



UNIVERSITY OF CRETE
SCHOOL OF MEDICINE

Ο ρόλος βιοδραστικών ενώσεων στην προστασία έναντι ασθενειών και στην θεραπεία

Χρήστος Τσατσάνης

School of Medicine, University of Crete,
Heraklion, Crete, Greece





- 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



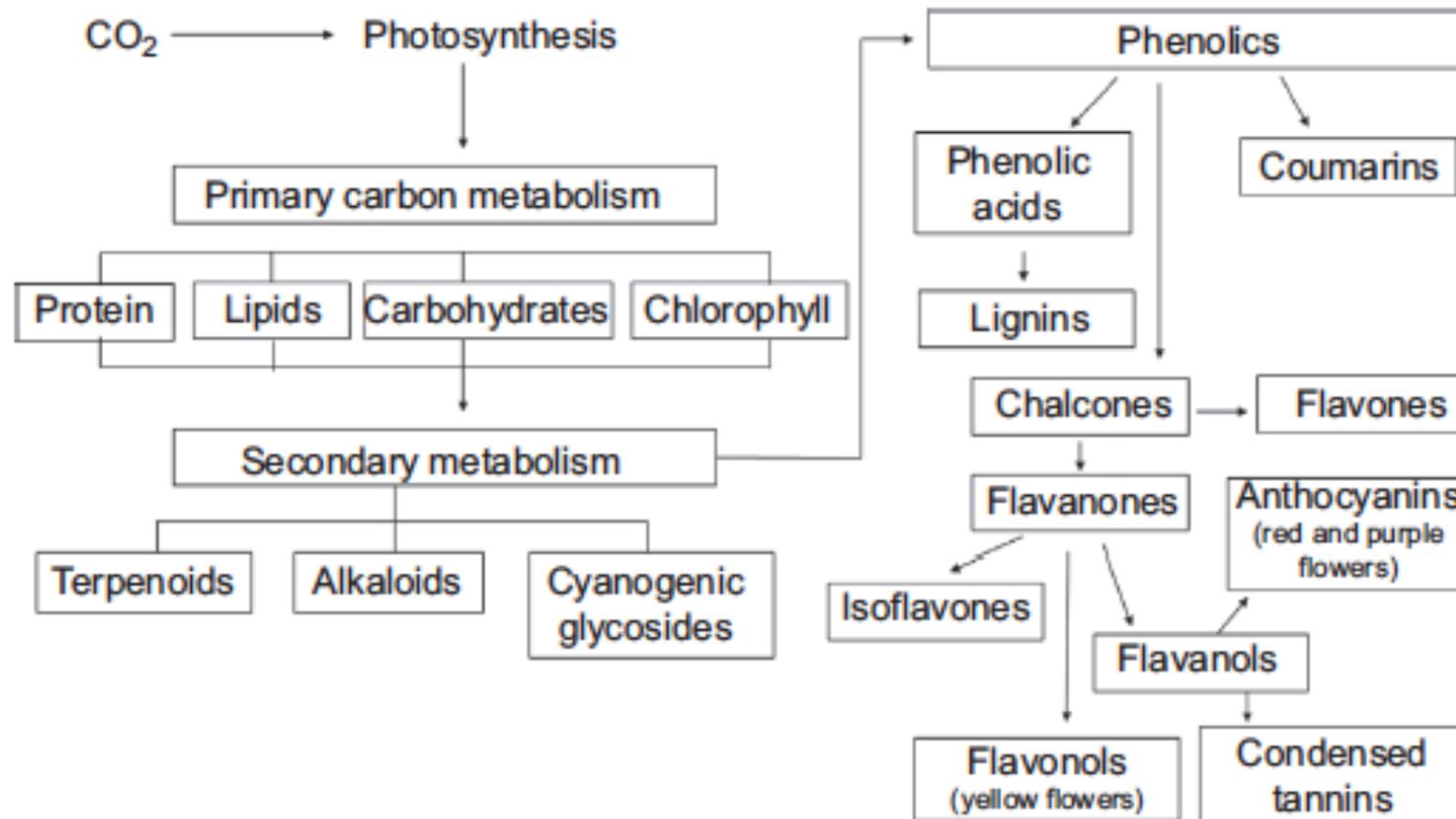
Βιοδραστικές ενώσεις: δευτερογενείς μεταβολίτες

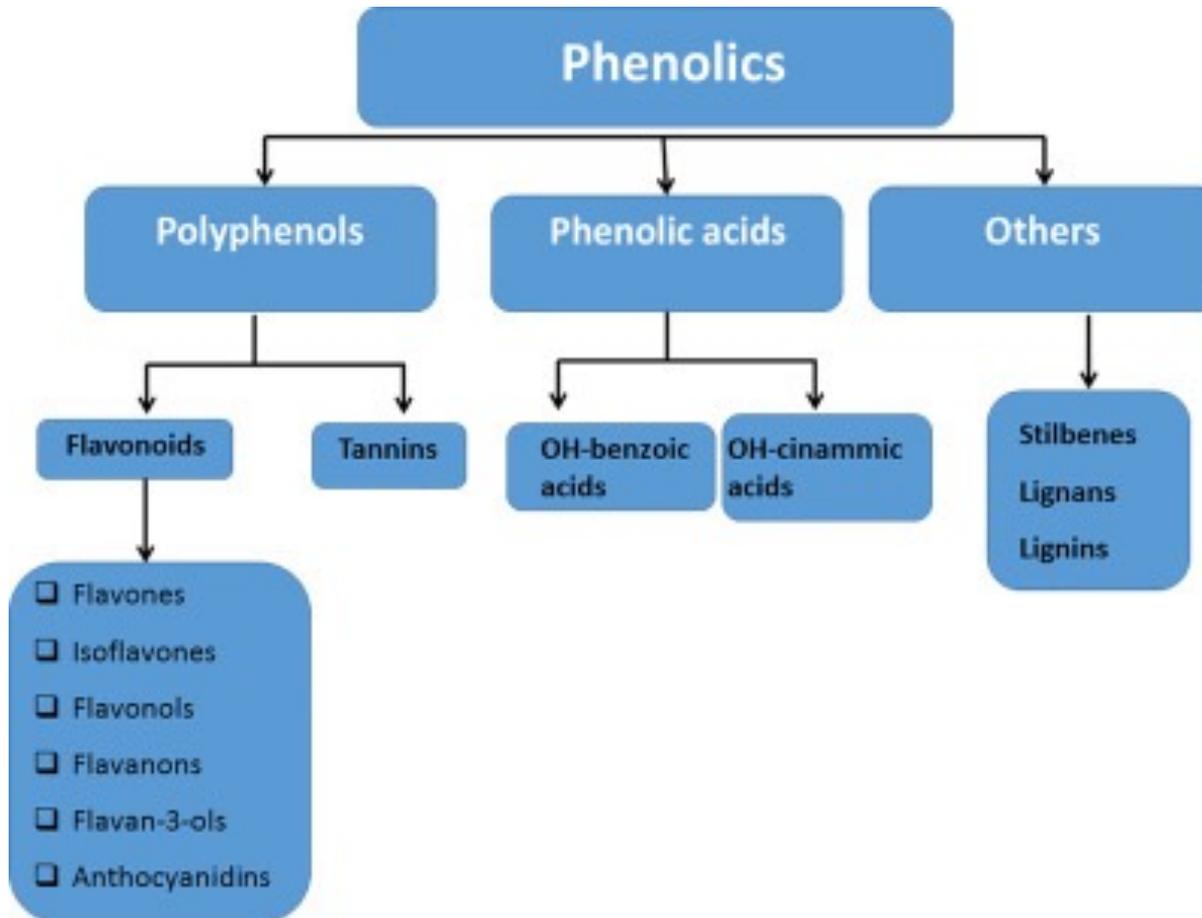
- phenolic and polyphenolic compounds
- flavonoids
- terpenoids
- nitrogen-containing alkaloids
- sulfur-containing compounds

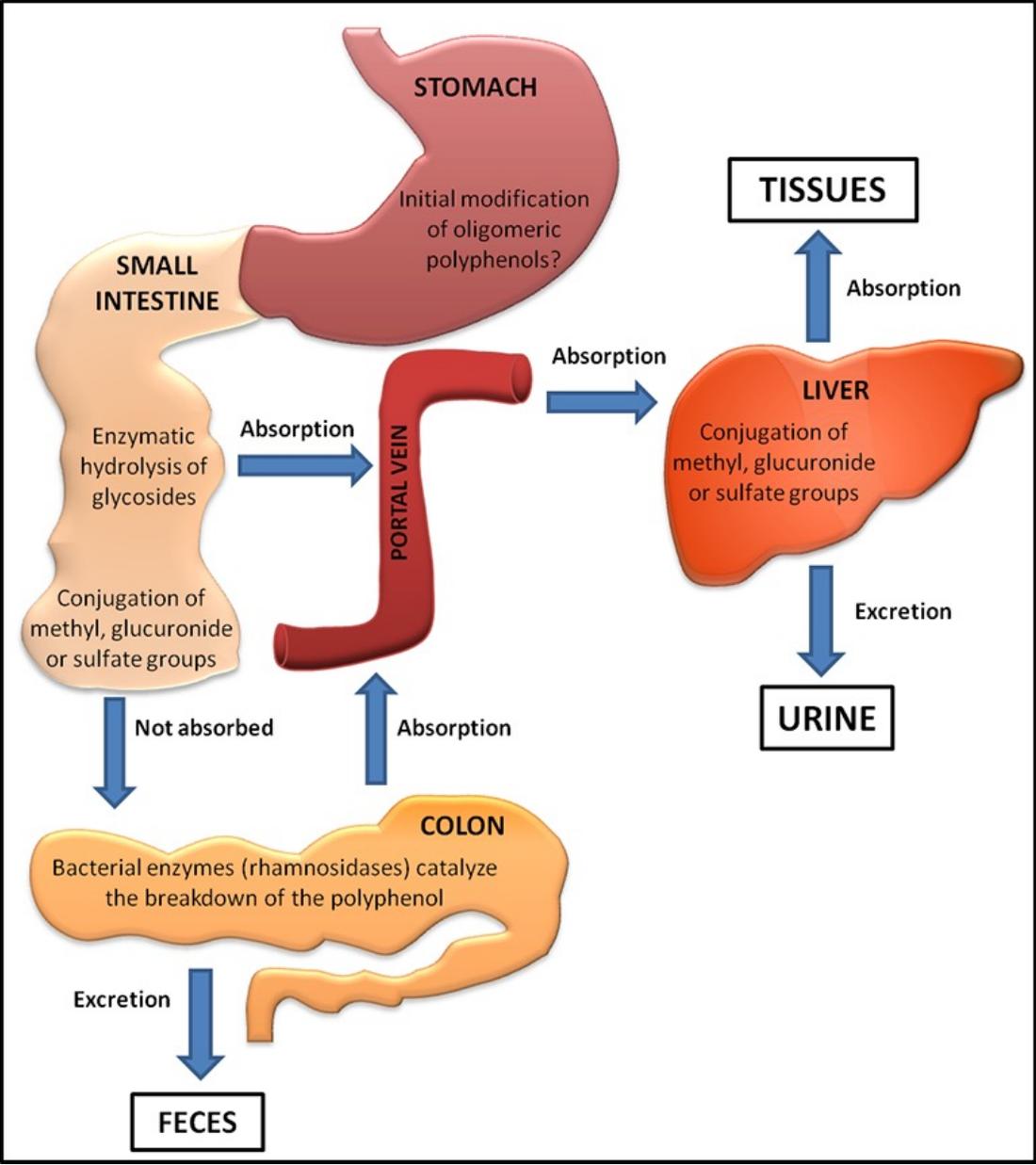
Λειτουργούν σαν σηματοδοτικά μόρια, για προσέλκυση εντόμων ή ζώων, προστατεύουν απο οξείδωση και υπεριώδη ακτινοβολία, προστατεύουν απο παθογόνα



Βιογενεση και μεταβολισμος φαινολών









Βιοδραστικές ενώσεις: flavonoids

- Η μεγαλύτερη ομάδα φαινολικών μεταβολιτών
- Βασική τους δράση είναι η αναστολή οξειδωσης.
- Έχουν:
 - αντι-ική
 - Αντι-διαβητική
 - Αντι-καρκινική δράση

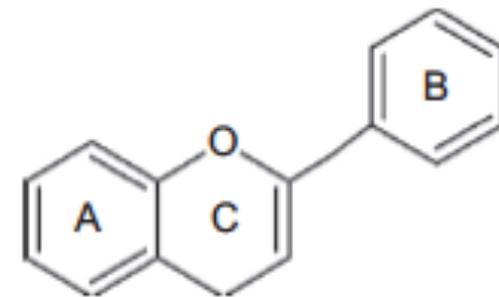


Figure 2.3
Structure of a flavonoid molecule.



Βιοδραστικές ενώσεις: terpenes

Αντι-οξειδωτική δράση

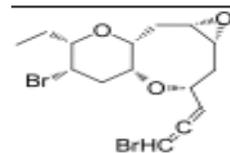
Αντι-φλεγμονώδη δράση

Κυτταροστατική δράση

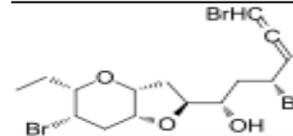
Activity of algae-derived terpenes

Compound NKUAMAR	IC50 (μM)
156	23.03 +/- 3.731
157	12.4 +/- 1.094
158	37.39 +/- 2.514
159	No action <62.5 μM
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

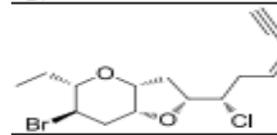
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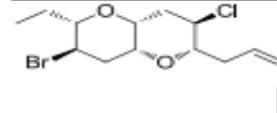
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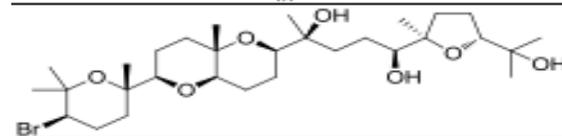
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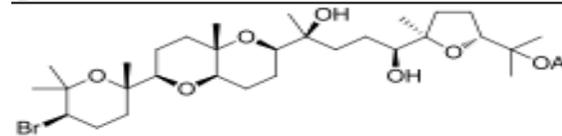
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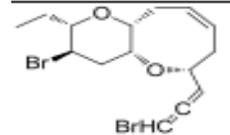
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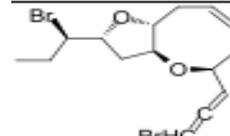
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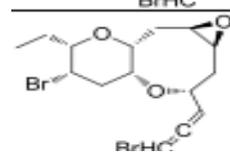
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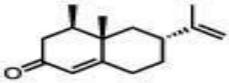
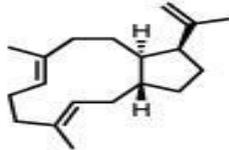
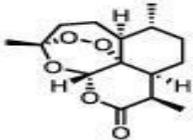
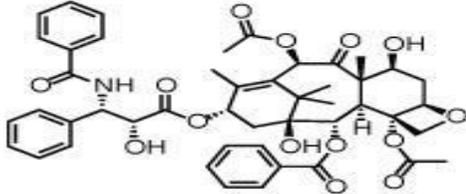
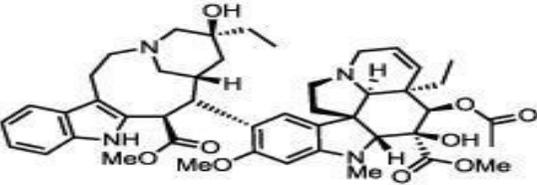


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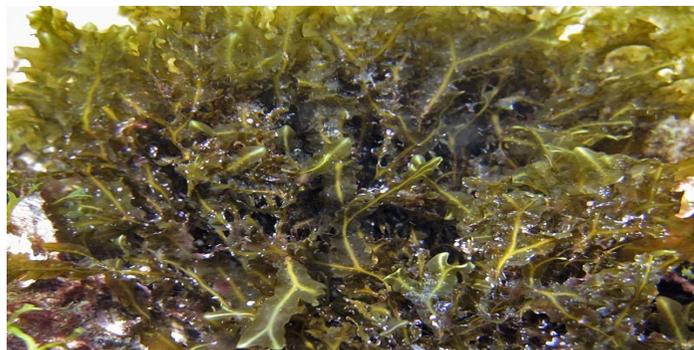
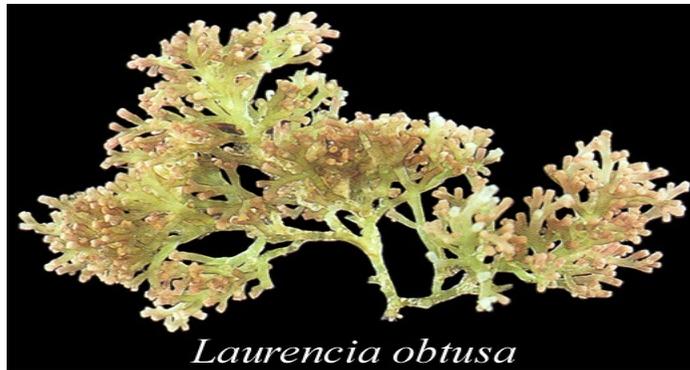


Natural source	Terpene	Structure	New method of production	
 <p>Grapefruit</p>	Nootkatone		Bioconversion of valencene using P450 in yeast	anti-insect aromatic
 <p>Brown algae</p>	Dolabellatriene		CotB2 derivative in <i>E. coli</i>	αντιμικροβιακό (πολυανθεκτικά)
 <p>Sweet wormwood</p>	Artemisinin		Yeast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

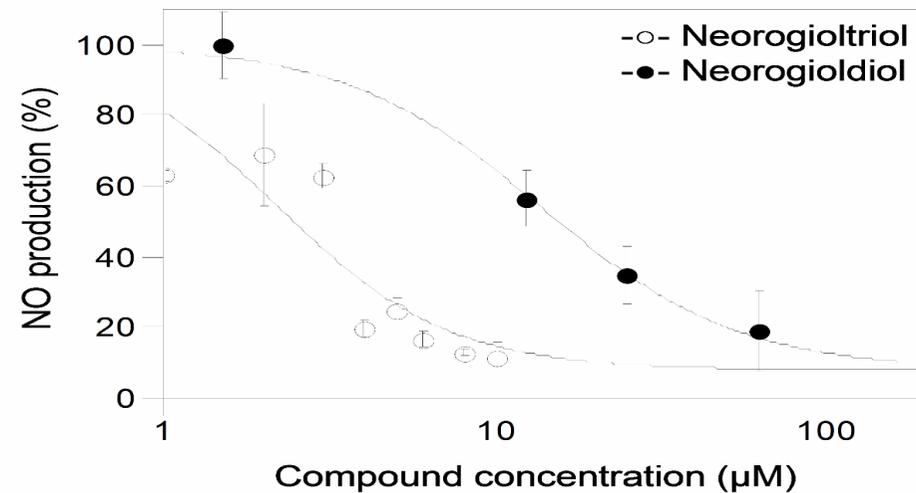
Cell cycle arrest	Apoptosis	Autophagy	Differentiation	Anti-angiogenesis	Anti-metastasis	Anti-MDR	Chemoprevention	Terpenoids	Mechanisms
								D-limonene	Inhibition of HMG-CoA reductase and CoA synthesis, etc.
								Cantharidin	Inhibition of serine/threonine PP1 and PP2A, etc.
								Artemisinin and 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-1 α , etc.
								Andrographolide	Inhibition of NF- κ B, JAK-STAT, PI3K, HSP90 and MMPs, etc.
								Oridonin	Downregulation of AP-1 and inhibition of NF- κ B 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- κ B, etc.
								Lycopene	Scavengers of ROS, inhibition of MMP2 and u-PA, etc.



