ivanova[19]; Meisel[59]
Bovine milk	*Enterococcus faecalis* TH563 and *Lb. delbrueckii* ssp. *bulgaricus* LA2	Unidentified	Immunostimulatory, ACE-inhibitory	Regazzo *et al.*[60]
Egg white	Alcalase	Arg-Val-Pro-Ser-Leu	ACE-inhibitory	Liu *et al.*[58]
Rice endosperm	Neutrase	Phe-Arg-Asp-Glu-His-Lys-Lys; and Lys-His-Asp-Arg-Gly-Asp-Glu-Phe	Antioxidative	Zhang *et al.*[61]
Sweet potato juice	Thermoase PC10F, Protease S andProleather FG-F	Ile-Thr-Pro; Ile-Ile-Pro; Gly-Gln-Tyr; Ser-Thr-Tyr-Gln-Thr	ACE-inhibitory	Ishiguro *et al.*[62]

Lb., *Lactobacillus;* ACE, angiotensin converting enzyme.

Βιοδραστικές ενώσεις σε θαλάσσιους οργανισμούς: φύκη

Table 6.1 Distribution of main bioactive phenolic compounds in marine algae.

Algal group	Class of phenolic compounds	Algal species
Rhodophyceae	Bromophenols	*Pterocladia capillacea*,[b] *Odonthalia corymbifera*,[c] *Rhodomela confervoides*,[d] *Jania rubens*[e]
	Terpenoids	*Laurencia* sp.,[f] *Callophycus serratus*[g]
	MAAs[a]	*Porphyra* sp.[h]
	Tichocarpols	*Tichocarpus crinitus*[i]
Phaeophyceae	Phlorotannins	*Eisenia bicyclis*,[j,k] *Ecklonia cava*,[j,k] *Ecklonia kurome*,[j,k] *Ecklonia stolonifera*,[l] *Ishige okamurae*,[m] *Eisenia arborea*[n]
	Bromophenols	*Padina arborescens*,[o] *Sargassum siliquastrum*,[o] *Lobophora variegata*[o]
	Meroditerpenoids	*Sargassum fallax*[p]
	Colpol	*Colpomenia sinuosa*[q]
Chlorophyceae	Bromophenols	*Codium fragile*,[b] *Avrainvillea longicaulis*,[b] *Avrainvillea nigricans*,[b] *Avrainvillea rawsonii*[b]
	MAAs	*Prasiola* spp.[r]
	Coumarins	*Dasycladus vermicularis*[s]
	Vanillic acid	*Cladophora socialis*[t]

Αντιοξειδωτικοί παράγοντες: ασκορβικό οξύ (βιταμινη C), τοκοφερόλες (βιταμινη E), β-καροτένη

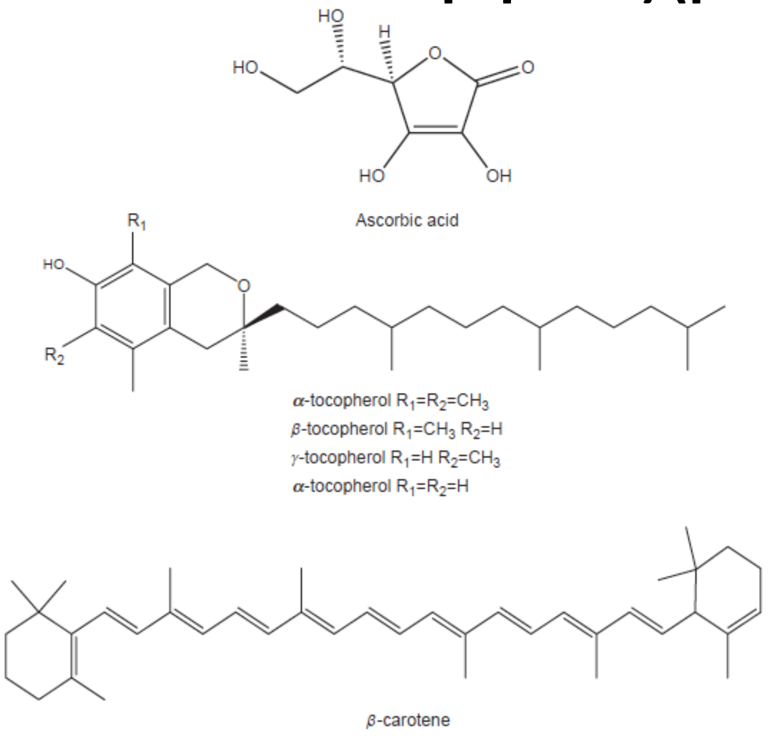
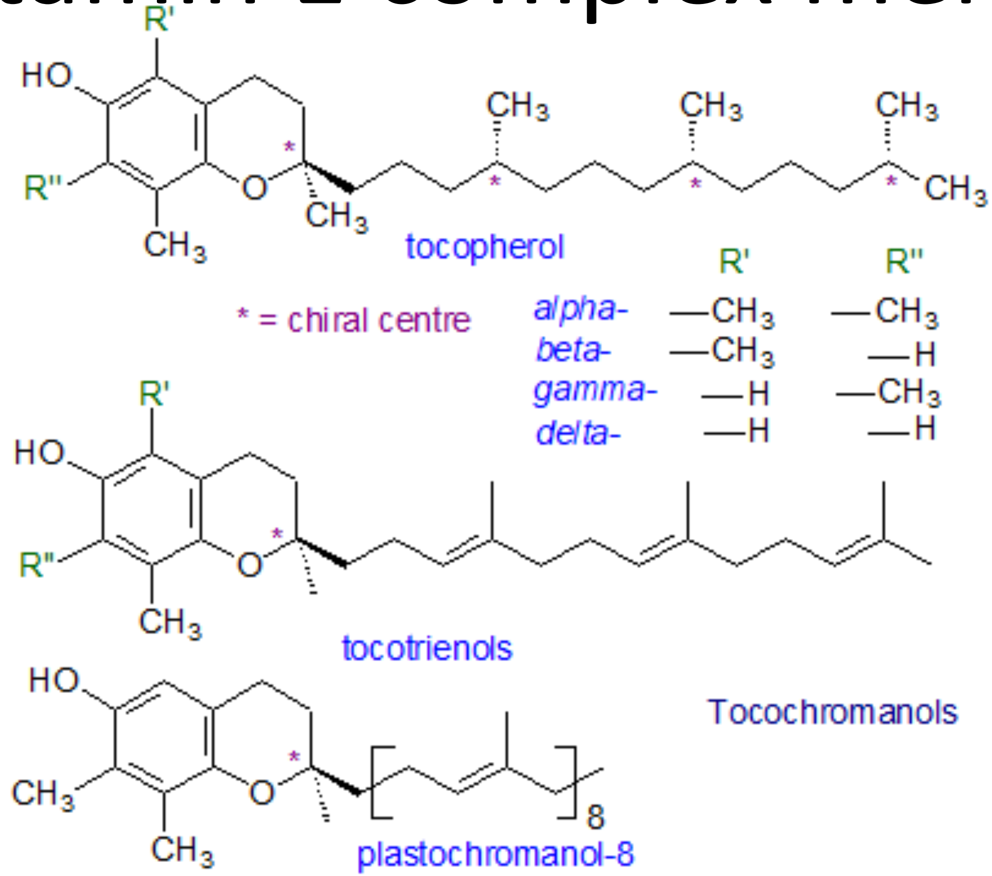


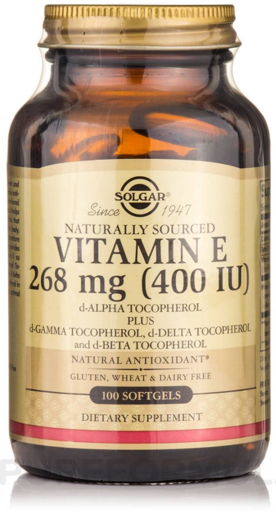
Figure 1.1
Ascorbic acid, tocopherols, and β-carotene as natural products with antioxidant activity.

vitC: αντιοξειδωτική δράση
vitE: εμποδίζει οξείδωση λιπών
β καροτένη: αντιοξειδωτική δράση

