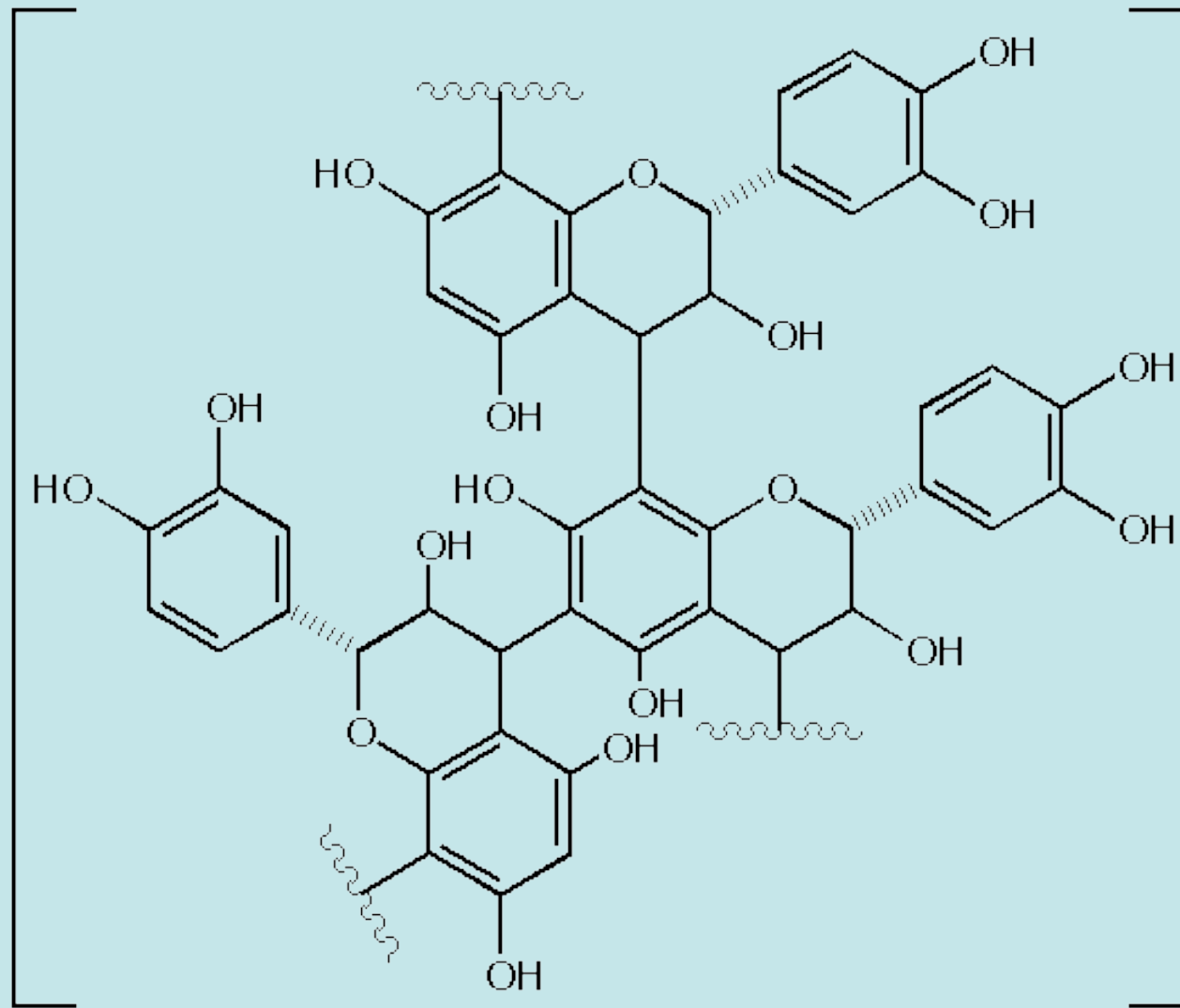


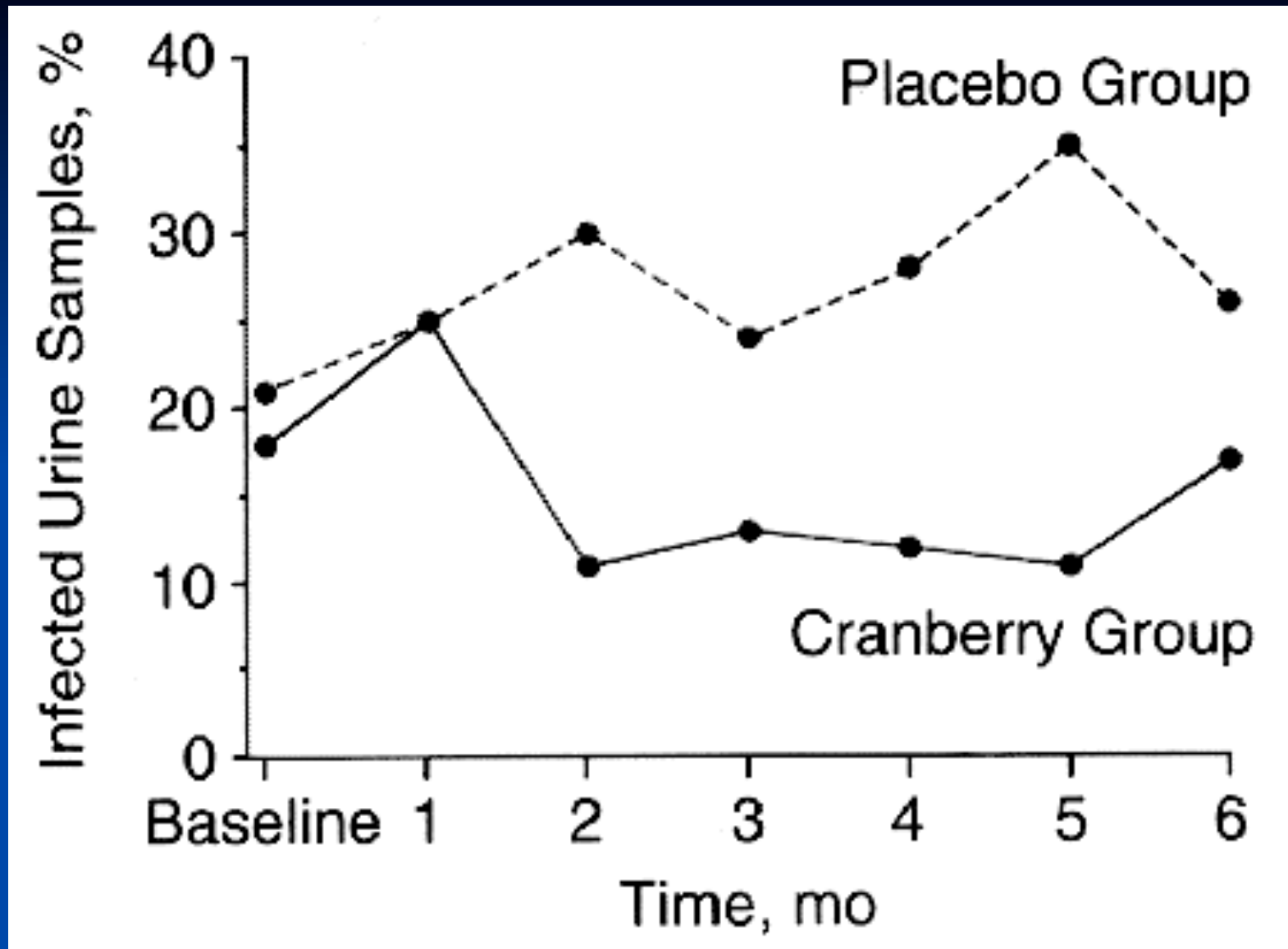
# Cranberry

- *Vaccinium macrocarpon*-cultivated in Washington
- Long history of use
- The mechanism was thought to be urine acidification
- Now *E. coli* (other pathogens also) adhesion inhibitors are known to be present but not in other juices. Several proanthocyanidins are likely the active compounds
- Need about 8-16 oz (240-480ml) of juice (not drink or cocktail)
- Less evidence for efficacy of cranberry capsules although adherence to a juice regimen can be difficult



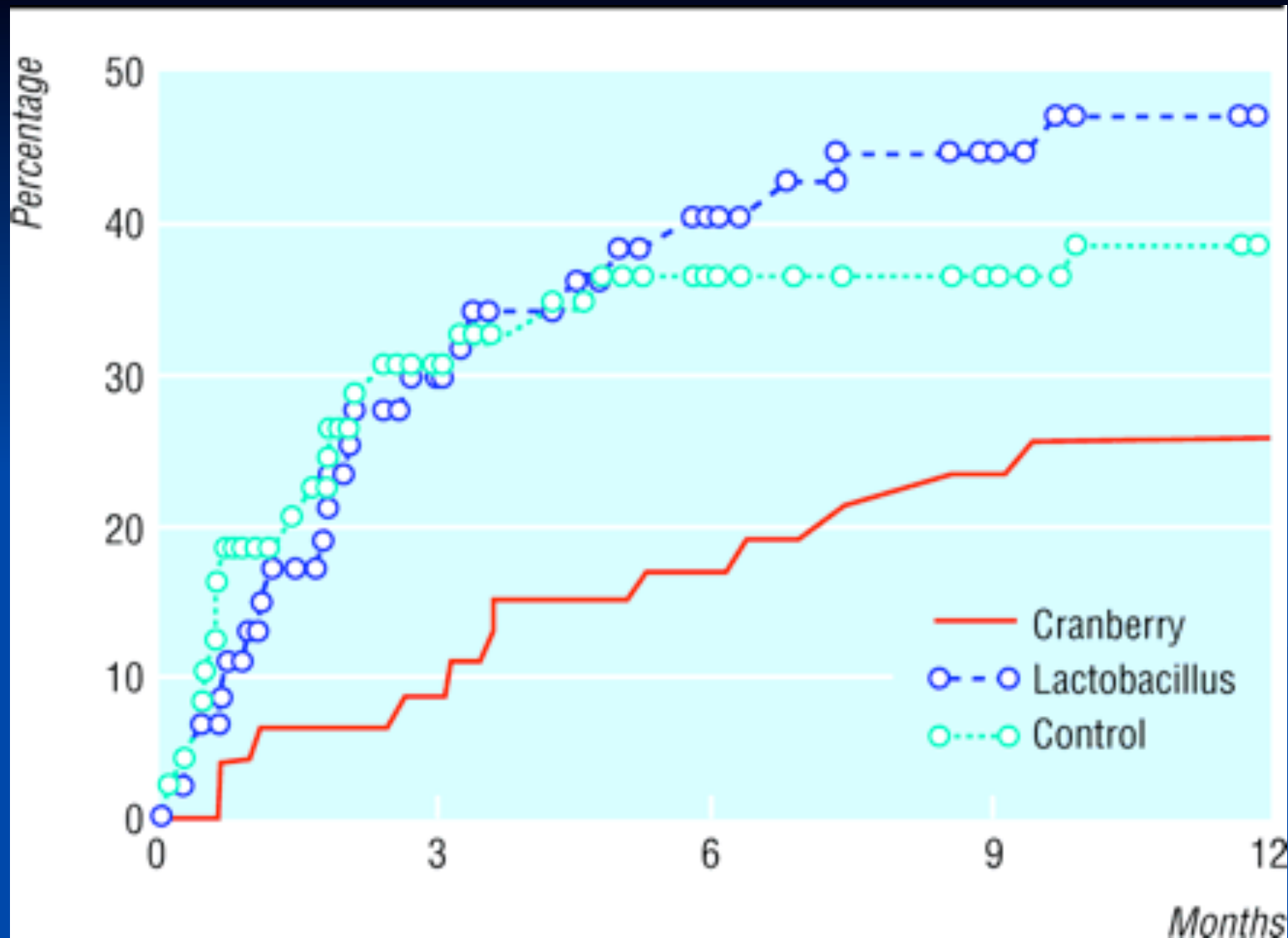
Proanthocyanidin oligomer

- Evidence for effectiveness in UTI **treatment** is weak
- Will acidify urine and contains high oxalic acid levels so that kidney stones could be a risk
- Cranberry juice will also reduce urine pH and ammonia odor.
- One study showed enhanced eradication of *H. pylori* when added to an antibiotic regimen.



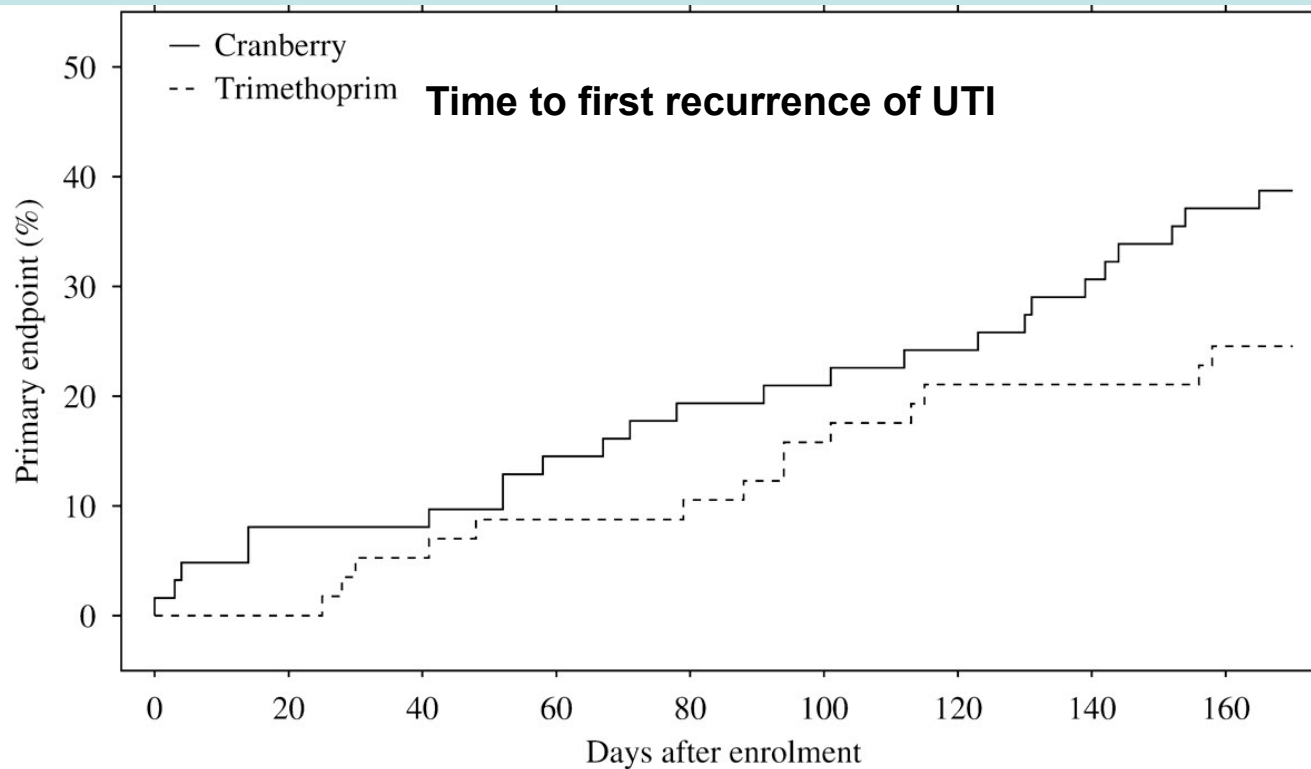
N=153; 300ml/d of juice; Avorn et al. JAMA  
1994;271:751-754.

First  
UTI in  
12  
months



Kontiokari et al. BMJ 2001;322:1571 n=150 50ml (7.5g) of cranberry concentrate (diluted)(also had some logenberry juice)

- A recent Cochrane Review (Jepson RG, Craig JC. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev (2008) CD001321) of 10 trials indicated support for cranberries and UTI prevention in younger women. Antimicrobials also work.
- “there is some evidence from two good quality RCTs that **cranberry** juice may decrease the number of symptomatic UTIs over a 12 month period in younger women” ; high dropout rates using juice.



**Cranberry**

69    65    64    60    57    56    54    50    46    44

**Trimethoprim**

68    68    65    63    62    59    56    56    54    54

Log-rank test:  $\Delta = 2.7, \chi^2(2.7, 1) P = 0.100$

**McMurdo, M. E. T. et al. J. Antimicrob. Chemother. 2009 63:389-395; doi:10.1093/jac/dkn489 n-135 women over 45; at least 2 prior UTI in 12 mos; used capsules 500mg extract (Cran-Max)**

Study in older women

## ■ Summary

## *Cranberry*

- **Efficacy:** reasonable evidence for benefit for **PREVENTION** of UTI.
- **Safety:** good but could be risky for those that form kidney stones easily. Has salicylates.
- **Drug interactions:** little effect on CYP or warfarin INR although several case reports indicate INR increase therefore be careful
- **Product selection:** need the juice? capsules are easier to take and have no sugar; Use the most concentrated product.
- **Questions remaining include**
  - *Does cranberry juice help with Helicobacter pylori?*
  - *Other infections? Help in dental caries?*
- **GWE:** *I recommend a trial of high potency cranberry capsules for recurrent UTI before using antimicrobials*

# Soy-

- **Botany-Glycine max-legume**
- contains isoflavones that act as estrogen mimics (phytoestrogens), e.g genistein, daidzein, that bind to estrogen receptors in a competitive manner
  - Isoflavones are present in many plants but soy beans; soy milk and tofu are especially rich sources
  - other sources (mainly legumes):fennel seeds, red clover, yam, black beans, licorice
  - 1 cup of soybeans=about 300mg of isoflavones
  - consumption in Japan is ~50mg/d isoflavones

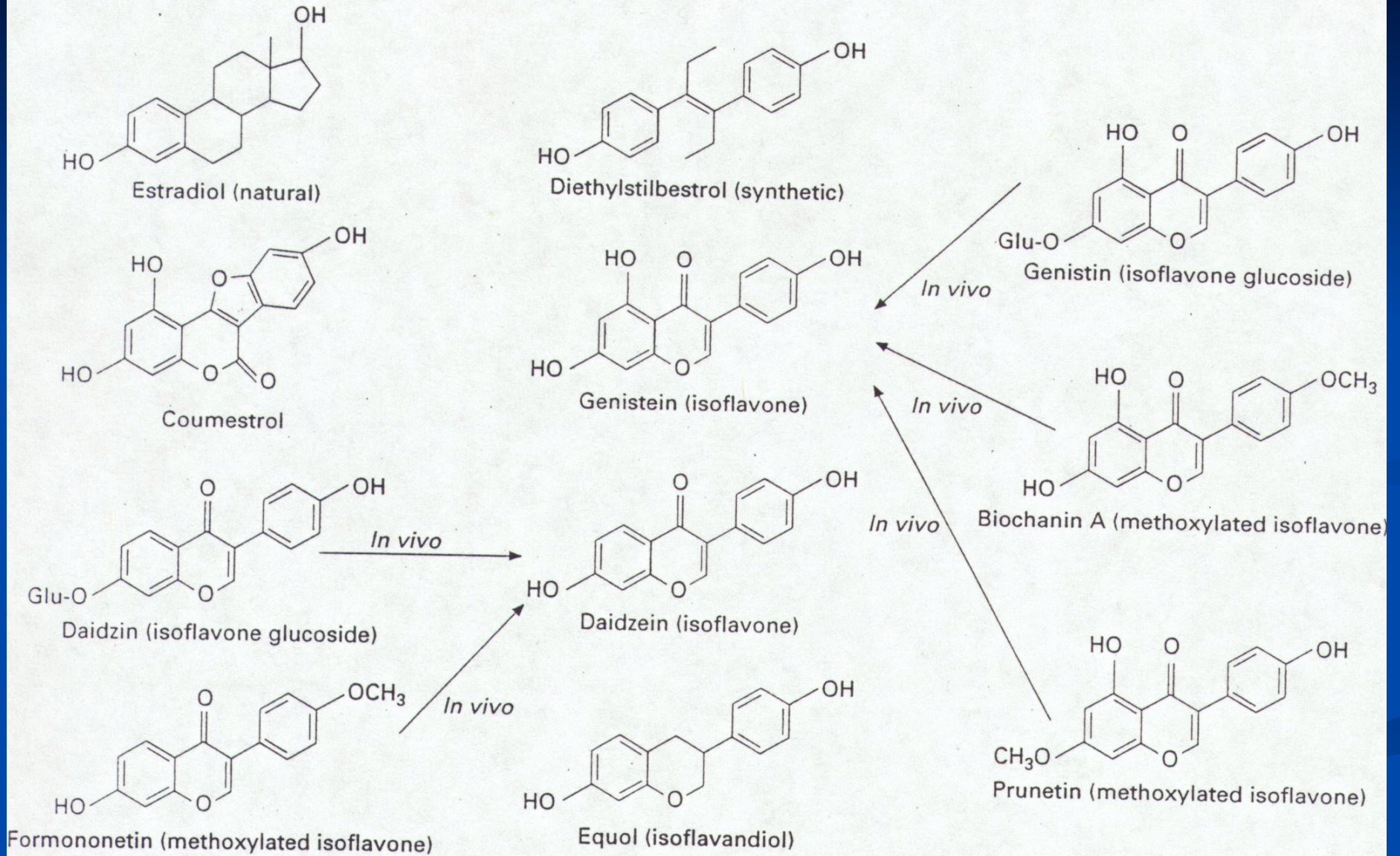
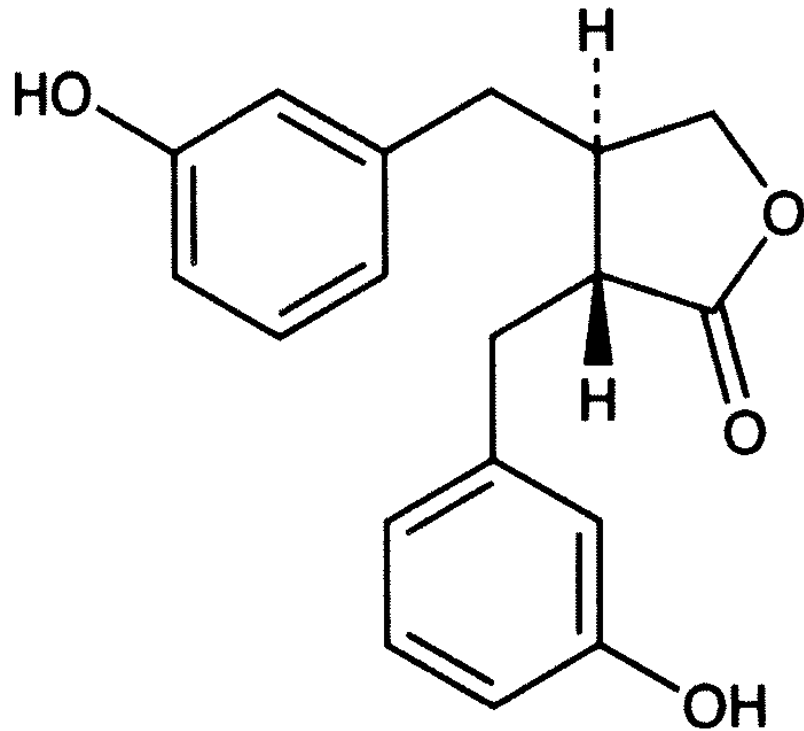


Fig. 5. Structural similarity of oestrogens and phytoestrogens.

# Soy

- also contains lignans
  - are phenylpropanoid dimers with antioxidant and free radical scavenging properties
  - present in many plants but especially soy beans and flaxseed and red clover
  - Some evidence that ingestion of lignans may decrease risk of some cancers (breast)
  - act like phytoestrogens



Gum, mp 141-143°. uv max (ethanol): 227, 261 nm (log  $\epsilon$  4.66, 4.64).