Example: anti-inflammatory actions of terpenes from algae



Dictyopteris membranacea

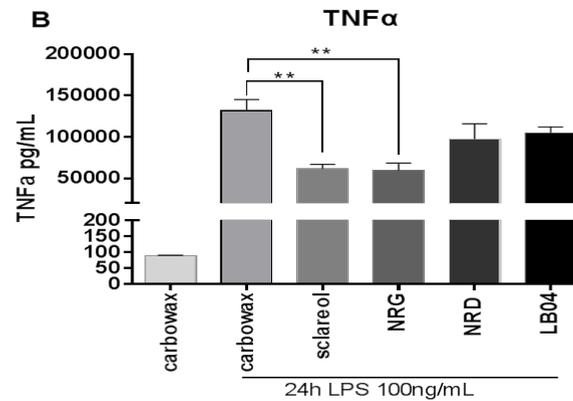
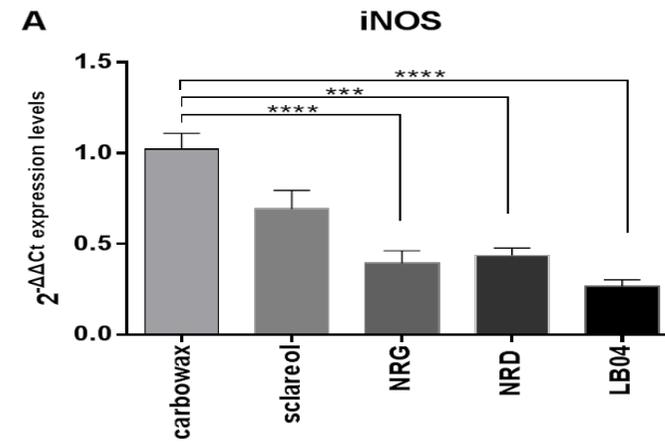
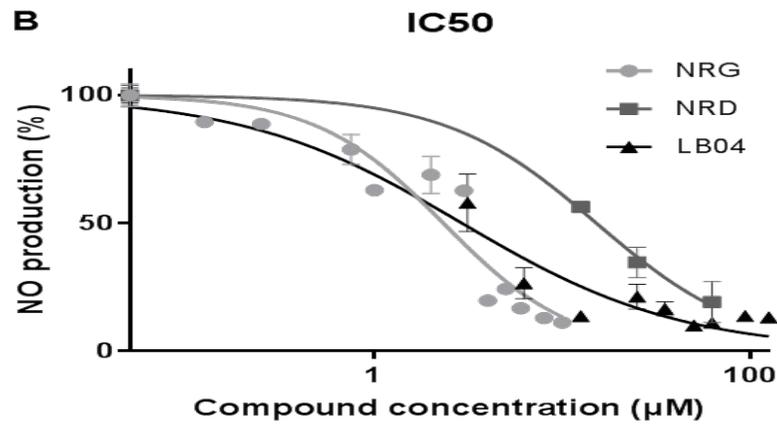


Compound	IC50
NRG	2.24 ± 2.29 µM
NRD	13.77 ± 2.81 µM

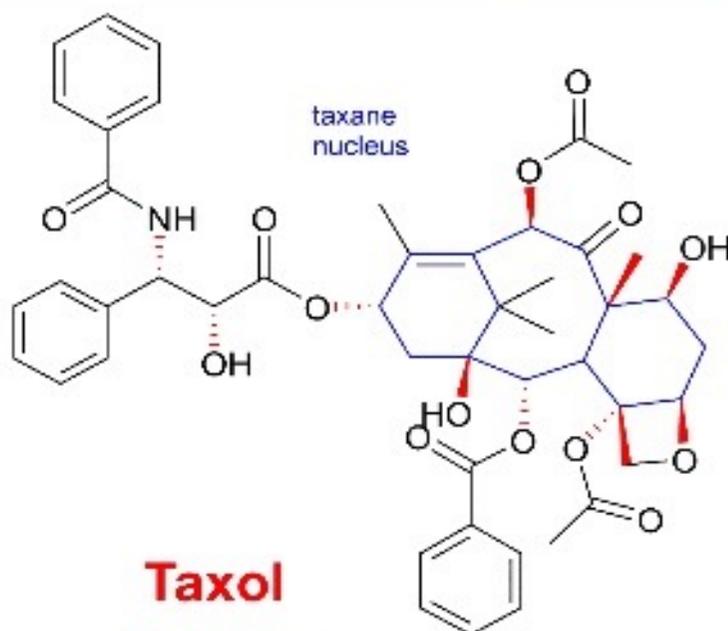
Daskalaki et al, Supported by EU and Greek National funds



Βιοδραστικότητα τερπενίων σαν αντιφλεγμονώδεις παράγοντες



Anticancer drugs: Taxol (Paclitaxel)

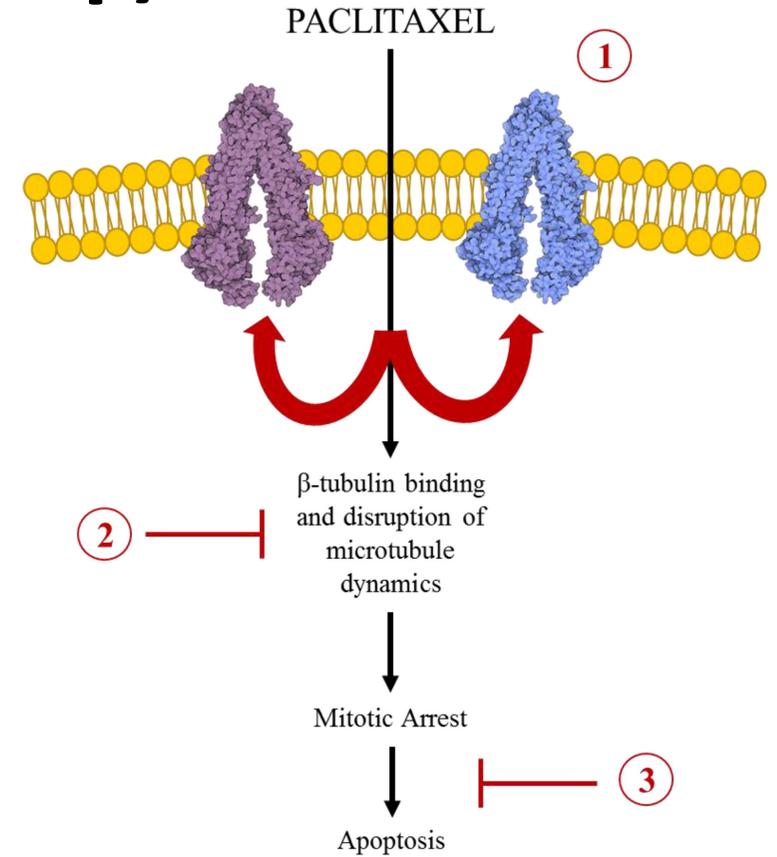
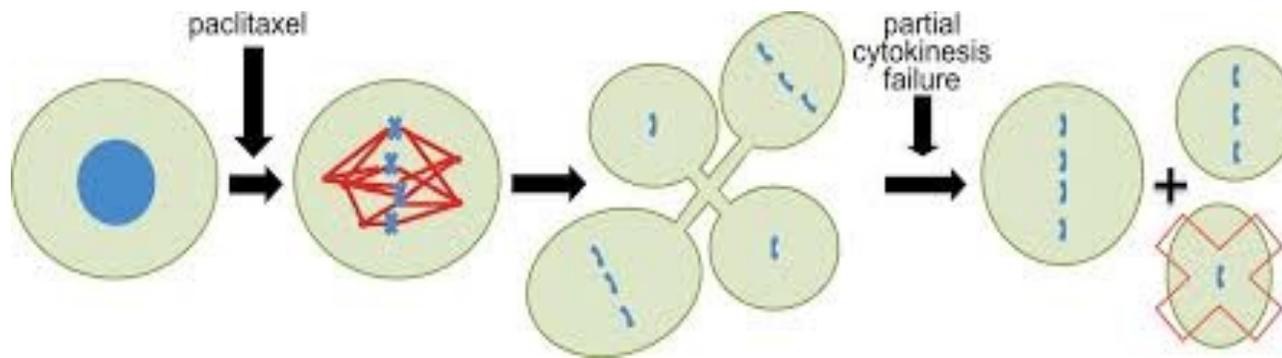


(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12b*S*)-9-(((2*R*,3*S*)-3-benzamido-2-hydroxy-3-phenylpropanoyl)oxy)-12-(benzoyloxy)-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-3,4,4a,5,6,9,10,11,12,12a-decahydro-1*H*-7,11-methanocyclodeca[3,4]benzo[1,2-*b*]oxete-6,12b(2a*H*)-diyl diacetate

- **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

<i>Development stage</i>	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



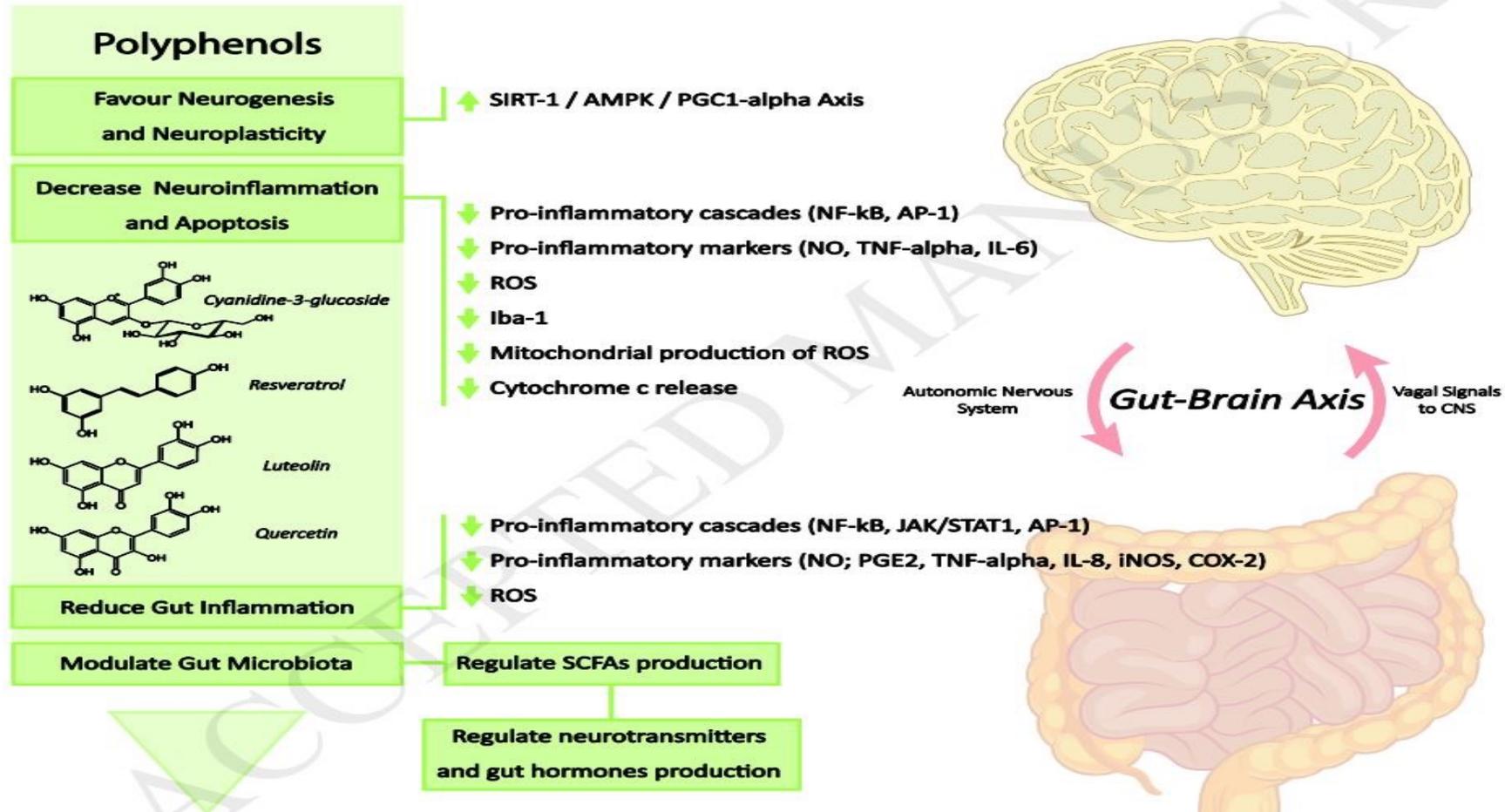
Therapeutic categories of natural product-derived drug development

Therapeutic categories of natural product-derived drugs at different stages of development

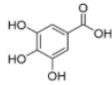
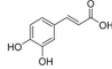
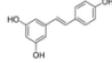
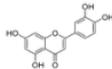
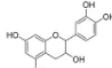
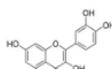
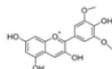
<i>Therapeutic area</i>	Preclinical	Phase I	Phase II	Phase III	Pre-registration	Total
Cancer	34	15	26	9	2	86
Anti-infective	25	4	7	2	2	40
Neuropharmacological	6	3	9	4	0	22
Cardiovascular/gastrointestinal	9	0	5	6	0	20
Inflammation	6	2	9	1	0	18
Metabolic	7	3	6	1	0	17
Skin	7	1	2	0	0	10
Hormonal	3	0	2	1	0	6
Immunosuppressant	2	2	0	2	0	6
Total	99	30	66	26	4	225



Polyphenolic compounds

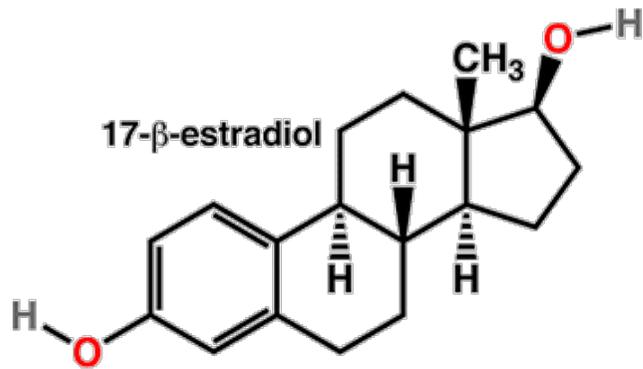


Polyphenols present in red wine

Group	Subclass	Main Representatives	Range in mg/L	Characteristic Structure
Non-flavonoid	Hydroxybenzoic acids	Gallic, ellagic, parahydroxybenzoic, protocatechuic, vanillic and 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

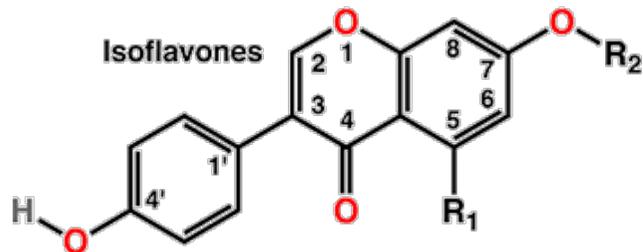


Phytoestrogens



What human estrogen looks like

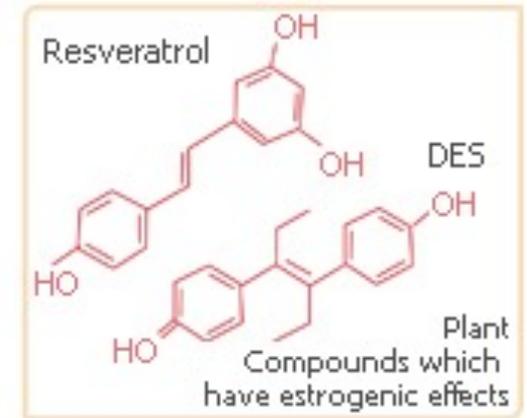
This is estradiol, one of the three forms of estrogen found in women (the other two are estrone and estriol)



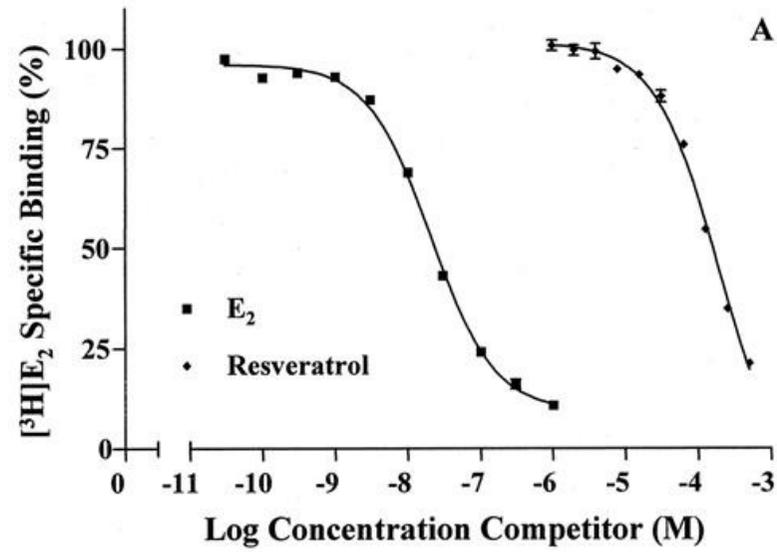
What plant estrogen looks like

Isoflavones are the most common type found in plants

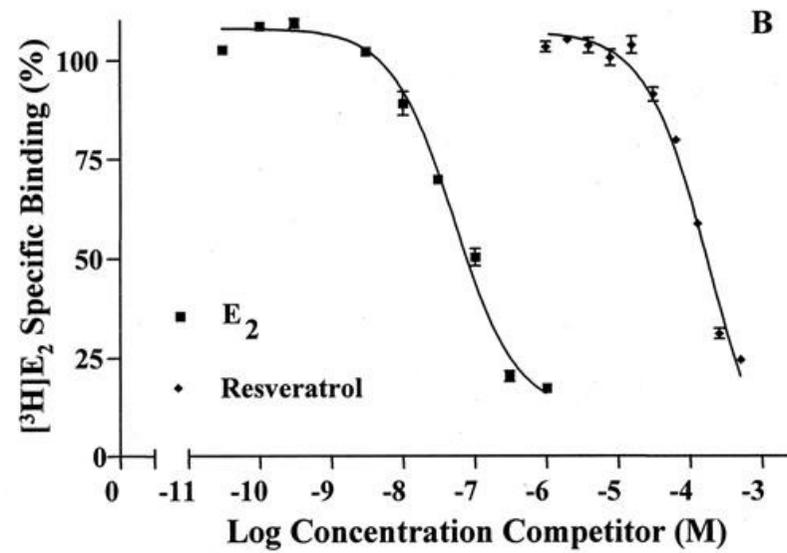
	R ₁	R ₂
daidzein	H	H
formononetin	H	CH ₃
genistein	OH	H
biochanin A	OH	CH ₃