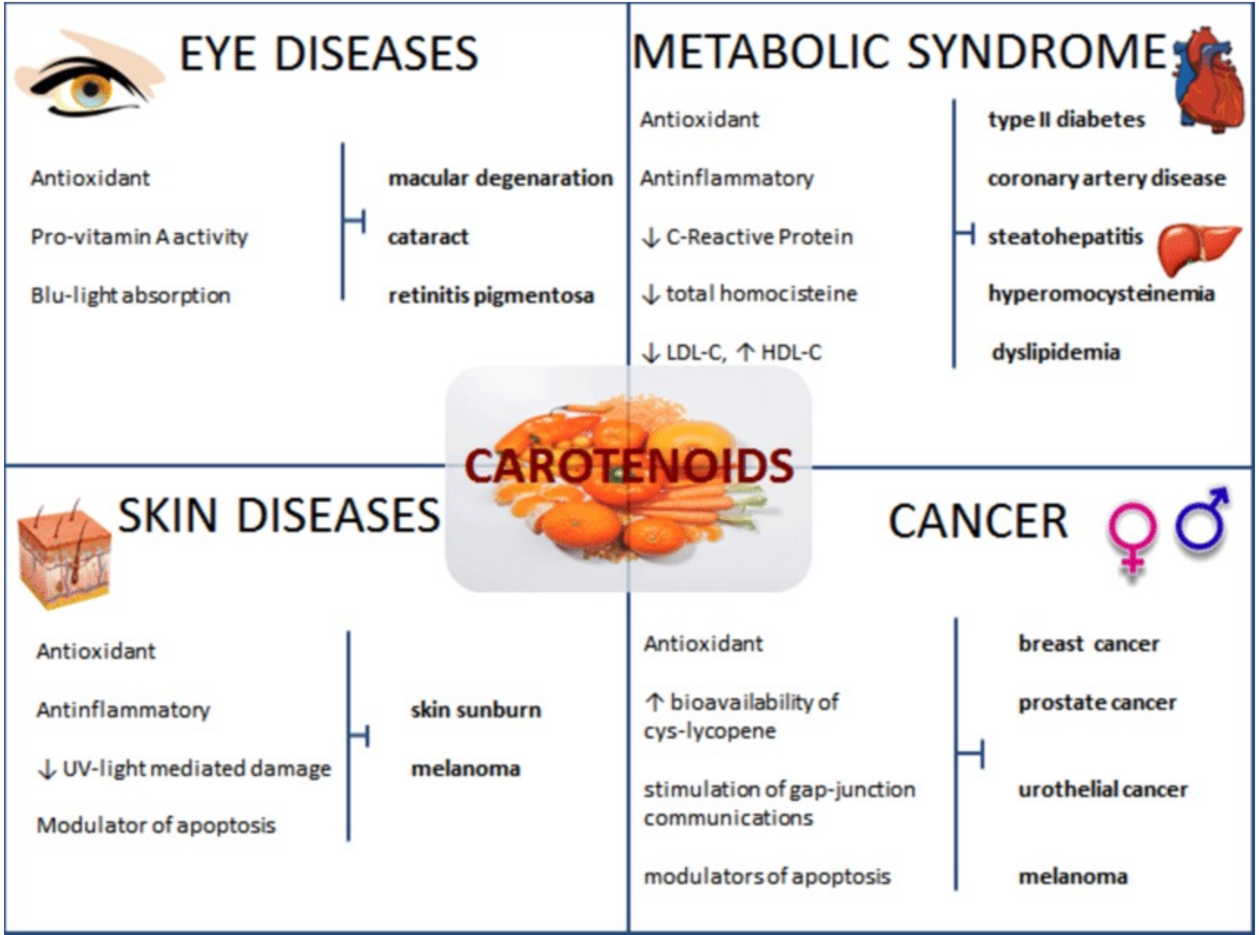
Vitamin E complex members



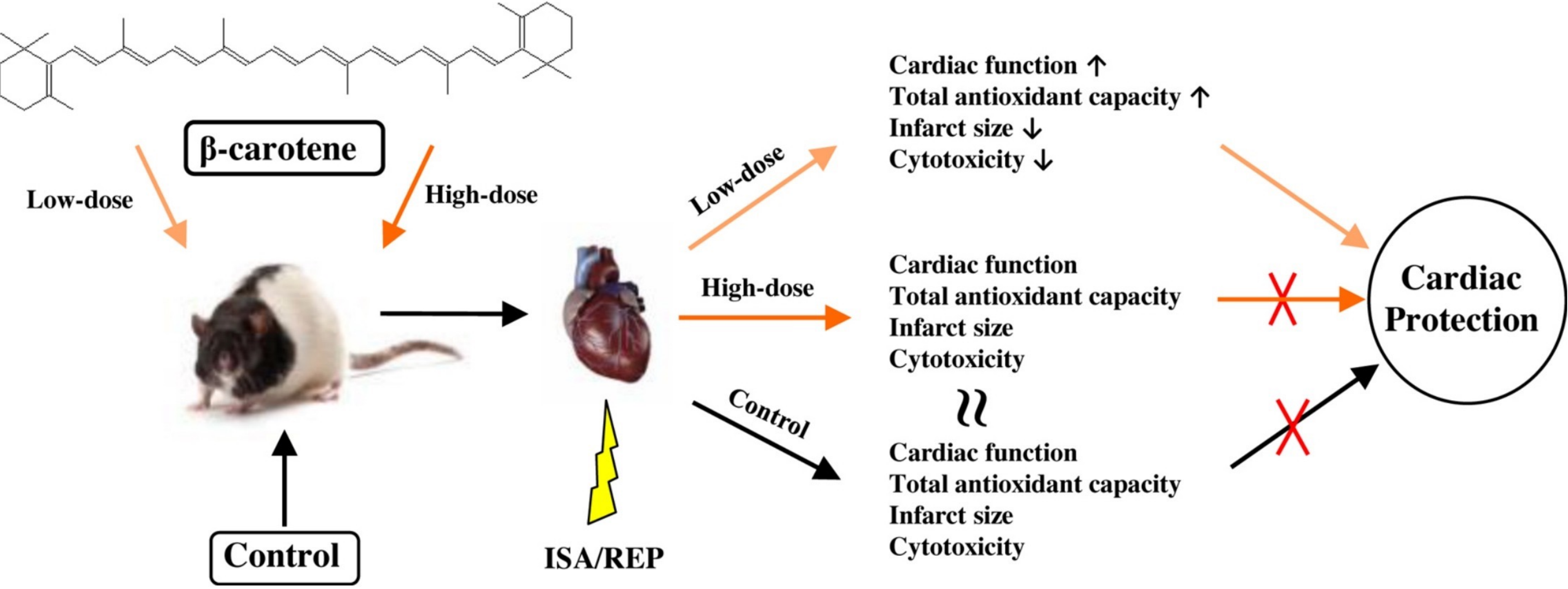
	R'	R''
alpha-	—CH_3	—CH_3
beta-	—CH_3	—H
gamma-	—H	—CH_3
delta-	—H	—H



β-carotene (BC), a lipid-soluble tetraterpene precursor to vitamin A

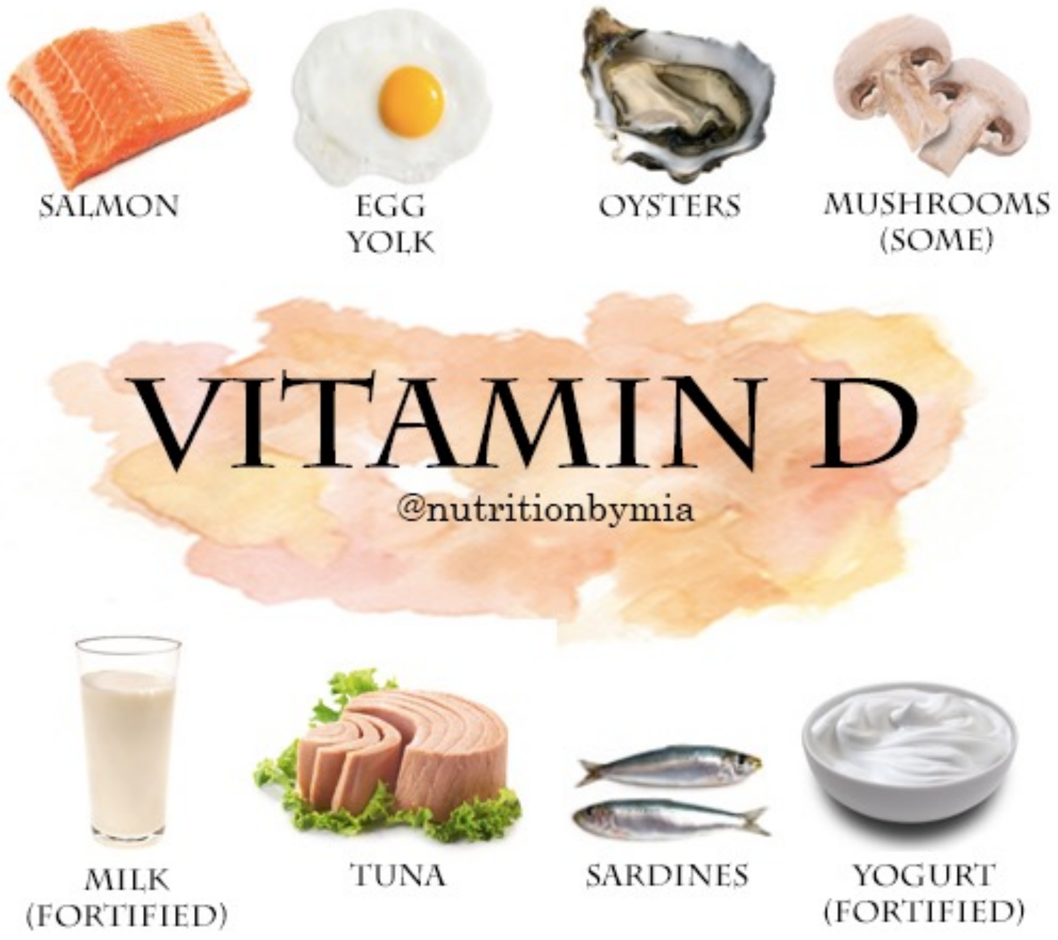


Dose-dependent action of b-carotene in cardioprotection



Vitamin D

- synthesized in the skin as pro-vitamin D
- activated in the liver and kidney by hydroxylation (1,25 di-hydroxy-vitD)
- Is present in fish fat (salmon)


SALMON
EGG YOLK
OYSTERS
MUSHROOMS (SOME)
VITAMIN D
@nutritionbymia
MILK (FORTIFIED)
TUNA
SARDINES
YOGURT (FORTIFIED)

Επιθυμητά επίπεδα vitD στον ορρό

- Φυσιολογικά επίπεδα: >20 ng/ml (50 nmol/L)
- Ανεπάρκεια (insuffiency): 10-20 ng/ml (30-50 nmol/L) (↑ALP, ↑PTH)
- Έλλειψη (deficiency): < 10 ng/ml (< 30 nmol/L) (συμπτωματική ραχίτιδα)
- Τοξικότητα: > 100 ng/ml (> 250 nmol/L) (↑Ca ορού και ούρων, ↓PTH)

Φιλανδική μελέτη

Περίπου **1400** άτομα που τα παρακολούθησαν για 22 χρόνια.
Στους **άνδρες, αλλά όχι στις γυναίκες**, οι υψηλότερες συγκεντρώσεις βιταμίνης 25(OH)D στον ορό συμβάδιζε με μειωμένο κίνδυνο εμφάνισης ΣΔ κατά 72% (adjustment for smoking, body mass index, physical activity, and education).