Enterolactone (example of a lignan)

## Isoflavone Pharmacology

- Isoflavones (IF) act as weak estrogenic compounds. Are essentially SERMs
- IF are competitive inhibitors of estrogen. If estrogen is high (premenopause), then will displace; if low (postmenopause) then will be an estrogen agonist.
- Bind to estrogen receptor B (bone, vascular) better than ER-A (reproductive)
- Have effects other than receptor action. Decrease aromatase, 3 $\beta$  and 17 $\beta$ -hydroxysteroid dehydrogenase, enzymes that convert precursor steroids to potent estradiol.
- Are antioxidants

## Isoflavones (continued)

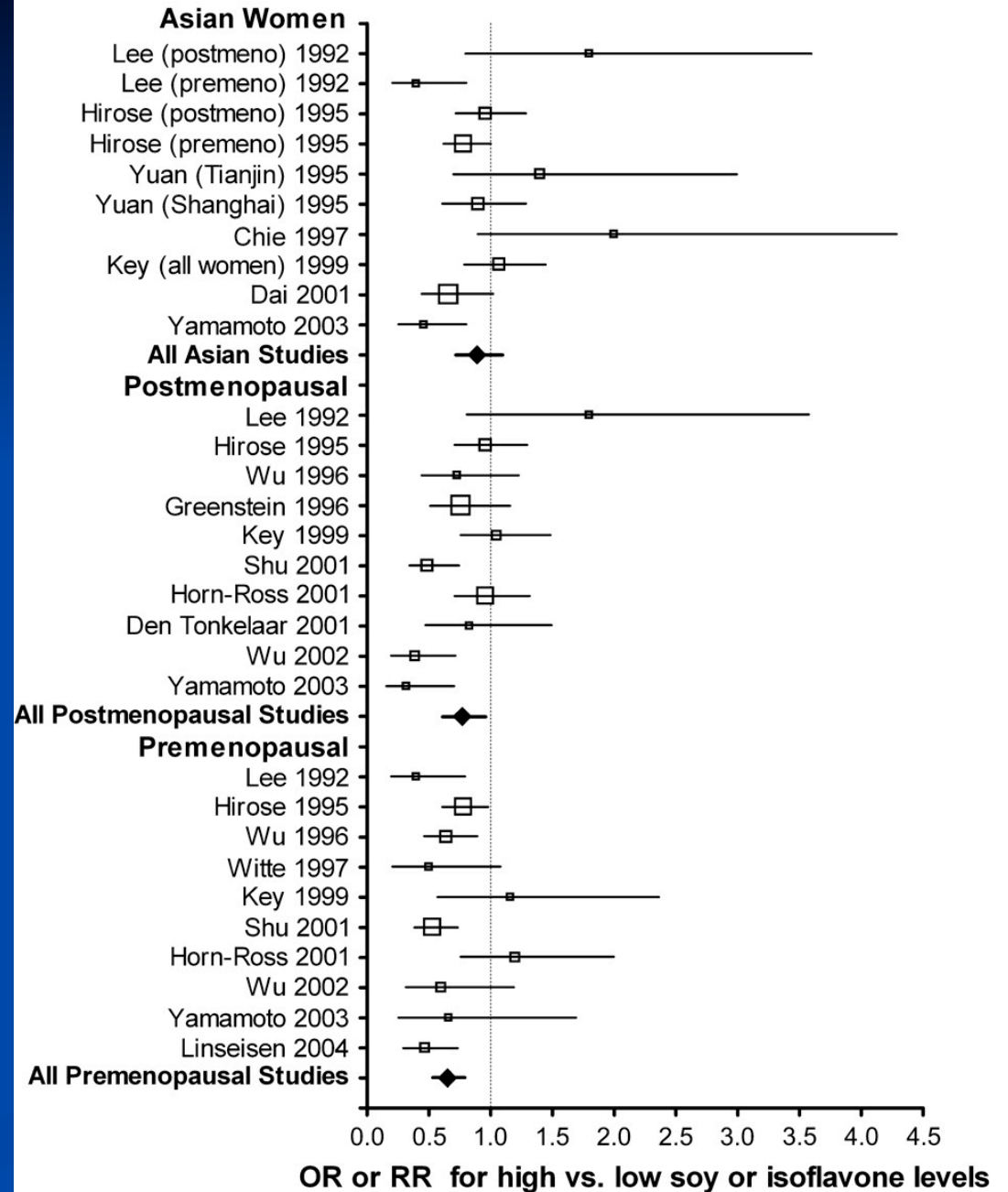
<u>Product</u>	<u>mg isoflavones/100g</u>
Raw soybeans	~100
Soy protein	100-300
Soy milk	10
Soy flour	199
Cooked soybeans	55
Tempeh	44
Tofu	31
Soy noodles	9

## Soy Effects on Cancers

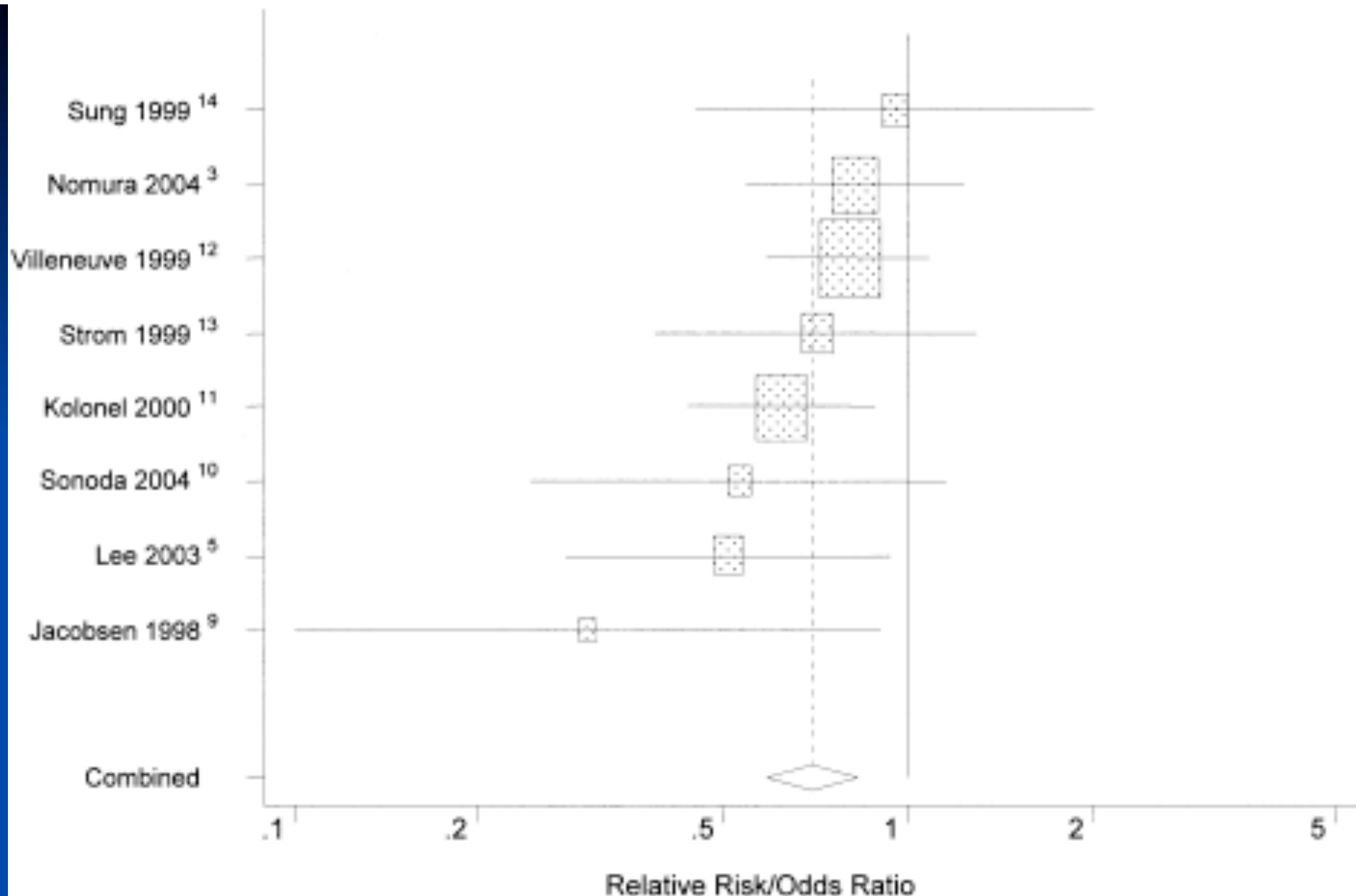
- Long consumption of soy associated with lower rates of breast, endometrial and prostate cancers.
- Animal studies show that high soy protein in diets will reduce incidence and development of several cancers
- Breast cancer
  - No long term **prospective** studies
  - In vitro, genistein and daidzein stimulate breast cancer growth in low conc but inhibit at high conc.
  - In mice, genistein increased growth rate of estrogen dependant and estrogen independent implanted tumors and antagonizes tamoxifen but at high concentrations the reverse was true.
  - In mice, genistein or soy given prior to the cancer will protect

Trock et al. J. Nat. Cancer  
Inst 2006;98:459-471

### Association Between Soy and Breast Cancer Risk, by Population Subgroups



\* Premeno = premenopausal women, postmeno = postmenopausal women



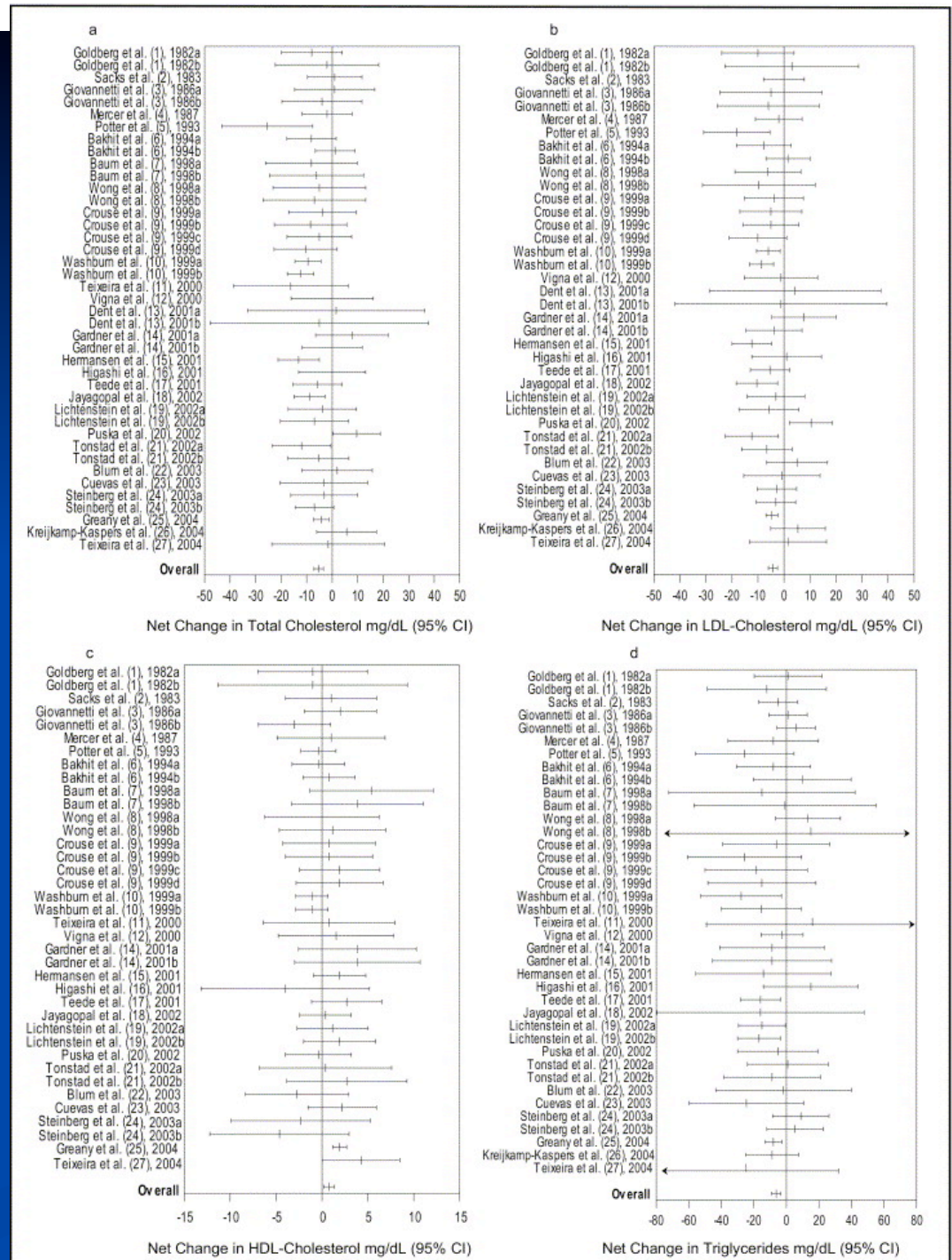
**Yan and Sptiznagel, Int. J. Cancer 2005;117: 667-669**  
**Prostate cancer risk vs intake**

## Soy Effects on Heart Disease Risks

- Soy diets associated with normalization of lipid profiles
  - Decreased total cholesterol (~9%), LDL (~13% decrease), increased HDL (small), triglycerides (~10% decrease) improved arterial dilation and compliance
- Soy modestly lowers BP
- In animal studies, soy without isoflavones did not affect lipids
- FDA now allows foods with 6.25g of soy protein per serving to state “consuming 25g of soy protein daily, as part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease”
- May need 20-50g/day of soy in diet for benefit; intake is low in Western countries and not correlated with cardio risk
- Isoflavones alone may not work as well

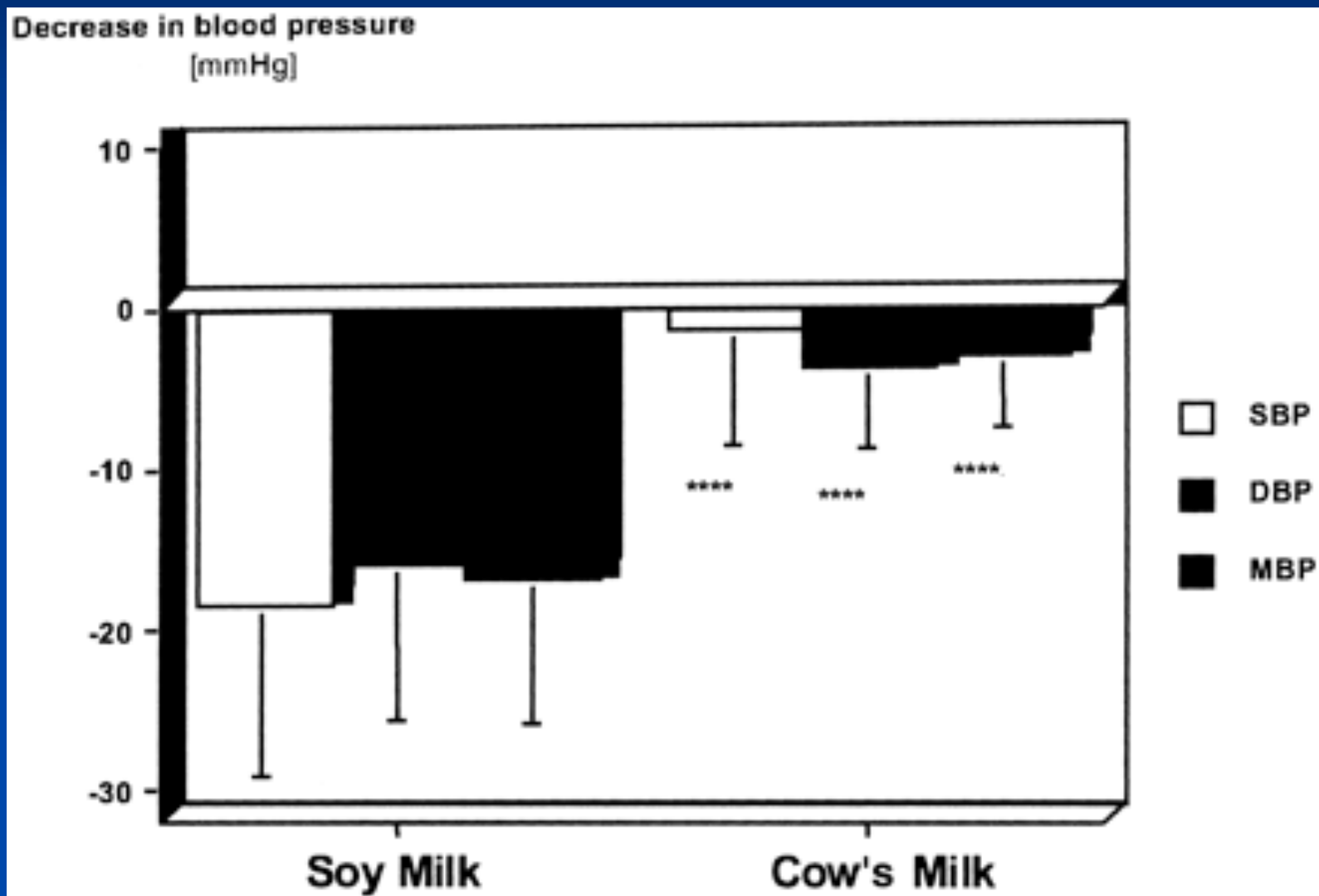
# Reynolds et al. Am J Cardiol 2006;98:633-40.

47 studies included



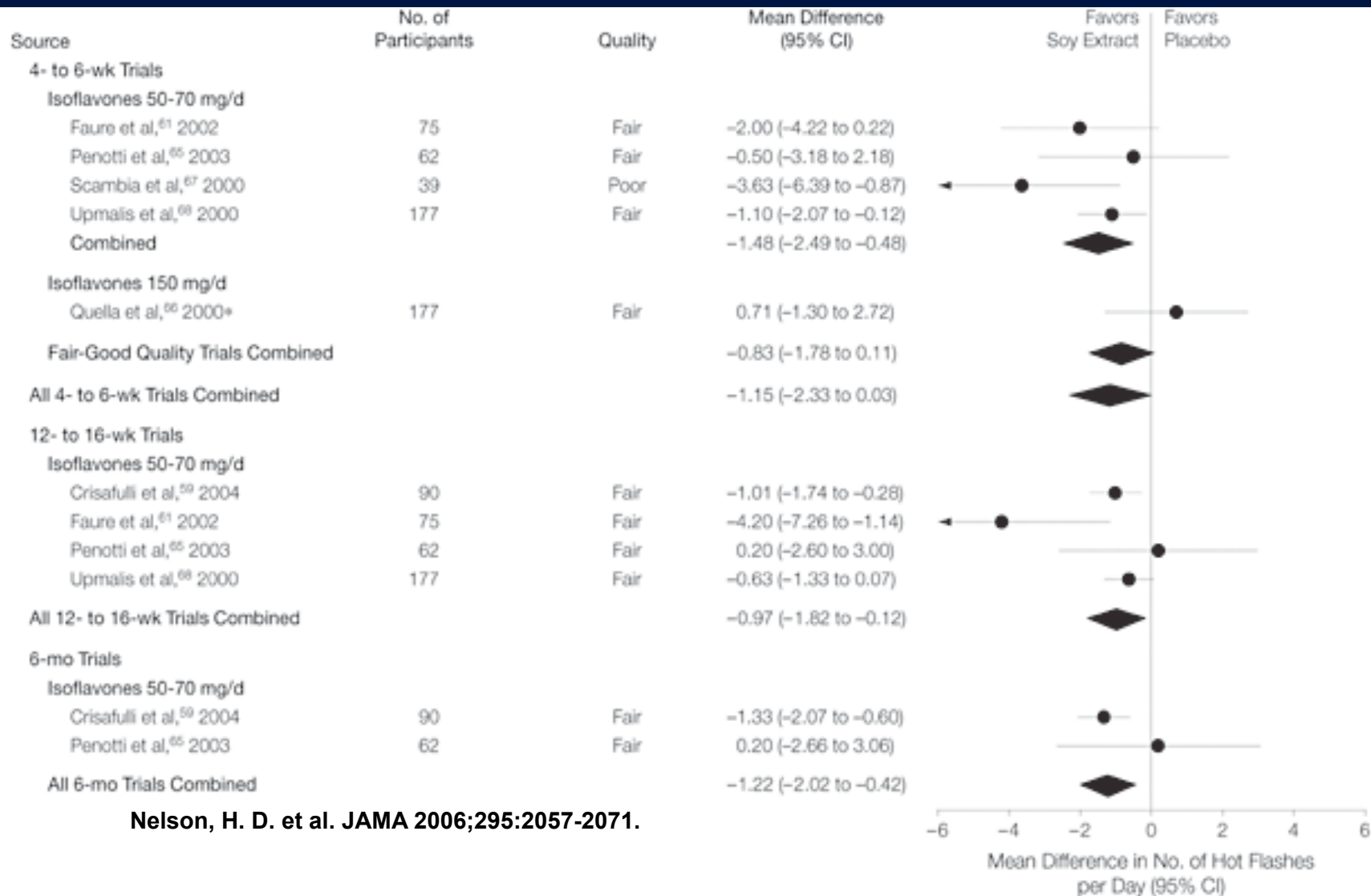
Rivas et al. J. Nutr 2002;132:1900-1902

Soy milk vs cow's milk for 3 mos; n=40



## Soy and Menopausal and Postmenopausal problems

- can soy replace HRT?
- Hot flashes and other symptoms: soy flour as well as higher doses of soy isoflavones (100mg/d) have been tested. The results are generally positive for mild benefit. A big placebo effect is seen in the published studies.
- Osteoporosis- Studies show only a very small increase, at best, in bone mineral density with soy or isoflavone supplements.



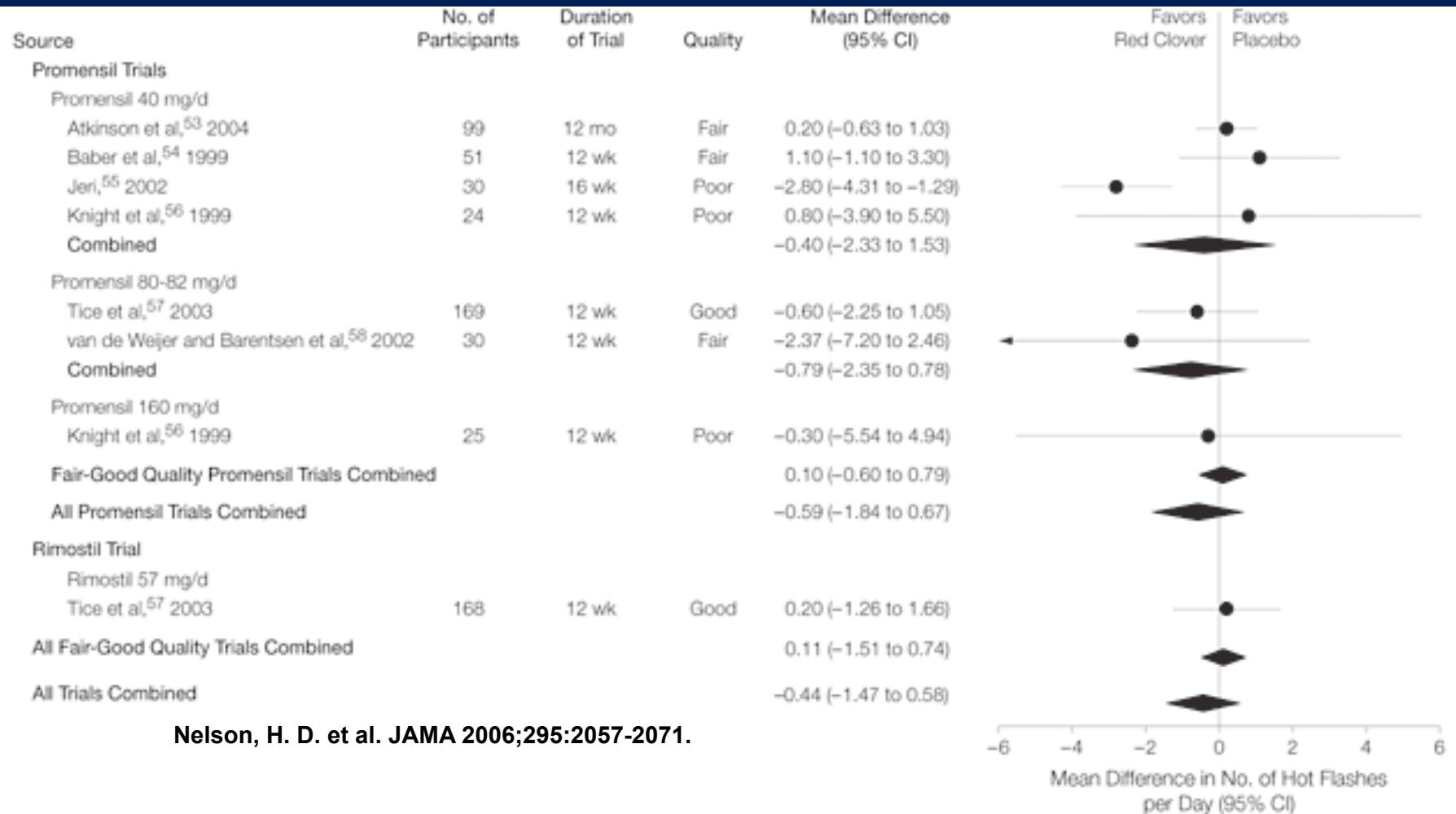
Nelson, H. D. et al. JAMA 2006;295:2057-2071.

# Hot flashes in menopausal women

Copyright restrictions may apply.