ER α

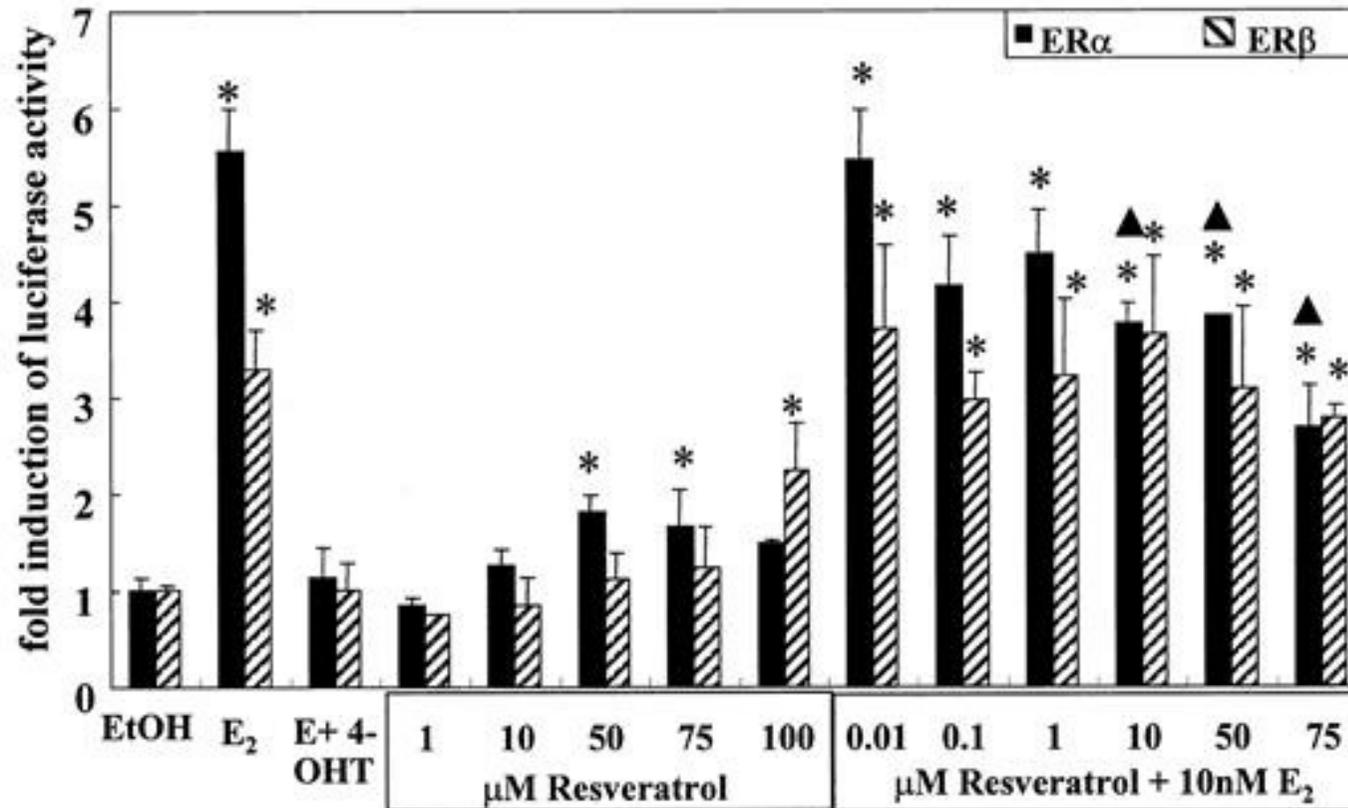


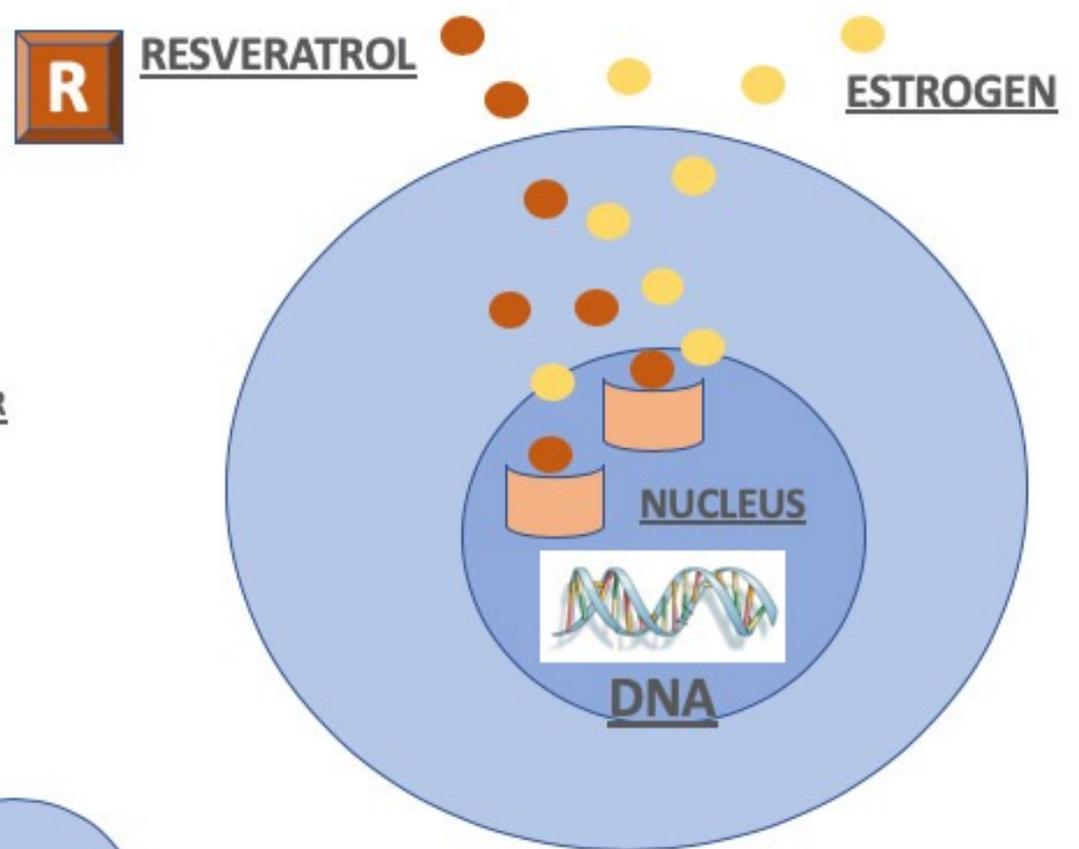
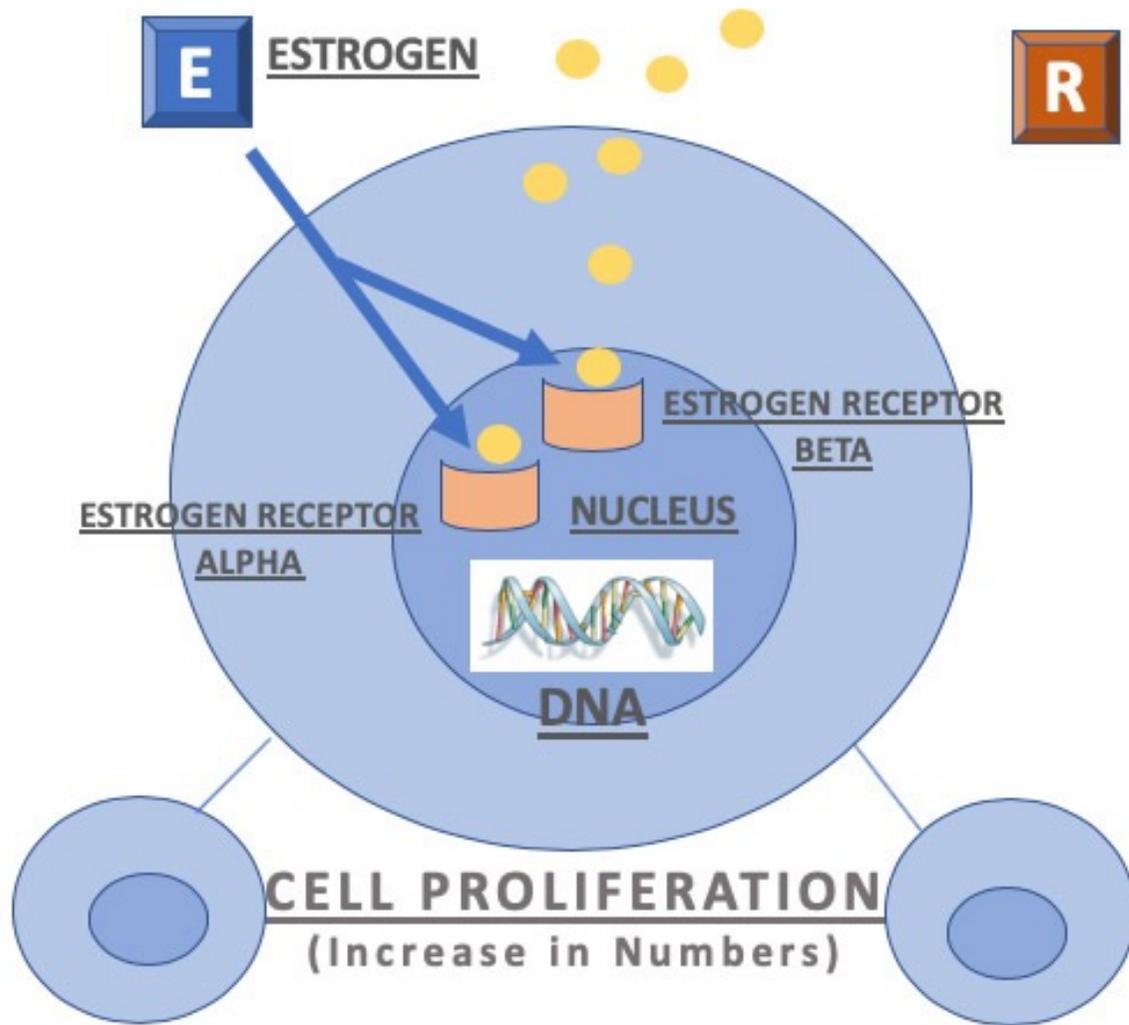
ER β





Resveratrol activates ER but antagonizes E2 action





Graphic: ResveratrolNews.com

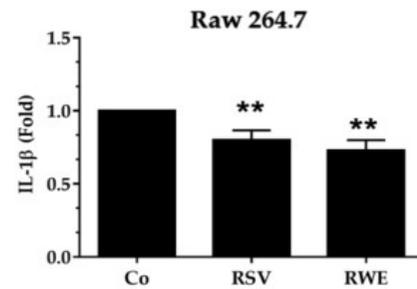
ESTROGEN RECEPTORS AND RESVERATROL



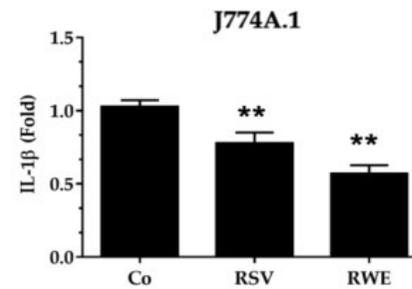
Effect of resveratrol on IL-1 secretion

RWE/RSV->LPS

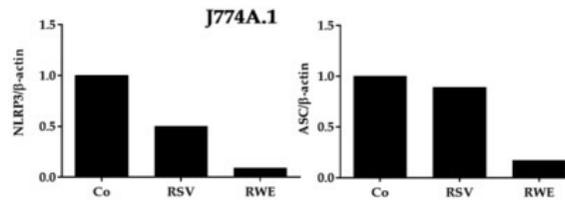
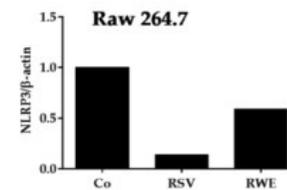
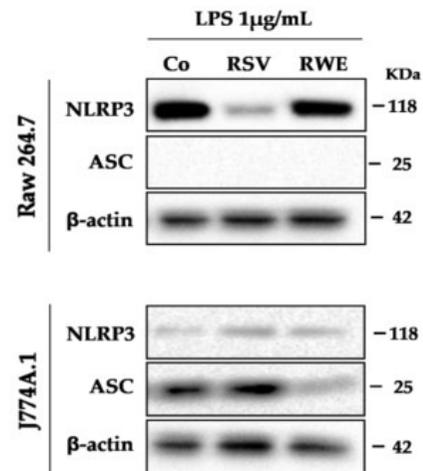
(a)



(b)

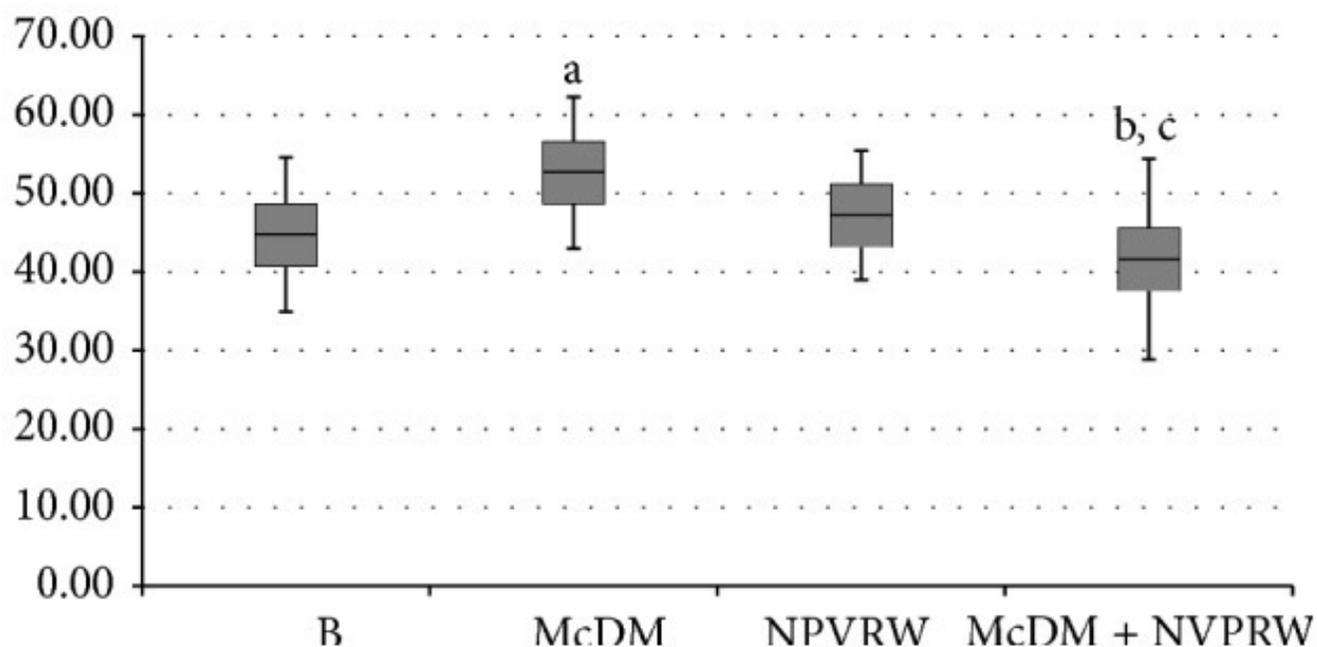


(c)





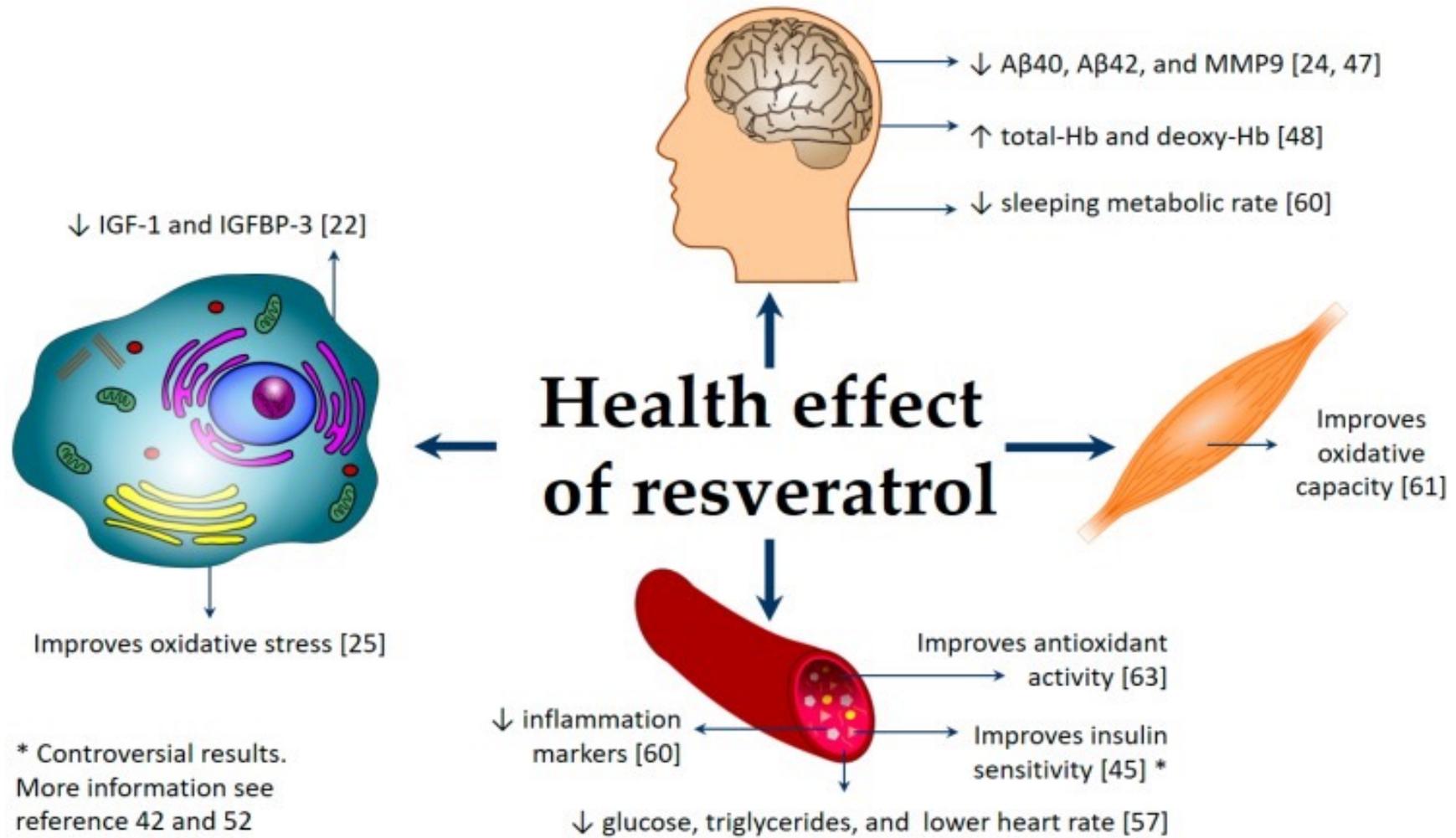
Changes in LDL Oxidative Status and Oxidative and Inflammatory Gene Expression After Red Wine Intake in Healthy People: A Randomized Trial



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 ($P > 0.05$).