TABLE 3. Pooled Relative Odds of Type 2 Diabetes Comparing the Highest and the Lowest Quartiles of Serum Vitamin D[a] According to Sex

	No. Cases	No. Controls	OR (95% CI)	P for Trend	P for Heterogeneity
Model A[b]					
Men	188	451	0.49 (0.23–1.03)	0.01	0.39
Women	224	535	0.71 (0.34–1.49)	0.20	0.20
Model B[b]					
Men	185	441	0.28 (0.10–0.81)	<0.001	0.44
Women	220	528	1.14 (0.60–2.17)	0.89	0.64
Model C[b]					
Men	140	333	0.18 (0.03–0.97)	<0.001	0.50
Women	167	437	1.12 (0.32–3.96)	0.92	0.11
Model D[b]					
Men	183	438	0.28 (0.05–1.43)	0.01	0.23
Women	220	523	1.42 (0.71–2.84)	0.75	0.66

[a]Measured from controls.
[b]As described in Table 2 footnotes.

Knekt, P., M. Laaksonen, et al. (2008). "Serum vitamin D and subsequent occurrence of type 2 diabetes." Epidemiology 19(5): 666-71

Η vitD προστατεύει απο εμφάνιση διαβήτη τύπου 1

Φιλανδική **τυχαιοποιημένη παρεμβατική** μελέτη σε **10,366** παιδιά.

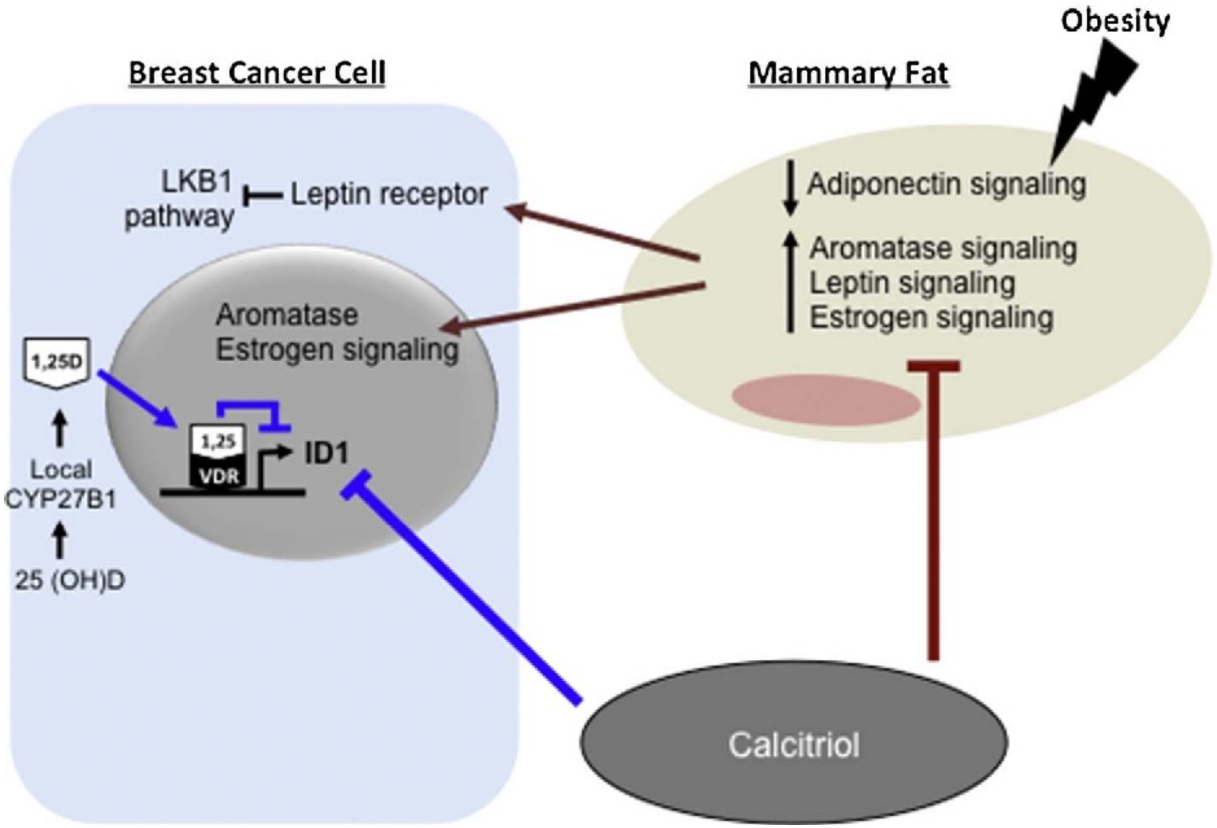
- Χορήγηση **2000 IU D3 / μέρα** κατά το πρώτο έτος της ζωής και παρακολούθηση του πληθυσμού αυτού κατά τα επόμενα 31 χρόνια
- Ο κίνδυνος εμφάνισης ΣΔ τύπου 1 μειωμένος κατά **80%.**
- Στα παιδιά με χαμηλά επίπεδα βιταμίνης D, ο κίνδυνος εμφάνισης διαβήτη ήταν **200%.**

.

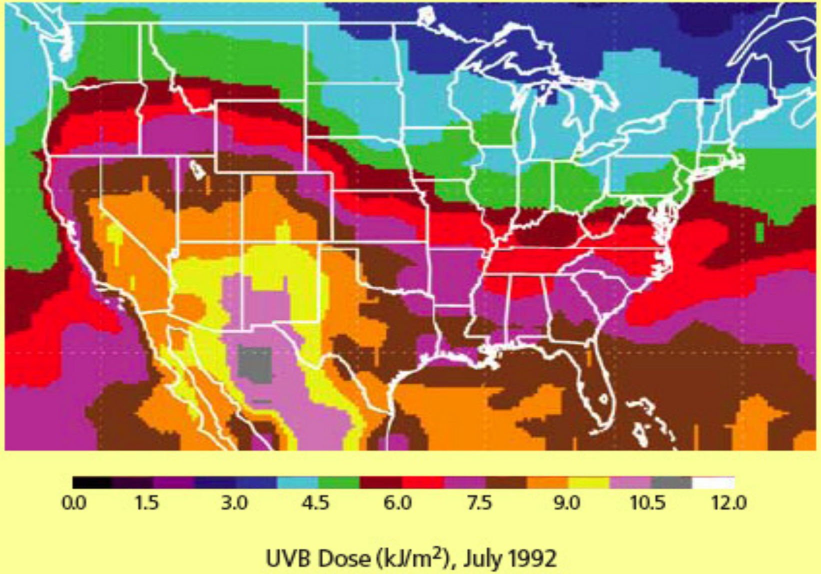
Dietary vitamin D supplementation is associated with reduced risk of type 1 diabetes. Ensuring adequate ωitamin D supplementation for infants could help to reverse the increasing trend in the incidence of type 1 diabetes.

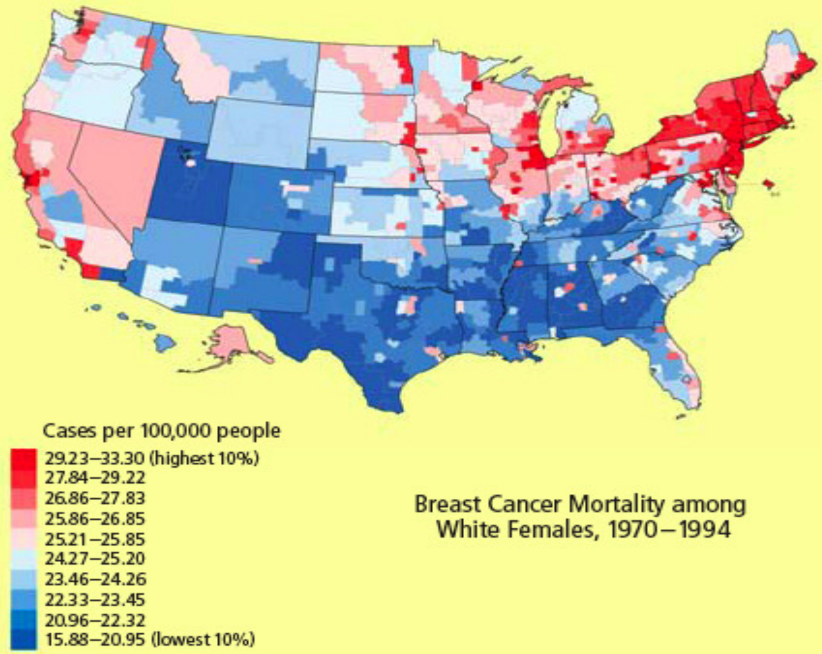
Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM. Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet. 2001 Nov 3;358(9292):1500-3.