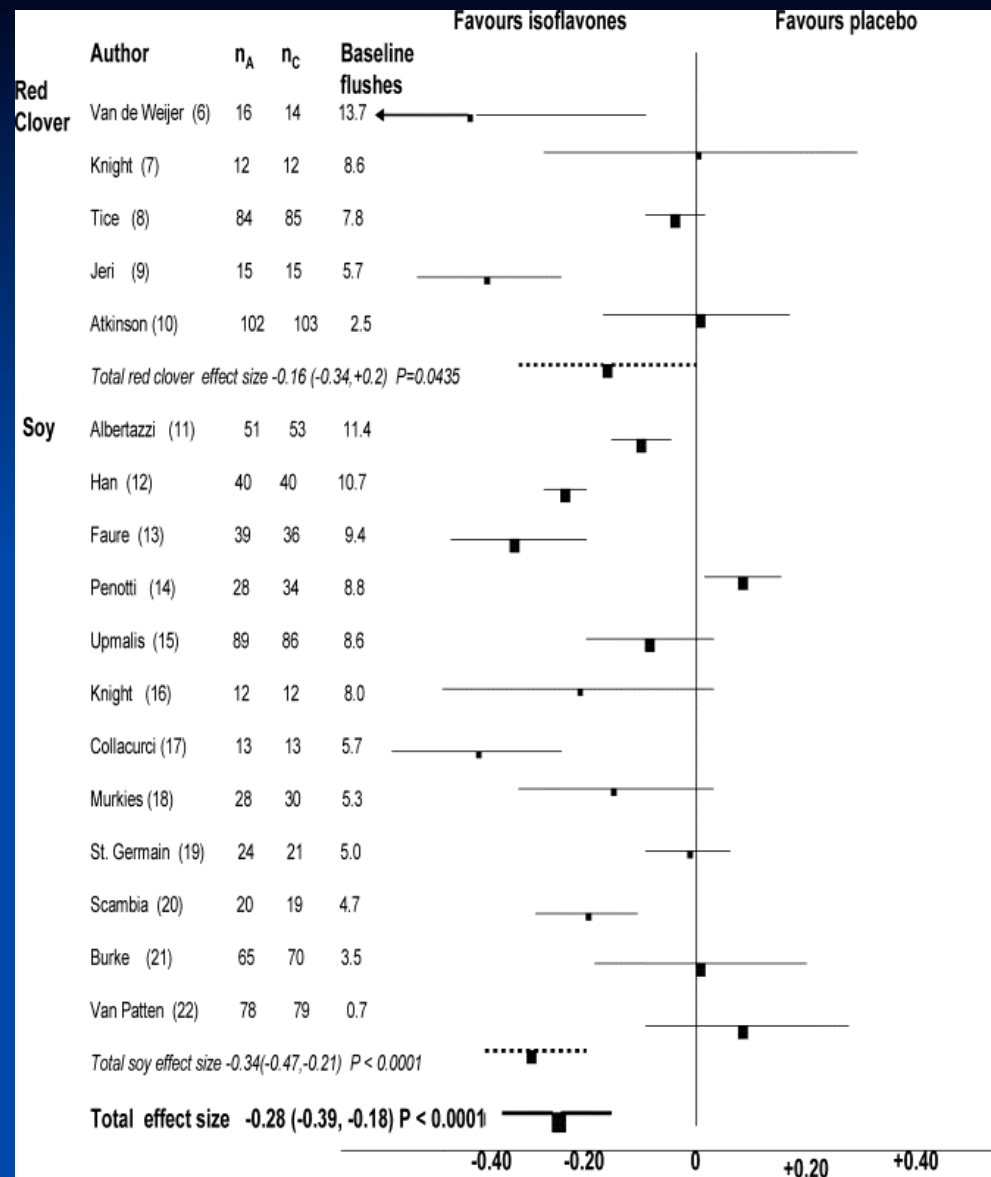
## Trials of Red Clover Isoflavone Extracts



Nelson, H. D. et al. JAMA 2006;295:2057-2071.

## Red clover isoflavones (Promensil)

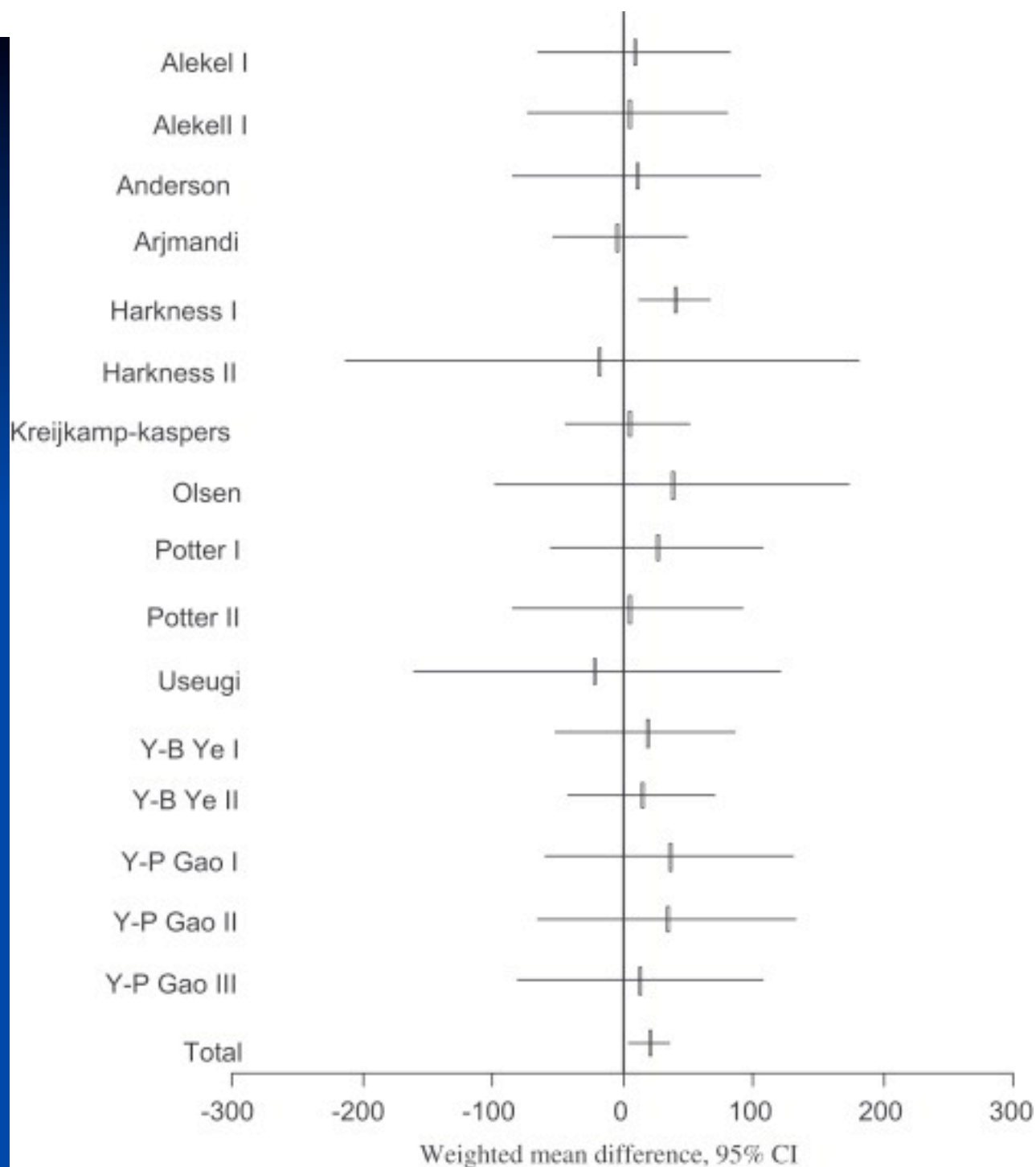
Copyright restrictions may apply.

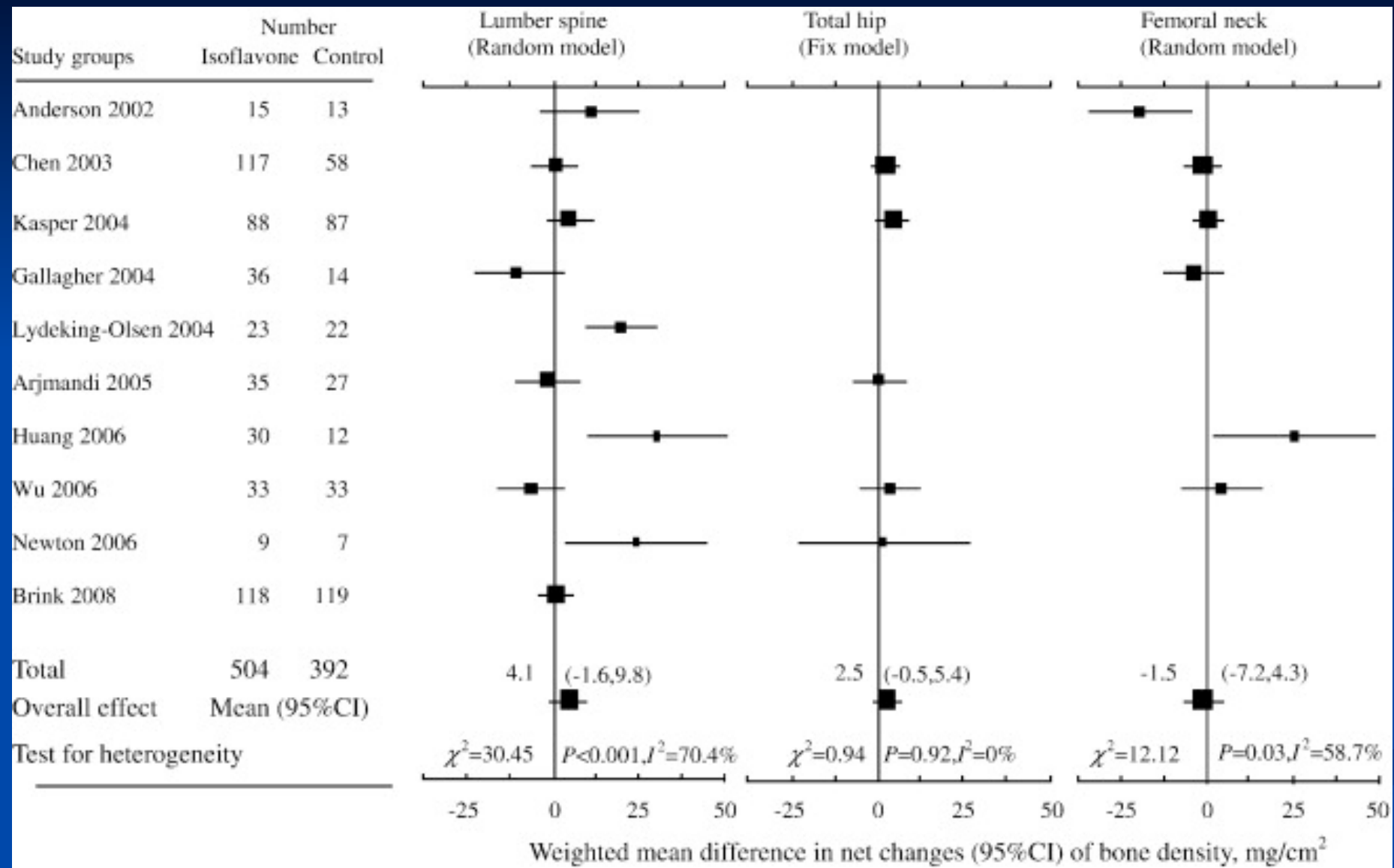


Howes et al. *Maturitas*. 2006;55:203-11

Ma et al. Clinical  
Nutrition  
2008;27:57-74

10 studies on Bone  
Mineral Density in  
menopausal  
women





## Risks and Interactions

- Can be allergenic for some
- Soy isoflavones can inhibit thyroid synthesis
- Soy use in breast cancer patients
  - Dietary soy may be OK but probably best to avoid supplements.
  - Studies generally show no benefit of soy vs placebo in hot flashes associated with breast cancer therapy with tamoxifen (e.g., Van Patten et al. J Clin Oncol 2002;20:1449-1455).
- Drug Interactions- not to be given with tamoxifen; isoflavones inhibit CYP in vitro but probably not in vivo

# Other Effects of Soy

- Diabetes- may improve glucose tolerance
- Diabetes- may improve neuropathy and kidney function
- Memory – may see improvement
- Men-prostate- may be slightly protective; no effect on PSA
- Women-may improve immune function

## **Other herbals used for menopausal symptoms**

**Red clover**- contains lignans and isoflavones; some studies show benefit for menopausal symptom relief, others no benefit

**Black cohosh**- does not affect endometrium but may relieve hot flashes and other menopausal symptoms; may build bone; may not be contraindicated in breast cancer and treatment regimens. More later

**Flaxseed and Flaxseed oil** – some evidence for benefit

**Evening primrose oil**- not consistent evidence for benefit

**Chasteberry**- helps in PMS but ? for menopause

**Dong quai**- no observed benefit in one good study

**Yam**- is a scam

**Topical progesterone**- works but risks same as HRT?

## ■ Summary

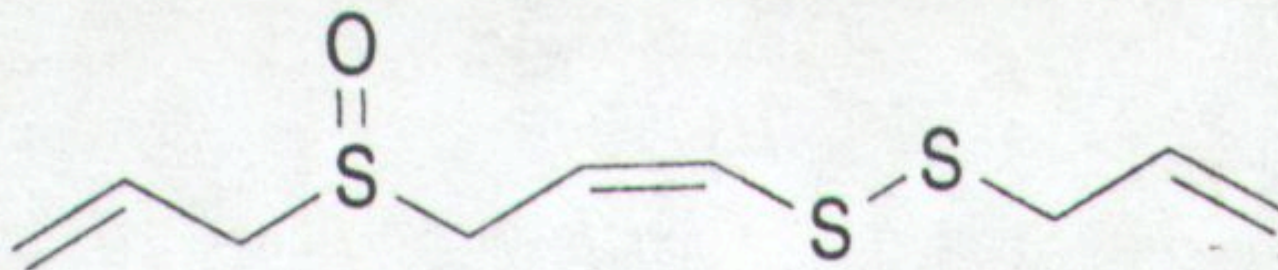
### *Soy*

- **Efficacy:** increased soy ingestion may decrease hot flashes and other postmenopausal symptoms; Only a tiny improvement in bone. Soy has cardiovascular and cancer prevention benefits. Isoflavones probably are the active components but the results with isoflavones alone are not as impressive.
- **Safety:** good, but use in estrogen receptor positive breast cancer may be risky; for infants is OK but low in vitamins
- **Drug interactions:** not with tamoxifen
- **Product selection:** Soy=best; Isoflavones OK
- **Dose:** about 20-40g of soy protein. This contains 30-50mg of isoflavones.
- **Questions remaining** include
  - *How much benefit? Safety in breast cancer?*
- *GWE: I suggest diet soy is good; supplements (soy or isoflavone) worth a try for menopausal symptoms but otherwise not impressive*

# •Garlic

- History
- Chemistry
  - organosulfur compounds
    - alliin
    - allicin
    - Ajoene
    - S-allylcysteine
    - interconversions and odor

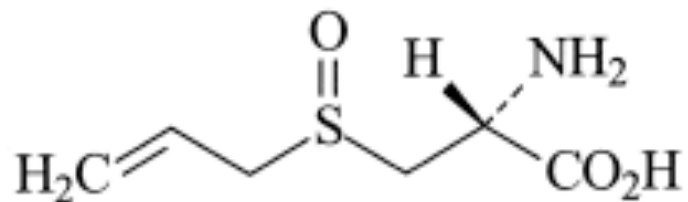




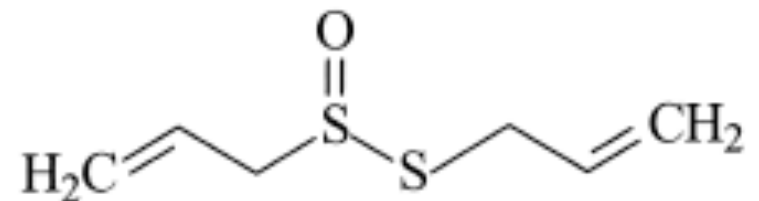
(Z)-Ajoene

2-Propenyl 3-(2-propenylsulfinyl)-1-propenyl disulfide

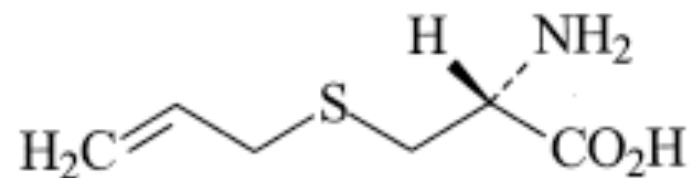
Ajoene and like allylsulfides are major components of garlic oil



**Alliin**



**Allicin**



**S-Allyl-L-Cysteine**

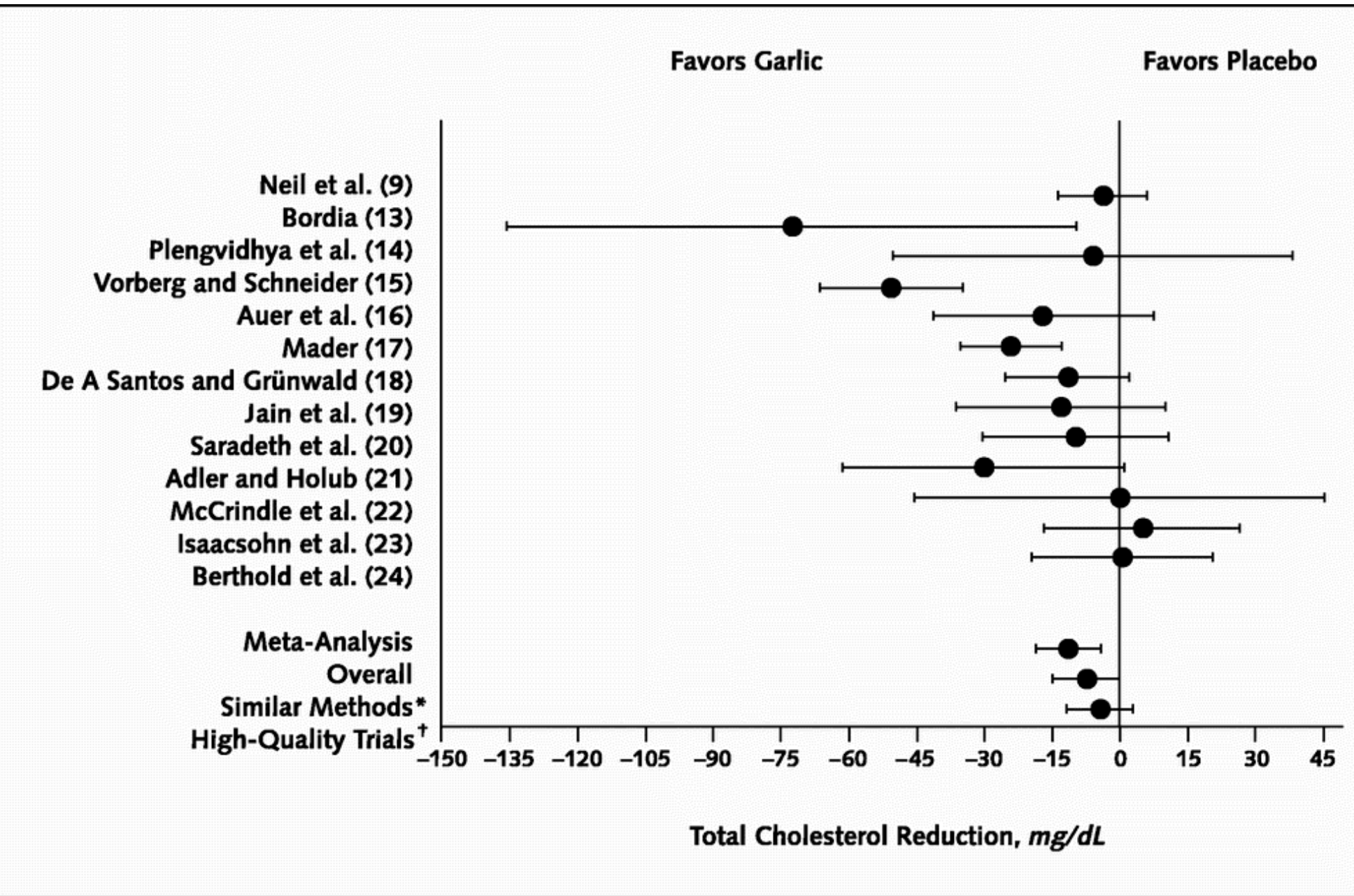
S-allylcysteine and like compounds are major components of aged garlic

# •Pharmacology

- cholesterol lowering
- decrease atherosclerosis
- triglyceride lowering
- antihypertensive
- antimicrobial
- insecticide
- increased fibrinolysis
- decreased plaque size
- decreased platelet aggregation
- increased catalase and glutathione peroxidase
- decreased cancer induction (animal studies)

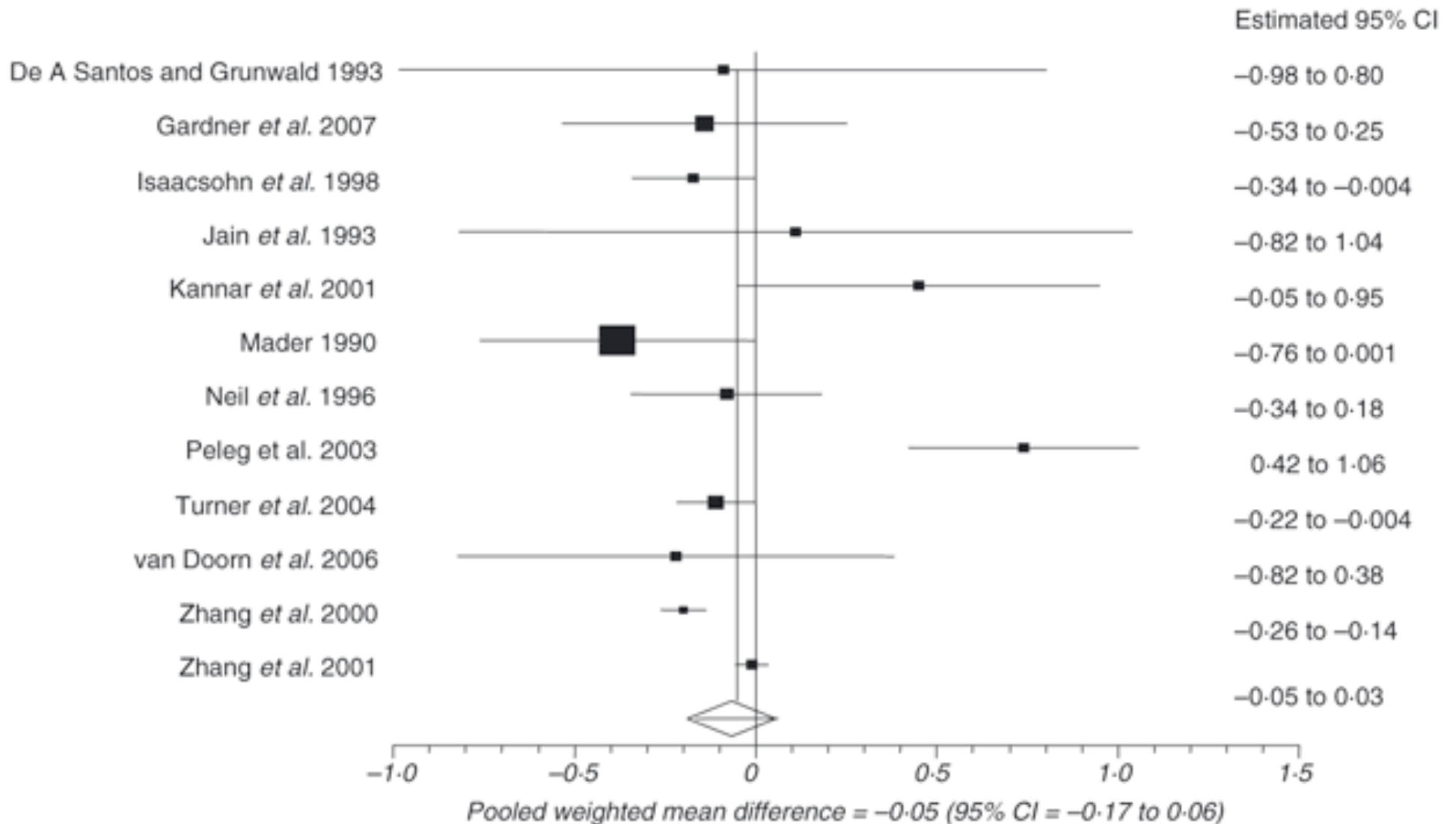
## cholesterol lowering

- most early studies (>40) show lowering effects but studies are often not of high quality
- Meta-analyses of earlier studies have shown a cholesterol lowering effect of 10%, triglycerides of 10% and LDL of 11%. (Ann Int Med 119:599-605,1993;J R Coll Physicians-London 28:39-45,1994, Ann Int Med 133:420-429, 2000, J Am Acad Nurse Prac 2003;15:120-128) but many available studies are lacking in quality



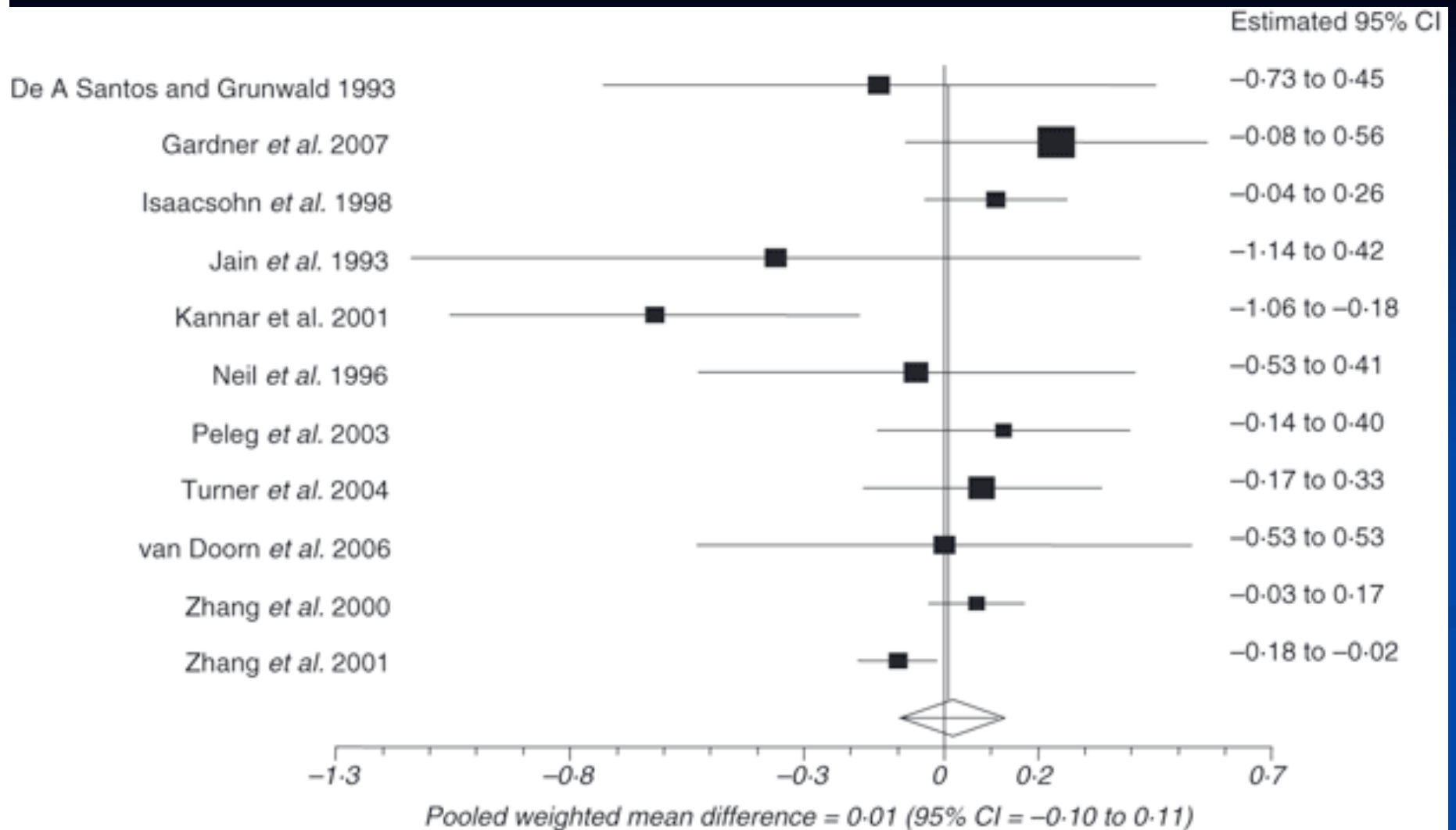
## lipid lowering

- Recent well designed studies show no effect on cholesterol lowering (see next slides)
- Kwai story
- Kanner et al (J Am Coll Nutr 2001;20:225-231) used a high potency, enteric coated garlic powder prep for 12 weeks to lower total and LDL cholesterol (n=46, 9.6mg/d allicin);
- Gardner et al (Gardner, C. D. et al. Arch Intern Med 2007;167:346-353) tested raw garlic and 2 well described commercial products and showed no benefit.