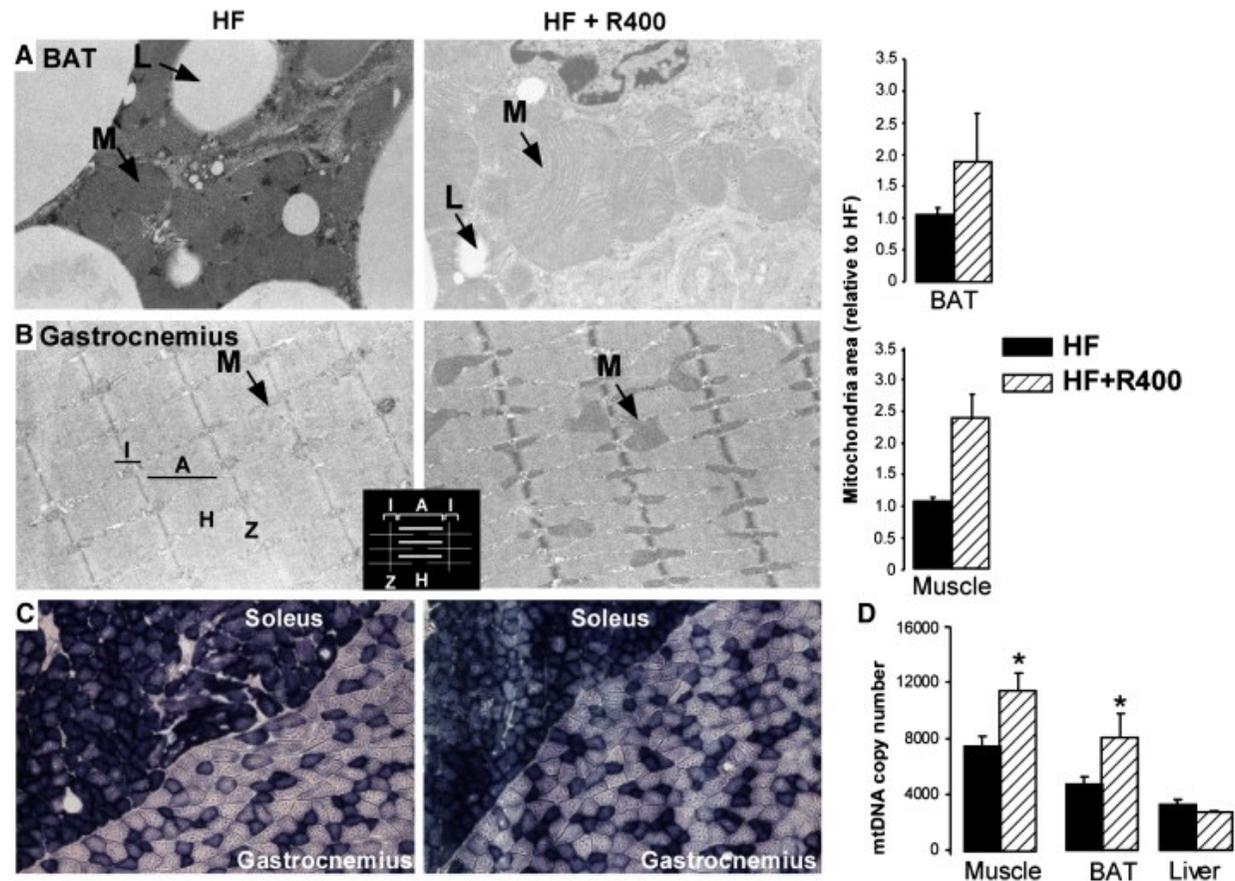
Total of 30 participants

Mediators Inflamm, 2015, 317348





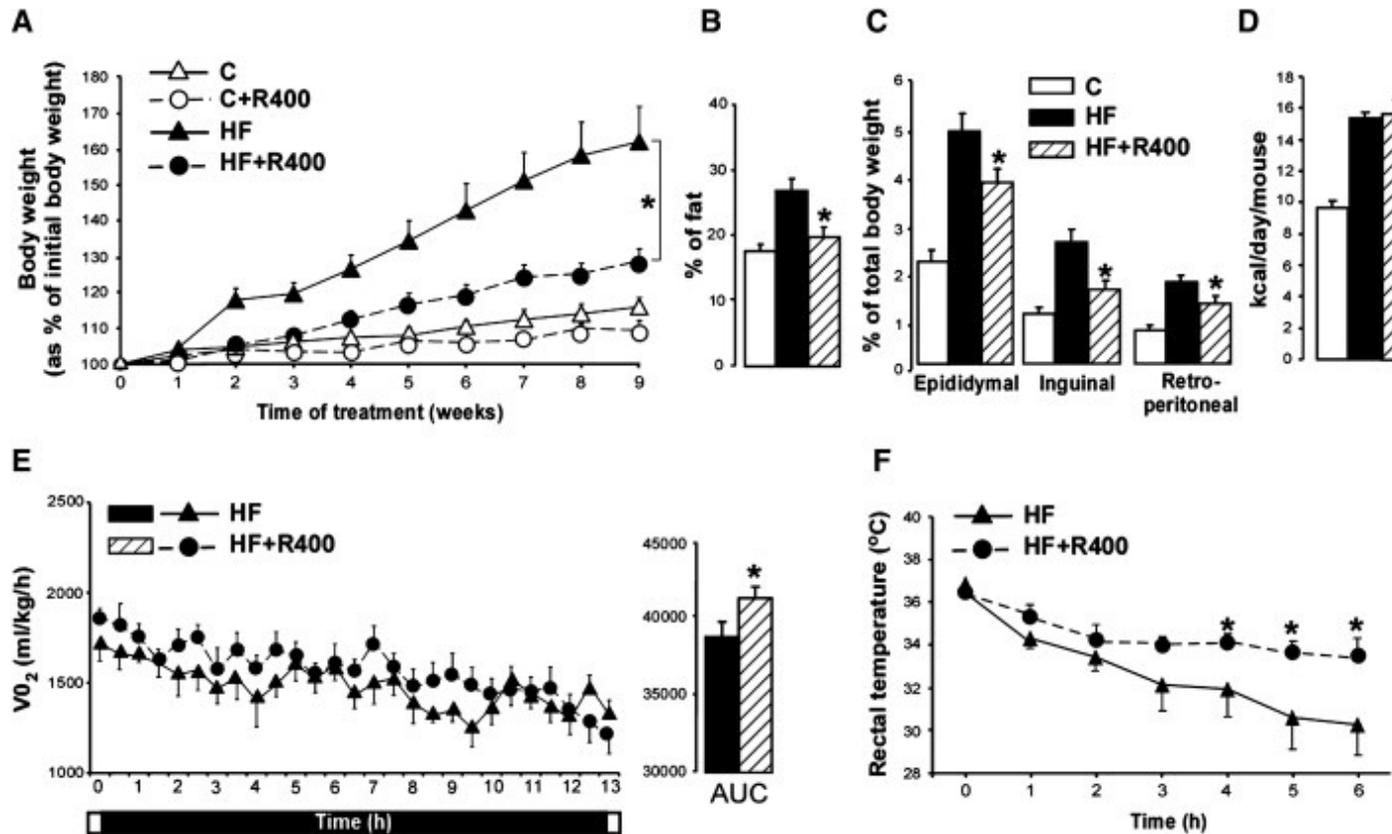
Resveratrol induces mitochondrial activity in BAT and muscle



Cell, 2006, 167:1109

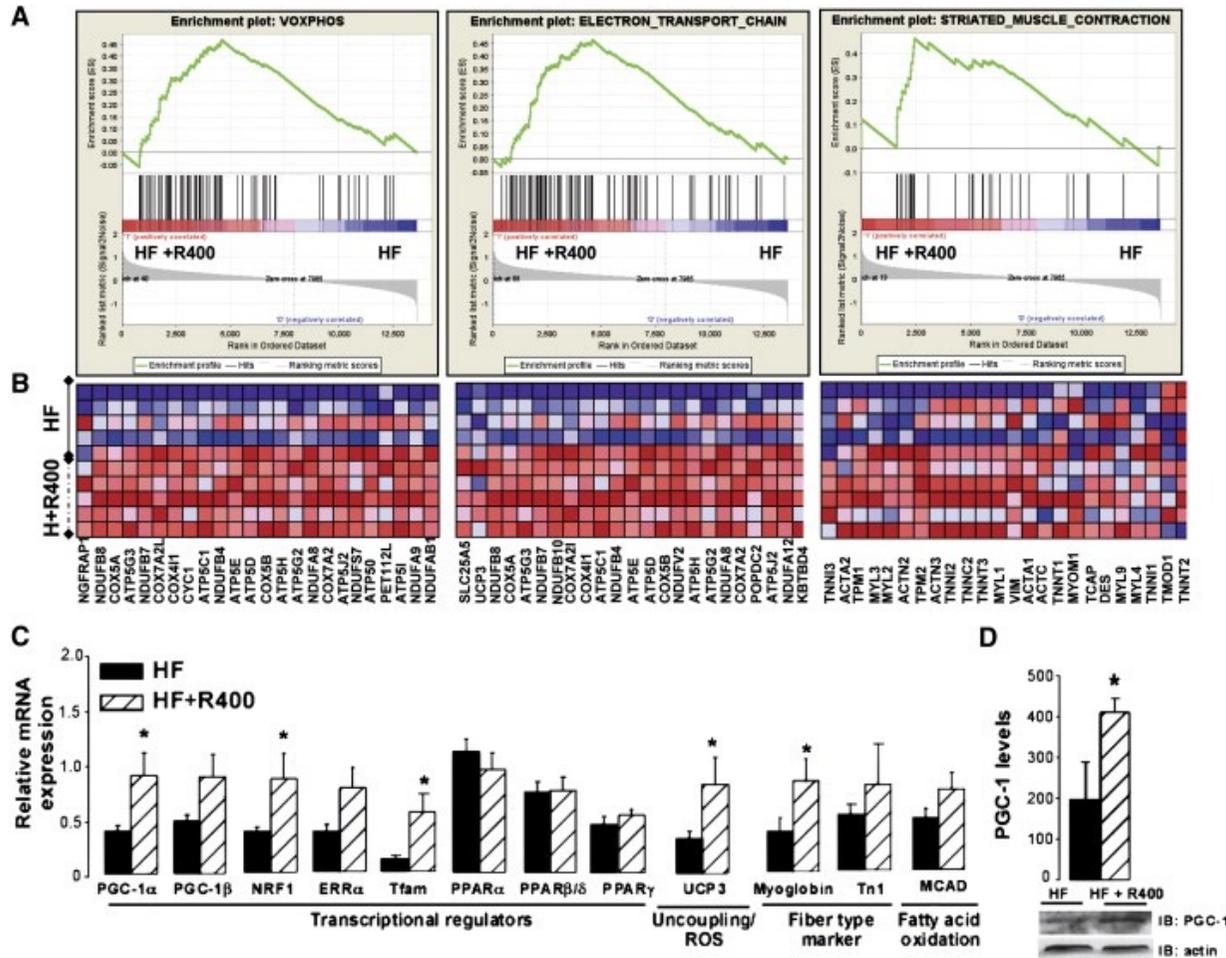


Resveratrol prevents diet-induced obesity in mice





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





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 risk** 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 <i>RASSF-1</i> 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

[npj Precision Oncology](#) volume 1,
Article number: 35 (2017)

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

Resveratrol: where we stand in therapy

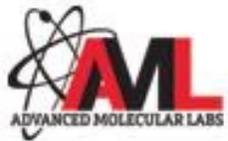
- Limited bioavailability
- Gastrointestinal side effects (over 1g/day)
- Toxicity, particularly nephrotoxicity

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

Reduced toxicity: Targeted nanoparticles (lipid based)



Phytoandrogens



**BEST
NATURAL
TESTOSTERONE
SUPPLEMENT**

BASED ON LATEST SCIENTIFIC RESEARCH



NEW!

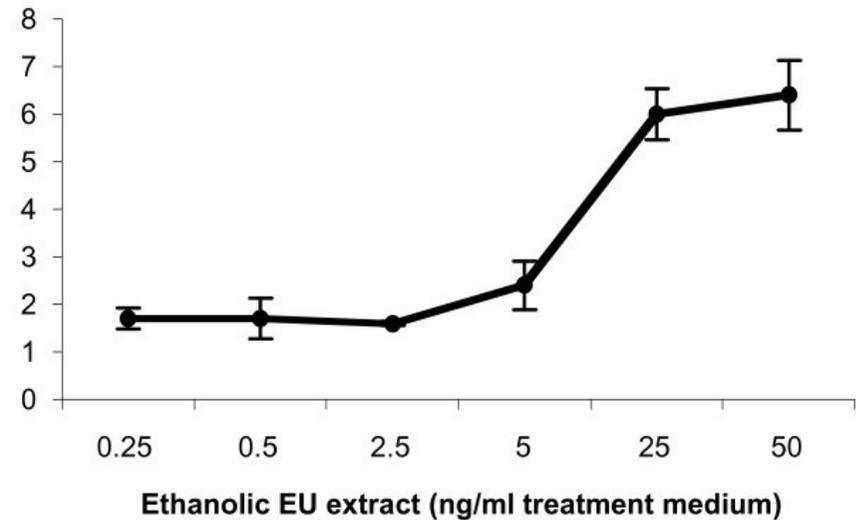




Eucommia ulmoides – Chinese herbs

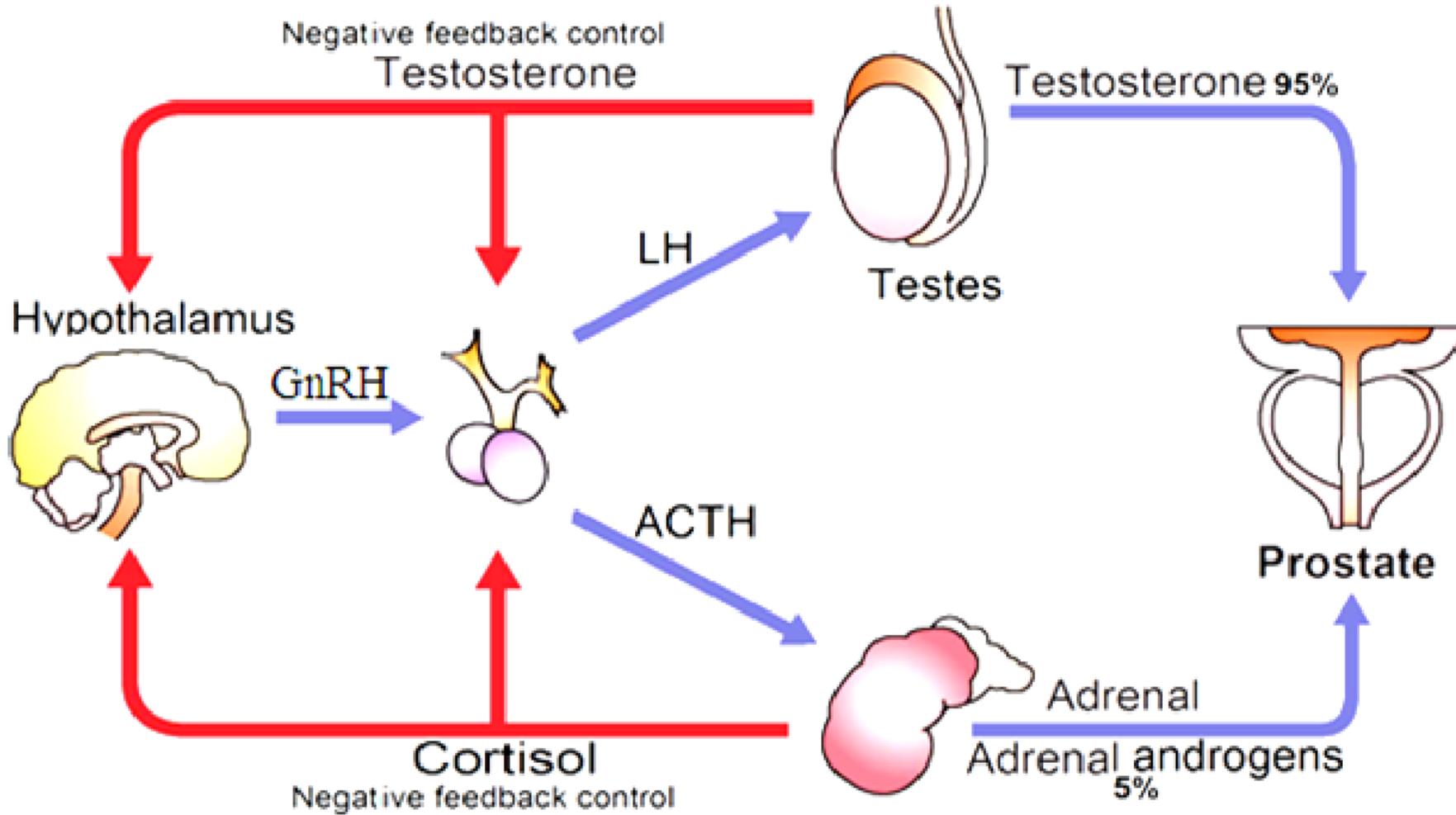


Binding to AR





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

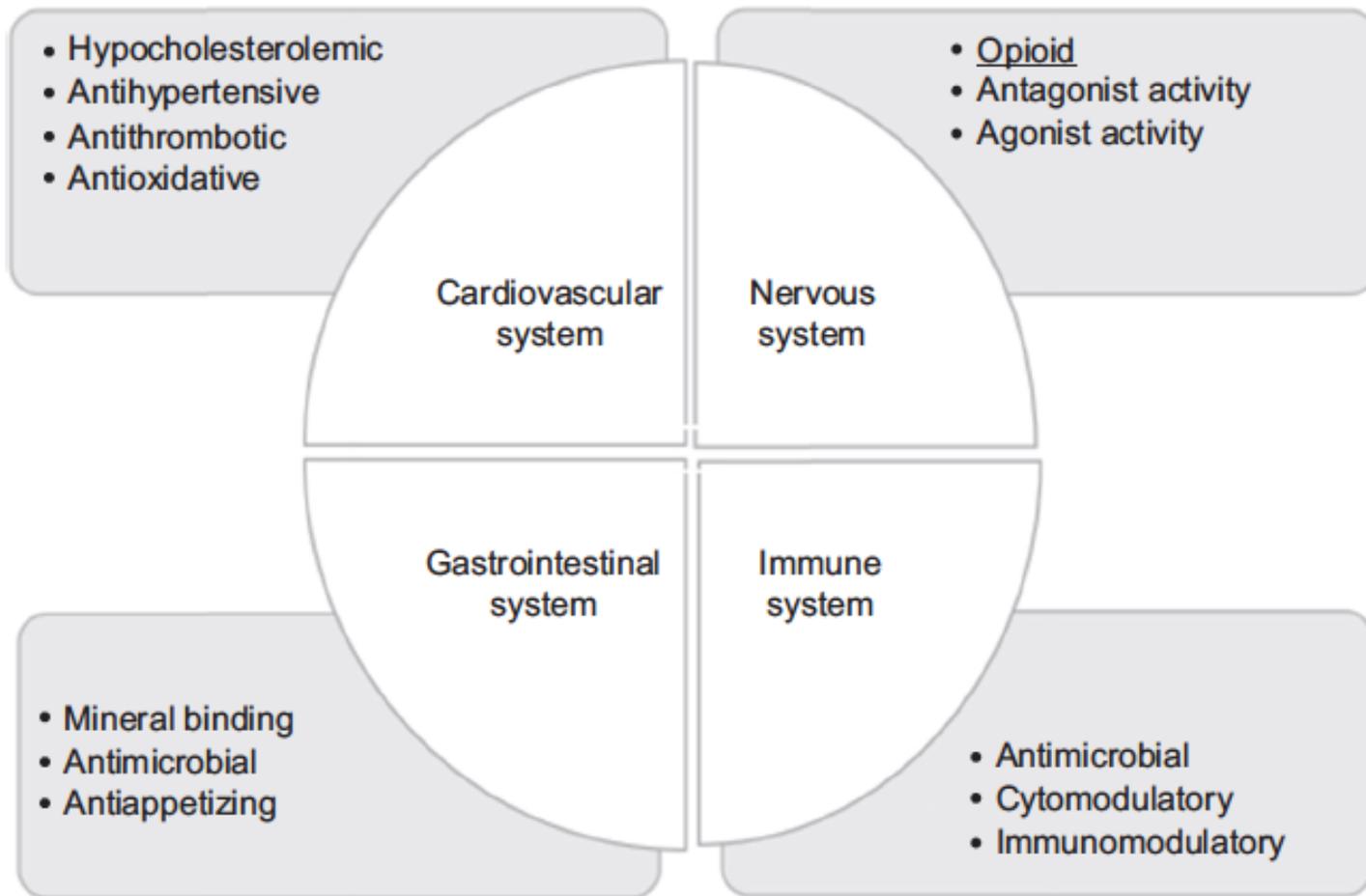


Δράσεις βιοδραστικών πεπτιδίων

- 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: CARLNCVPKGTSNTETCPCYASLHSCRKYG
- 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	α_{s2} -casein f(203–208)	Antimicrobial; antihypertensive; antioxidant	Atanasova and Ivanova ¹⁹
Bovine milk	<i>Lb. helveticus</i>	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) β -casein f(60–70)	Immunostimulatory, opioid agonist; ACE-inhibitory	Atanasova and Ivanova ¹⁹ ; Meisel ⁵⁹
Bovine milk	<i>Enterococcus faecalis</i> TH563 and <i>Lb. delbrueckii</i> ssp. <i>bulgaricus</i> 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	Neutrased	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 and Proleather 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.