Η vitD καταστελλει κυτταρα καρκίνου του μαστού

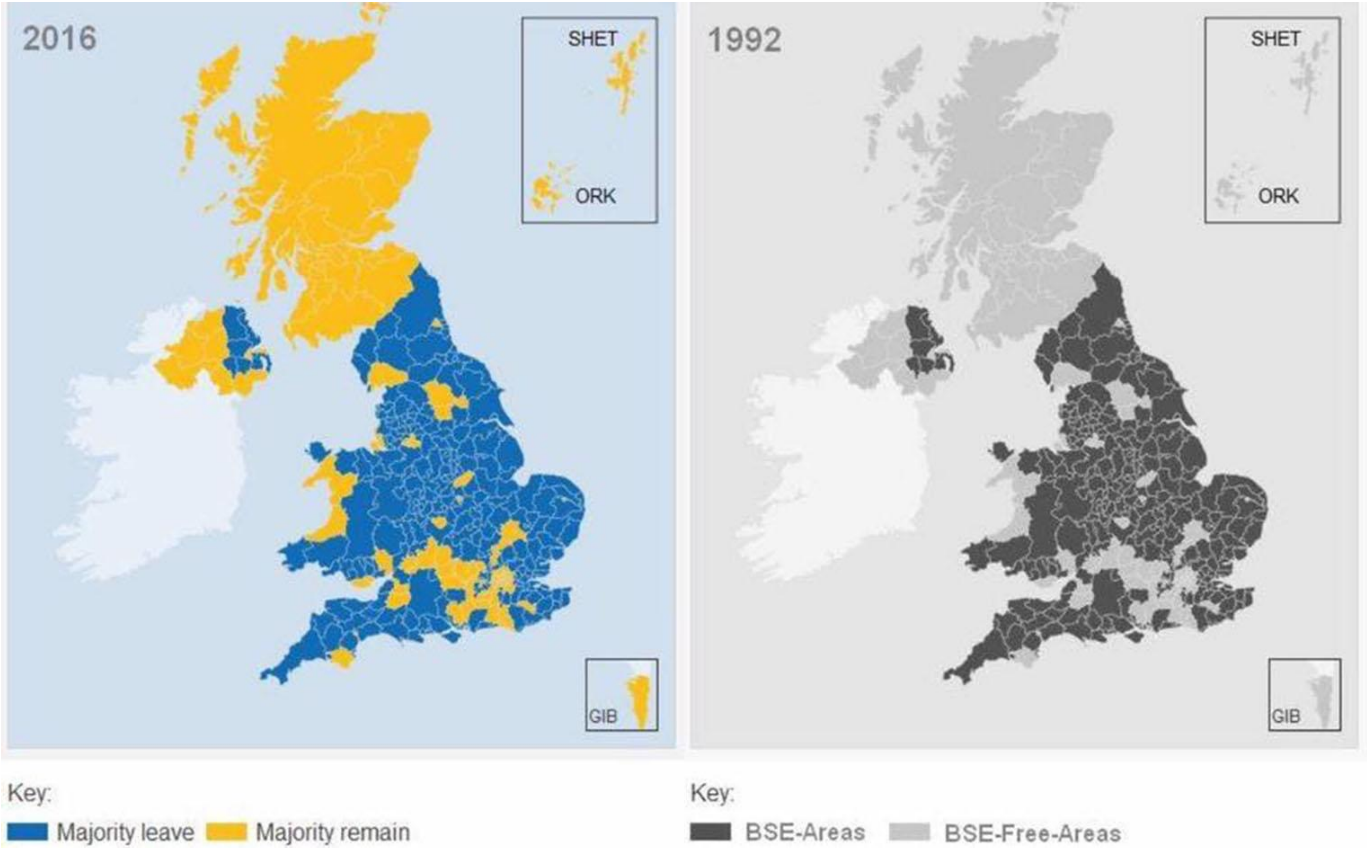


Επίπτωση καρκίνου μαστού και έκθεση σε ηλιοφάνεια

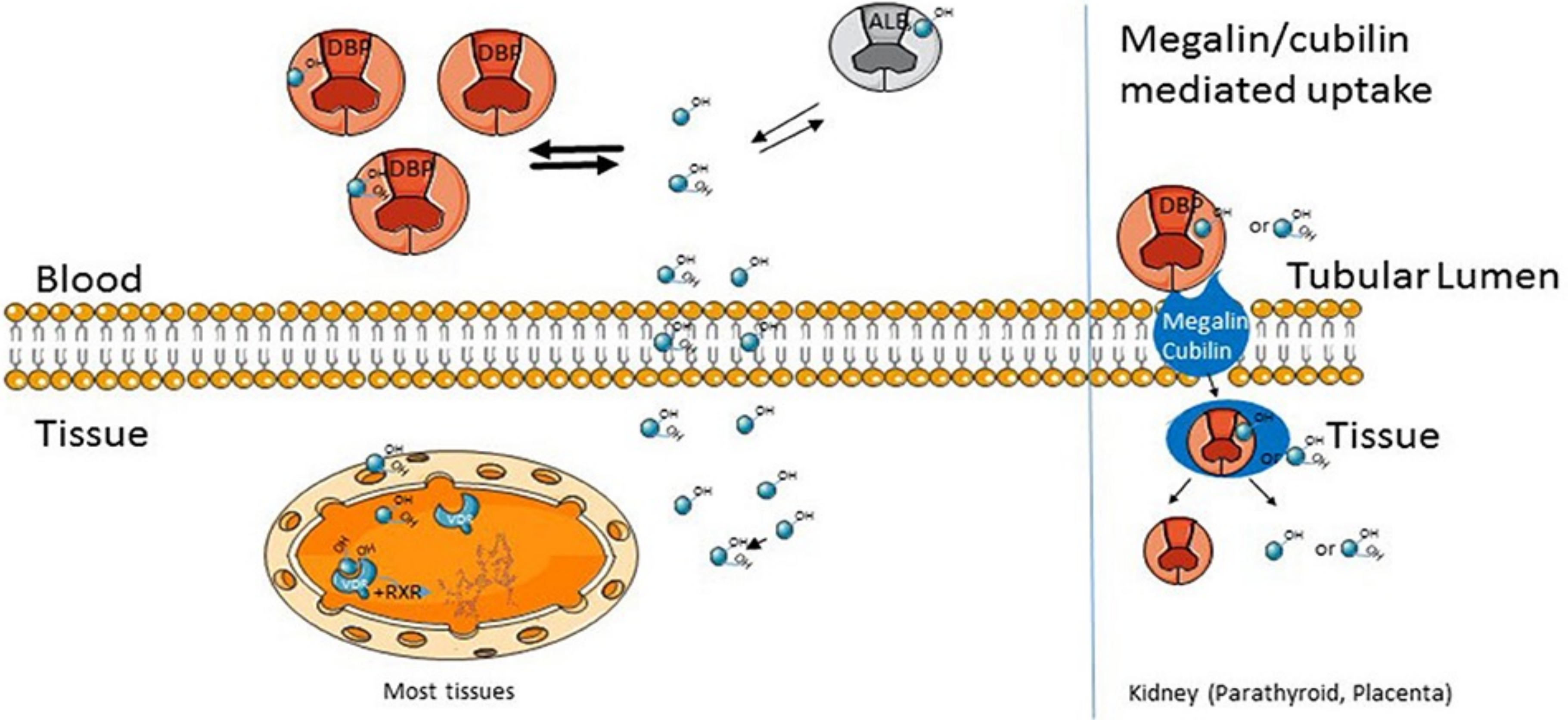




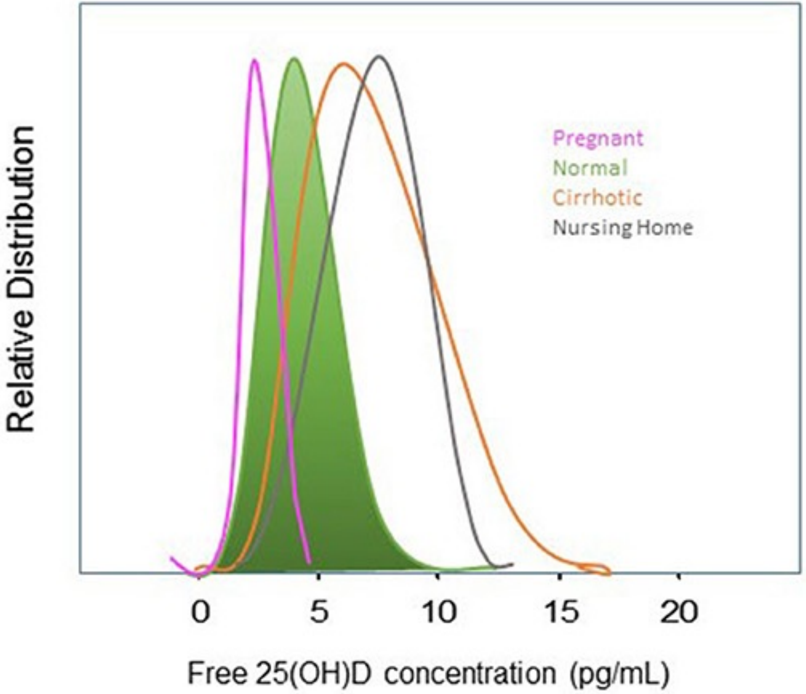
Mad cow disease and brexit



VitD circulates free and bound on vitD-BP

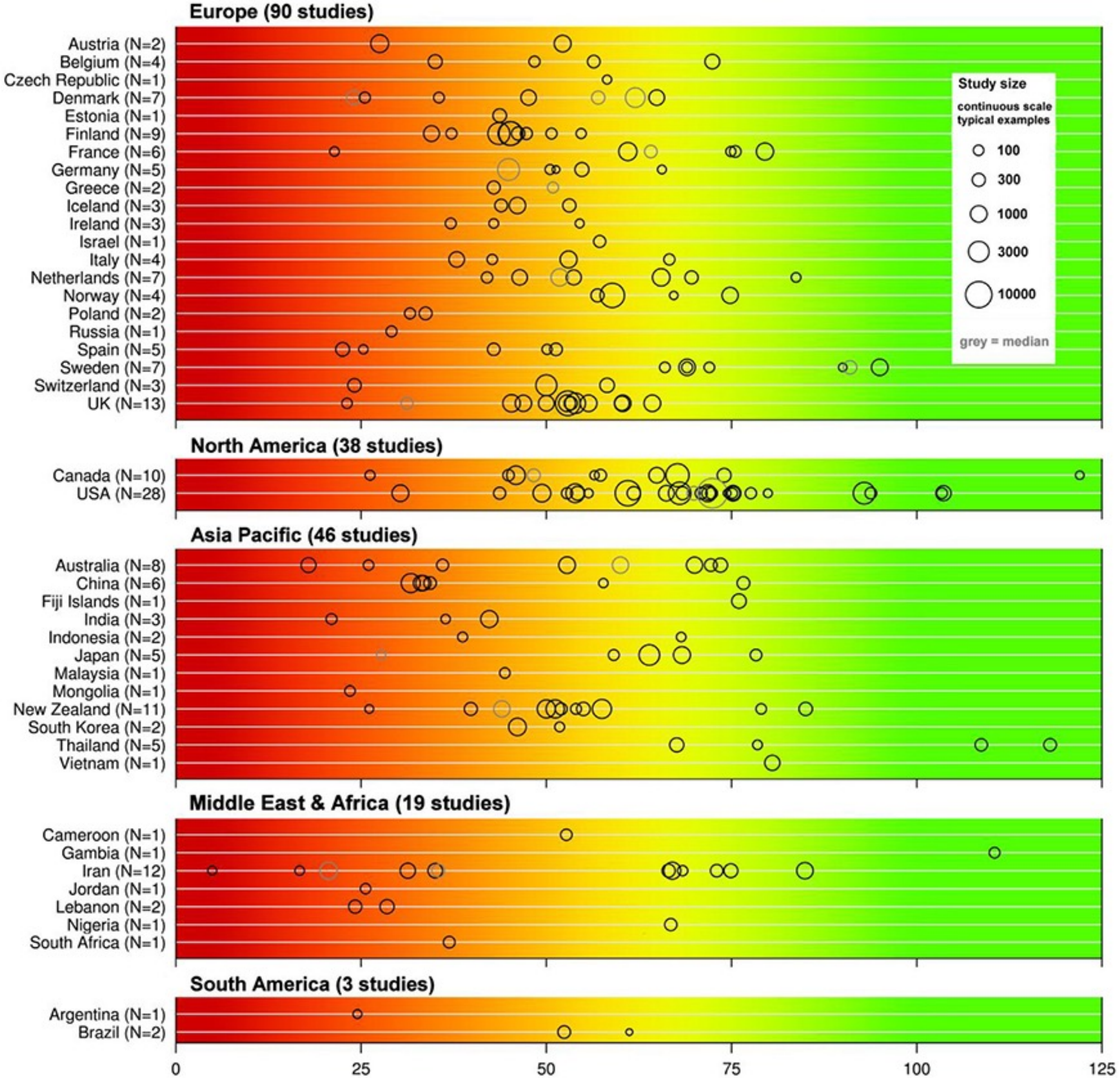


Distribution of free 25(OH)D in Adults and Selected Patient Groups

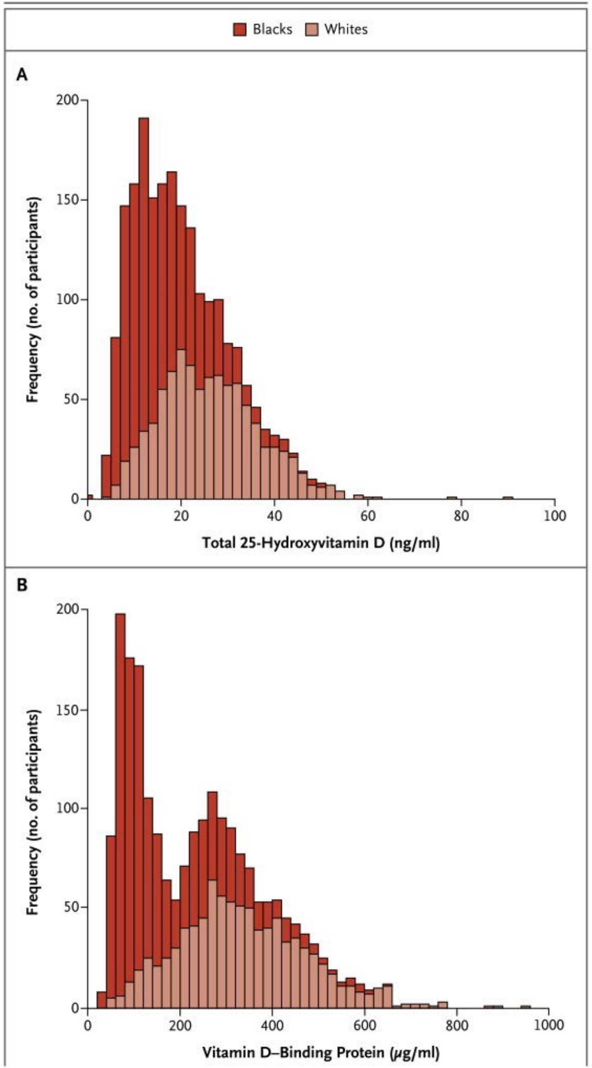


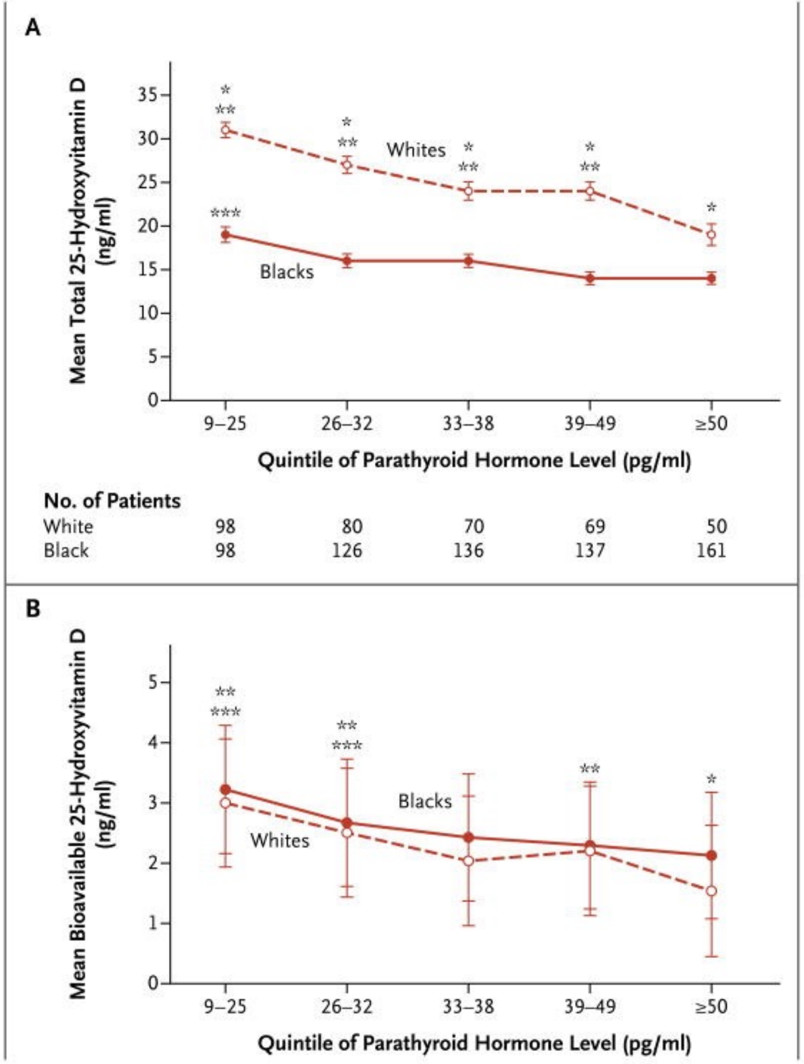
VitD levels in different populations

meta-analysis



VitD binding protein and bioavailable vitD