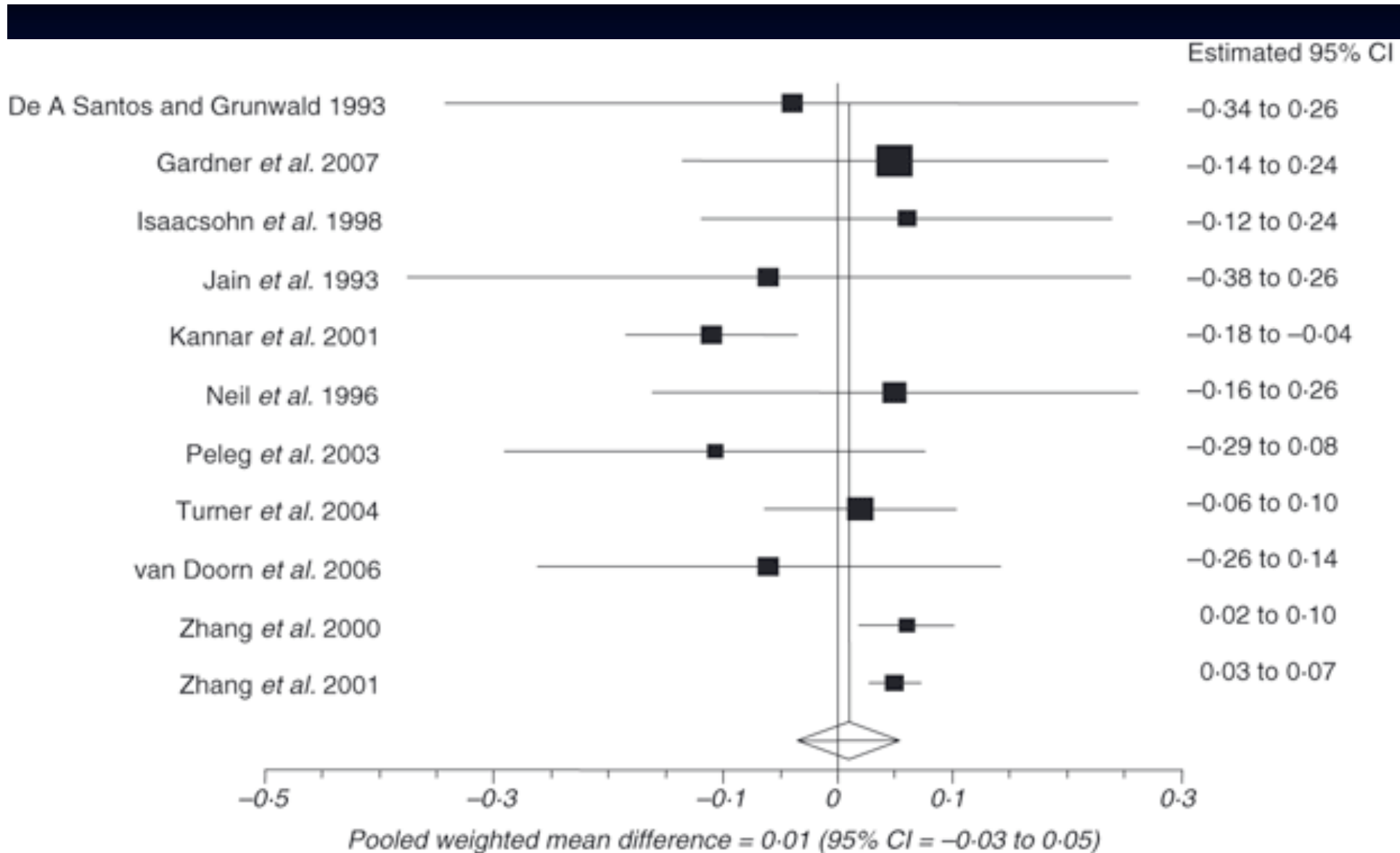
Khoo YS and Aziz Z J Clin Pharm Ther. 2009 Apr;34:133-45

Total cholesterol



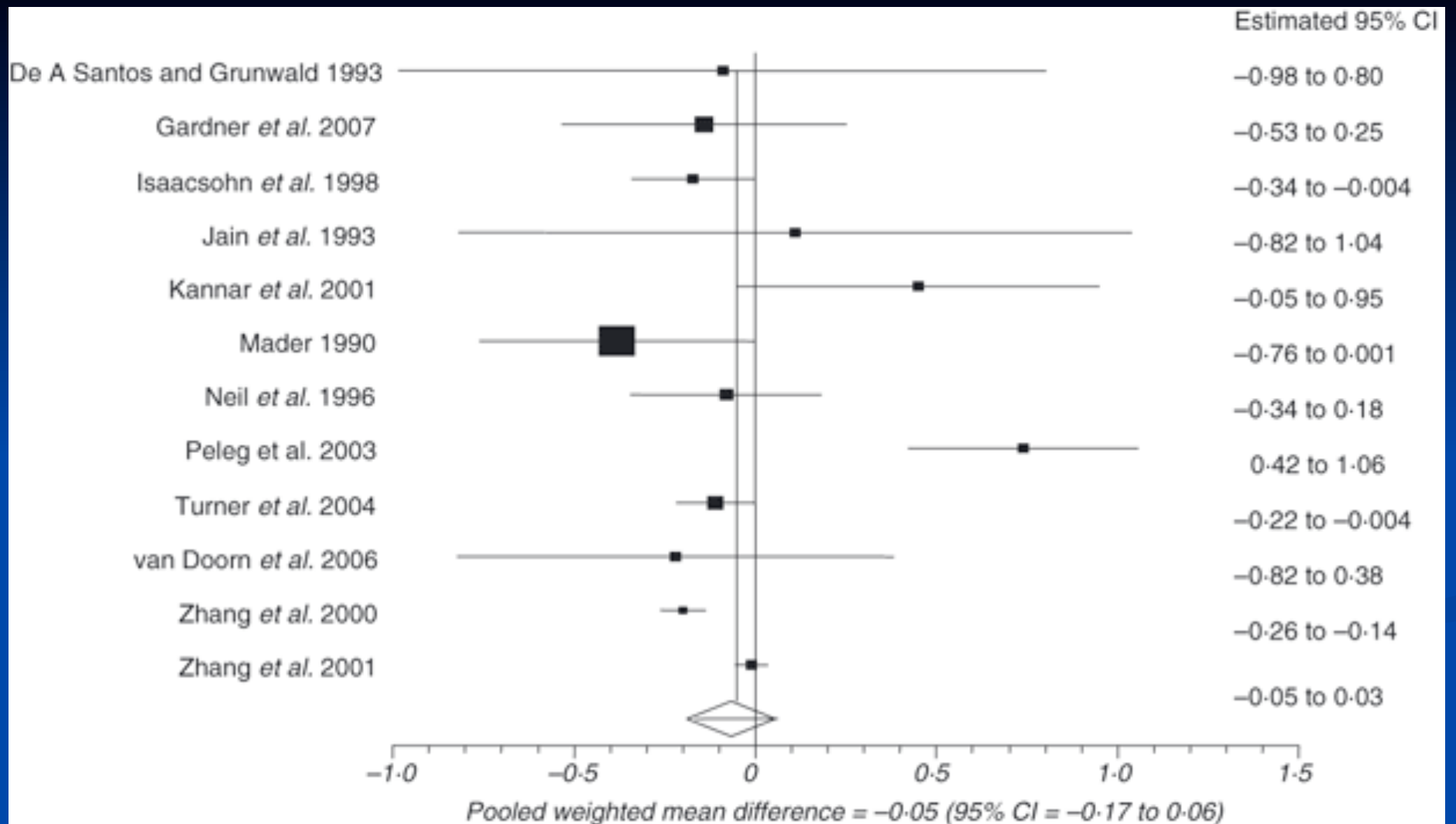
Khoo YS and Aziz Z J Clin Pharm Ther. 2009 Apr;34:133-45

LDL cholesterol



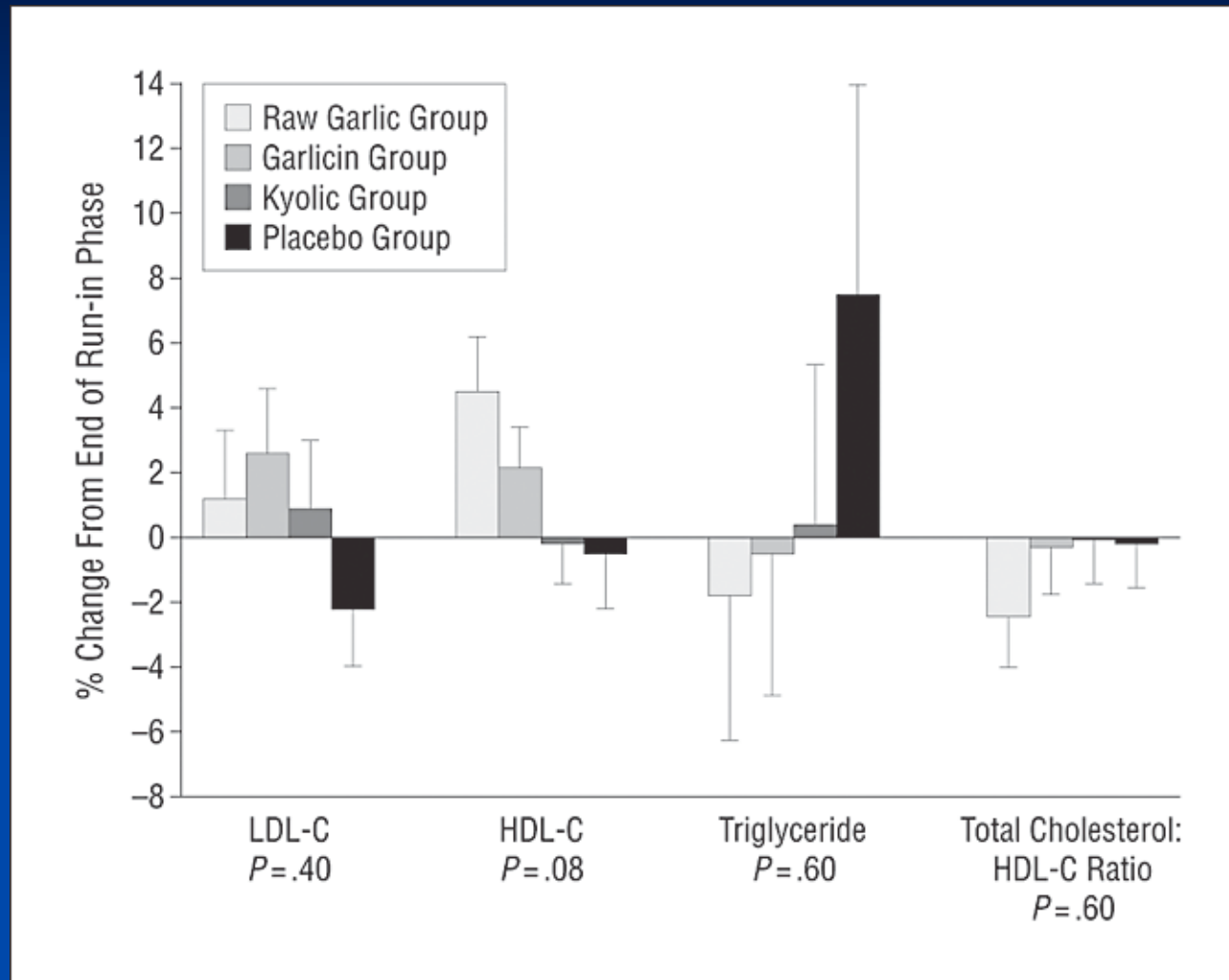
Khoo YS and Aziz Z J Clin Pharm Ther. 2009 Apr;34:133-45

HDL cholesterol



Khoo YS and Aziz Z J Clin Pharm Ther. 2009 Apr;34:133-45  
triglycerides

## Six-month percent change (mean and SE) relative to the end of the run-in phase in participants with available data



Gardner, C. D. et al. Arch Intern Med 2007;167:346-353.

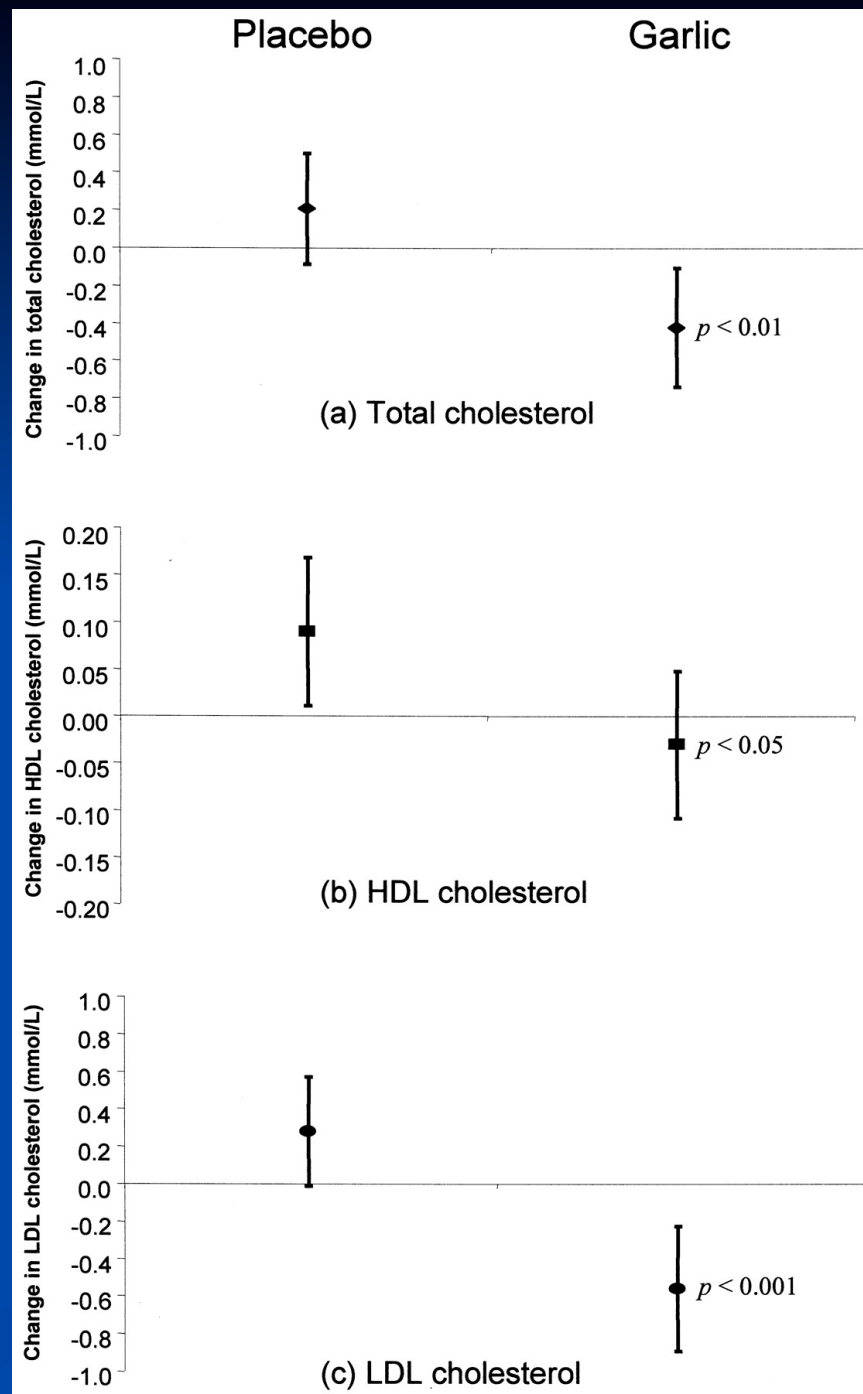
Kanner et al. J Am  
College Nutr  
2001;20:225-231.

N=42

EC garlic powder tab  
standardized to 2.4mg  
allicin/tab

Dose: 2 BID or 9.6mg  
allicin/d for 12 weeks

Diet modification run-in  
period of 1-2 weeks prior  
to study

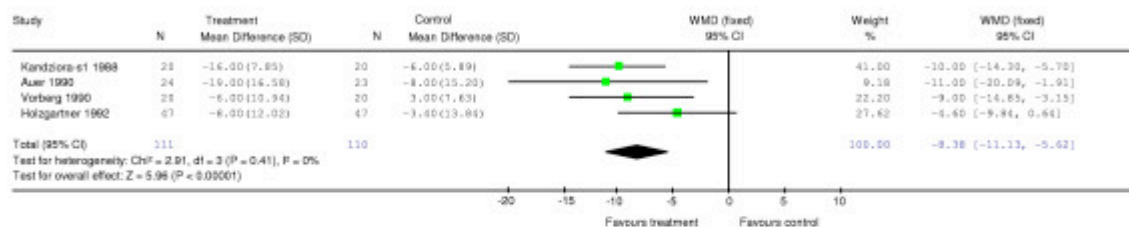


# Other beneficial garlic effects in heart and vascular disease

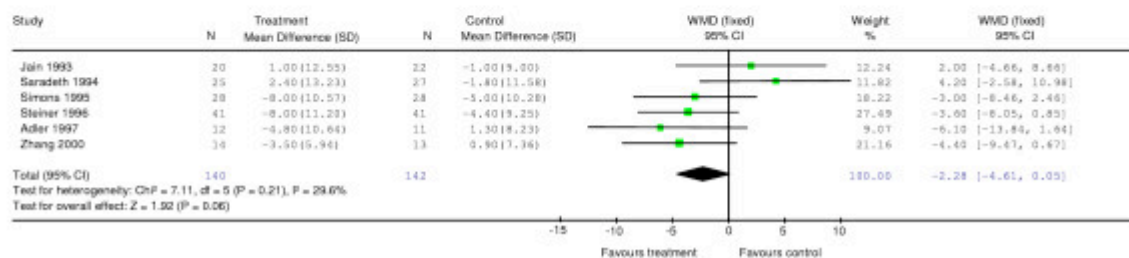
- One study showed decrease in plaque size (n=152, 48mos) compared to placebo (Koscielny et al. *Atherosclerosis* 144:237-249,1999)
- Another study indicated that chronic garlic intake increased the elasticity of the aorta (*Circulation* 1997;96:2649-2655)
- Small reduction in systolic and diastolic blood pressure
- Garlic has modest platelet adhesion inhibition effects

# Ried et al. BMC Cardiovasc Disord 2008;8:13

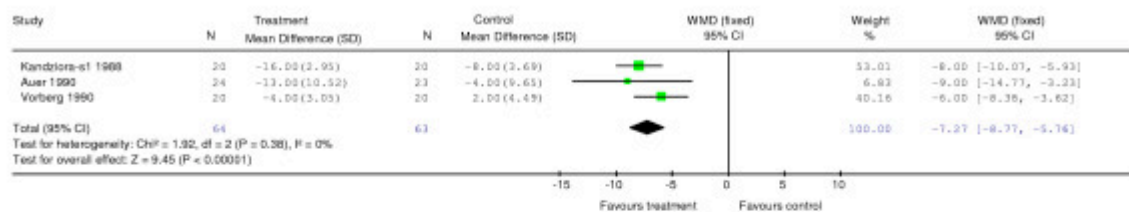
## A) SBP hypertensive subgroup



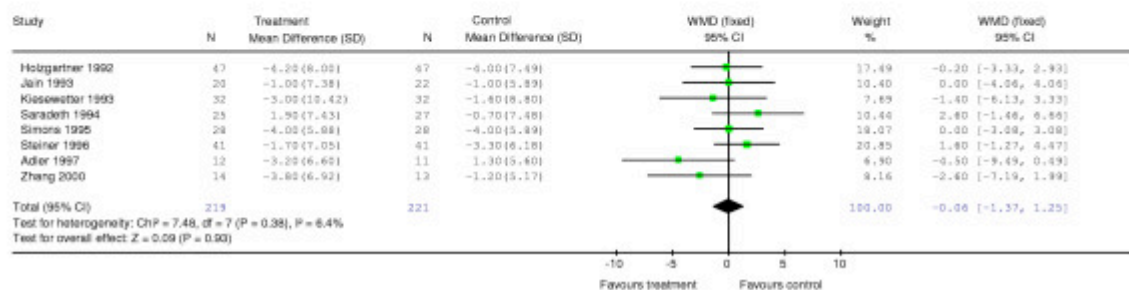
## B) SBP normotensive subgroup



## C) DBP hypertensive subgroup



## D) DBP normotensive subgroup



# Other garlic benefits?

## ■ Evidence - cancer

- A meta-analysis showed modest protective effects for diet intake for colorectal RR=0.69 and stomach cancers (RR=0.53) Fleischauer et al. Am J Clin Nutr 2000 Oct;72(4):1047-52.
- However, supplements did not reduce precancerous lesions. Yu, YC et al. J Natl Cancer Inst. 2006 Jul 19;98(14):945-6.

## ■ Evidence - infections

- A 12 weeks use of a potent garlic supplement reduced the incidence of the common cold compared to placebo (n=146); Rx 24 colds vs placebo 65 colds. Recovery was faster in the Rx. Josling P. Advances in Therapy 2001;18:189-193. Other studies underway?
- 0.6% cream of ajoene may help with tinea infections.

## ■ Insect Repellent

- Lab studies no (Rajan et al. Med Vet Entomol 2005;19:84-89.) ; field studies maybe (RR=0.7, 1.2g/d in crossover study in Swedish military) Stjernberg et al. JAMA 2000;248:831.