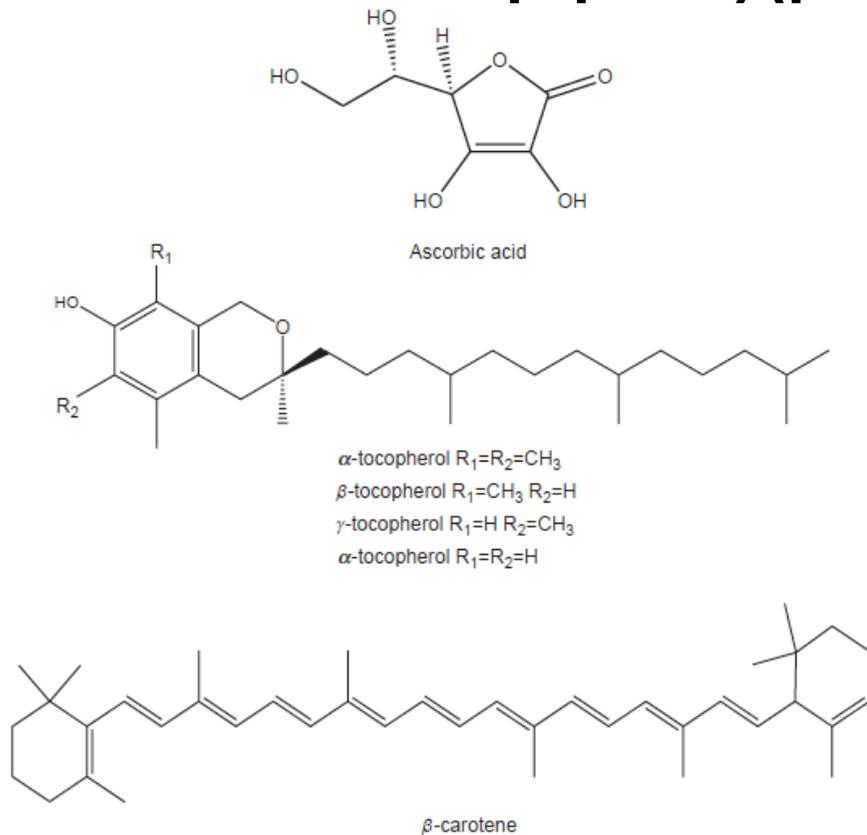
Βιοδραστικές ενώσεις σε θαλάσσιους οργανισμούς: φύκη

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

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



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



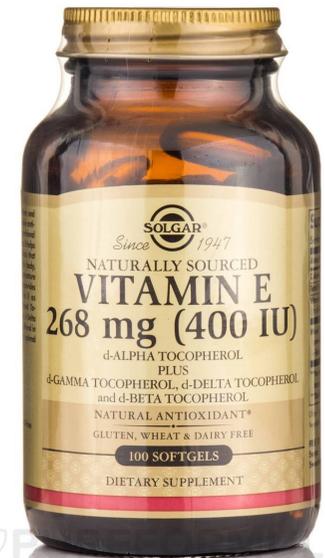
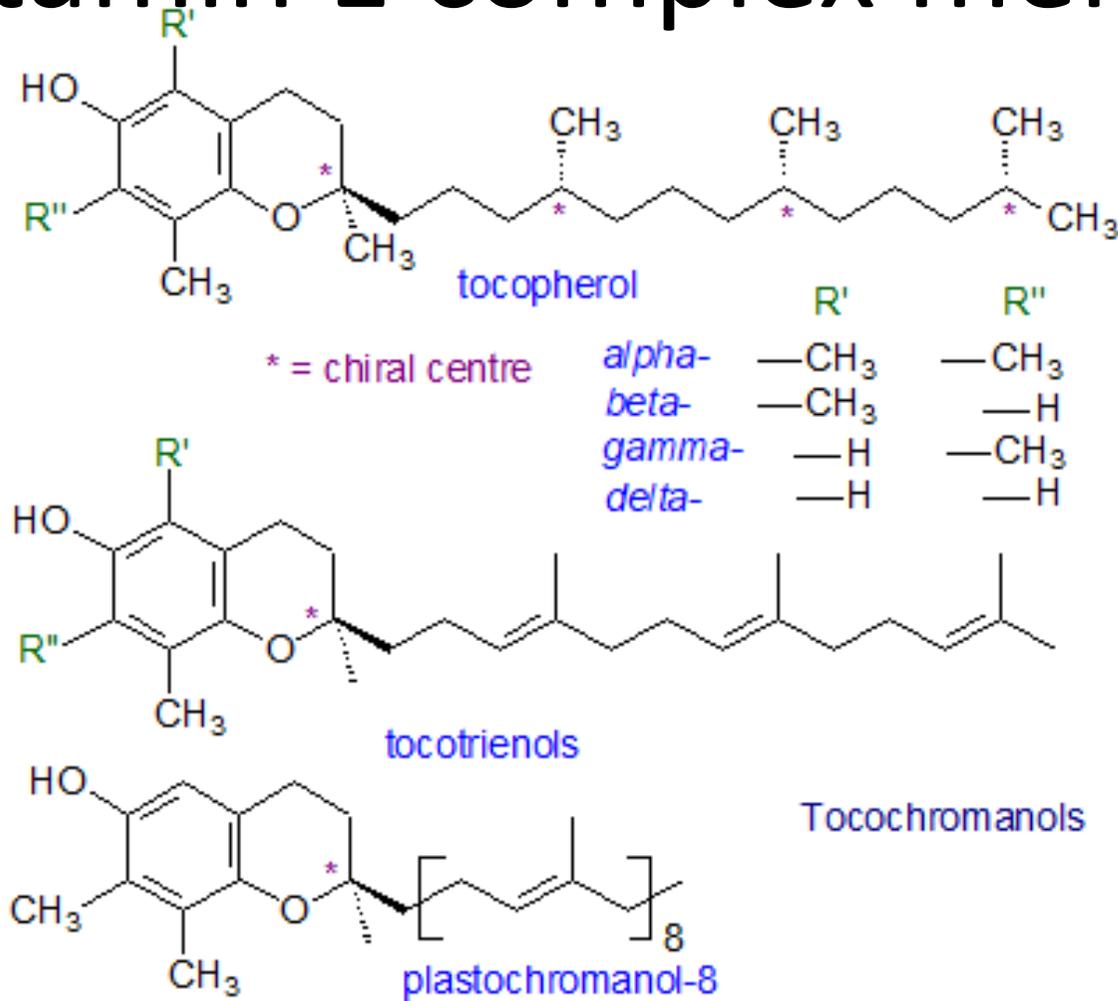
vitC: αντιοξειδωτική δράση
vitE: εμποδίζει οξείδωση λιπών
β καροτένη: αντιοξειδωτική δράση

Figure 1.1

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

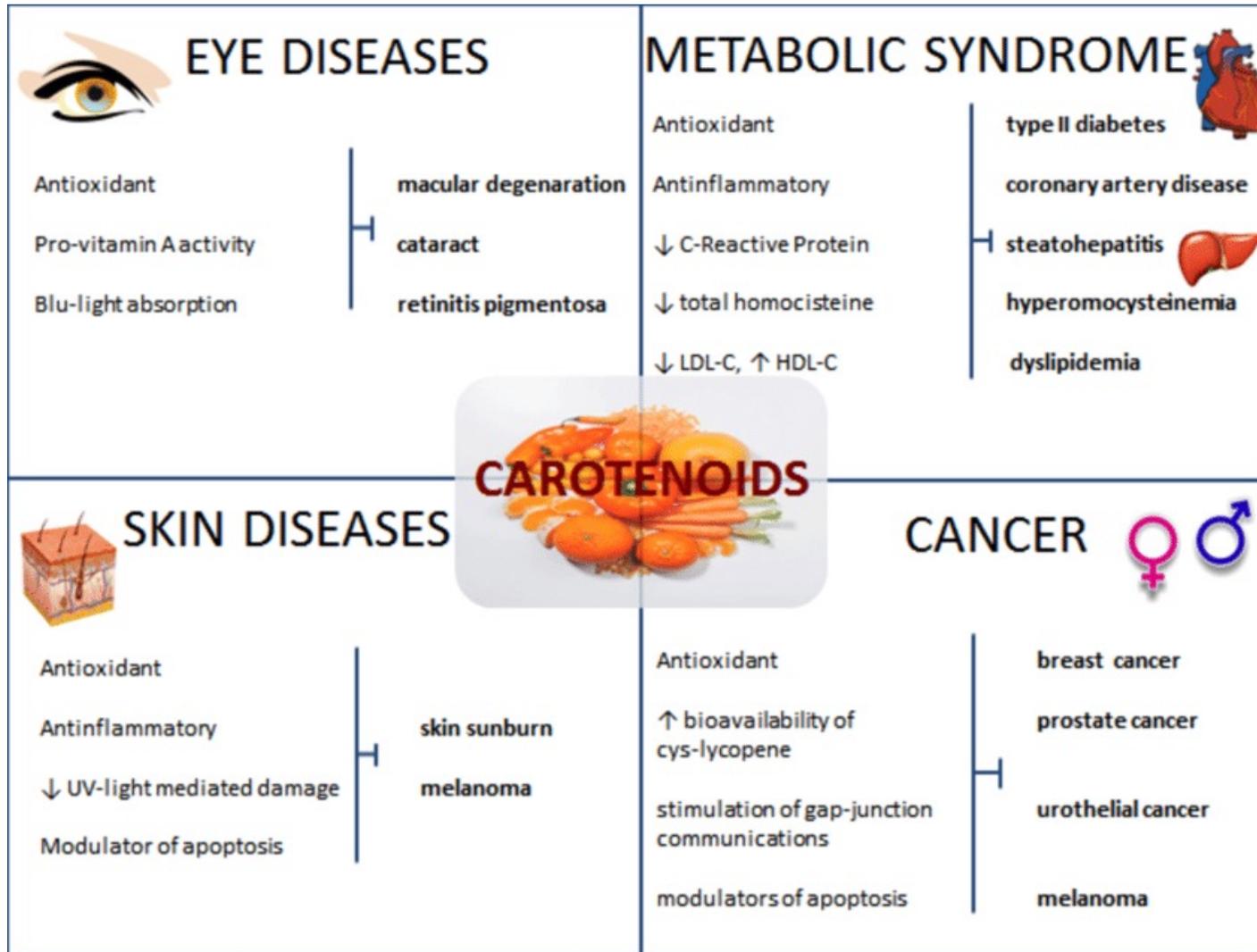


Vitamin E complex members



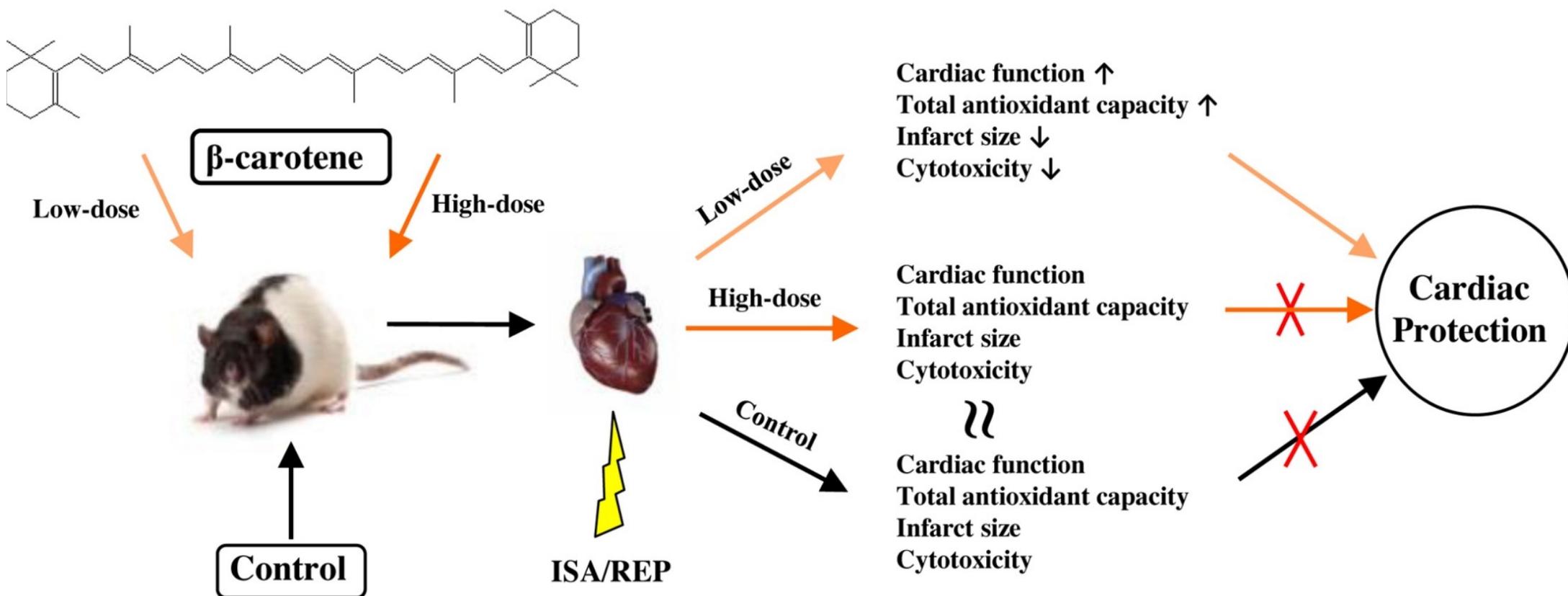


β -carotene (BC), a lipid-soluble tetraterpene precursor to vitamin A





Dose-dependent action of b-carotene in cardioprotection



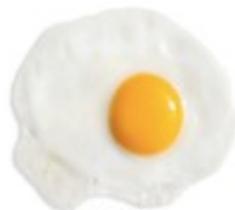


Vitamin D

- 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 (insufficiency): 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

^aMeasured from controls.

^bAs 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.

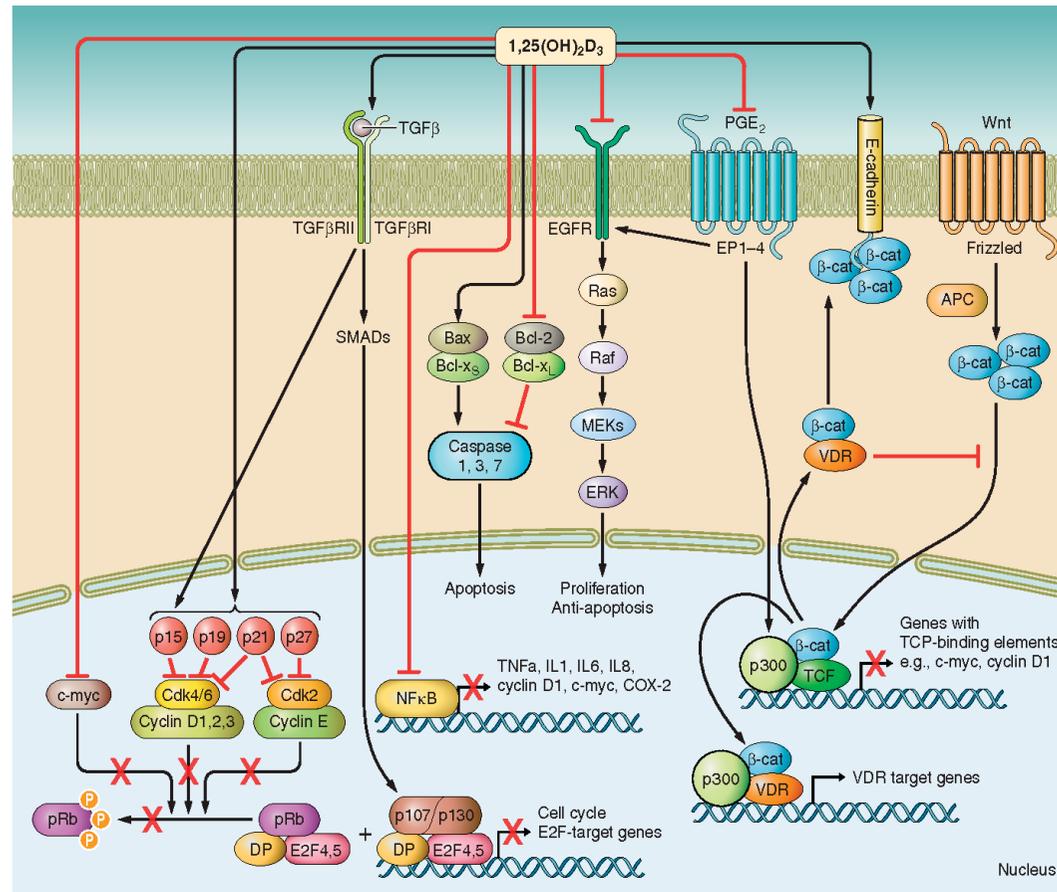
- Χορήγηση **2000 IU D3 / μέρα** κατά το πρώτο έτος της ζωής και παρακολούθηση του πληθυσμού αυτού κατά τα επόμενα 31 χρόνια
- Ο κίνδυνος εμφάνισης ΣΔ τύπου 1 μειωμένος κατά **80%**.
- Στα παιδιά με χαμηλά επίπεδα βιταμίνης D, ο κίνδυνος εμφάνισης διαβήτη ήταν **200%**.

Dietary vitamin D supplementation is associated with reduced risk of type 1 diabetes. Ensuring adequate vitamin 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.