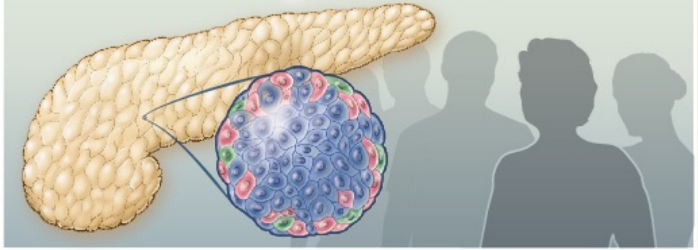


The NEW ENGLAND JOURNAL of MEDICINE

Vitamin D and Prevention of Type 2 Diabetes

DOUBLE-BLIND, RANDOMIZED TRIAL

2423 Overweight or obese adults with prediabetes



	Vitamin D_3 (4000 IU/day)	Placebo
		
	(N = 1211)	(N = 1212)
Progression to new-onset diabetes	293 Patients	323 Patients

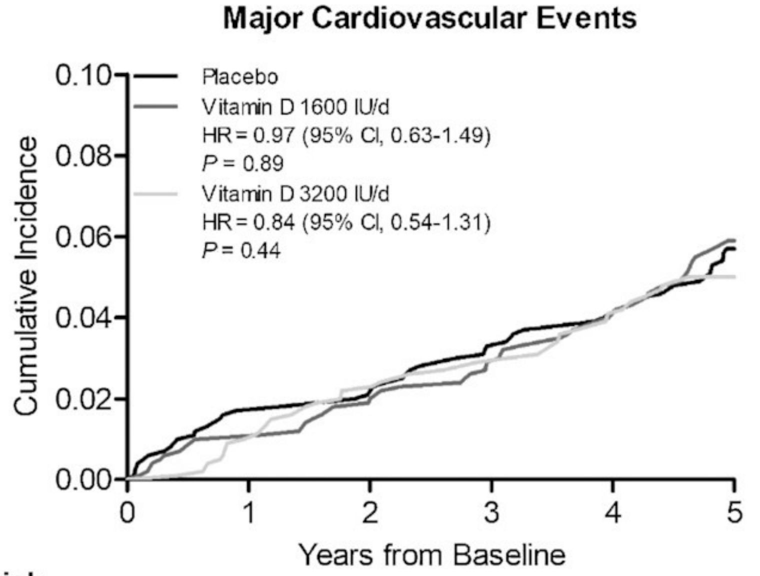
HR, 0.88; 95% CI, 0.75–1.04 (P=0.12)

No significant between-group differences in adverse events

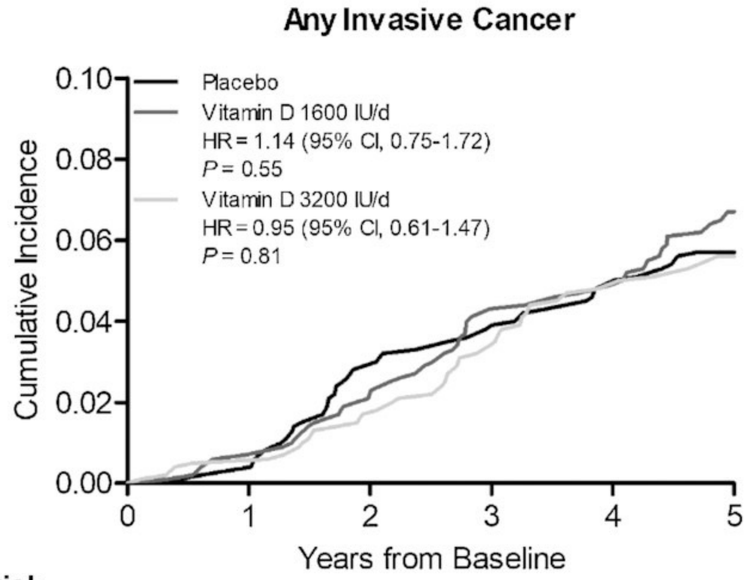
Risk of new-onset diabetes not significantly lower with vitamin D than with placebo