# Garlic

## ■ Adverse effects

- Nothing special

## ■ Drug interactions:

- platelet anti-adhesion effects; careful with aspirin and warfarin
- Reduced AUC of saquinavir in volunteers. May induce p-glycoprotein (more later) but effect may be product dependant. Avoid garlic supplement use with anti HIV therapies

## ■ Summary

## *Garlic*

- **Efficacy:** the literature is conflicting for use in hyperlipidemia and hypertension; possible mild benefit if excellent product is used; other cardiovascular benefits are possible.
- **Safety:** good
- **Drug interactions:** warfarin; possibly aspirin and other antiplatelet adhesion drugs; not with HIV drugs
- **Product selection:** avoid Kwai? Suggest enteric coated garlic powder tablets standardized to about 2mg allicin/tab.
- **Dose:** equivalent of about 4g (2-4 cloves) of fresh garlic per day (~8-12mg allicin). Want >4mg allicin delivered past the stomach
- **Questions remaining** include
  - *Who can benefit from use; Other uses?*
- *GWE: Dietary garlic is good. I am not impressed with the health benefits of garlic supplements.*

# Saw palmetto

## ■ Botany

- *Serenoa repens*, Sabal, American dwarf palm tree, cabbage palm

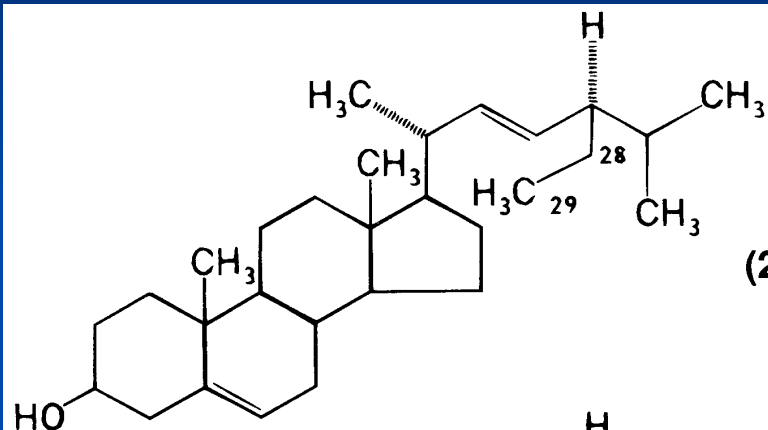
## ■ History

## ■ Chemistry

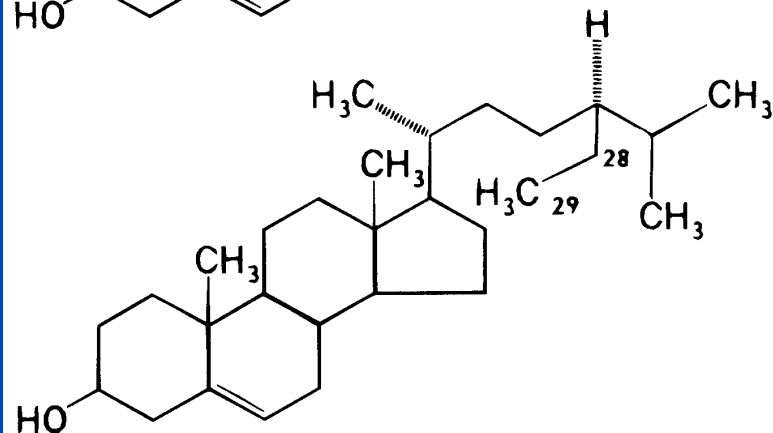
- fatty acids
- sitosterols
- flavones, isoflavones, coumestrans<sup>#</sup>

## ■ Pharmacology

- lipid extracts of berry inhibit testosterone 5 $\alpha$ -reductase and therefore conversion of testosterone to dihydrotestosterone

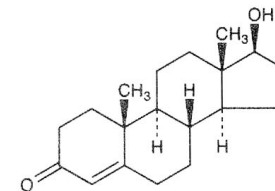


**Stigmasterol**  
**(22E)- Stigmasta-5,22-dien-3β-ol**



**β-Sitosterol**  
**Stigmast-5-en-3β-ol**

9322. **Testosterone.** (17β)-17-Hydroxyandrost-4-en-3-one; Δ<sup>4</sup>-androst-17β-ol-3-one; *trans*-testosterone; Andro; Mertestate; Oreton; Testoderm; Testolin; Testro AQ; Virsterone. C<sub>19</sub>H<sub>28</sub>O<sub>2</sub>; mol wt 288.43. C 79.12%, H 9.78%, O 11.09%. Principal hormone of the testes, produced by the interstitial cells. Major circulating androgen; converted by 5α-reductase in androgen-dependent target tissues to 5α-dihydrotestosterone which is required for normal male sexual differentiation. Also converted by aromatization to estradiol, *q.v.* Isolated from bull testes: David *et al.*, *Z. Physiol. Chem.* **233**, 281 (1935). Prepn from cholesterol and confirmation of structure: A. Butenandt, G. Hanisch, *Ber.* **68**, 1859 (1935); *idem.*, *Z. Physiol. Chem.* **237**, 89 (1935); from dehydroandrosterone: L. Ruzicka, A. Wettstein, *Helv. Chim. Acta* **18**, 1264 (1935); from mixed esters: L. Ruzicka *et al.*, *ibid.* 1478. Crystal structure: P. J. Roberts *et al.*, *J. Chem. Soc., Perkin Trans. II* **1973**, 1978. Historical review: J. M. Hoberman, C. E. Yesalis, *Sci. Am.* **272**, 76-81 (Feb. 1995). Review of role in aging males: F. E. Kaiser, J. E. Morley, *Neurobiol. Aging* **15**, 559-563 (1994); of clinical relevance in females: R. S. Rittmaster, *Am. J. Med.* **98**, Suppl. 1A, 17S-21S (1995).



Needles from dil acetone, mp 155°. [α]<sub>D</sub><sup>24</sup> +109° (c = 4 in alc). uv max: 238 nm. Insol in water. Sol in alcohol, ether, and other organic solvents.

Acetate, C<sub>21</sub>H<sub>30</sub>O<sub>3</sub>, mp 140-141°. 17β-Cyclopentanepropionate, C<sub>27</sub>H<sub>40</sub>O<sub>3</sub>, *testosterone cypionate*, *depAndro*, *Depotest*, *Depo-Testosterone*, *Depovirin*, *Per-testis*, *Virilon*. Pharmacology: A. C. Ott *et al.*, *J. Clin. Endocrinol. Metabol.* **12**, 15 (1952). Crystals, mp 101-102°. [α]<sub>D</sub><sup>25</sup> +87° (CHCl<sub>3</sub>). Sol in oils.

Ethanate, C<sub>26</sub>H<sub>40</sub>O<sub>3</sub>, *Andro LA*, *Androtardyl*, *Delatestryl*, *Everone*, *Primoteston*, *Testinon*, *Testo-Enant*. Prepn: Junkmann *et al.*, U.S. pat. 2,840,508 (1958 to Schering AG). Comprehensive description: K. Florey, *Anal. Profiles Drug Subs.* **4**, 452-465 (1975). Crystals, mp 36-37.5°.

Isobutyrate, C<sub>23</sub>H<sub>34</sub>O<sub>3</sub>, *Perandren M*. Propionate, C<sub>22</sub>H<sub>32</sub>O<sub>3</sub>, *Anertan*, *Enarmon*, *Neo-Hombreol (amp.)*, *Orchisterone*, *Perandren (amp.)*, *Synandrol*, *Synandrol Testosterone*, *Viramona*. Prepn: H. Koester *et al.*

# Saw palmetto

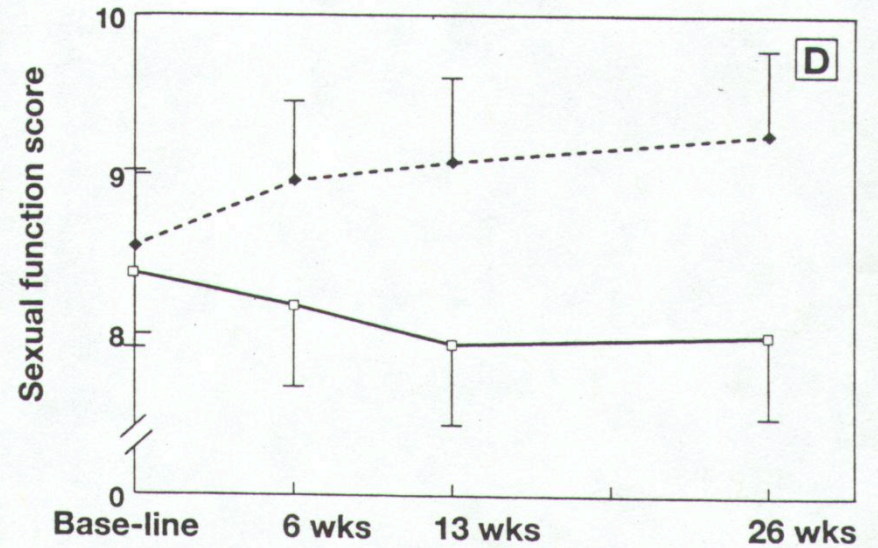
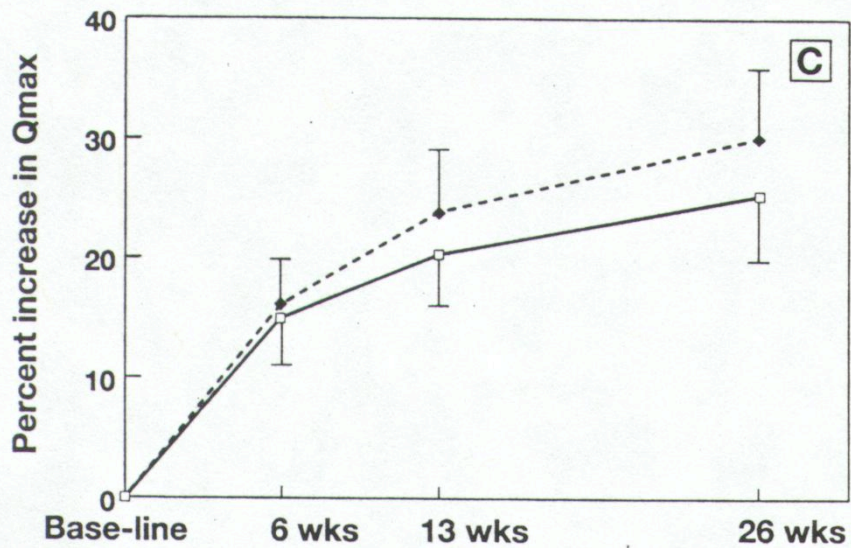
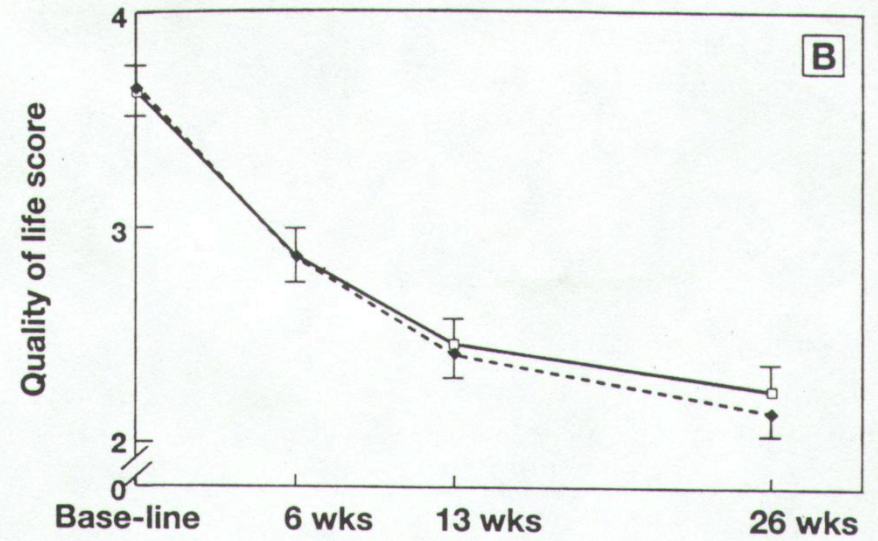
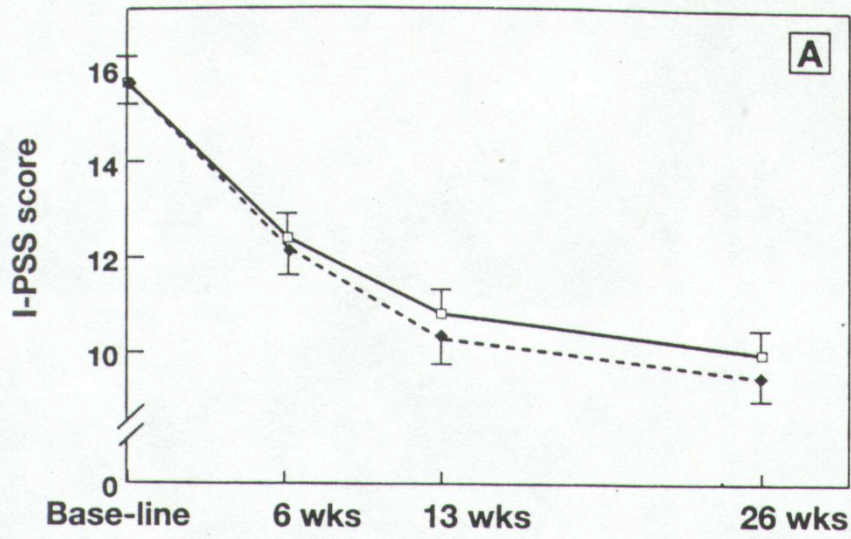
## ■ Pharmacology (continued)

- block binding of DHT to receptors
- block nuclear not cytosolic estrogenic, progestogenic and androgenic receptors in prostate
- inhibit cyclooxygenase (one report of a bleed) and 5-lipoxygenase thereby decreasing inflammation
- inhibit prolactin at receptor level
- inhibit testosterone metabolism in prostate tissues in vitro
- observations: no big plasma changes in hormones. No PSA changes. Favorable cytological changes occur in the prostate.

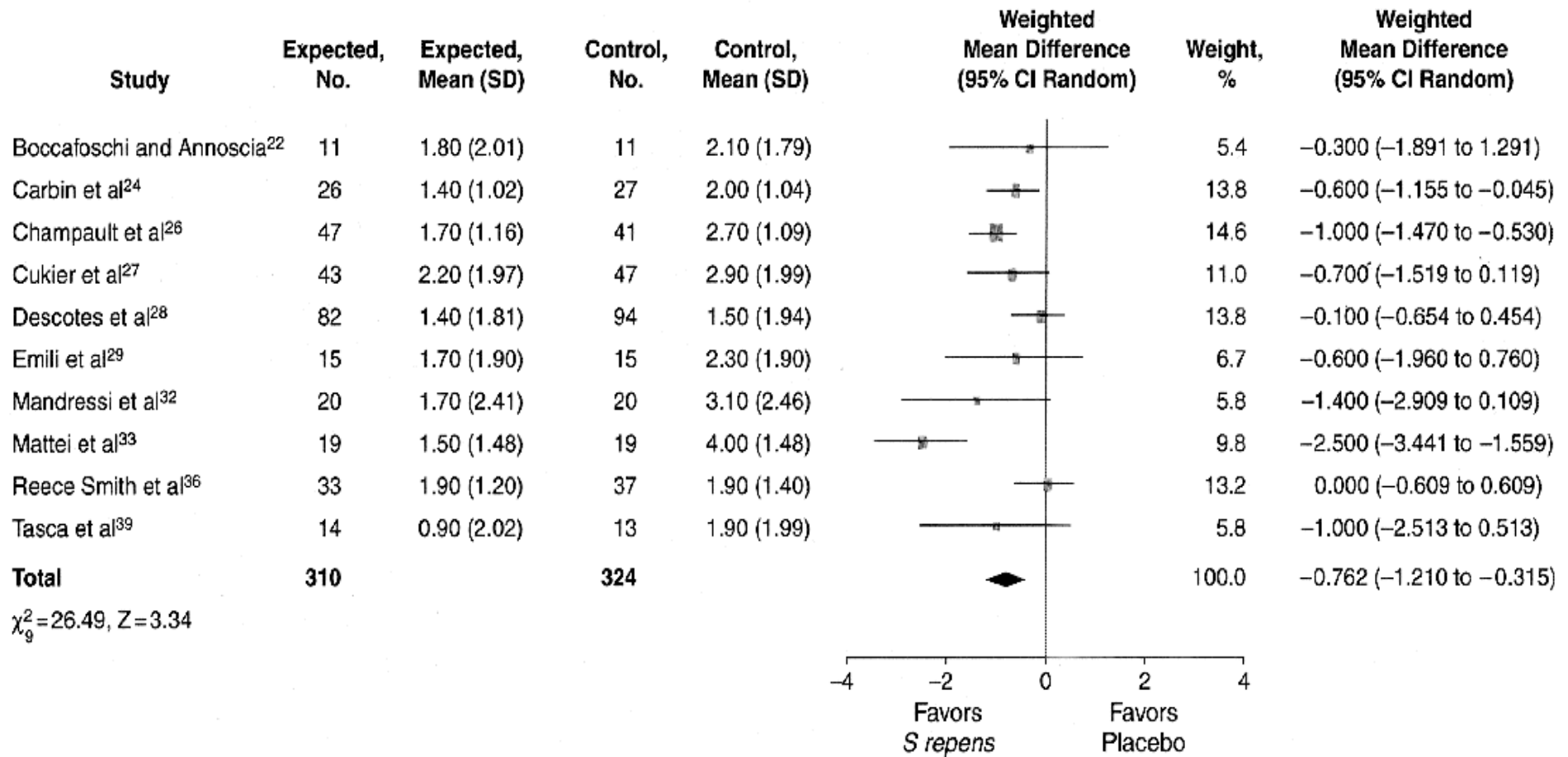
# •Saw palmetto

## Evidence for efficacy in BPH

- Vs Active control
  - Carraro et al (Prostate 1996;29:231-240)
    - multicentered European randomized trial of 1098 patients
    - compared Permixon ( hexane extract of saw palmetto) vs. finasteride (Proscar)
  - Debruyne et al. Comparison of a phytotherapeutic agent(Permixon) with an alpha-blocker (Tamsulosin): a one-year randomized international study. *Eur Urol.* 2002;41:497-507. same
- Vs placebo
  - Most studies but not all (see recent Bent study) have showed benefit vs placebo, e.g. study by Gerber et al. (Urology 2001;58:960-5)



**Fig. 1.** Mean total IPSS (A), mean quality of life score (B), percentage of increase in mean peak urinary flow (C), and mean sexual function score (D), in men with BPH receiving either 320 mg Permixon® (open squares) or 5 mg finasteride (solid diamonds) ( $\pm 0.95$  confidence intervals).



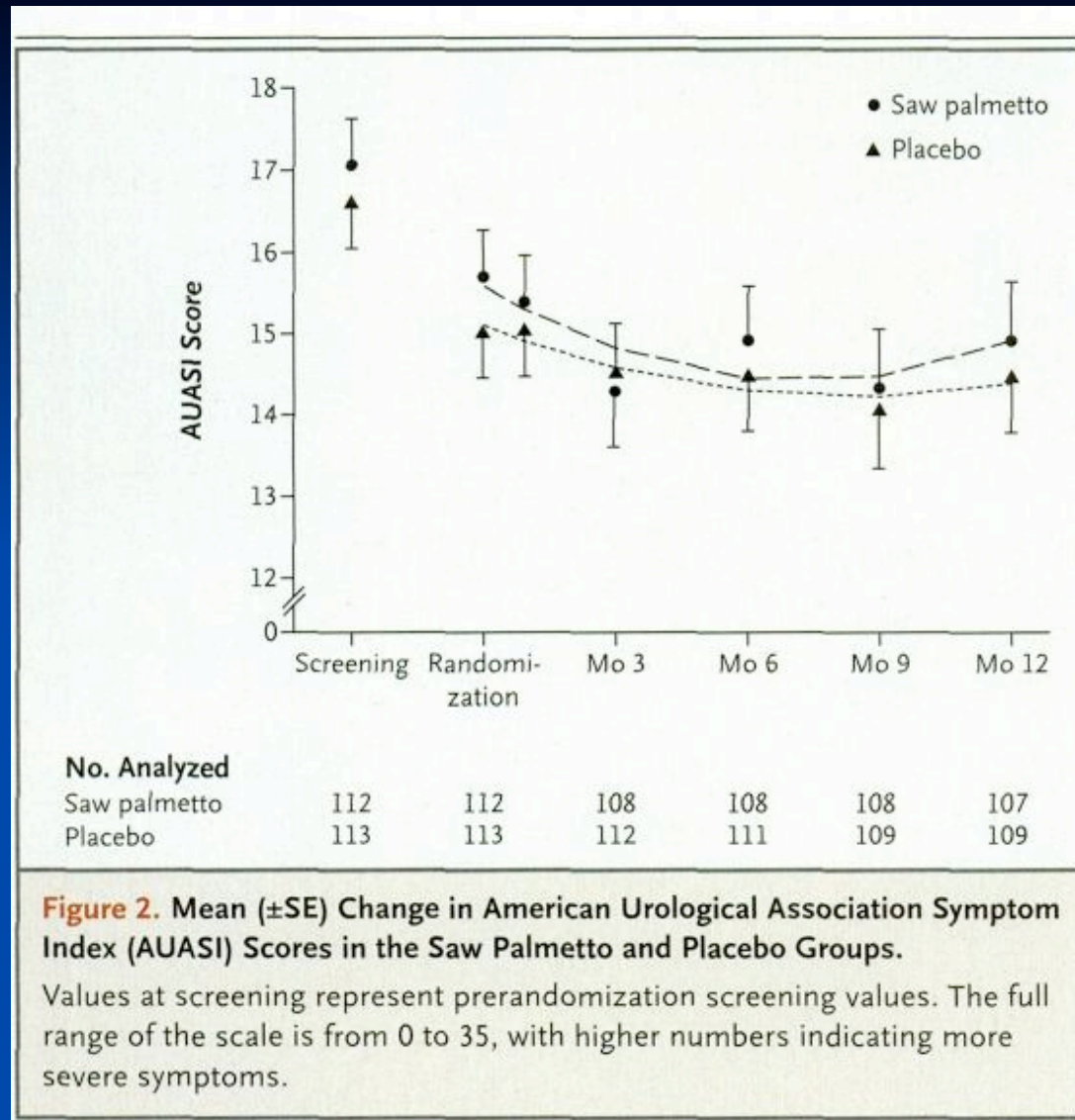
From Wilt et al. JAMA 280:1604-1609, 1998

**TABLE I. Changes in International Prostate Symptom Score and quality-of-life score in men treated with saw palmetto and placebo for 6 months**

	Initial	2 Months	4 Months	Final	Change
Symptom score					
Saw palmetto	16.7 ± 4.9	13.1 ± 4.6	12.0 ± 5.1	12.3 ± 5.5	-4.4 ± 5.9
Placebo	15.8 ± 4.8	12.4 ± 5.2	13.3 ± 5.4	13.6 ± 6.6	-2.2 ± 5.4
					<i>P</i> = 0.038
Quality-of-life score					
Saw palmetto	3.3 ± 1.1	3.0 ± 1.4	2.6 ± 1.2	2.6 ± 1.5	-0.7 ± 1.5
Placebo	3.1 ± 1.3	2.8 ± 1.1	2.8 ± 1.3	2.8 ± 1.2	-0.3 ± 1.1
					<i>P</i> = 0.20

*Data presented as the mean ± SD.*

Gerber et al. Urology 2001;58:960-965



Bent et al. NEJM 2006;354:557-566 n=255 Rx for 12 mos. Used Indena carbon dioxide extract product yielding 160mg/capsule (91% fatty acids). One BID.



■ **Chronic noninfective prostatitis**-no benefit

■ **Adverse effects:**

–one report of hemorrhage during surgery

–due to prolactin inhibition and some isoflavone content, avoid in pregnancy and lactation

■ **Dose:** 160mg twice a day or 320mg q d of a 85-95% lipid extract

## ■ Summary

## *Saw Palmetto*

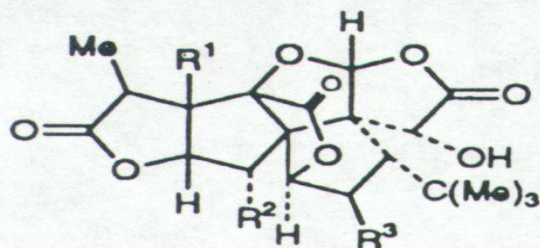
- **Efficacy:** overall evidence in reducing symptoms of BPH
- **Safety:** good; one report of hemorrhage during surgery; avoid in pregnancy
- **Drug interactions:** none noted so far
- **Product selection:** want standardized extract containing 85-95% fatty acids and sterols
- **Dose:** about 160mg of extract BID for treatment; some use 320mg q d
- **Questions remaining include**
  - *Will saw palmetto prevent BPH and even prostate cancer? Maybe avoid CO2 extract?*
- *GWE: Get exam to rule out cancer then for BPH, give it a try for 6 months before using stronger drugs*

## Pygeum and BPH

- not as well studied as saw palmetto
- extract of the bark of an evergreen tree (*Prunus africana*) found in Africa
- tree nearly endangered so use is not to be encouraged
- saw palmetto is cultivated
- studies support its use for BPH (e.g. Wilt et al. *Cochrane Database Syst Rev.* 2002;(1):CD001044); takes a few months to work
- products should be standardized to contain 14% triterpenes and 0.5% docosanol
- dose: 100mg qd is therapeutically equivalent to 50mg BID
- no special safety problems; better than Saw palmetto??  
Combination products with Saw palmetto better??