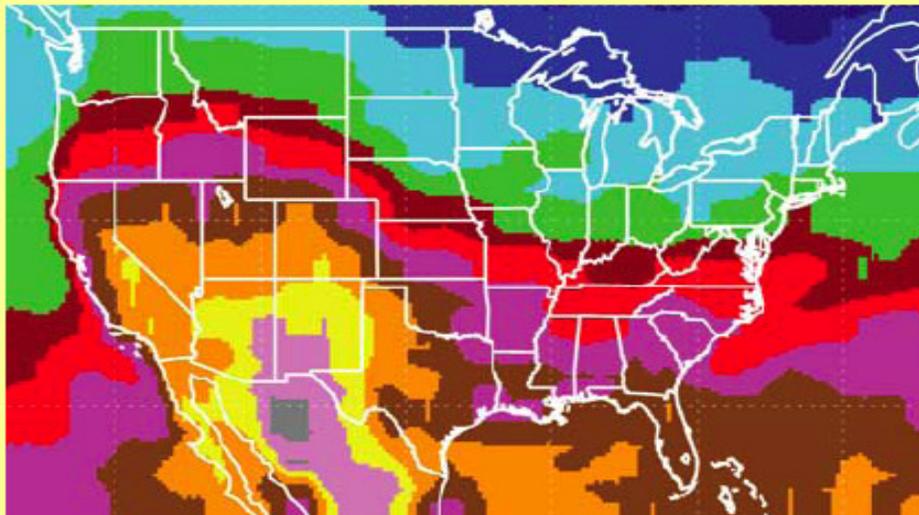


Η vitD σηματοδοτεί σε κυτταρα καρκίνου



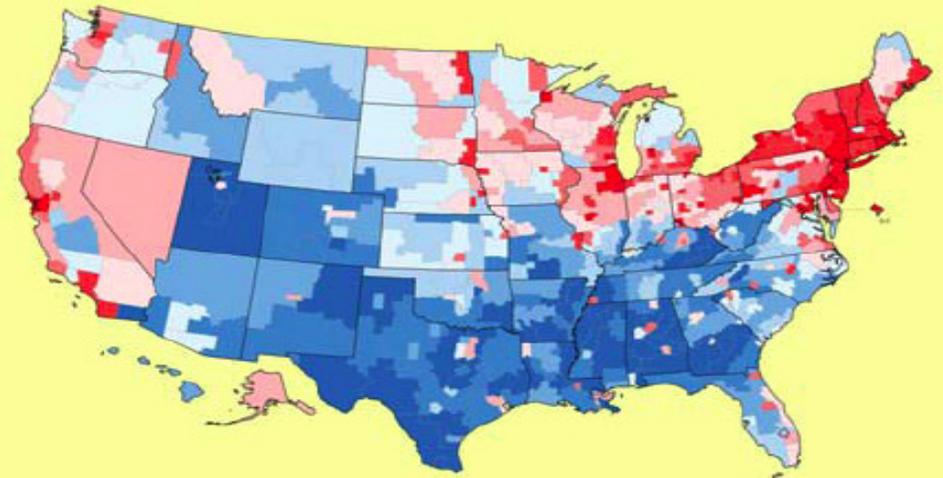


Επίπτωση καρκίνου μαστού και έκθεση σε ηλιοφάνεια

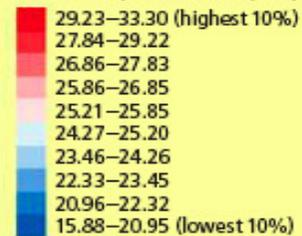


0.0 1.5 3.0 4.5 6.0 7.5 9.0 10.5 12.0

UVB Dose (kJ/m^2), July 1992



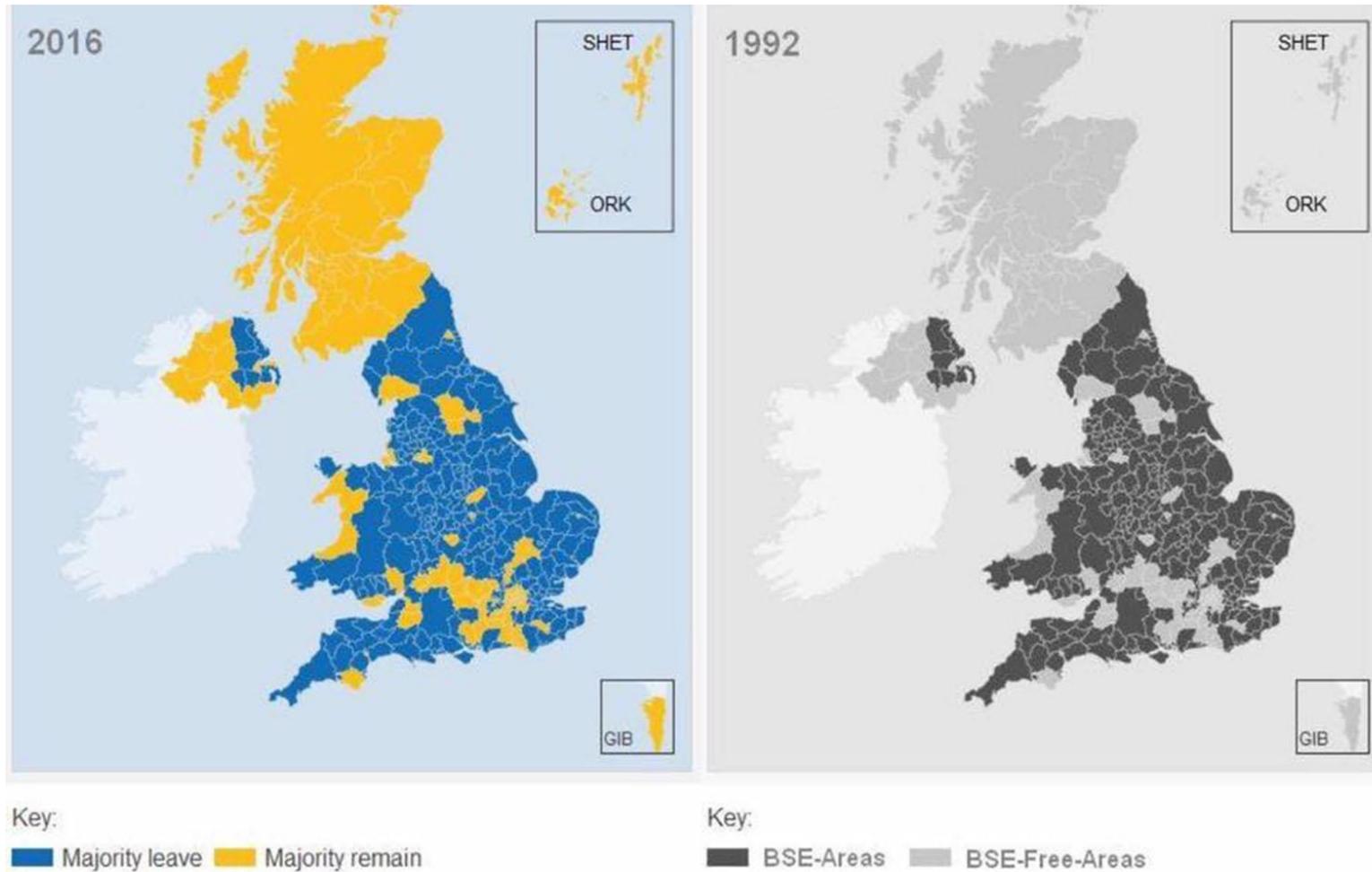
Cases per 100,000 people



Breast Cancer Mortality among
White Females, 1970–1994

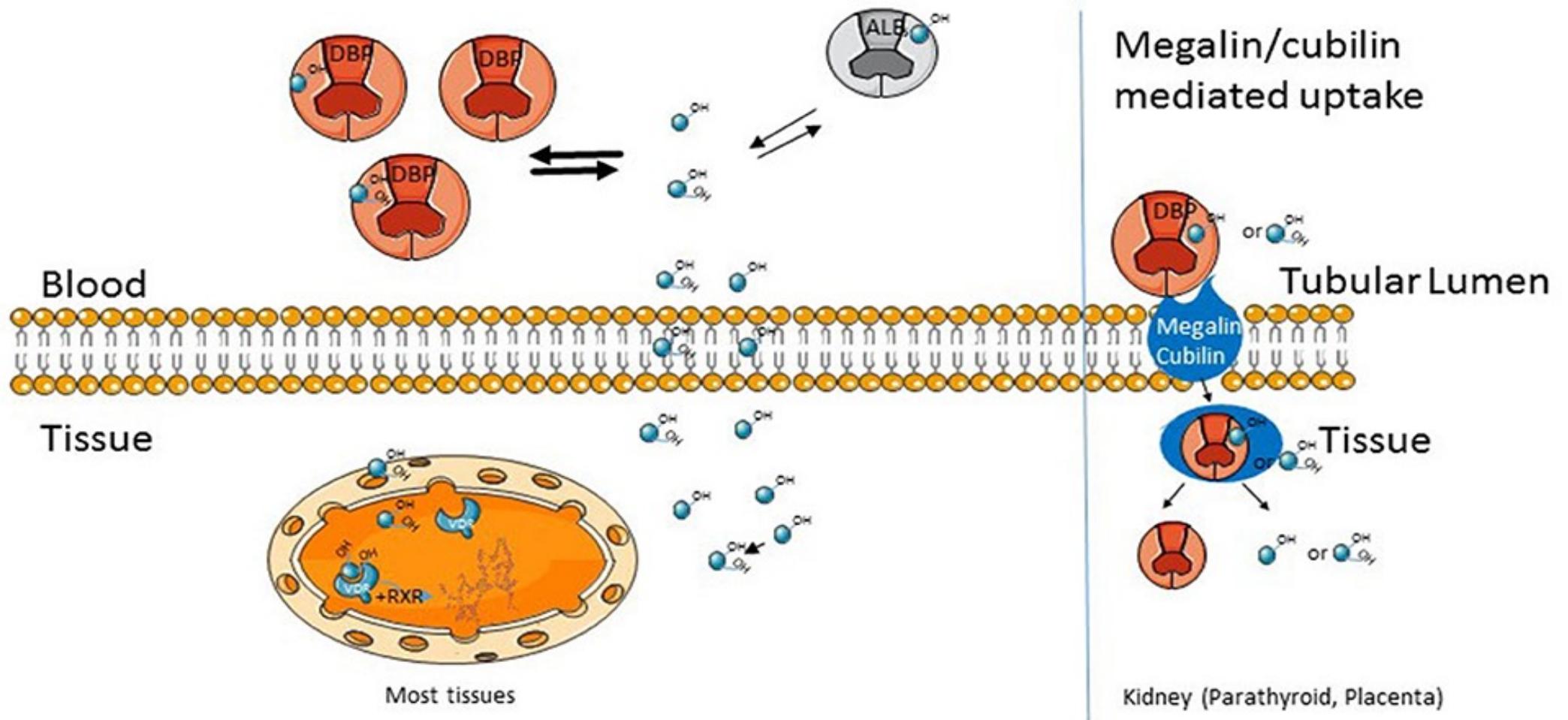


Mad cow disease and brexit



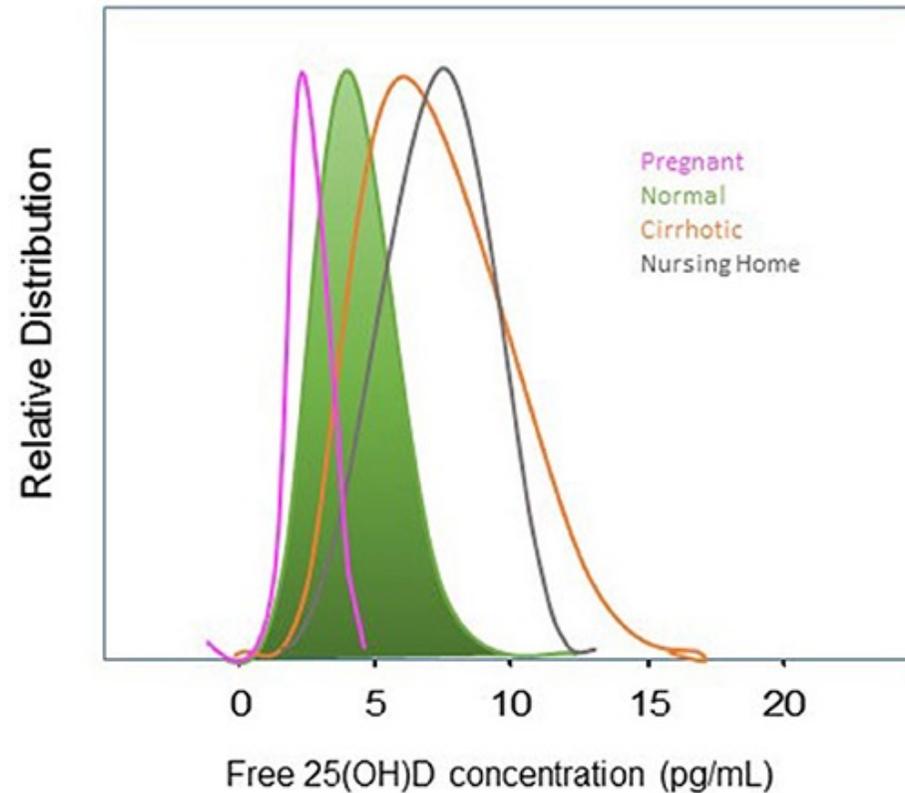


VitD circulates free and bound on vitD-BP

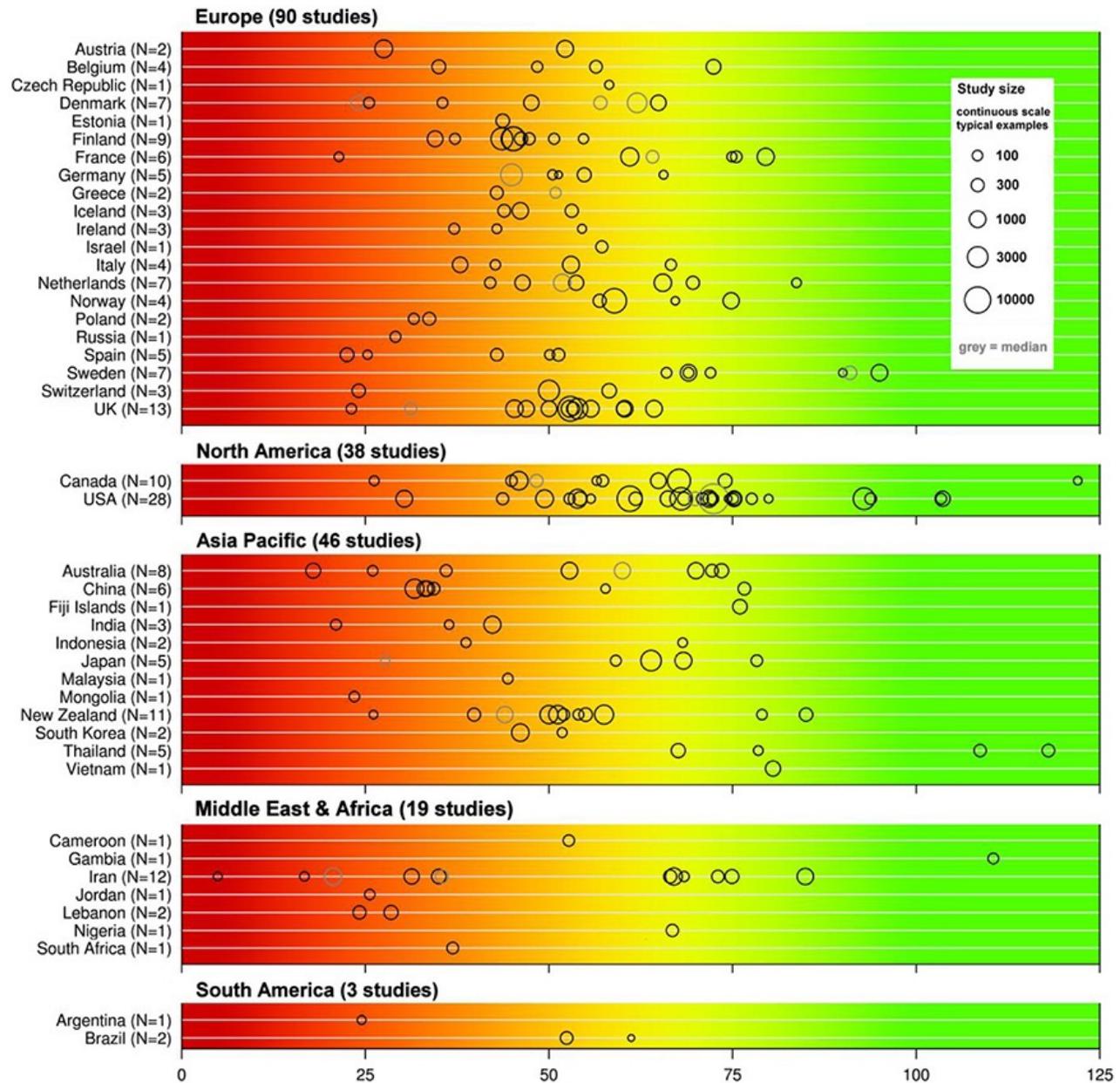




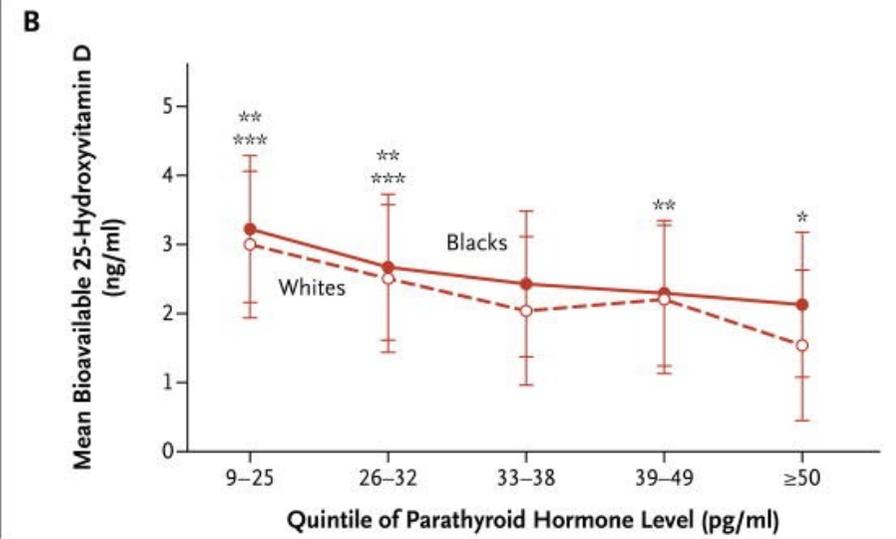
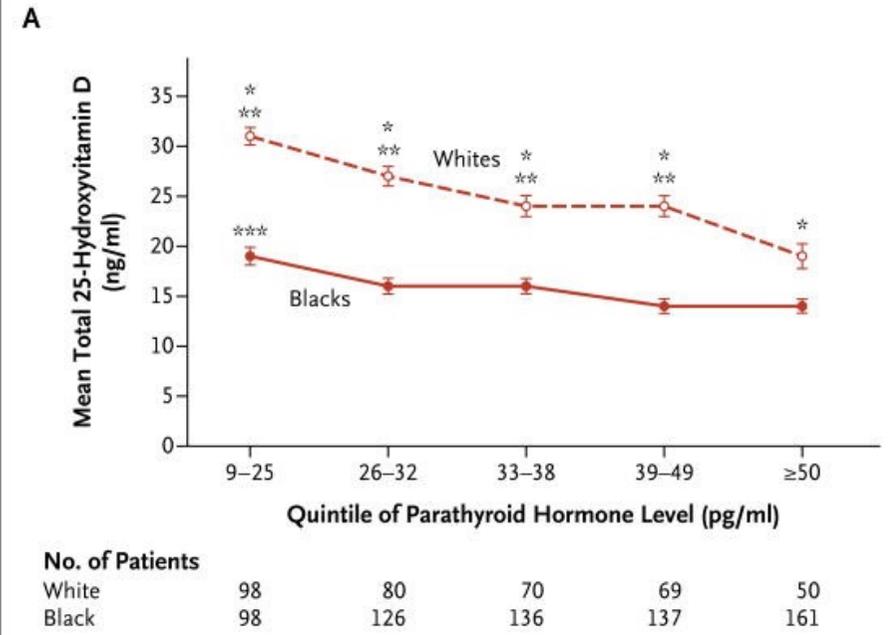
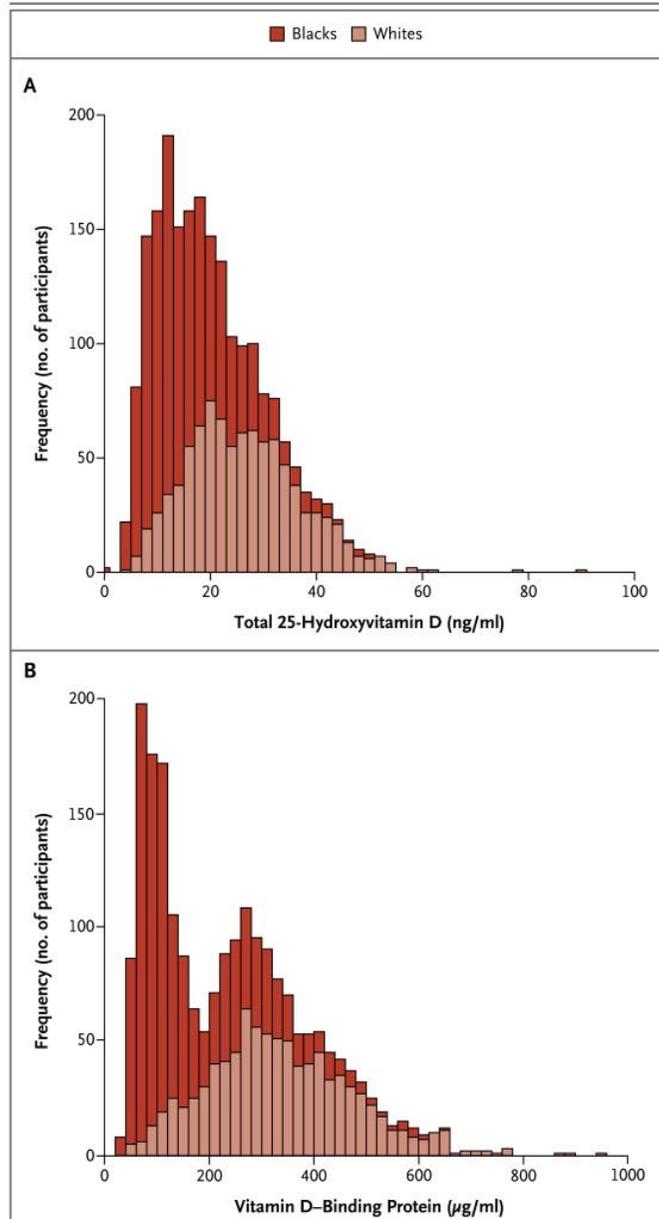
Distribution of free 25(OH)D in Adults and Selected Patient Groups



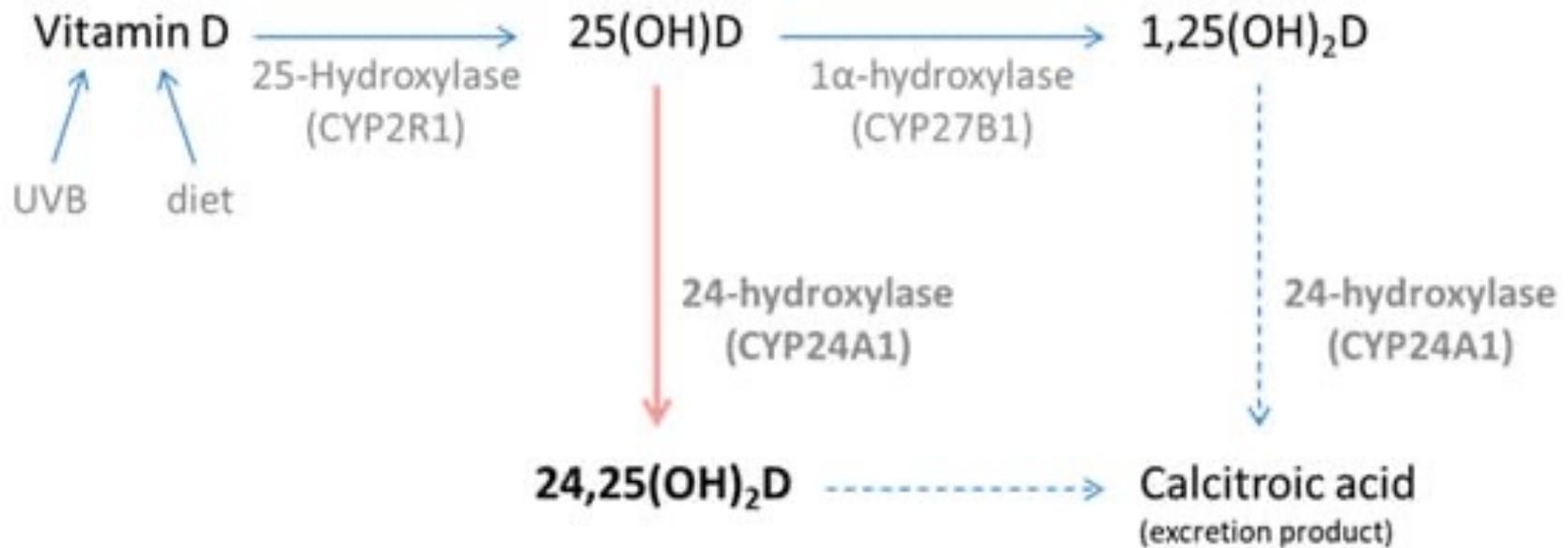
VitD levels in different populations meta-analysis