A.G. Pittas et al. 10.1056/NEJMoa1900906

Effect of vitD supplementation on Cardiovascular disease and Cancer



No. at risk						
Placebo	830	780	702	659	625	598
1600 IU/d	832	783	718	676	648	616
3200 IU/d	833	786	721	671	633	616



No. at risk						
Placebo	830	780	702	659	625	598
1600 IU/d	832	783	718	676	648	616
3200 IU/d	833	786	721	671	633	616

2495participants: male participants ≥60 years and post-menopausal female participants ≥65 years from a general Finnish population who were free of prior CVD or cancer

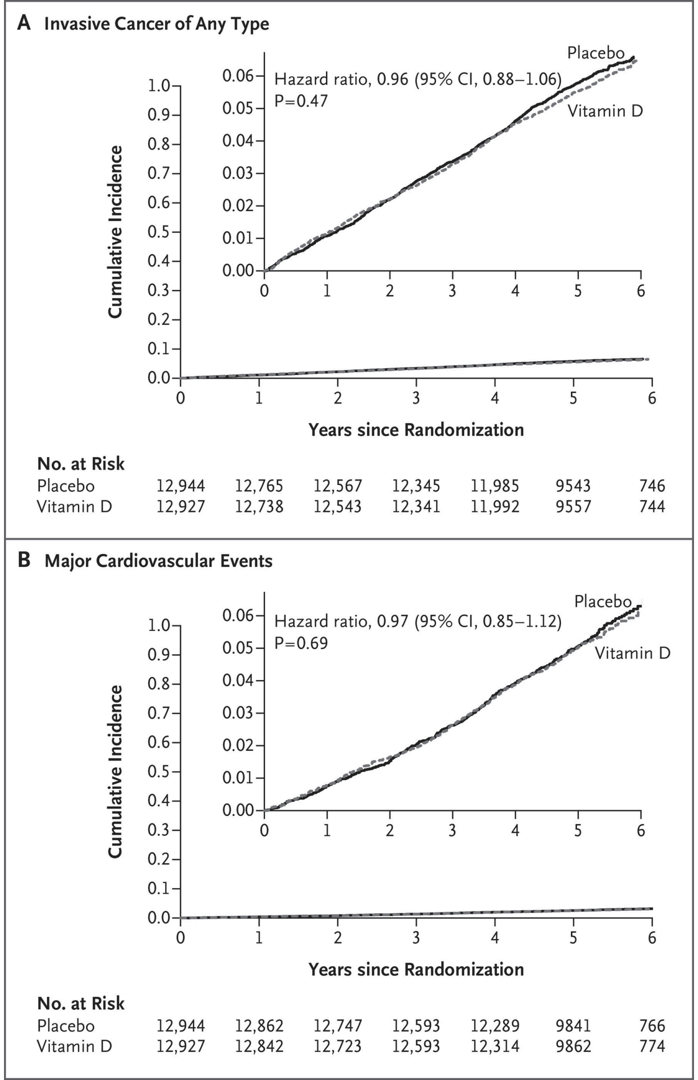
The American Journal of Clinical Nutrition, Volume 115, Issue 5, May 2022, Pages 1300–1310, https://doi.org/10.1093/ajcn/nqab419

VitD and marine Ω3 supplementation for 5 years VITAL study

25,871 participants, including 5106 black participants men 50 years of age or older and women 55 years of age or older in the United States.

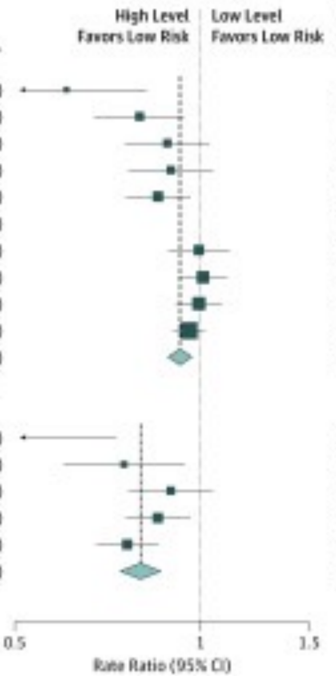
Conclusion: Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

N Engl J Med 2019; 380:33-44
DOI: 10.1056/NEJMoa1809944



Association of 25OH-VitD serum levels with fractures

Source	Baseline 25-Hydroxyvitamin D, nmol/L	Cases No./Total Participants, No.	Degree of Adjustment	Rate Ratio (95% CI)	Weight, %
Any fracture					
Looker,[28] 2013	59.8	525/4749	+++	0.61 (0.45-0.82)	1.3
Buchebner et al,[29] 2014	62.0	349/1044	+++	0.80 (0.67-0.95)	4.2
Barbour et al,[30] 2012	60.6	247/2614	++++	0.88 (0.75-1.04)	4.7
Robinson-Cohen et al,[31] 2011	62.8	244/2294	++++	0.90 (0.76-1.05)	4.7
Holvik et al,[32] 2013	55.9	1175/2613	++	0.85 (0.75-0.97)	7.9
Steingrimsdottir et al,[33] 2014	53.6	261/5764	++++	0.76 (0.68-0.86)	8.6
Cauley et al,[34] 2011	53.5	1132/2264	++++	0.99 (0.88-1.12)	8.9
Swanson et al,[36] 2015	62.3	432/1000	++++	1.01 (0.92-1.11)	13.6
Roddam et al,[37] 2007	81.0	730/2175	+++	0.99 (0.91-1.09)	15.5
Julian et al,[38] 2016	58.1	1183/14624	++++	0.96 (0.90-1.02)	30.6
All		6278/39 141		0.93 (0.89-0.96)	100.0
Subtotal (Q = 31.0, *df* = 9, $P < .001$; $I^2 = 71.0\%$)					
Hip fracture					
Looker,[28] 2013	59.8	287/4749	+++	0.53 (0.38-0.73)	4.7
Cauley et al,[34] 2011	57.8	400/800	++++	0.75 (0.60-0.95)	9.4
Robinson-Cohen et al,[31] 2011	62.8	244/2294	++++	0.90 (0.76-1.05)	19.1
Holvik et al,[32] 2013	55.9	1175/2613	++	0.85 (0.75-0.97)	32.1
Steingrimsdottir et al,[33] 2014	53.6	261/5764	++++	0.76 (0.68-0.86)	34.7
All		2367/16 220		0.80 (0.75-0.86)	100.0
Subtotal (Q = 10.0, *df* = 4, $P = .04$; $I^2 = 59.9\%$)					



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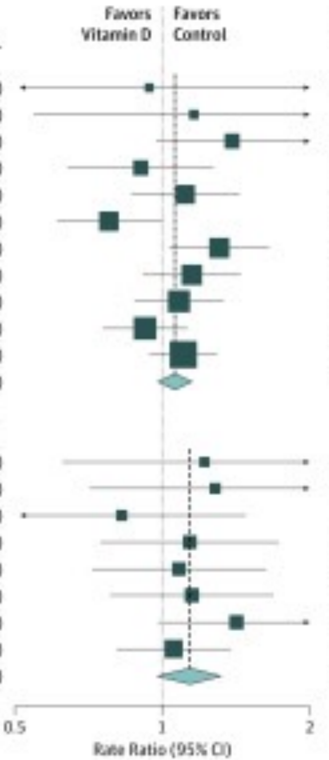
Effect of VitD+Ca^{++} Supplementation in fractures

Source	Vitamin D: Treatment	Vitamin D: Events, No./Total Participants, No.	Control: Events, No./Total Participants, No.	Risk of Bias	Rate Ratio (95% CI)	Weight, %
Any fracture						
Glendenning et al,[39] 2012	150 000 IU/3 mo	10/353	10/333	High	0.94 (0.39-2.29)	0.8
Larsen et al,[40] 2018	20 000 IU/wk	15/256	13/255	Unclear	1.16 (0.54-2.48)	1.0
Law et al,[41] 2006	100 000 IU/3 mo	66/1762	53/1955	High	1.39 (0.97-2.01)	4.5
Meyer et al,[42] 2002	400 IU/d	69/569	76/575	High	0.90 (0.64-1.28)	4.9
Lips et al,[43] 1996	400 IU/d	135/1291	122/1287	High	1.12 (0.86-1.45)	8.9
Trivedi et al,[44] 2003	100 000 IU/4 mo	119/1345	149/1341	High	0.78 (0.61-1.00)	9.6
Sanders et al,[45] 2010	500 000 IU/y	171/1131	135/1127	High	1.31 (1.03-1.67)	10.4
Khaw et al,[46] 2017	100 000 IU/mo	156/2558	136/2550	Low	1.15 (0.91-1.46)	10.8
Grant et al,[47] 2005	800 IU/d	208/1343	192/1332	High	1.08 (0.88-1.35)	13.0
Lyons et al,[48] 2007	100 000 IU/4 mo	205/1725	218/1715	High	0.92 (0.76-1.14)	14.2
Smith et al,[49] 2007	300 000 IU/y	306/4727	279/4713	High	1.11 (0.93-1.30)	21.9
All		1460/17060	1383/17183		1.06 (0.98-1.14)	100.0
Subtotal (Q = 14.5, df = 10, P = .15; I^2 = 31.1%)						
Hip fracture						
Sanders et al,[45] 2010	500 000 IU/y	19/1131	15/1127	High	1.22 (0.64-2.48)	4.7
Law et al,[41] 2006	100 000 IU/3 mo	24/1762	20/1955	High	1.28 (0.73-2.41)	6.1
Trivedi et al,[44] 2003	100 000 IU/4 mo	21/1345	24/1341	High	0.83 (0.48-1.57)	6.2
Grant et al,[47] 2005	800 IU/d	47/1343	41/1332	High	1.14 (0.75-1.75)	12.0
Meyer et al,[42] 2002	400 IU/d	50/569	47/575	High	1.08 (0.71-1.63)	12.6
Lips et al,[43] 1996	400 IU/d	58/1291	48/1287	High	1.15 (0.82-1.79)	14.4
Smith et al,[49] 2007	300 000 IU/y	66/4727	44/4713	High	1.42 (1.03-2.18)	15.4
Lyons et al,[48] 2007	100 000 IU/4 mo	112/1725	104/1715	High	1.06 (0.82-1.42)	28.6
All		397/13893	343/14045		1.14 (0.98-1.32)	100.0
Subtotal (Q = 3.0, df = 7, P = .89; I^2 = 0.0%)						