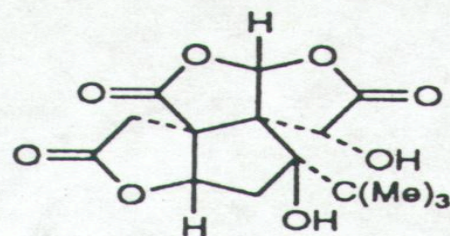
# Ginkgo biloba

- Botanical Aspects
- History
- Chemistry
  - *bioflavonoid glycosides*  
*quercetin, kaempferol, isorhamnetin*
  - *terpenoids*  
*Ginkgolides A,B,C,J*  
*bilobalide*

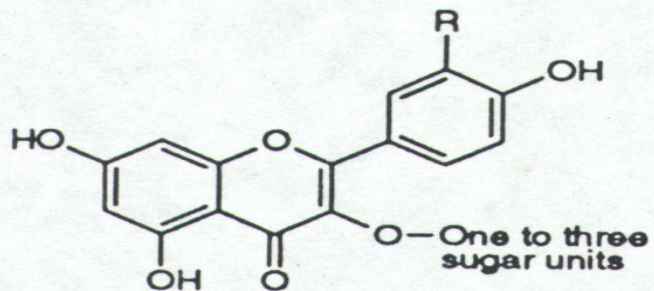


Ginkgolide structures

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
Ginkgolide A;	OH	H	H
Ginkgolide B;	OH	OH	H
Ginkgolide C;	OH	OH	OH
Ginkgolide J;	OH	H	OH
Ginkgolide M;	H	OH	OH



Bilobalide

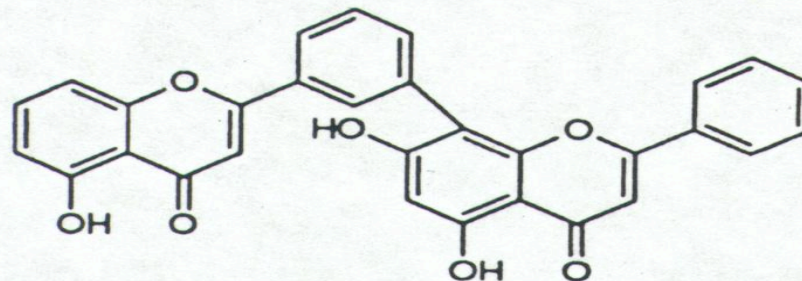


Flavonol structures

Kaempferol derivatives; R = H

Quercetin derivatives; R = OH

Isorhamnetin derivatives; R = OMe



Amentoflavone

Fig. 23.5. Some constituents of *Ginkgo biloba* leaves

# • *Ginkgo biloba*

## ■ Pharmacology

- Antioxidant/antiinflammatory
- Free radical scavenger
- Anti amyloid formation (in vitro)
- Anti PAF (ginkgolide B)-
  - Decreased platelet activation by collagen (ex-vivo human study)
- Complex effects on insulin responses to glucose load (increased in normals but decreased in diabetics)
- Vasodilation
- Lower blood pressure
- Increased capillary blood flow, decreased blood viscosity
- Stimulation of endothelium-derived relaxing factor
- Increased nitric oxide and decreased endothelin-1 in vivo
- Neuroprotective effects and neurotransmitter modulations (animal and in vitro studies)

## Common Uses

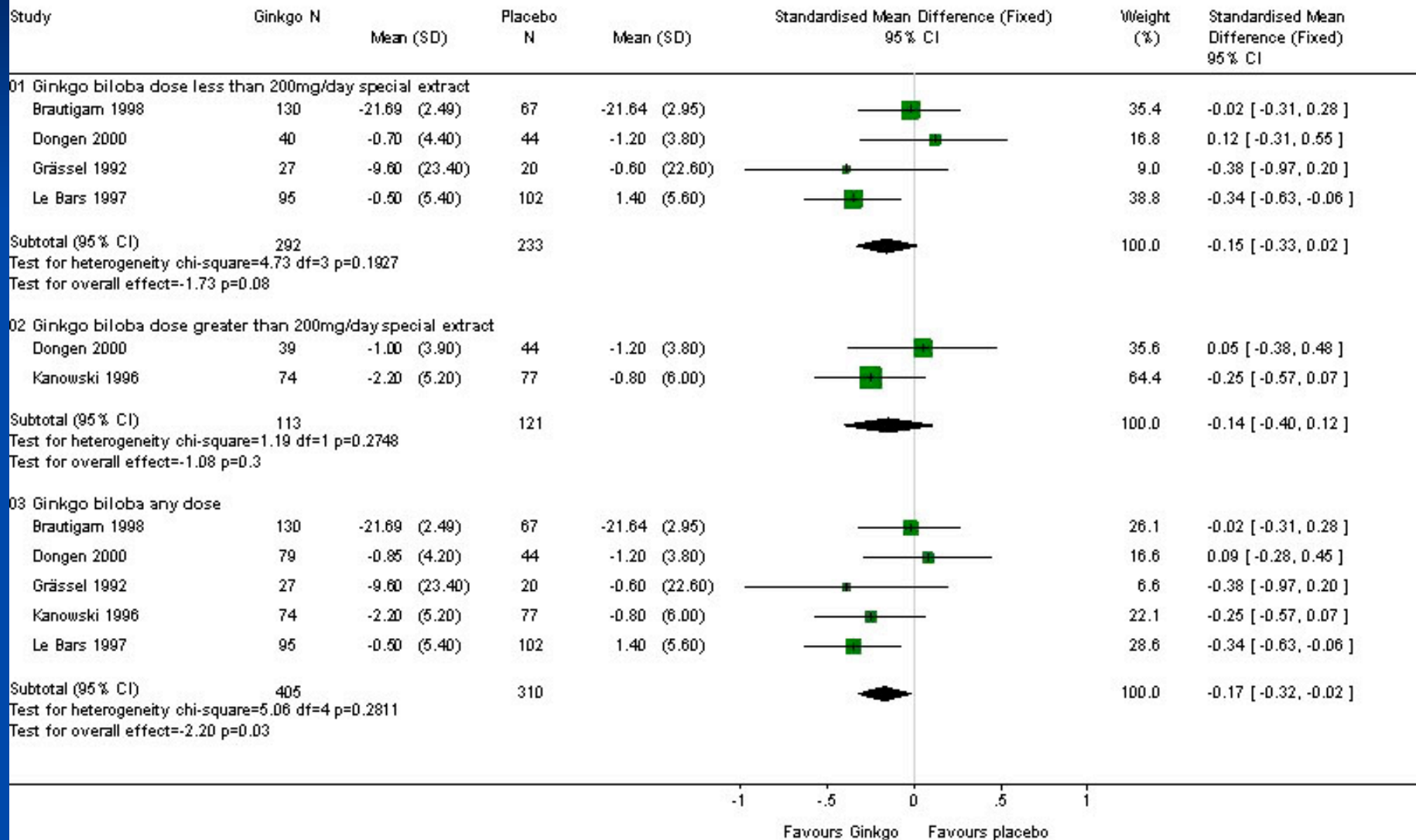
- Claudication (peripheral vascular disease)
- Dementia treatment (multi-infarct and Alzheimer's)
- Cerebral insufficiency
- Age-associated memory impairment
- Memory enhancement (in healthy patients)
- Tinnitus
- Altitude (mountain) sickness
- Vertigo
- Macular degeneration
- Premenstrual syndrome (PMS)
- Decreased libido and erectile dysfunction
- Depression and seasonal affective disorder (SAD)
- Chemotherapy adjunct (reduce adverse vascular effects)
- Multiple sclerosis
- Glaucoma
- Acute ischemic stroke

# Ginkgo and Dementia, Alzheimer's Disease

- >30 double blind, placebo controlled trials evaluating ginkgo have been published. Most early studies show ginkgo to be better than placebo. The recent NIH funded GEM study (n=3069) showed no prevention properties. One similar large trial in Europe has yet to be completed.

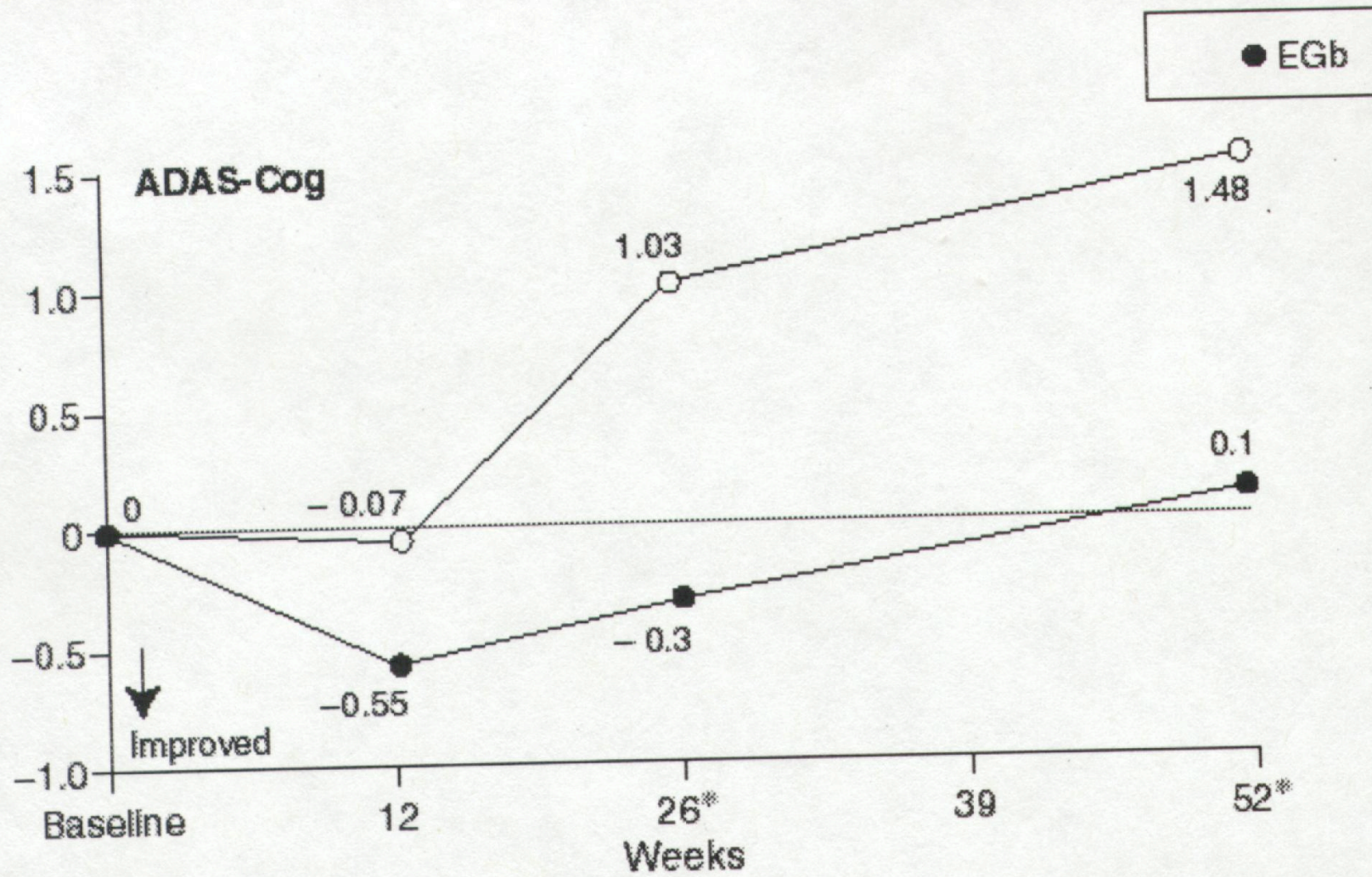
# Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of cognitive impairment and dementia: a meta-analysis of randomized trials. Am J Med 2000;108(4):276-281.

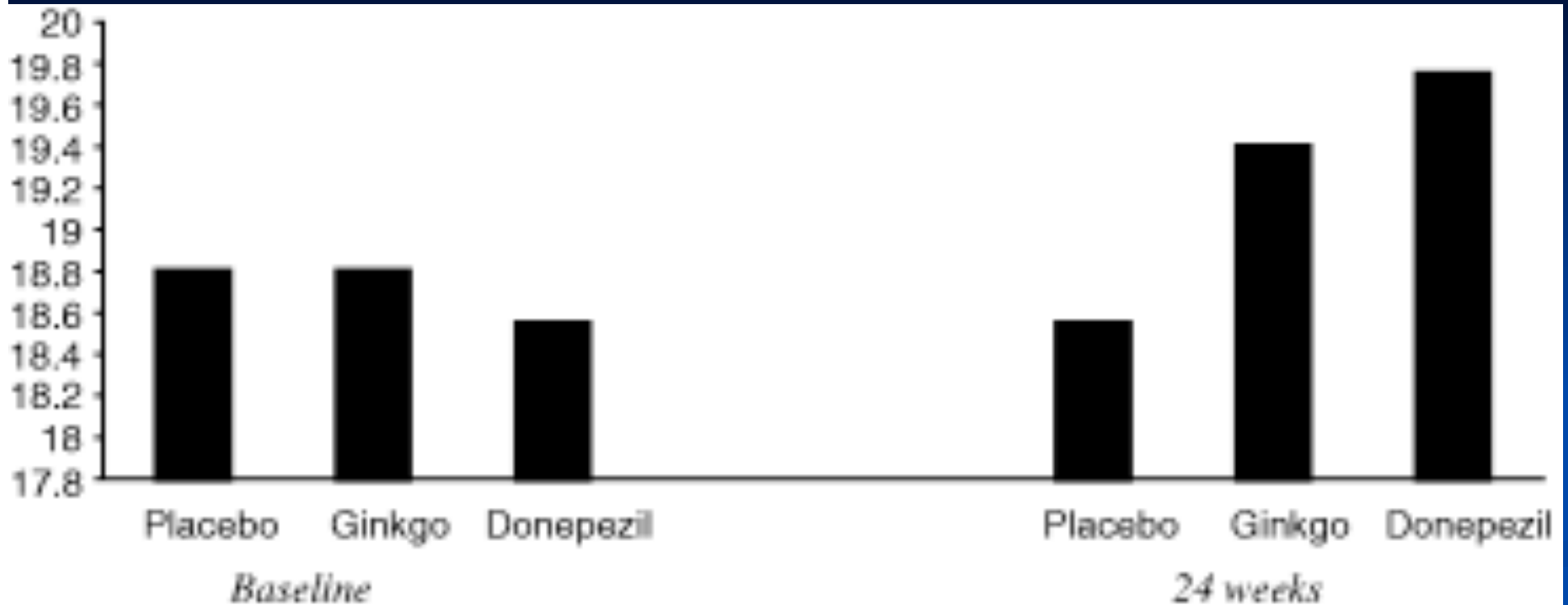
Review: Ginkgo Biloba for Cognitive Impairment and Dementia  
 Comparison: 01 Ginkgo biloba vs placebo  
 Outcome: 11 Cognition (change from baseline after treatment of 24 weeks)



# Ginkgo - JAMA article

- LaBars et al., JAMA 278:1327-1332, 1997 (Oct 22)
  - USA study 6 research centers
  - N=309 1 year
  - 202 evaluable at 52 weeks
    - In ginkgo group 24% had 4 point improvement on ADAS-Cog vs 14% in placebo group
    - adverse effects: same as placebo
  - Large dropout rate
  - conclusions: modest improvement, improvement recognized by caregivers

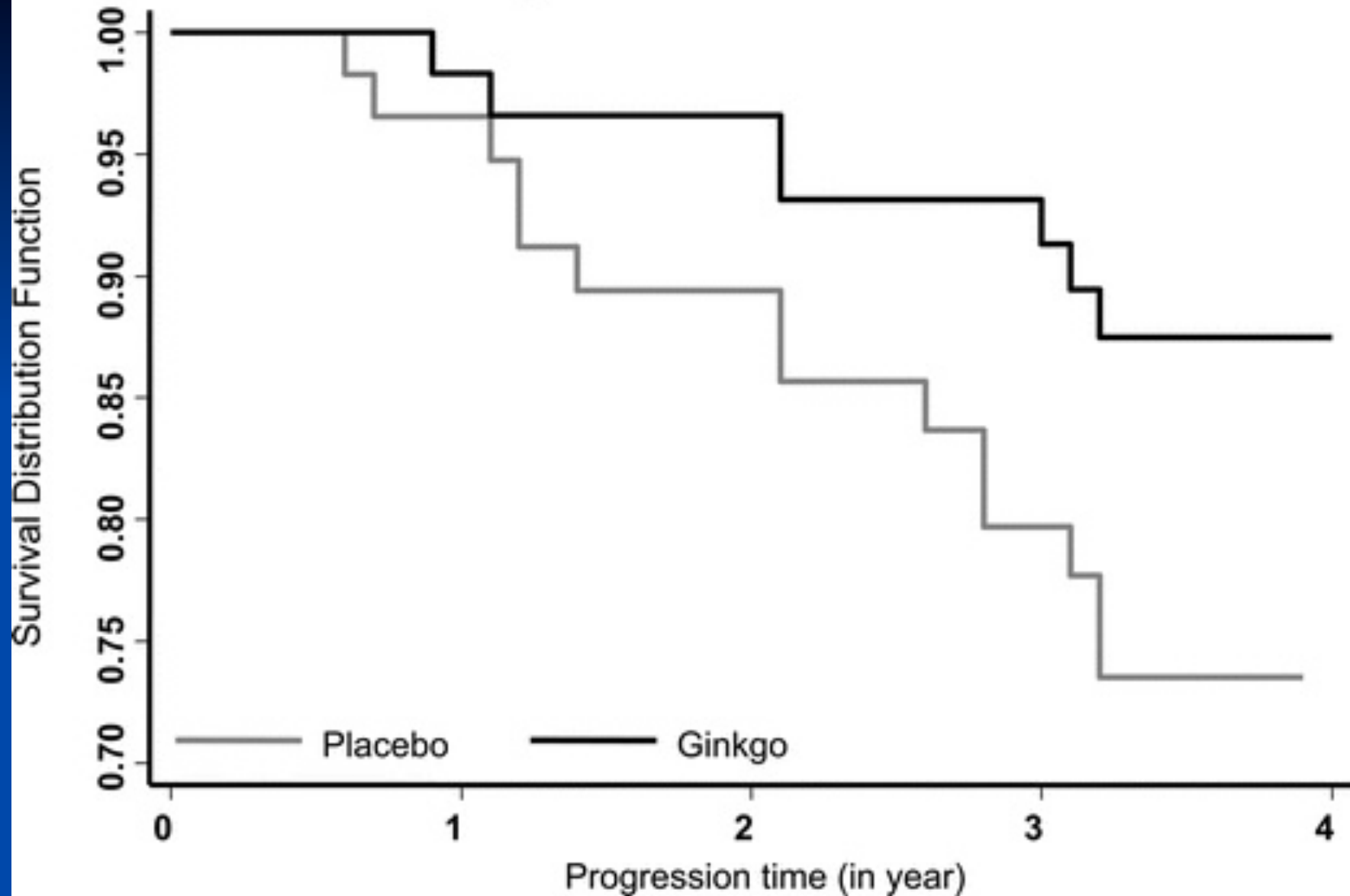




- Mini-mental state exam scores EGb761 160mg/d n=76

- Mazza, M., Capuano, A., Bria, P. & Mazza, S.  
Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study.  
*European Journal of Neurology* 2006;**13** (9): 981-985.

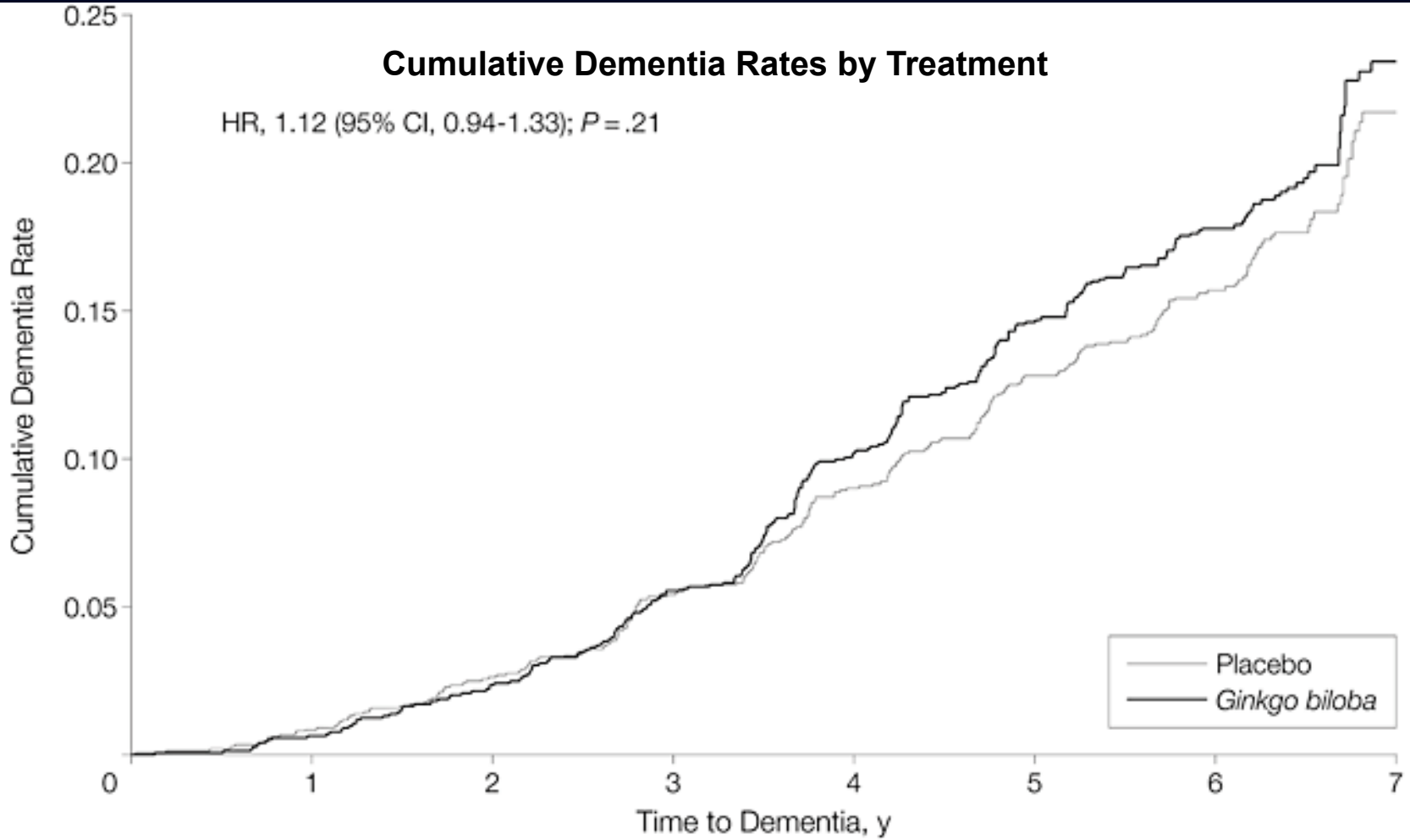
## Outcome: Progression from CDR=0 to CDR=0.5



Dodge et al. Neurology 2008;70:1809-1817 n=118 2yr (used Thorne Research GBE 80mg TID; all over 85 years of age)

### Cumulative Dementia Rates by Treatment

HR, 1.12 (95% CI, 0.94-1.33); P = .21



No. at risk

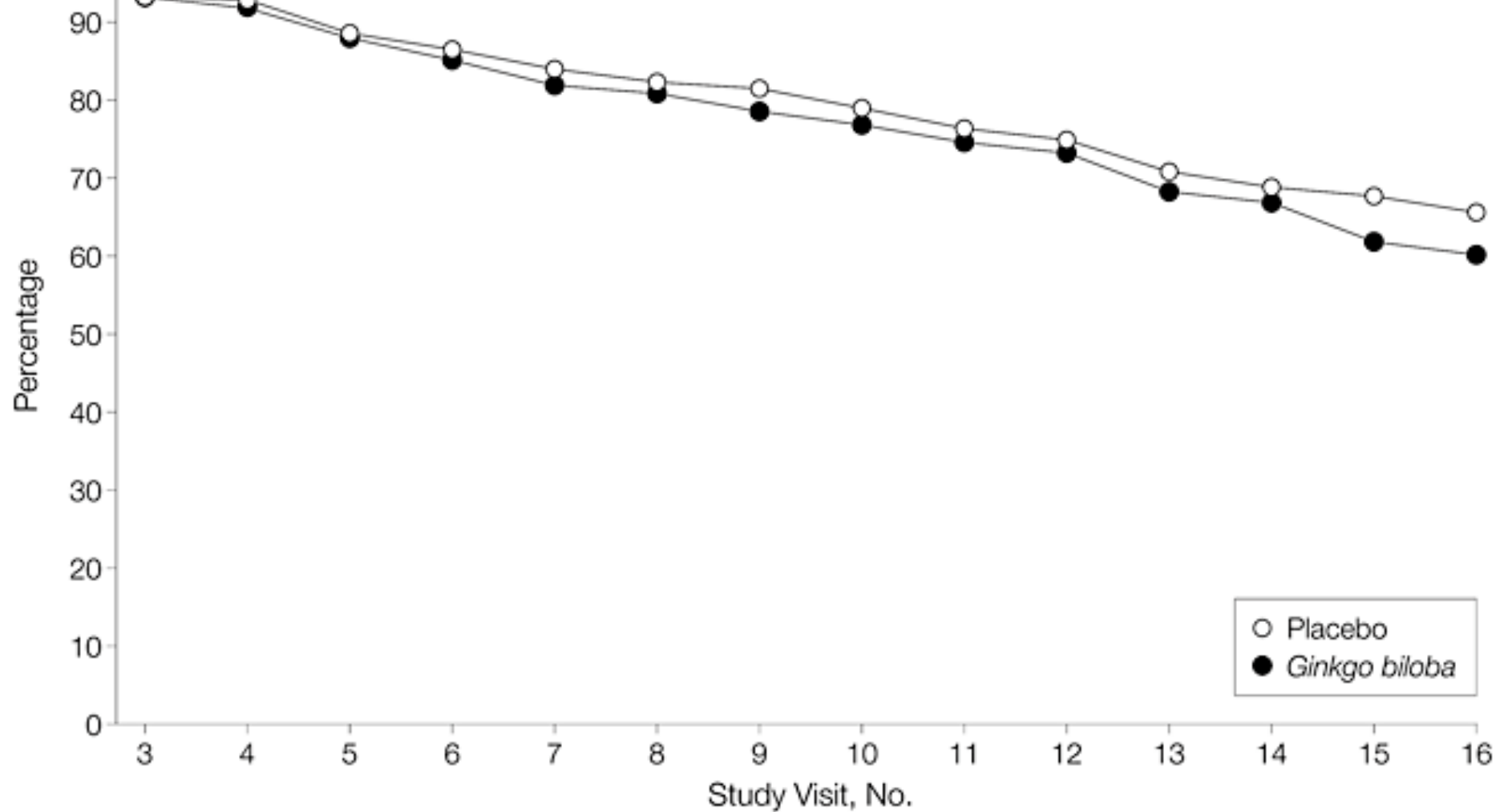
Placebo	1524	1485	1423	1342	1243	1148	792	81
<i>G biloba</i>	1545	1521	1458	1369	1254	1129	775	97

DeKosky, S. T. et al. JAMA 2008;300:2253-2262.