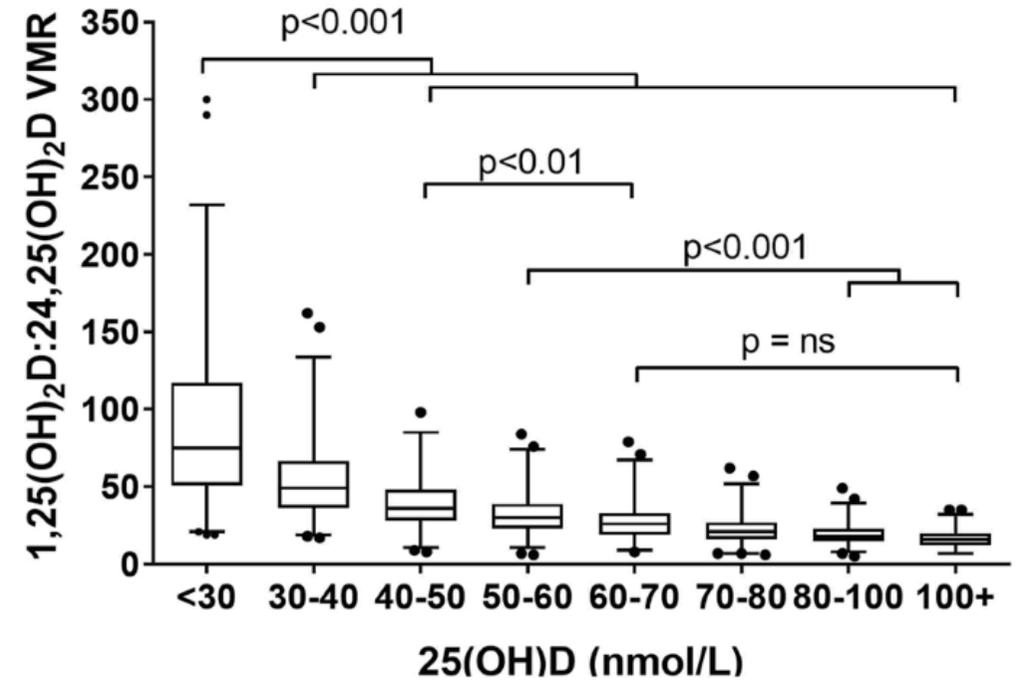
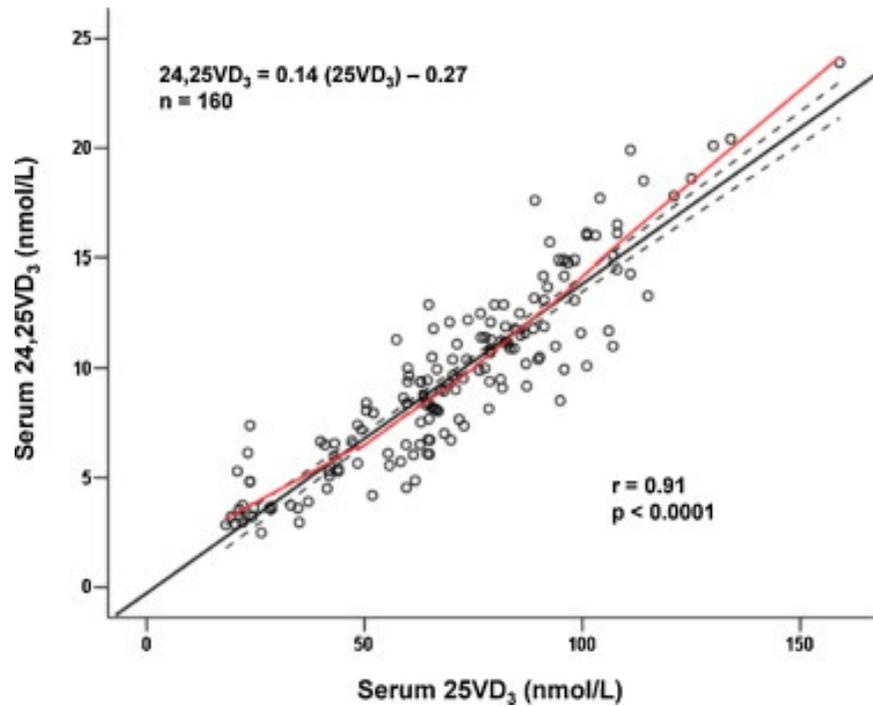
VitD binding protein and bioavailable vitD



Inactivation of vitD by hydroxylation at 24OH



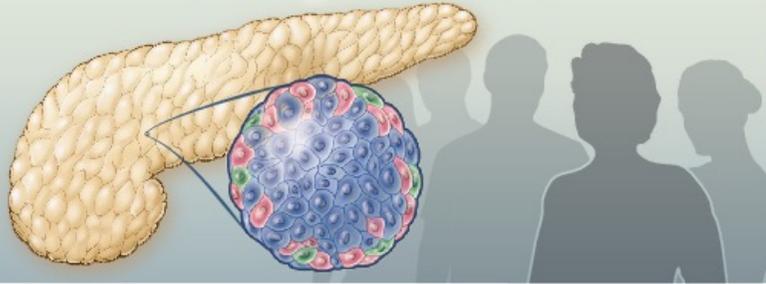
Serum 24,25 vitD increases when 25OhVitD is high



Vitamin D and Prevention of Type 2 Diabetes

DOUBLE-BLIND, RANDOMIZED TRIAL

2423 Overweight or obese adults
with prediabetes



Vitamin D₃
(4000 IU/day)



(N = 1211)

Placebo



(N = 1212)

**Progression to
new-onset diabetes**

**293
Patients**

**323
Patients**

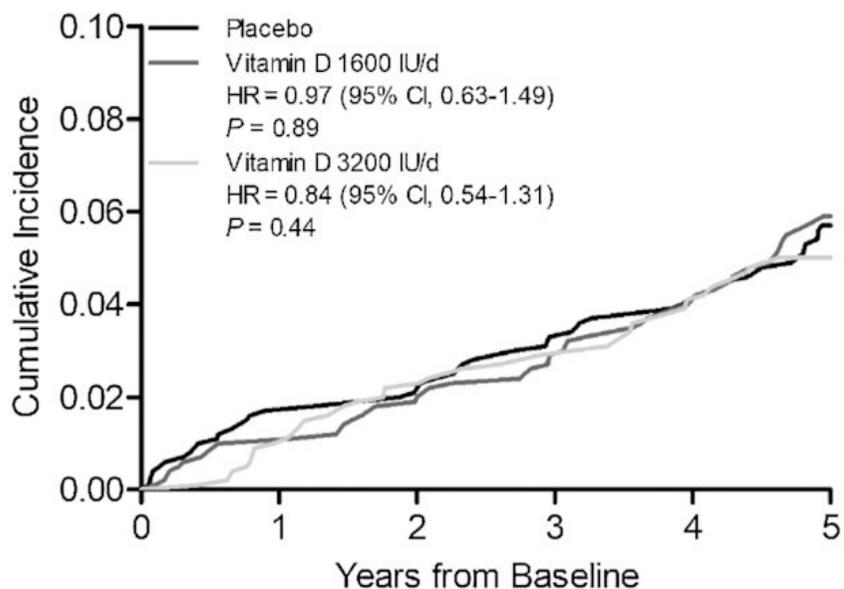
HR, 0.88; 95% CI, 0.75–1.04 (P=0.12)

No significant between-group differences in adverse events

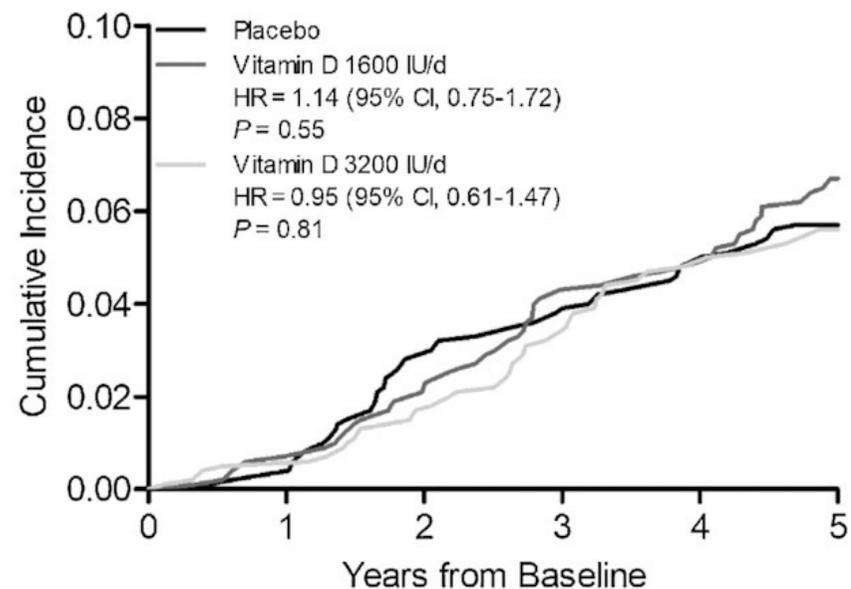
Risk of new-onset diabetes not significantly lower with vitamin D
than with placebo

Effect of vitD supplementation on Cardiovascular disease and Cancer

Major Cardiovascular Events



Any Invasive Cancer



No. at risk

	0	1	2	3	4	5
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

	0	1	2	3	4	5
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

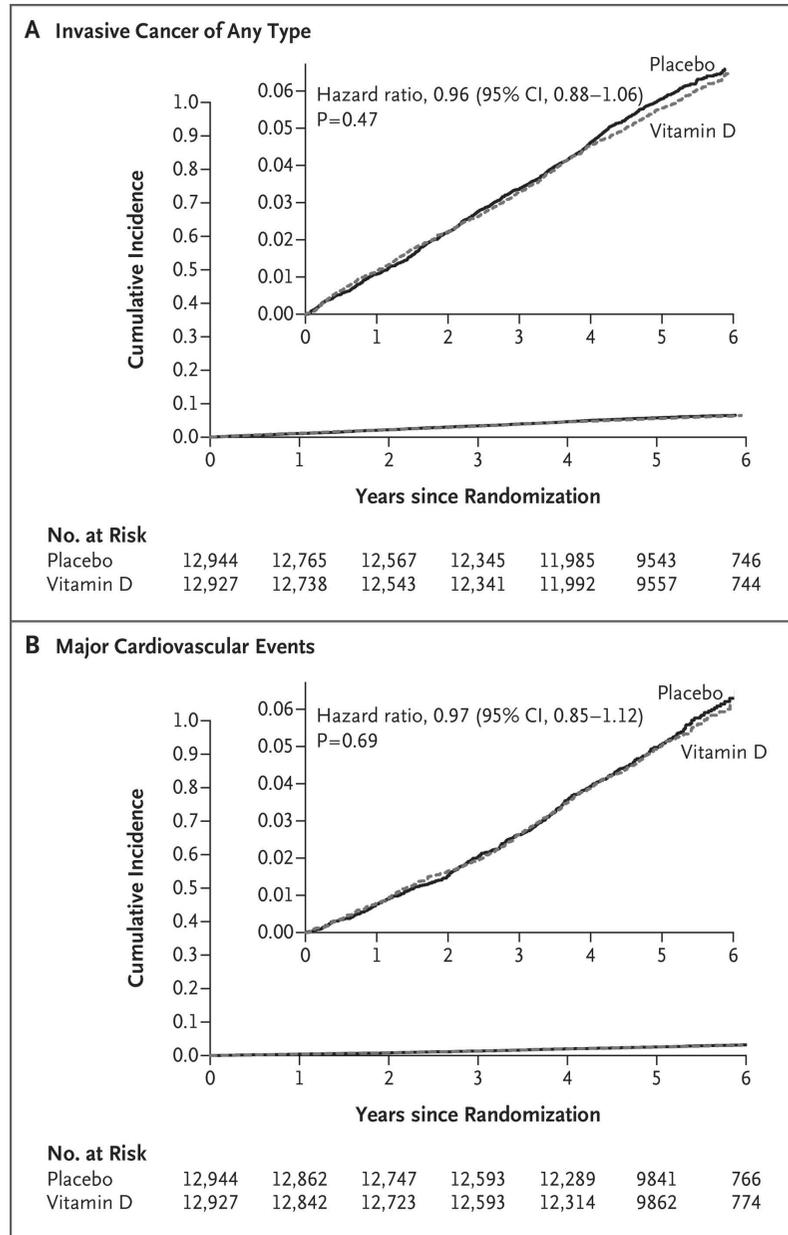
2495 participants: male participants ≥ 60 years and post-menopausal female participants ≥ 65 years from a general Finnish population who were free of prior CVD or cancer

VitD and marine $\Omega 3$ supplementation for 5 years VITAL study

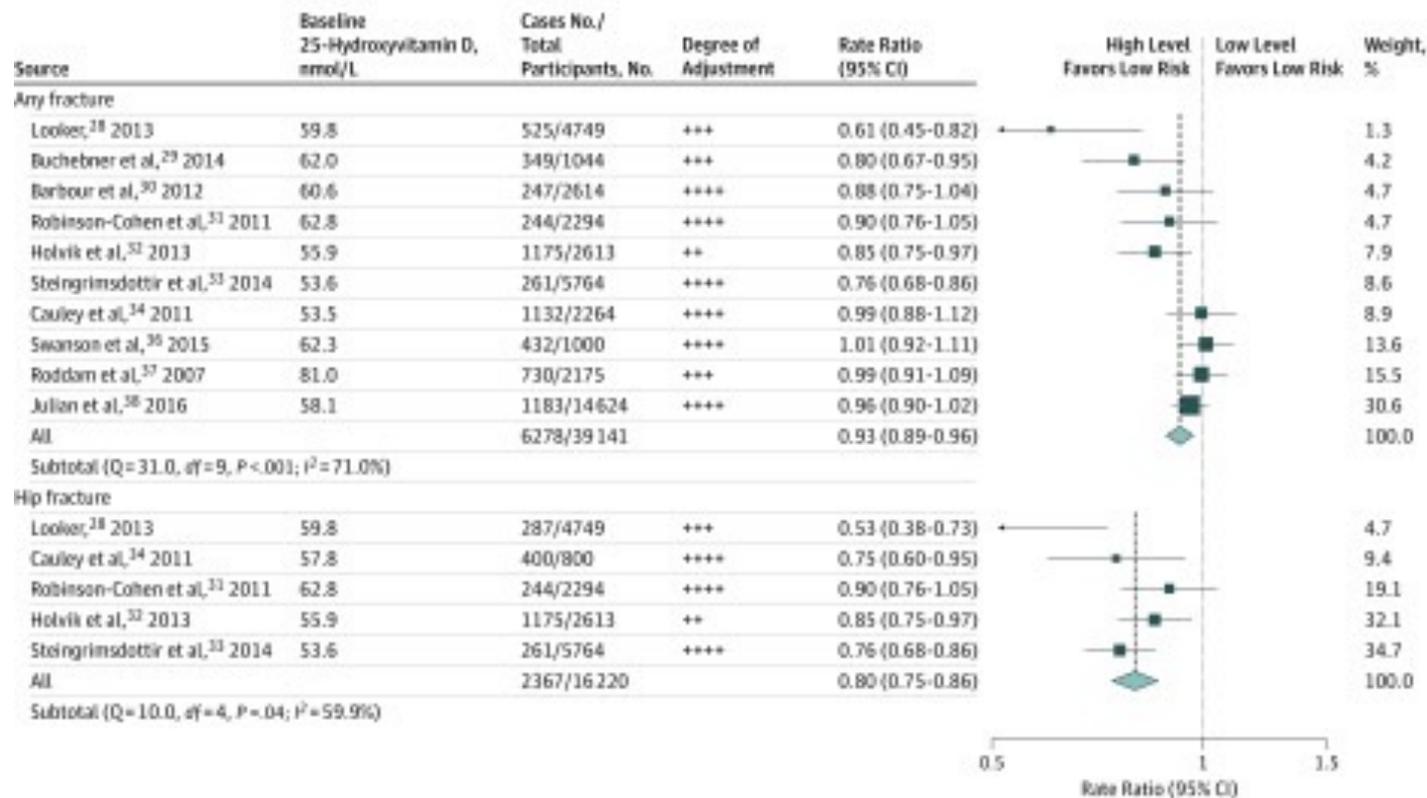
25,871 participants, including 5106 black participants men 50 years of age or older and women 55 years of age or older in the United States.