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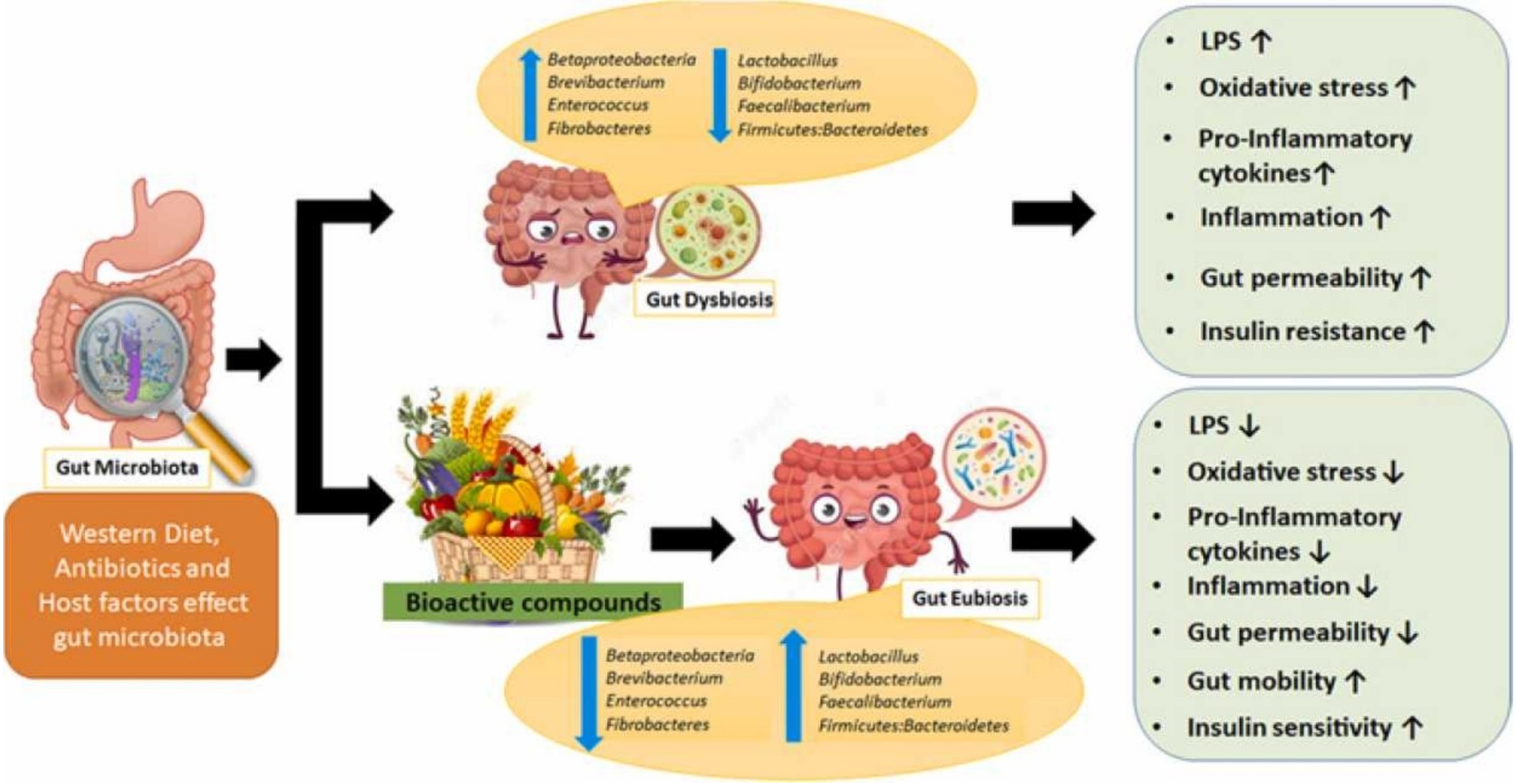
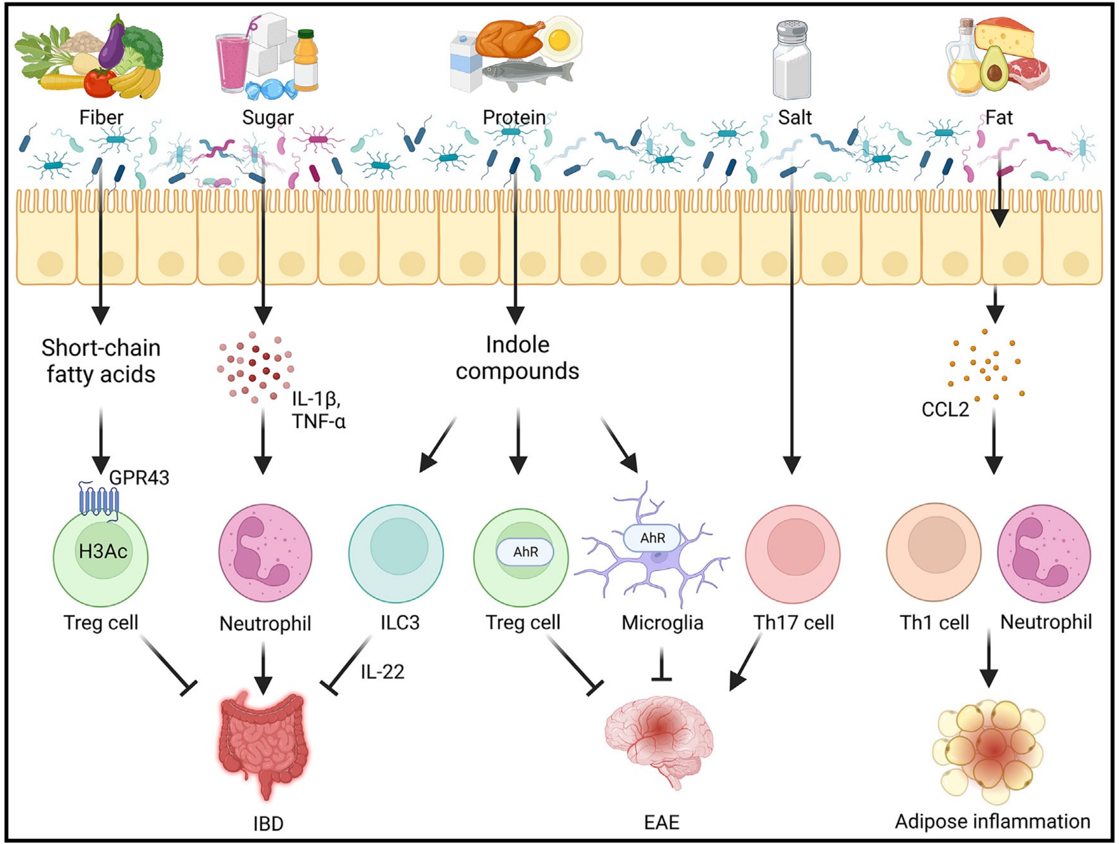
Modulation of the gut microbiota from bioactive compounds

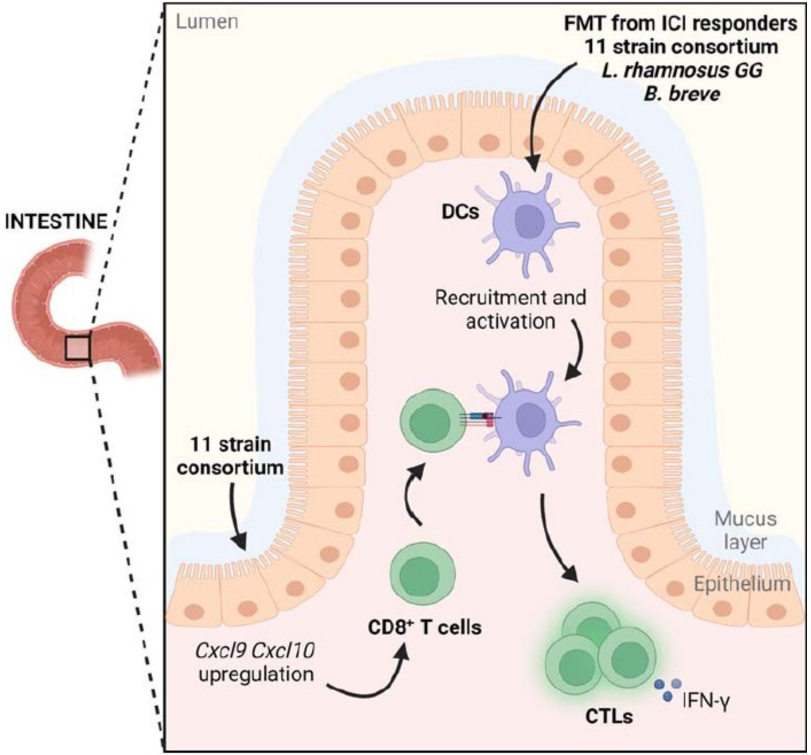


Dietary impact of microbiota products in the immune system



Immunity, Jan 9, 2024

Impact of microbiome-derived metabolites to cancer Immunotherapy



Trends in Immunology

Examples of metabolite concentrations in human tumors				
Metabolite	Sample type	Cancer type	ICI antibody treatment	Correlation with ICI treatment response
Butyrate Propionate	Fecal	NSLC	Anti-PD-1	High fecal concentration associated with response
Acetate Butyrate Propionate	Fecal	Solid tumors	Anti-PD-1	High fecal concentration associated with response
Butyrate Propionate	Serum	Melanoma	Anti-CTLA-4	High serum concentration negatively corelated with clinical outcome
Nicotinic acid	Fecal	NSLC	Anti-PD-1	Increased concentrations in the feces of prolonged responders (PFS >12 months)
Alanine Pyruvate	Serum	NSLC	Anti-PD-1	Decreased serum concentrations associated with response
Lysine	Fecal	NSLC	Anti-PD-1	Increased concentrations in the feces of prolonged responders (PFS >12 months)
3-Hydroxyanthranilic acid	Plasma	NSLC	Anti-PD-1	Low concentrations associated with longer PFS
Anacardic acid	Fecal	Melanoma	Anti-CTLA-4/anti-PD-1	High concentrations of anacardic acid associated with response
2-Pentanone	Fecal	NSLC	Anti-PD-1	Associated with early progression of tumor
Tridecane	Fecal	NSLC	Anti-PD-1	Associated with early progression of tumor
Primary bile acids (muricholic acid, α- and β-muricholic acids) Secondary bile acids (ursodeoxycholic acid, ursocholic acid, tauroursodeoxycholic acid, and taurohyocholic acid)	Fecal	Unresectable hepatocellular carcinoma	Anti-PD-1	Significantly dominant in the feces of patients with objective response to ICI treatment