No. with incident dementia

Placebo	13	26	40	50	51	36	30
<i>G biloba</i>	10	26	47	66	60	40	27

## Cumulative Adherence to Assigned Study Tablets by Scheduled 6-Month Follow-up Visit (Excluding Death and Incident Dementia)



DeKosky, S. T. et al. JAMA 2008;300:2253-2262.

No. adherent

Placebo	1516	1492	1471	1433	1393	1358	1307	1267	1225	1177	1123	1005	654	246
G biloba	1540	1523	1502	1464	1437	1386	1340	1279	1212	1154	1101	996	635	239

**Table 3.** Specific Serious Adverse Events

Type	Specific Serious Adverse Events No. (%)		HR (95% CI)	P Value
	Placebo	<i>Ginkgo Biloba</i>		
Death	188 (12.3)	197 (12.8)	1.04 (0.85-1.26)	.72
Bleeding, total	140 (9.2)	138 (8.9)	0.97 (0.77-1.23)	.81
Gastrointestinal	77 (5.1)	83 (5.4)	1.06 (0.78-1.45)	.70
All other	71 (4.7)	64 (4.1)	0.89 (0.64-1.25)	.52
CHD total	204 (13.4)	211 (13.7)	1.02 (0.84-1.24)	.83
Myocardial infarction	76 (5.0)	90 (5.8)	1.18 (0.87-1.59)	.30
Angina	99 (6.5)	107 (6.9)	1.06 (0.81-1.40)	.65
Angioplasty	65 (4.3)	79 (5.1)	1.20 (0.87-1.67)	.27
CABG	49 (3.2)	51 (3.3)	1.02 (0.69-1.52)	.90
CHD death	47 (3.1)	48 (3.1)	1.01 (0.67-1.50)	.98
Stroke, total	71 (4.7)	80 (5.2)	1.12 (0.81-1.54)	.50
Ischemic	62 (4.1)	62 (4.0)	0.99 (0.70-1.41)	.96
Hemorrhagic	8 (0.5)	16 (1.0)	1.97 (0.84-4.61)	.12
Unknown	2 (0.1)	3 (0.2)		

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio.  
**DeKosky, S. T. et al. JAMA 2008;300:2253-2262.**

McCarney et al. *Int J Geriatr Psychiatry*. 2008 Dec;23(12):1222-30

**OBJECTIVES:** Doubt over the cost-effectiveness of the cholinesterase inhibitors in dementia has renewed interest in alternative treatments such as Ginkgo biloba. We aimed to determine the effectiveness and the safety profile of Ginkgo biloba for treating early stage dementia in a community setting. **METHODS:** We conducted a community-based, pragmatic, randomised, double-blind, parallel-group trial where participants were given a standardised extract of Ginkgo biloba (120 mg daily) or a placebo control for 6 months. Our primary outcomes were cognitive functioning (ADAS-Cog) and participant and carer-rated quality of life (QOL-AD). **RESULTS:** We recruited 176 participants, mainly through general practices. In the ANCOVA model with baseline score as a co-variate ( $n = 176$ ), Ginkgo did not have a significant effect on outcome at six months on either the ADAS-Cog score ( $p = 0.392$ ), the participant-rated QOL-AD score ( $p = 0.787$ ) nor the carer-rated QOL-AD score ( $p = 0.222$ ). **CONCLUSION:** We found no evidence that a standard dose of high purity Ginkgo biloba confers benefit in mild-moderate dementia over 6 months.

N=262  
Ginkgold  
60mg BID  
x 6 weeks

HUMAN PSYCHOPHARMACOLOGY

*Hum Psychopharmacol Clin Exp* 2002; 17: 267–277.

Published online 5 July 2002 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/hup.412

## A double-blind, placebo-controlled, randomized trial of *Ginkgo biloba* extract EGb 761<sup>®</sup> in a sample of cognitively intact older adults: neuropsychological findings

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<sup>2</sup>Virginia Neuropsychology Associates, Inc., Lynchburg, Virginia, USA

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There appears to be an absence of large-scaled clinical trials that have examined the efficacy of *Ginkgo biloba* extract on the neuropsychological functioning of cognitively intact older adults. The importance of such clinical research appears paramount in light of the plethora of products containing *Ginkgo biloba* that are currently being widely marketed to predominantly cognitively intact adults with claims of enhanced cognitive performances. The purpose of this research was to conduct the first known, large-scaled clinical trial of the efficacy of *Ginkgo biloba* extract (EGb 761<sup>®</sup>) on the neuropsychological functioning of cognitively intact older adults. Two hundred and sixty-two community-dwelling volunteers (both male and female) 60 years of age and older, who reported no history of dementia or significant neurocognitive impairments and obtained Mini-Mental State Examination total scores of at least 26, were examined via a 6-week, randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, clinical trial. Participants were randomly assigned to receive either *Ginkgo biloba* extract EGb 761<sup>®</sup> ( $n = 131$ ; 180 mg/day) or placebo ( $n = 131$ ) for 6 weeks. Efficacy measures consisted of participants' raw change in performance scores from pretreatment baseline to those obtained just prior to termination of treatment on the following standardized neuropsychological measures: Selective Reminding Test (SRT), Wechsler Adult Intelligence Scale-III Block Design (WAIS-III BD) and Digit Symbol-Coding (WAIS-III DS) subtests, and the Wechsler Memory Scale-III Faces I (WMS-III FI) and Faces II (WMS-III FII) subtests. A subjective Follow-up Self-report Questionnaire was also administered to participants just prior to termination of the treatment phase. Analyses of covariance indicated that cognitively intact participants who received 180 mg of EGb 761<sup>®</sup> daily for 6 weeks exhibited significantly more improvement on SRT tasks involving delayed (30 min) free recall ( $p < 0.04$ ) and recognition ( $p < 0.01$ ) of noncontextual, auditory-verbal material, compared with the placebo controls. The EGb 761<sup>®</sup> group also demonstrated significantly greater improvement on the WMS-III FII subtest assessing delayed (30 min) recognition ( $p < 0.025$ ) of visual material (i.e. human faces), compared with the placebo group. However, based on the significant difference ( $p < 0.03$ ) found between the two groups' pretreatment baseline scores on the WMS-III FII, this result should be interpreted with caution. An examination of the participants' subjective ratings of their overall abilities to remember by treatment end on the Follow-up Self-report Questionnaire also revealed that significantly more ( $p = 0.05$ ) older adults in the EGb 761<sup>®</sup> group rated their overall abilities to remember by treatment end as 'improved' compared with the placebo controls. Overall, the results from both objective, standardized, neuropsychological tests and a subjective, follow-up self-report questionnaire provided complementary evidence of the potential efficacy of *Ginkgo biloba* EGb 761<sup>®</sup> in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 60 years of age and over. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — *Ginkgo biloba* extract; neuropsychological; cognitive; memory; elderly; clinical trial

N=203 >60  
years old, 40mg  
Ginkoba TID x 6  
weeks

## Ginkgo for Memory Enhancement A Randomized Controlled Trial

Paul R. Solomon, PhD

Felicity Adams, BA

Amanda Silver, BA

Jill Zimmer, BA

Richard DeVeaux, PhD

**S**OME OVER-THE-COUNTER TREATMENTS are marketed as having the ability to improve memory, attention, and related cognitive functions. These claims are generally not supported by well-controlled clinical studies. Ginkoba claims to "enhance mental focus and improve memory and concentration."<sup>1</sup> Several published studies reported beneficial effects of ginkgo on cognition. These studies, however, either report cognitive improvement in only 1 of many memory tests administered<sup>2,3</sup> or report cognitive enhancement in cognitively impaired clinical populations such as patients with cerebrovascular or Alzheimer disease.<sup>4,5</sup> In contrast, advertising claims imply that the compound is broadly beneficial to those both with and without clinically significant cognitive impairments. Specific advertising claims cite more than 50 clinical trials that demonstrate benefit centered around concentration and memory. These studies were conducted for periods ranging from 14 days to 2 months. The manufacturer claims benefit with "at least 4 weeks of uninterrupted use."<sup>6</sup>

The purpose of the present study was to evaluate ginkgo in healthy elderly volunteers in a randomized, double-blind, placebo-controlled trial using standardized tests of memory, learning, attention and concentration, and expressive language as well as subjective ratings by participants and family.

**Context** Several over-the-counter treatments are marketed as having the ability to improve memory, attention, and related cognitive functions in as little as 4 weeks. These claims, however, are generally not supported by well-controlled clinical studies.

**Objective** To evaluate whether ginkgo, an over-the-counter agent marketed as enhancing memory, improves memory in elderly adults as measured by objective neuropsychological tests and subjective ratings.

**Design** Six-week randomized, double-blind, placebo-controlled, parallel-group trial.

**Setting and Participants** Community-dwelling volunteer men (n=98) and women (n=132) older than 60 years with Mini-Mental State Examination scores greater than 26 and in generally good health were recruited by a US academic center via newspaper advertisements and enrolled over a 26-month period from July 1996 to September 1998.

**Intervention** Participants were randomly assigned to receive ginkgo, 40 mg 3 times per day (n=115), or matching placebo (n=115).

**Main Outcome Measures** Standardized neuropsychological tests of verbal and non-verbal learning and memory, attention and concentration, naming and expressive language, participant self-report on a memory questionnaire, and caregiver clinical global impression of change as completed by a companion.

**Results** Two hundred three participants (88%) completed the protocol. Analysis of the modified intent-to-treat population (all 219 participants returning for evaluation) indicated that there were no significant differences between treatment groups on any outcome measure. Analysis of the fully evaluable population (the 203 who complied with treatment and returned for evaluation) also indicated no significant differences for any outcome measure.

**Conclusions** The results of this 6-week study indicate that ginkgo did not facilitate performance on standard neuropsychological tests of learning, memory, attention, and concentration or naming and verbal fluency in elderly adults without cognitive impairment. The ginkgo group also did not differ from the control group in terms of self-reported memory function or global rating by spouses, friends, and relatives. These data suggest that when taken following the manufacturer's instructions, ginkgo provides no measurable benefit in memory or related cognitive function to adults with healthy cognitive function.

JAMA. 2002;288:835-840

www.jama.com

### METHODS

#### Participants

Following approval by the Williams College institutional review board, participants were recruited from newspaper advertisements that solicited individuals who would participate in a study designed to improve memory. An initial telephone interview was conducted to determine if the participant was likely to meet entry criteria for the study. Those who passed the

screen provided informed consent and a medical history including current medications, neurologic or psychiatric

**Author Affiliations:** Department of Psychology (Dr Solomon and Ms Zimmer), Program in Neuroscience (Dr Solomon and Ms Adams, Silver, and Zimmer), Department of Mathematics and Statistics (Dr DeVeaux), Williams College, Williamstown, Mass; and The Memory Clinic, Southwestern Vermont Medical Center, Bennington (Dr Solomon).

**Corresponding Author and Reprints:** Paul R. Solomon, PhD, Bronfman Science Center, Williams College, 33 Hoxsey St, Williamstown, MA 01267 (e-mail: psolomon@williams.edu).

**Birks J, Grimley Evans J. Ginkgo biloba for cognitive impairment and dementia.**  
*Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD003120.

**There is no convincing evidence that Ginkgo biloba is efficacious for dementia and cognitive impairment**

Ginkgo biloba appears to be safe in use with no excess adverse effects compared with placebo. Many of the early trials used unsatisfactory methods, were small, and publication bias cannot be excluded.

Overall, evidence that Ginkgo has predictable and clinically significant benefit for people with dementia or cognitive impairment is inconsistent and unreliable. Of the four most recent trials to report results, three found no difference between Ginkgo biloba and placebo, and one reported very large treatment effects in favour of Ginkgo biloba.

*Ginkgo biloba* – peripheral circulation

Adapted from Vasa 27:106-110,1998

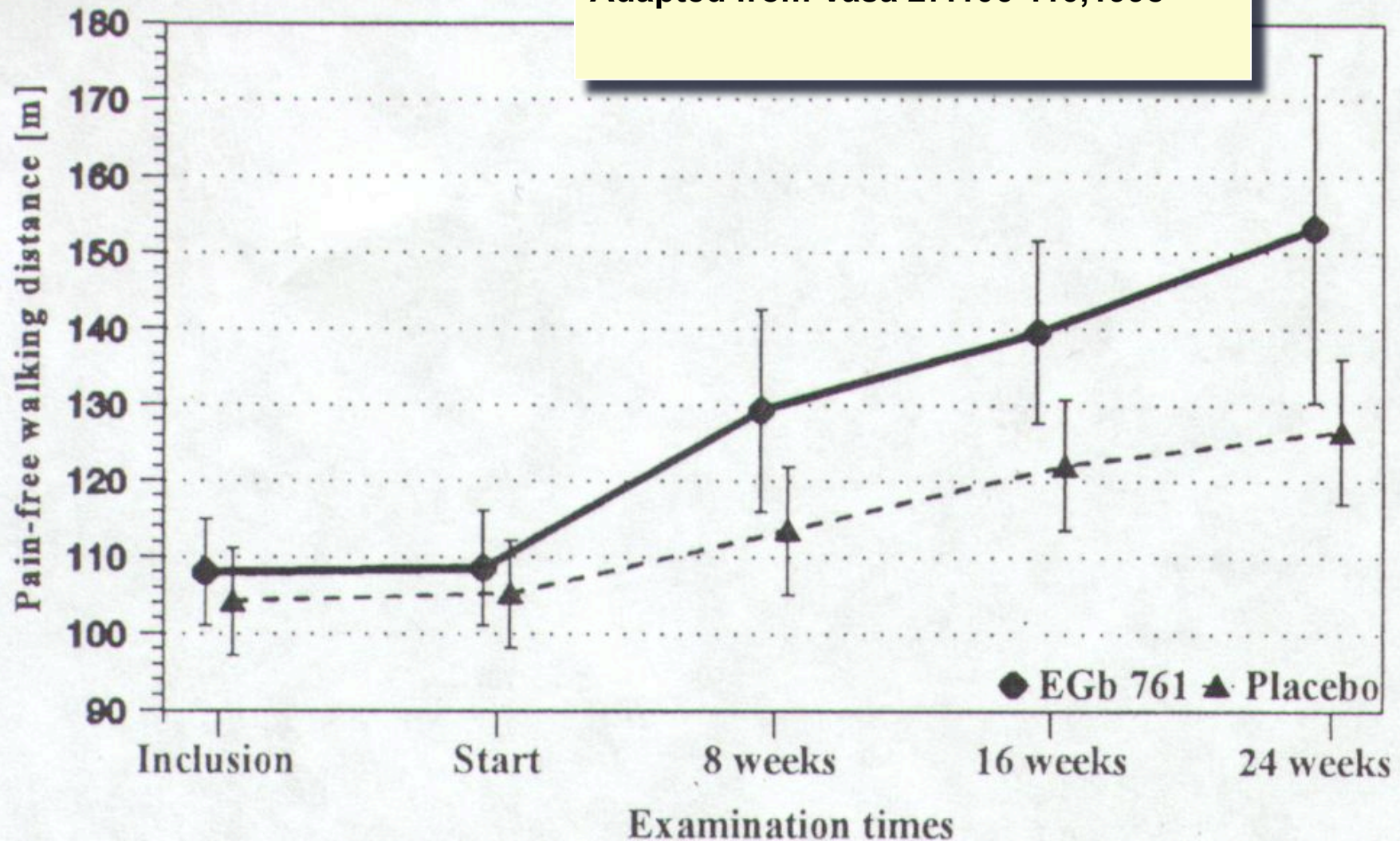
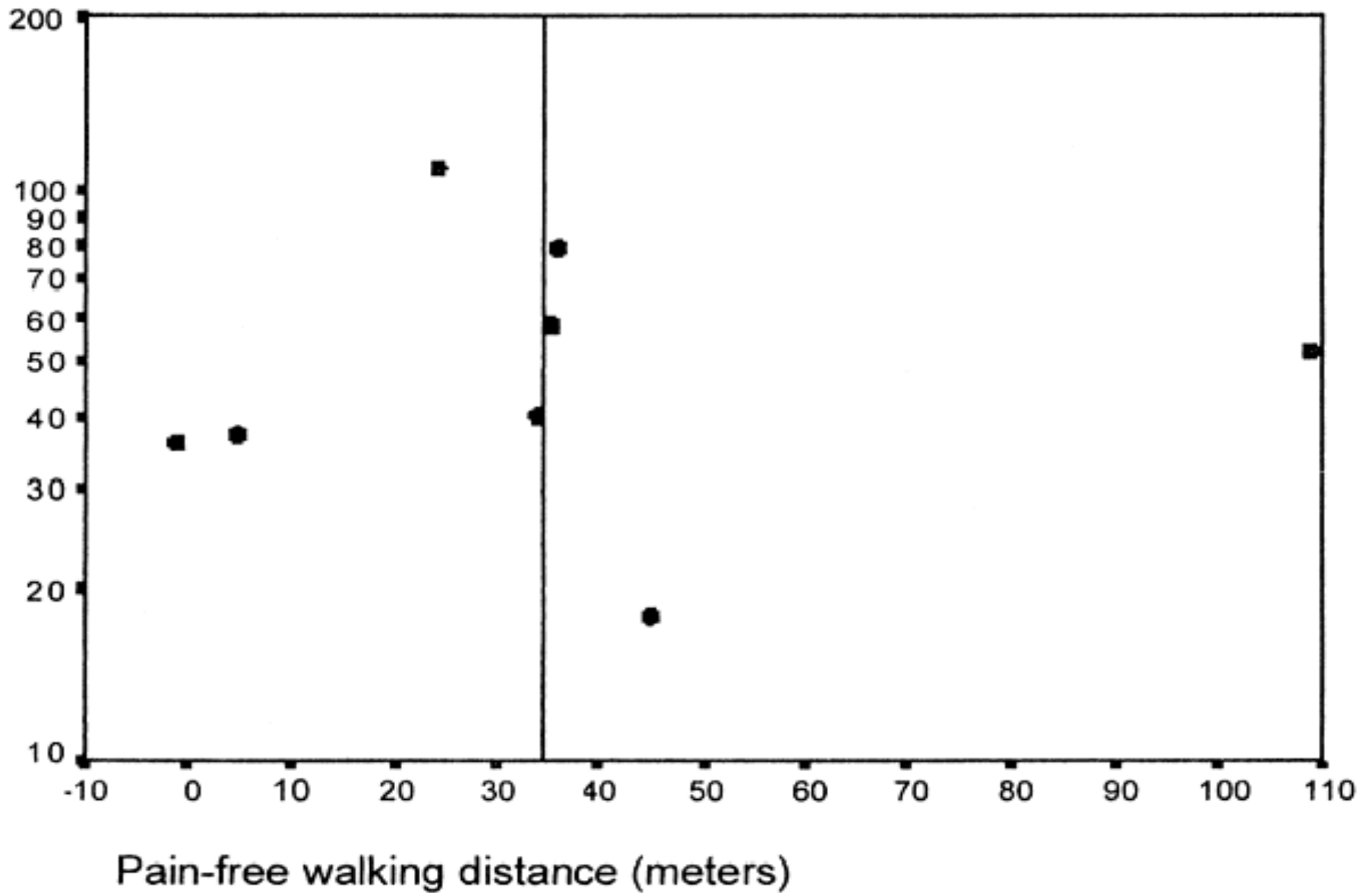


Fig. 1: Course of pain-free walking distance (m) at baseline, after 2 weeks placebo treatment and after 8, 16, and 24 weeks treatment with EGb 761 or placebo (arithmetic means with 95% confidence intervals).

## Sample size



Pittler and Ernst. Am J Med 108:276-281, 2000

1: Nicolai et al. Cochrane Database Syst Rev. 2009 Apr 15;(2):CD006888. **Ginkgo biloba for intermittent claudication.**

**CONCLUSIONS:** Overall, there is no evidence that *Ginkgo biloba* has a clinically significant benefit for patients with peripheral arterial disease.

# • *Ginkgo biloba*

## Other Uses (much less well studied)

- Impotence (associated with SSRI antidepressants) – several small studies show some improvement but others do not
- Tinnitus- (recent studies indicated no help, e.g. n=1121, BMJ 2001;322:73)
- Vertigo- several small studies showed improvement
- PMS- a study in France (n=165) indicated improvement
- prevent altitude sickness- (some but not all studies show benefit; start 1-2d prior and continue during trip)
- Macular degeneration-one study showed improvement
- A fixed combination of ginkgo and ginseng shows promise for beneficial effects on memory and (one study) attention deficit hyperactivity disorder

# • *Ginkgo biloba*

## Other Uses (much less well studied)

- Raynaud's Syndrome – one study showed decreased attacks
- Diabetic Retinopathy – one study showed improved color vision
- Glaucoma – one study showed improvement
- SAD – no benefit
- Activities of Daily Living in Older Adults – one study showed improvement
- Anxiety- one study showed improvement in young adults with anxiety
- MS- one study showed improvement in functionality in adults with MS

# Ginkgo

## Safety

Rare bleeds; recent large trial indicate a potential (trend) risk for ischemic stroke. Not seen in other studies.

Ginkgo seeds contain 4-methoxypyridoxine and can cause seizures. Two cases of seizure episodes associated with ginkgo extracts (contamination?)- maybe avoid ginkgo in the seizure prone

Ginkolic acids are toxic but removed during extract prep

## Drug interactions

Seems not to have effects on CYP in vivo (more later)

Possible additive effects with antiplatelet/adhesion drugs

Effects on insulin are complex-careful in diabetes

# Bleeds associated with ginkgo use

<u>Patient age</u>	<u>Ginkgo use</u>	<u>Other therapy</u>	<u>Bleed</u>	<u>ref</u>
70	1 week	Aspirin	Iris	1
78	2 mos	Warfarin	Intracerebral	2
33	2 years	None	Subdural	3
61	6 mos	None	Subarachnoid	4

1. NEJM 336:1108,1997
2. Neurology 50:1933-1934,1998
3. Lancet 352:36-37,1998
4. Neurology 46:1775-1776,1996

# *Ginkgo biloba*

## ■ Summary

- **Efficacy:** lack of strong evidence for benefit in dementia, poor memory and poor peripheral circulation
- **Safety:** good but watch for rare bleeding episodes, seizures? Stroke?
- **Drug interactions:** possibly warfarin, antiplatelet adhesion drugs; CYP 3A4 interactions are uncertain
- **Product selection:** look for EGb761 or LI 1370 extracts; these are the best studied; 24% flavone glycosides and 6% terpene lactones
- **Dose:** 1-2 60mg tabs, BID or 1 x120mg tab qd
- **Questions remaining :** many!
- *GWE: I was a former advocate for ginkgo use. The final answers are not in but recent evidence from good studies is not convincing for benefit. There may even be some risks. I no longer recommend ginkgo .*

# Echinacea

- **Botany**

- *Echinacea purpurea*, *E. augustifolia*, *E. pallida*

- **History**

-

# Echinacea

- 

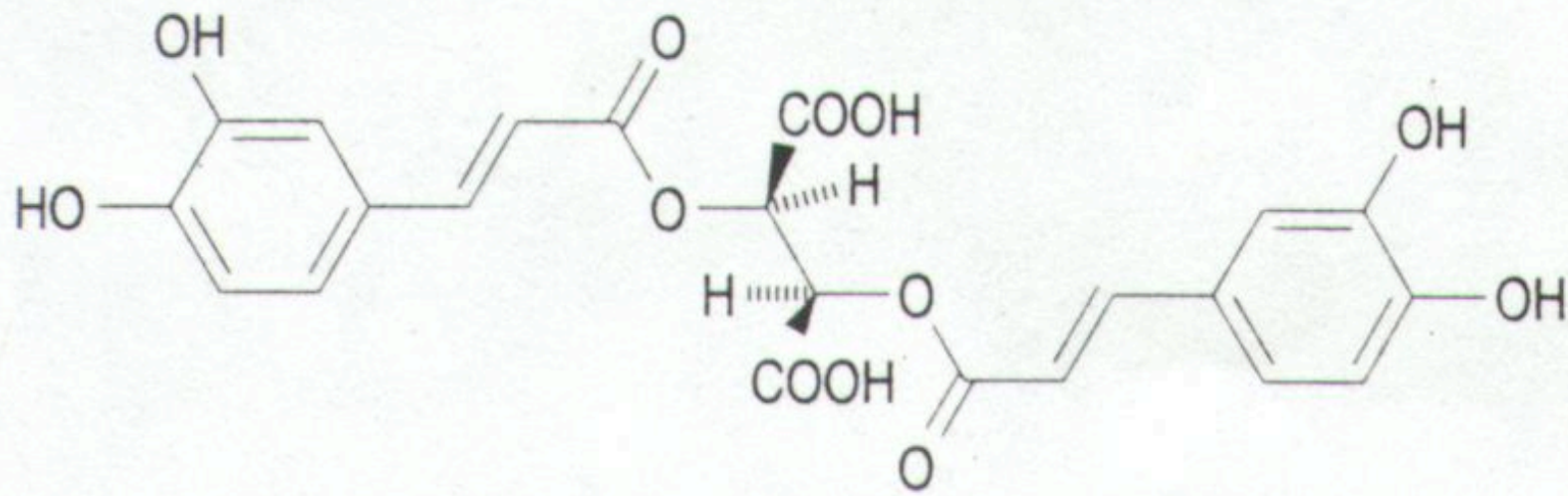
- **Chemistry**

- high molecular weight polysaccharides
  - heteroxylan
  - arabinogalactan
- phenylpropanoid - chicoric acid
- alkylamides
- flavonoids

- **Pharmacology**

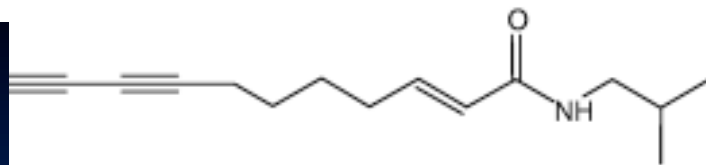
- phagocyte activation
- release of TNF, interleukin-1 and B2
- increase immune response
- local anaesthesia
- antimicrobial
- antioxidant

acids.