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

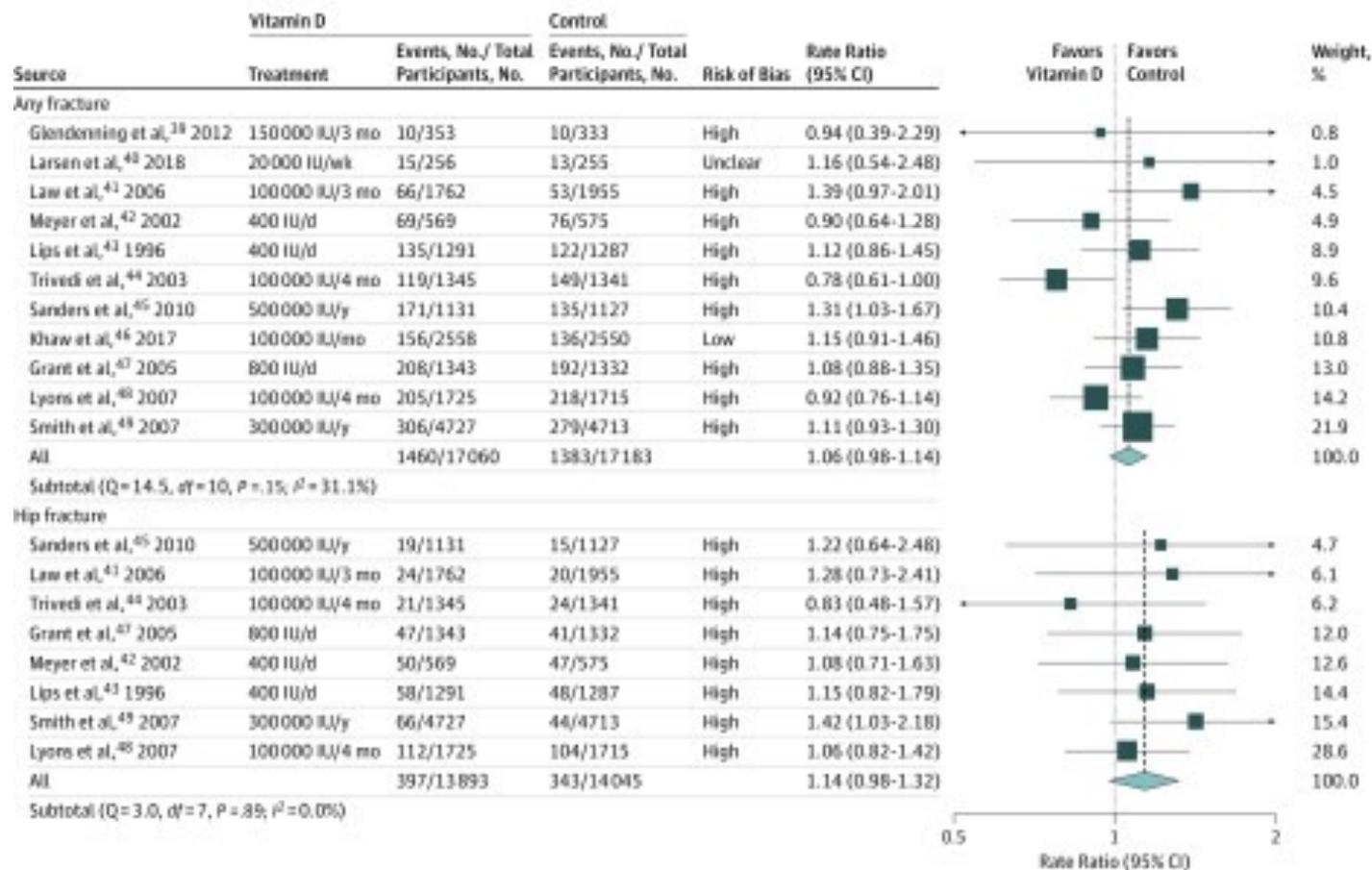
N Engl J Med 2019; 380:33-44
DOI: 10.1056/NEJMoa1809944



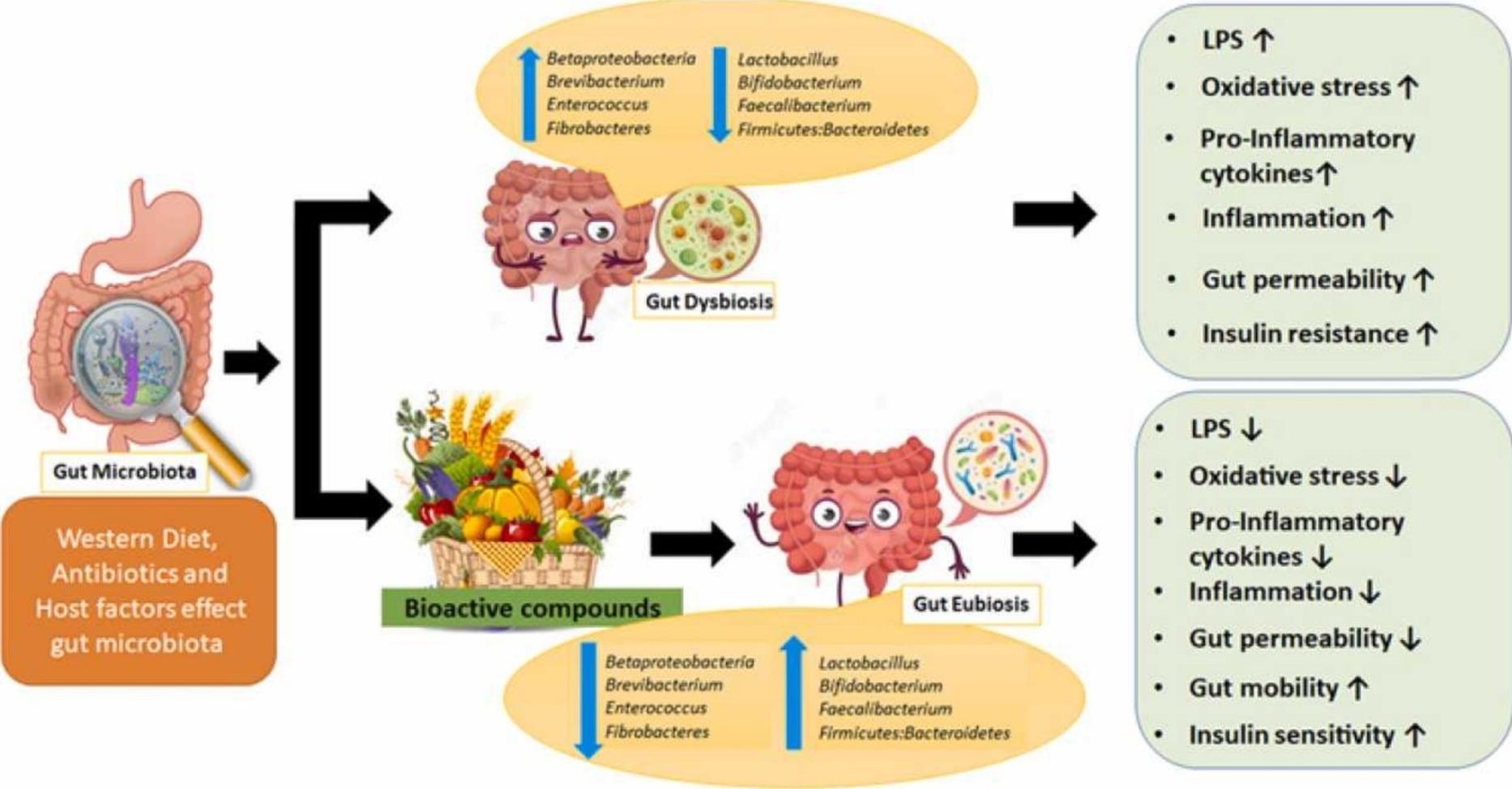
Association of 25OH-VitD serum levels with fractures



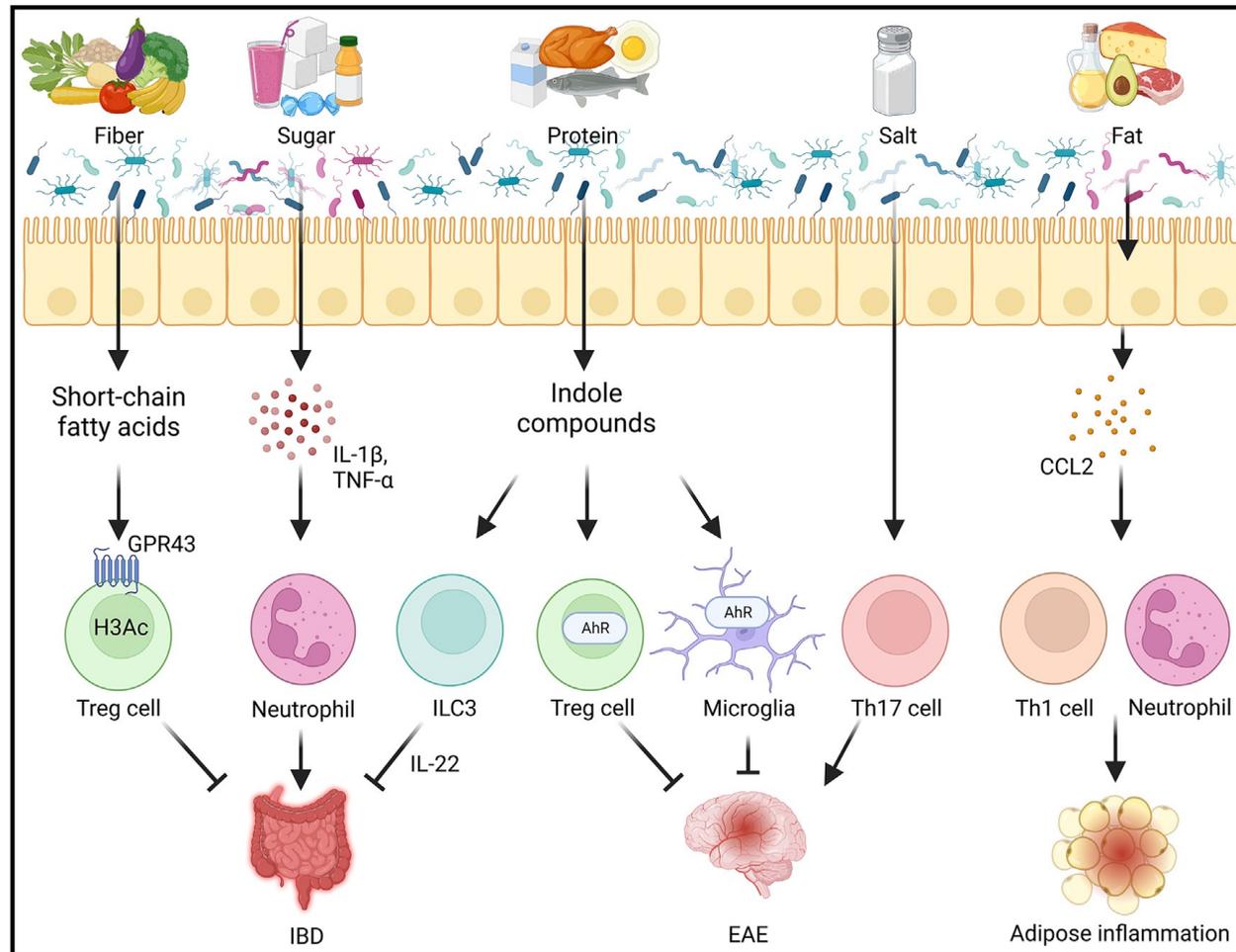
Effect of VitD+Ca⁺⁺ Supplementation in fractures



Modulation of the gut microbiota from bioactive compounds

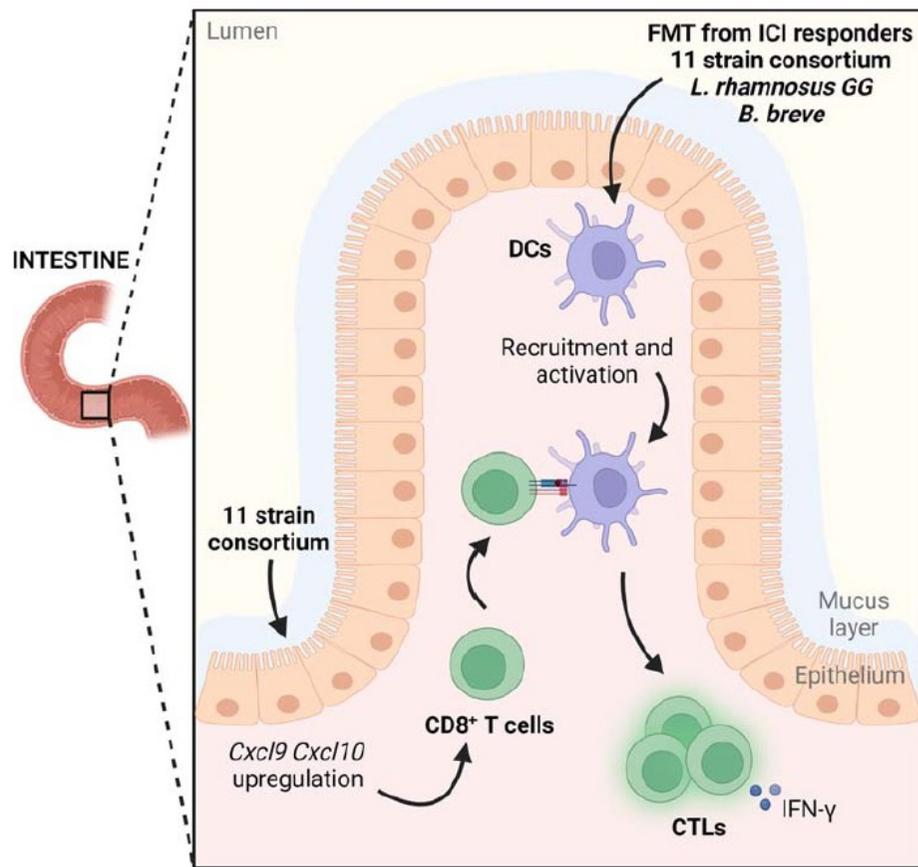


Dietary impact of microbiota products in the immune system



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	Fecal	NSLC	Anti-PD-1	High fecal concentration associated with response
Propionate				
Acetate				
Butyrate	Fecal	Solid tumors	Anti-PD-1	High fecal concentration associated with response
Propionate				
Butyrate				
Propionate	Serum	Melanoma	Anti-CTLA-4	High serum concentration negatively correlated with clinical outcome
Butyrate				
Nicotinic acid	Fecal	NSLC	Anti-PD-1	Increased concentrations in the feces of prolonged responders (PFS >12 months)
Alanine	Serum	NSLC	Anti-PD-1	Decreased serum concentrations associated with response
Pyruvate				
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)	Fecal	Unresectable hepatocellular carcinoma	Anti-PD-1	Significantly dominant in the feces of patients with objective response to ICI treatment
Secondary bile acids (ursodeoxycholic acid, ursocholic acid, tauroursodeoxycholic acid, and taurohychoic acid)				

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			

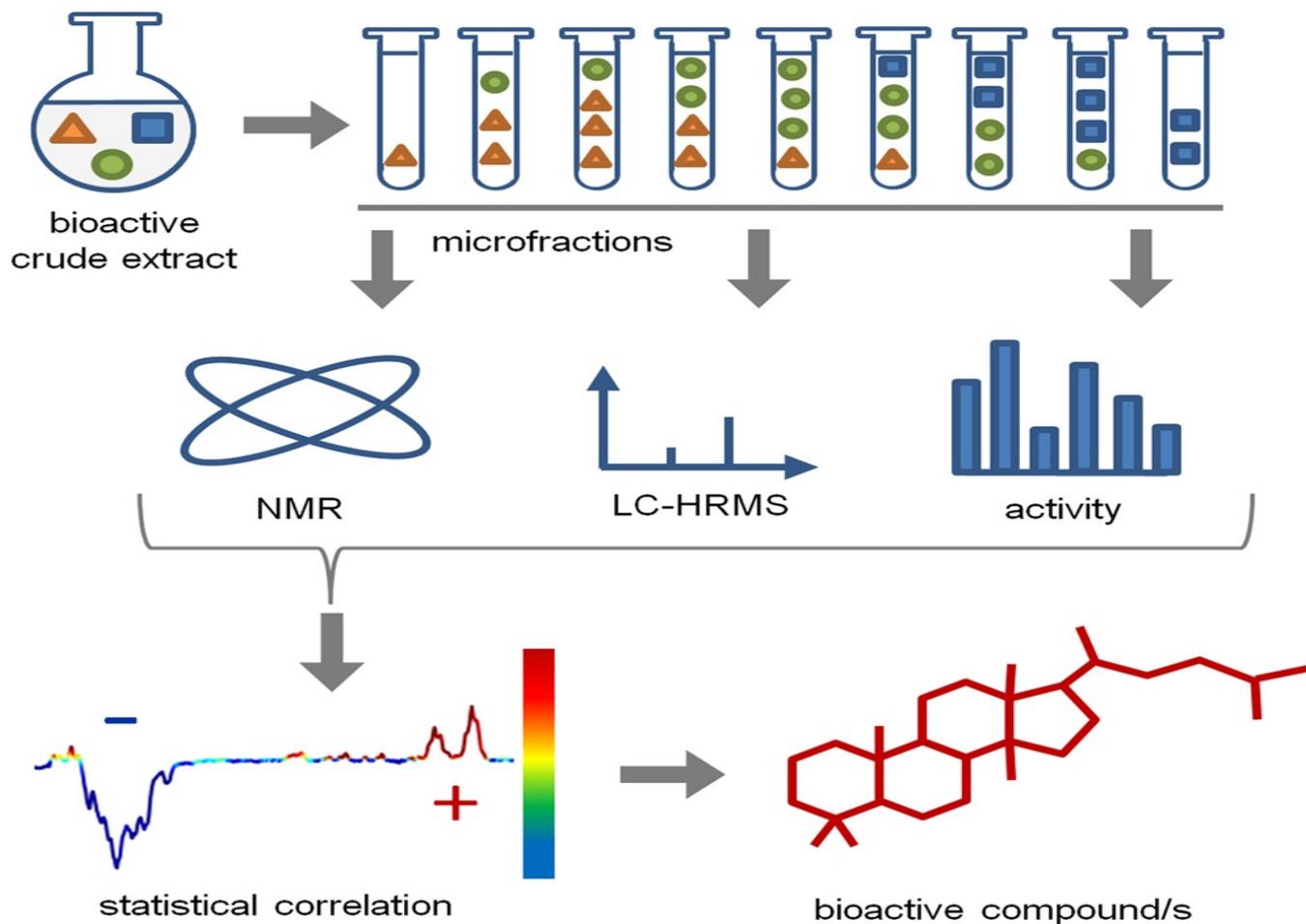


Βιοδραστικές ενώσεις

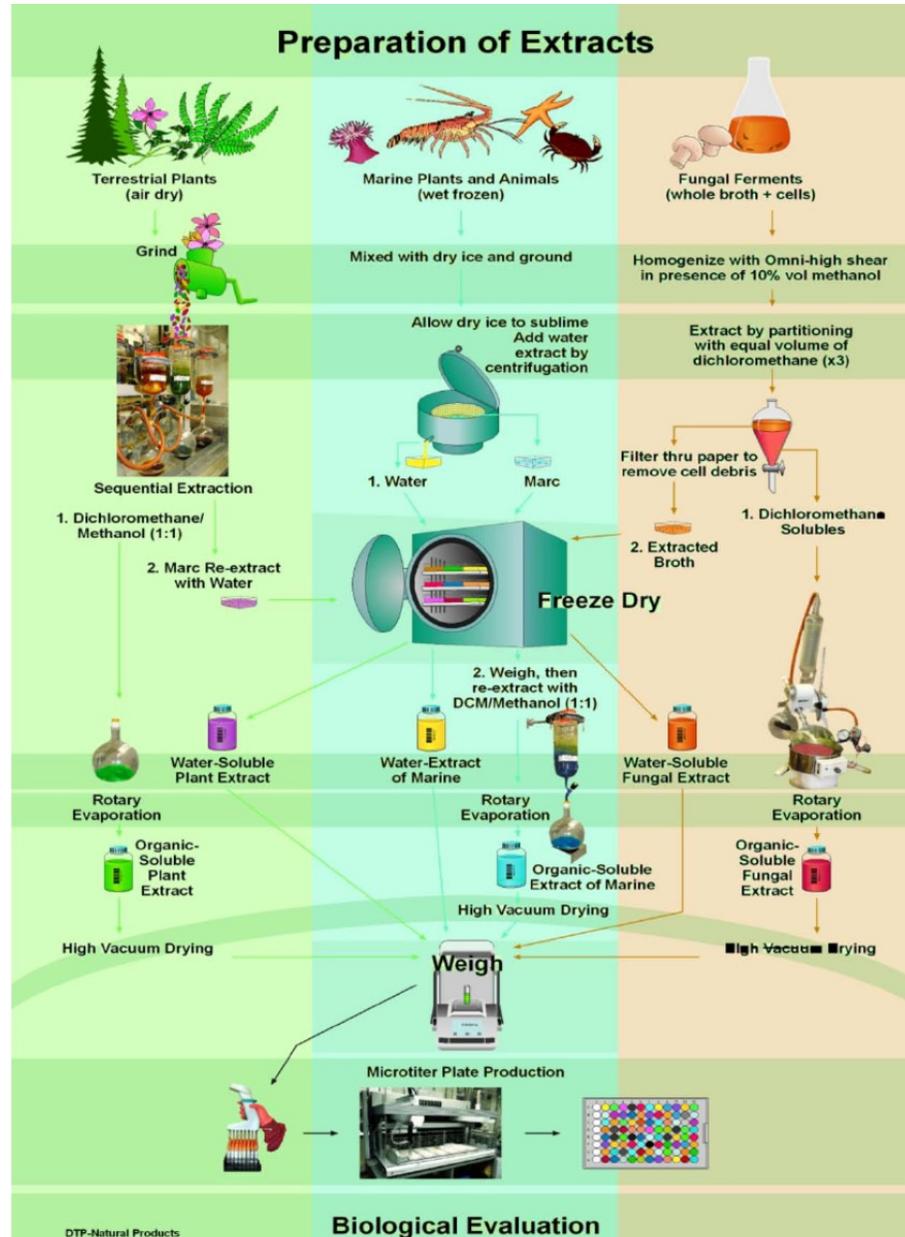
- Απομόνωση
- Χαρακτηρισμός δράσης
- Μελέτη σαν διατροφικό συμπλήρωμα ή φαρμακευτική ουσία



Απομόνωση νέων βιοδραστικών ενώσεων



Preparation of Extracts





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 ουσιών 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 ποιότητα της