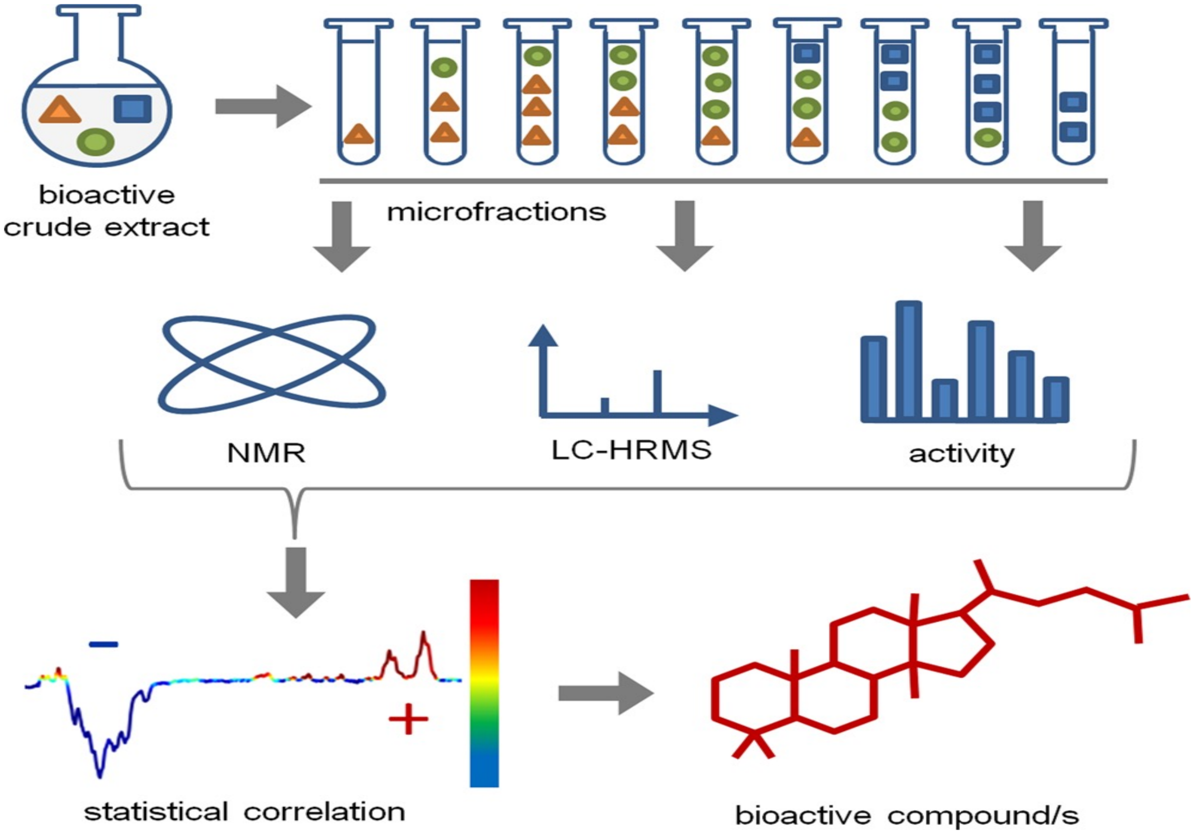
Microbiota-derived metabolites that affect anti-tumor responses

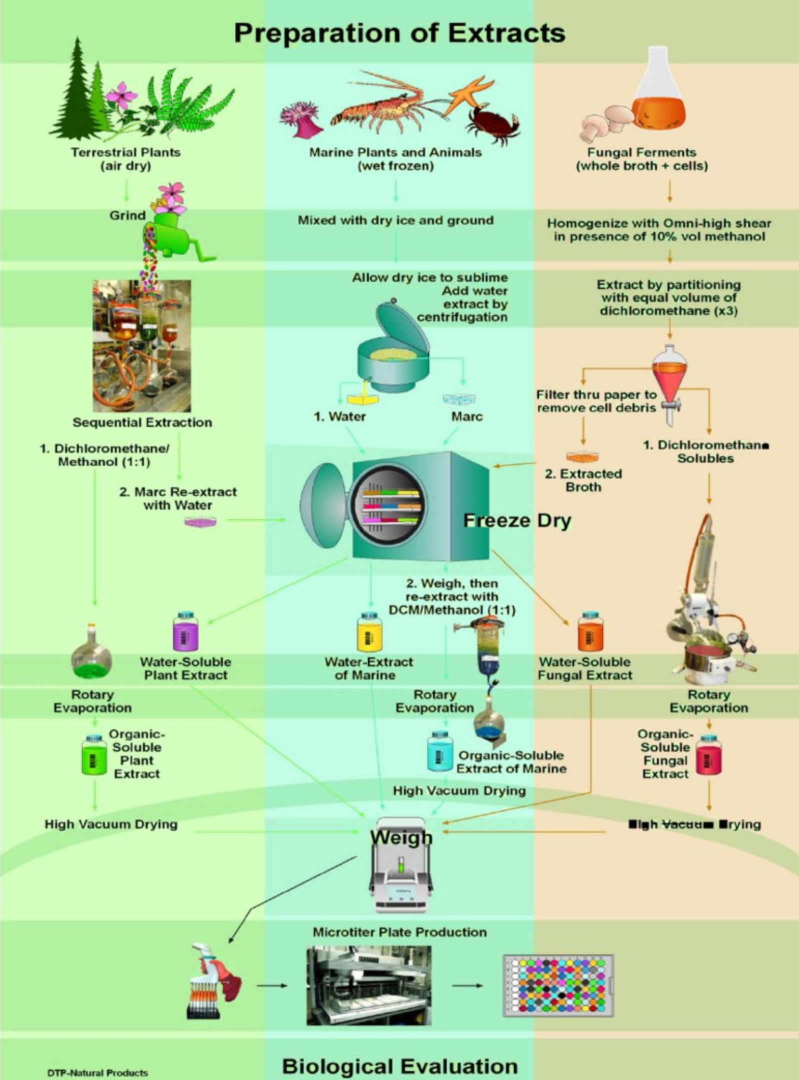
Examples of microbiota-derived metabolite concentrations in murine models			
Metabolite	Model	ICI antibody treatment	Correlation with ICI treatment response
Inosine	MC38 tumor-bearing mice	Anti-CTLA-4	Co-treatment with inosine or inosine-producing bacteria enhanced the efficacy of anti-CTLA-4
	B16-melanoma-bearing mice	Anti-PD-1	Co-treatment with inosine enhanced the efficacy of anti-PD-1
Inosine monophosphate and hypoxanthine	GF mice	None	Increased concentrations in cecal contents and sera of mice following inoculation with an 11-strain bacterial consortium
Mevalonate			
Dimethyl glycine			

Βιοδραστικές ενώσεις

- Απομόνωση
- Χαρακτηρισμός δράσης
- Μελέτη σαν διατροφικό συμπλήρωμα ή φαρμακευτική ουσία

Απομόνωση νέων βιοδραστικών ενώσεων




Preparation of Extracts
Terrestrial Plants (air dry)
Marine Plants and Animals (wet frozen)
Fungal Ferments (whole broth + cells)
Grind
Mixed with dry ice and ground
Homogenize with Omni-high shear in presence of 10% vol methanol
Allow dry ice to sublime Add water extract by centrifugation
Extract by partitioning with equal volume of dichloromethane (x3)
Sequential Extraction
1. Water
Marc
Filter thru paper to remove cell debris
1. Dichloromethane/ Methanol (1:1)
2. Marc Re-extract with Water
1. Dichloromethane Solubles
2. Extracted Broth
Freeze Dry
2. Weigh, then re-extract with DCM/Methanol (1:1)
Water-Soluble Plant Extract
Water-Extract of Marine
Water-Soluble Fungal Extract
Rotary Evaporation
Rotary Evaporation
Rotary Evaporation
Organic-Soluble Plant Extract
Organic-Soluble Extract of Marine
Organic-Soluble Fungal Extract
High Vacuum Drying
High Vacuum Drying
High Vacuum Drying
Weigh
Microtiter Plate Production
Biological Evaluation
DTP-Natural Products

Συμπεράσματα

- Βιοδραστικές ουσίες υπάρχουν σε όλες σχεδον τις τροφές
- Λιγες από αυτές έχουν εξειδικευμένη δράση- θεραπευτική
- Χαρακτηρισμός τους και απομόνωση βοηθά στη σύνθεση θεραπευτικών ουσιών
- Χαρακτηρισμός και κατανόηση δράσης βοηθά στην επιλογή διατροφικών συνηθειών
- Κατανόηση δράσης βιοδραστικών ουσιών βοηθά στην παρασκευή λειτουργικών τροφίμων
- Μεγάλες δόσεις βιοδραστικών ουσίων δύνανται να έχουν μη επιθυμητά αποτελέσματα
- Συνδιασμός βιοδραστικών ουσιών στα πλαίσια της διατροφής έχουν θετική επίδραση στην υγεία

Παντα να ελέγχετε τις πηγές της πληροφορίας και την ποιότητά της