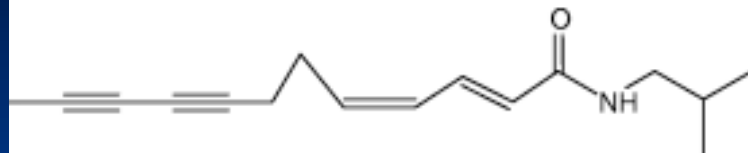


Chicoric acid

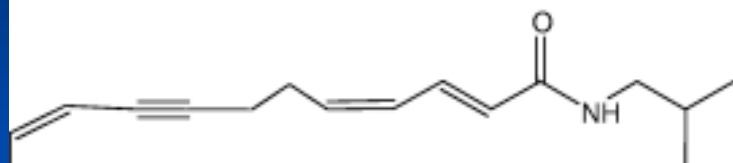
(1) (2E,4Z)-N-isobutylundeca-2,4-diene-8,10-diynamide  $m/z = 229$



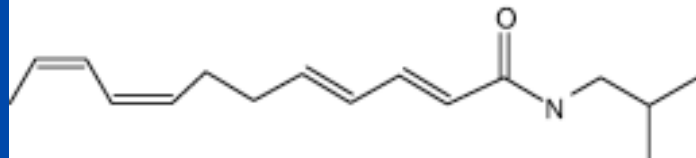
(2) (2E)-N-isobutylundeca-2-ene-8,10-diynamide  $m/z = 231$



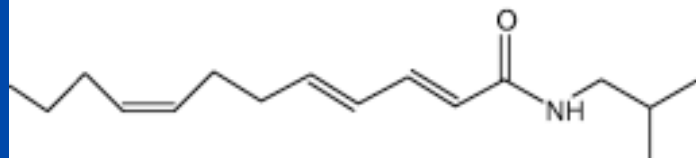
(3) (2E,4Z)-N-isobutyldodeca-2,4-diene-8,10-diynamide  $m/z = 243$



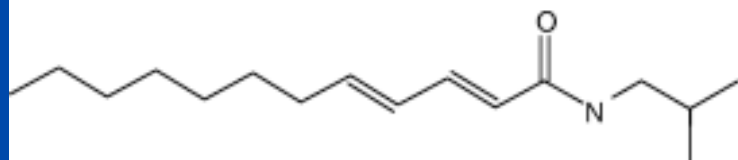
(4) (2E,4Z,8Z)-N-isobutyldodeca-2,4,10-triene-8-ynamide  $m/z = 245$



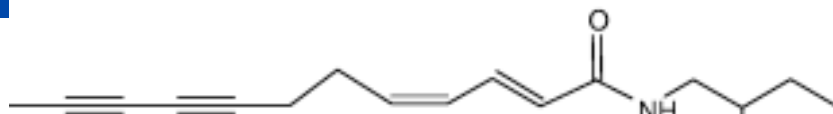
(5) (2E,4E,8Z,10Z)-N-isobutyldodeca-2,4,8,10-tetraenamide  $m/z = 247$

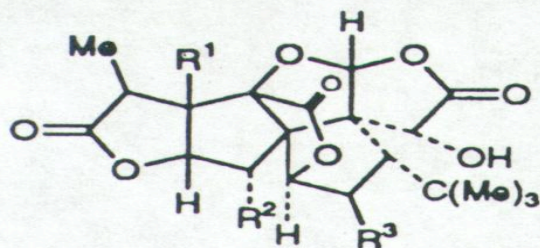


(6) (2E,4E,8Z)-N-isobutyldodeca-2,4,8-trienamide  $m/z = 249$



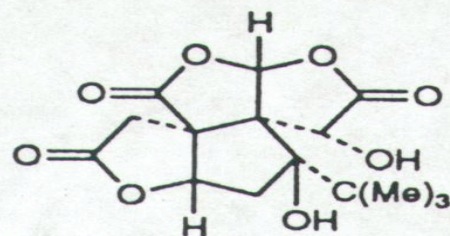
(7) (2E,4E)-N-isobutyldodeca-2,4-dienamide  $m/z = 251$



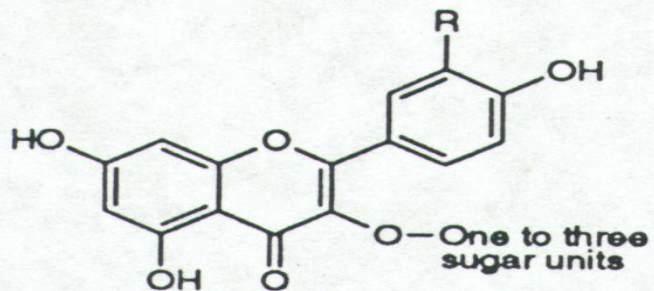


Ginkgolide structures

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>
Ginkgolide A;	OH	H	H
Ginkgolide B;	OH	OH	H
Ginkgolide C;	OH	OH	OH
Ginkgolide J;	OH	H	OH
Ginkgolide M;	H	OH	OH



Bilobalide

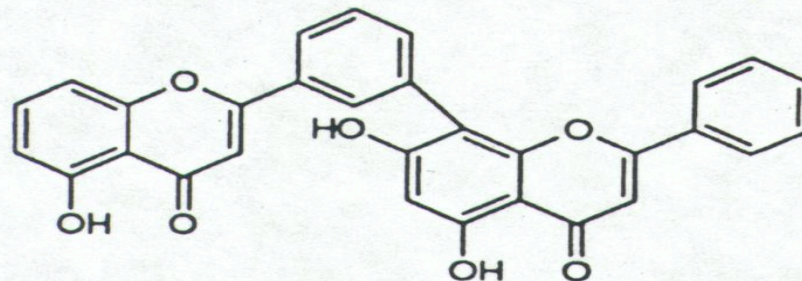


Flavonol structures

Kaempferol derivatives; R = H

Quercetin derivatives; R = OH

Isorhamnetin derivatives; R = OMe



Amentoflavone

Fig. 23.5. Some constituents of *Ginkgo biloba* leaves

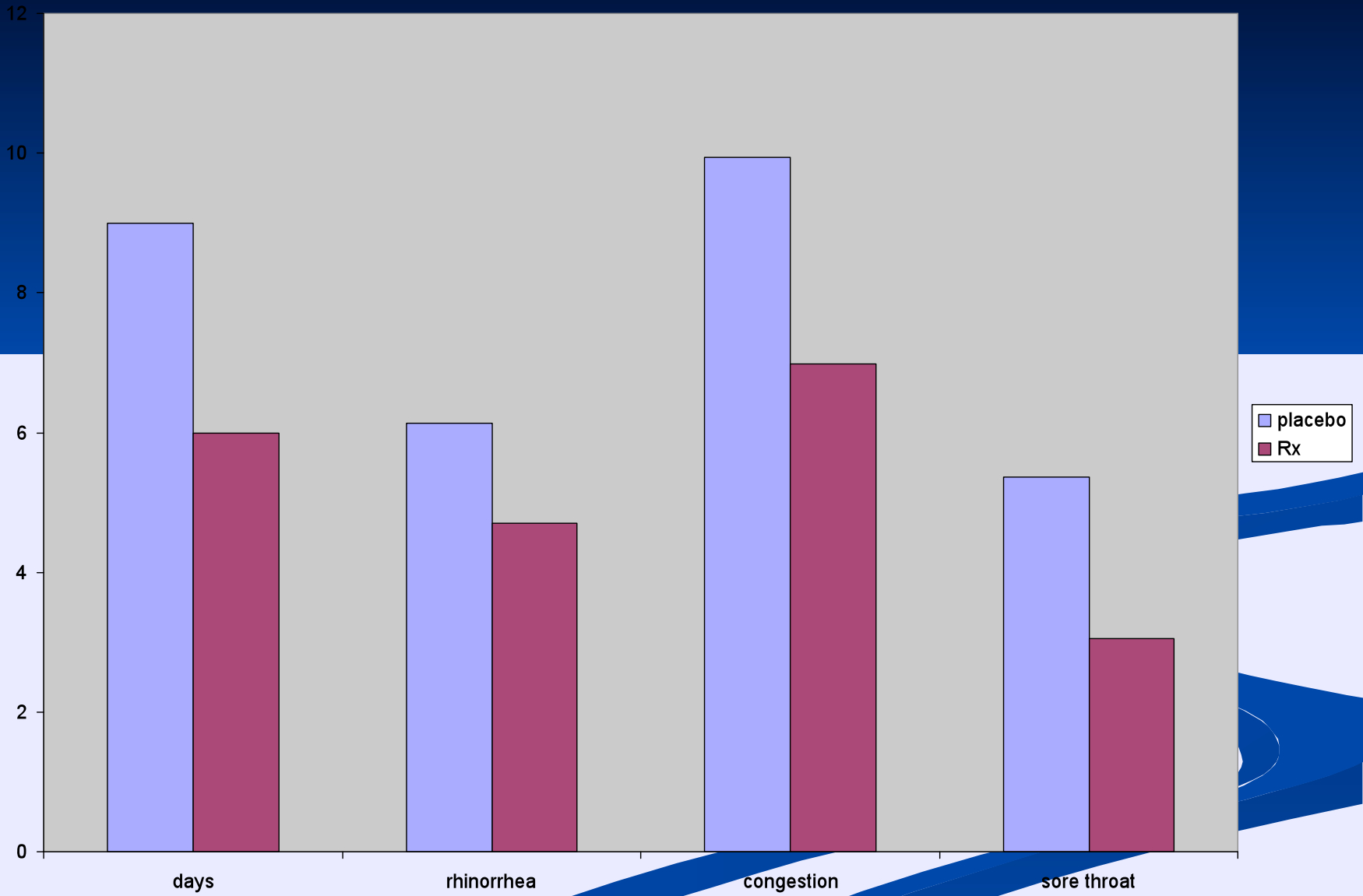
# Prevention of colds/flu

- Melchart et al., Archives of Family Medicine 7:541-545,1998
  - n=302, double blind, placebo controlled, randomized prevention trial in Germany
  - no difference in time to first cold (t=66 vs t=65 in the placebo (patients believed they had more benefit from echinacea, however)(p<.04)
- Grimm and Muller, Am J Med 106:138-143, 1999
  - similar prevention trial and results as above
- Turner et al., Antimicrob Agents Chemother 44:1708-1709, 2000
  - experimental cold prevention - no effect
- Bastyr study in Seattle

# •Echinacea-Treatment of Colds/Flu

- In a recent review, Linde et al. concluded that there is some evidence that preparations based on the aerial parts of *Echinacea purpurea* might be effective for the early treatment of colds in adults but results are not fully consistent. Linde K, Barrett B, Wolkart K, et al. Echinacea for preventing and treating the common cold. [Cochrane Database Syst Rev 2006;\(1\):CD000530.](#)  
.
- A study evaluated the pressed juice (5ml BID) of *E. purpurea* in 80 subjects. Days of illness in treated = 6 vs 9 in placebo ( $p=0.01$ ). Cold symptoms were less severe in Rx group. (Schulten et al, *Arzneim.-Forsch./Drug Research* 2001;51:563-568
- Brinkeborn et al (*Phytomedicine* 1999;6:1-5) reported a reduction in symptoms in treated compared to placebo in a large ( $n=246$ ) study. Used *E. purpurea* extract (95% herb, 5% root) or a concentrate of same or *E. purpurea* root extract. The aerial parts-based products showed benefit. The root extract did not.

### Echinacea and cold treatment



Schulten et al. *Arzneim-Forsch/Drug Research* 2001;51:563

n=80 p<0.05

## More recent studies

- Taylor et al. JAMA 2003;290:2824-2830. UW study in treating URI in children n= 407 no benefit (used pressed juice product)
- Yale and Liu Arch Intern Med 2004;164:1237-1241. Rx for colds in adults N=128 no benefit (used pressed juice)
- Goel et al. J Clin Pharm Ther 2004;29:75-83 N=282 adults. Used potent product (Echinilin) and high loading dose. Echinilin, a water/ethanol extract of *E. purpurea* plants contained alkamides/chicoric acid/polysaccharides in a concentration of 0.25/2.5/25 5 mg/ml in 40% ethanol. Got big benefit from treatment.
- Turner et al. N Engl J Med 2005;353:341-8. Used 3 different *E. augustifolia* root extracts. N=399 BUT only ~50/group. Low dose used. All given rhinovirus 39.

## **Study says Echinacea is not cold remedy**

**By Karen Kaplan**  
*Los Angeles Times*

Echinacea, the popular herbal remedy for fighting the common cold, does not ward off runny noses, sore throats or headaches, nor does it help speed recovery from cold symptoms, according to the results of a broad clinical trial published in today's New England Journal of Medicine.

The federally funded research was undertaken because more than 200 smaller studies had provided inconclusive and conflicting results about the benefits of the herbal remedy, which is derived from the purple coneflower.

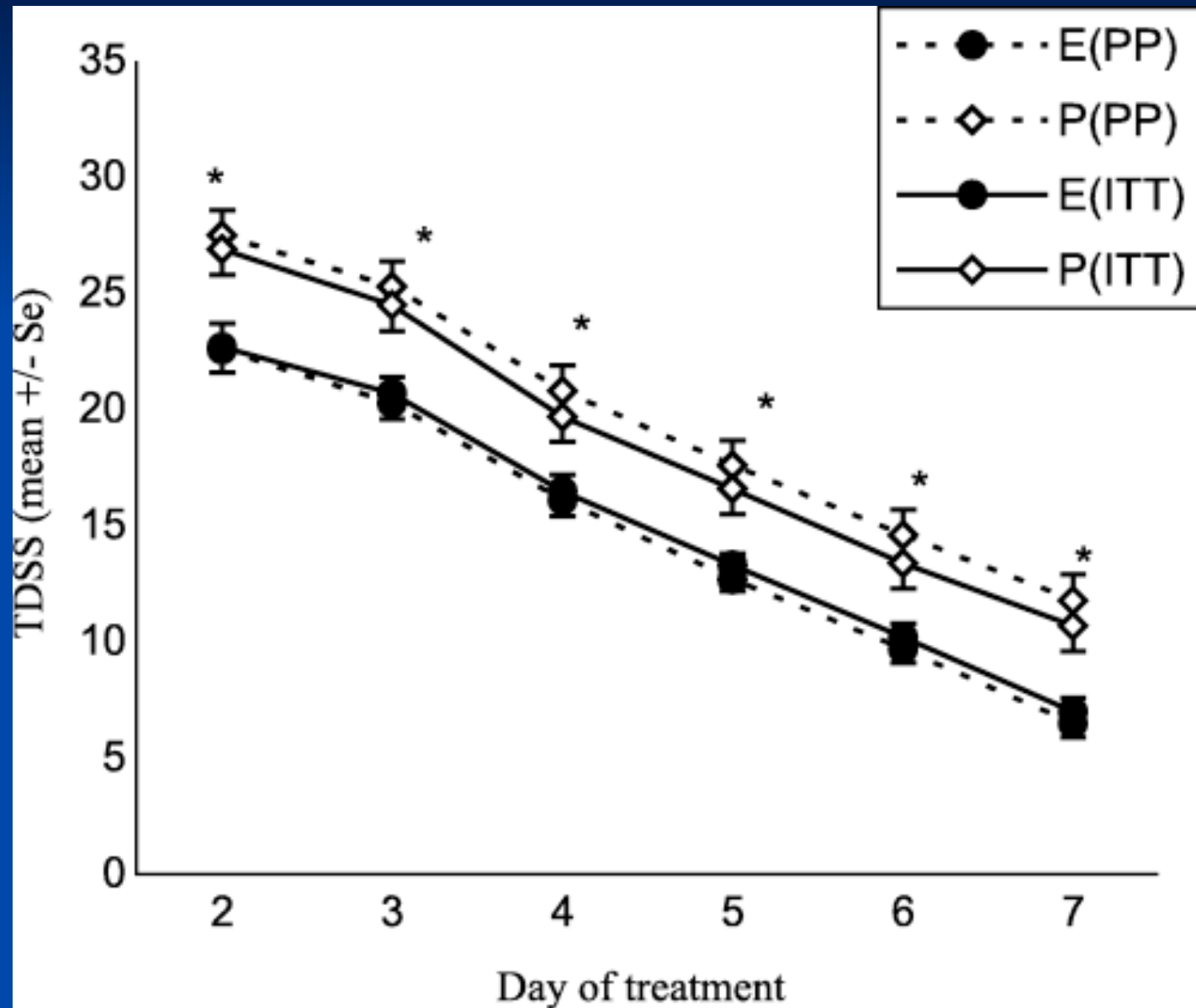
"We find no evidence that it actually does anything to common cold symptoms," said Dr. Ronald Turner, a professor of pediatrics at the University of Virginia School of Medicine and the study's lead author. "If that's the reason you're buying it, then you're wasting your money."

Echinacea enthusiasts said they do not think the results of the study merit such a clear-cut conclusion. They noted that Turner and his colleagues used only the root of one type of the plant and said the dosage given was too low.

Echinacea, a member of the same plant family as sunflowers and daisies, was used for hundreds of years by more than a dozen American Indian tribes to treat snakebites, toothaches, coughs and other ailments.

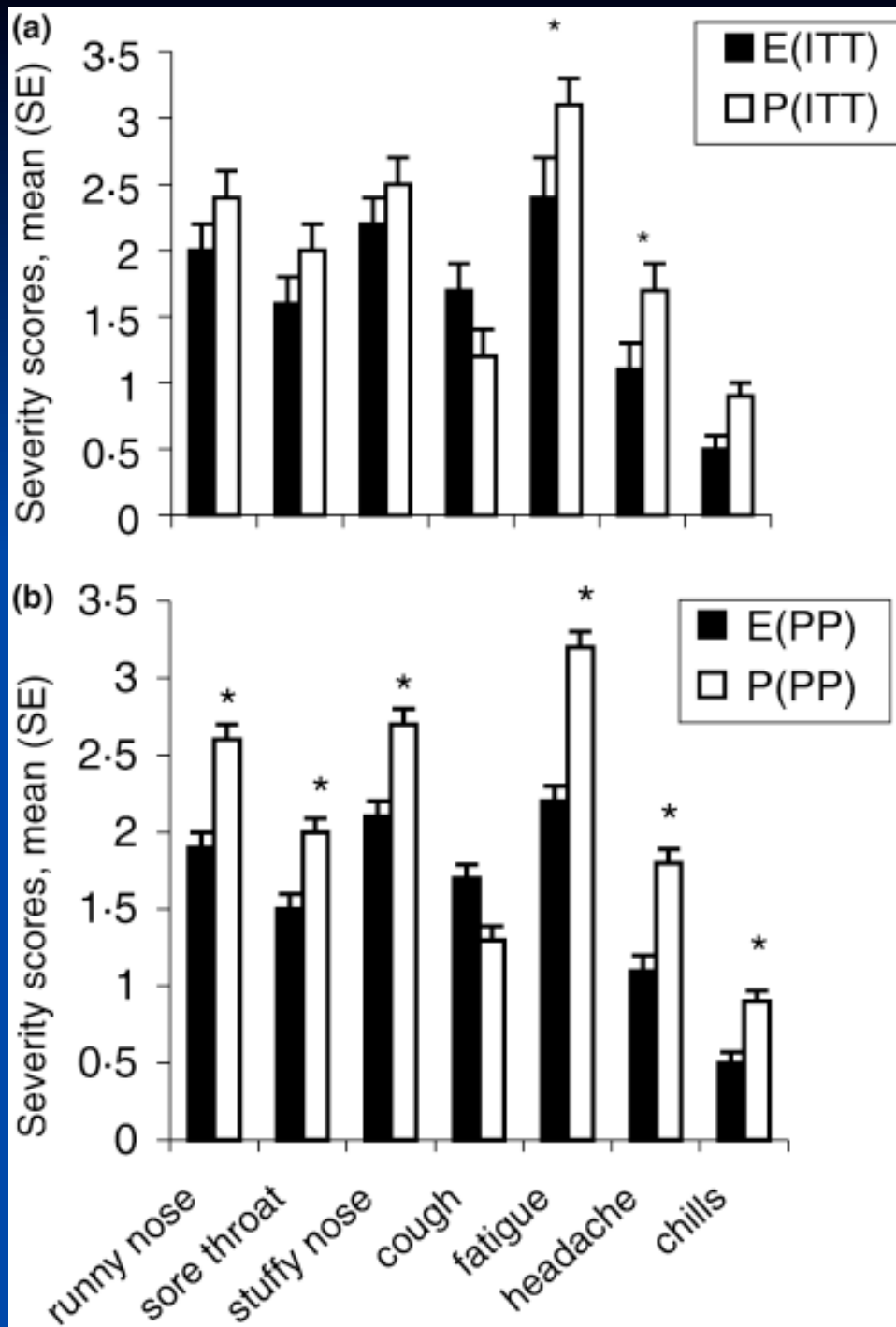
Americans spent \$153 million on echinacea products last year, making it one of the five best-selling herbs in the country, according to the Nutrition Business Journal, an industry publication.

Goel et al. J Clin Pharm Ther 2004;29:75-83 N=282 echinilin standardized; 10 stat then 1 qid



Goel et al. J  
Clin Pharm  
Ther  
2004;29:75-8  
3

N=282  
echinilin  
standardized;  
10 stat then 1  
qid



## NEWER INSIGHTS INTO THE PREVENTION OF THE COMMON COLD

**Table 5**

### When to Refer a Patient to a Physician<sup>4,12</sup>

- Coughing up a significant amount of mucus
- Shortness of breath
- Unusual lethargy/tiredness
- Inability to keep food or liquids down or poor fluid intake
- Increasing headache or facial or throat pain
- Severely painful sore throat that interferes with swallowing
- Fever >103°F (39.3°C)
- Chest or stomach pain
- Swollen glands in the neck
- Earache

with rheumatoid arthritis, lupus, or multiple sclerosis) or taking immunosuppressant medications.<sup>12</sup>

Airborne is an OTC combination of vitamins and herbs (including echinacea and vitamins A and C) intended to prevent and shorten the duration of common illnesses such as colds and flu. It has become popular in a short period of time, to the extent that stores often have trouble keeping it on the shelves. Generic versions are now available with the same ingredients in different packaging. There is no warning on the Airborne packaging relating to minimum or maximum dosing. But if taken as the label states ("take at the first sign of a cold symptom or before entering crowded environments and repeat every three hours as necessary"), eight doses of Airborne would provide *eight* times the recommended daily allowance of vitamin A, and would be at least four times the amount to start causing liver damage.<sup>35</sup>

Clinical trials have been inconsistent in their findings with regard to the effectiveness of zinc gluconate or acetate lozenges. Inconsistent results are likely attributable to reductions in the efficacy of zinc secondary to changes in formulation in efforts to mask the unpleasant properties of zinc.<sup>6,36</sup> Recent reports have demonstrated that treatment with zinc nasal gel is effective in reducing the duration and severity of common cold symptoms if taken within 24 hours of symptom onset.<sup>36</sup> Patients should be counseled to begin zinc at the very first sign of cold symptoms, and should continue until symptoms resolve or until otherwise advised.

data presently available. Therefore, the risk versus benefit ratio appears unfavorable for use of a product with potential for permanent anosmia.<sup>38</sup>

Many other botanicals have been studied for the prevention and treatment of the common cold. Such items include high lactoferrin whey protein, devil's claw, elderberry, ephedra, garlic, Panax ginseng, goldenseal, horehound, larch arabinogalactans, licorice, olive leaf extract, astragalus, baptisia, wild cherry, isatis, and yerba santa. None of these products has scientific evidence supporting their safety and efficacy. Pharmacists should not recommend these products to their patients.

**Myth:** *Herbal remedies are effective treatments for the common cold.*

**Fact:** *Echinacea and other herbs are receiving a great amount of publicity as cold remedies. Zinc lozenges are also said to cure colds quickly. However, the effectiveness and safety of these remedies have not been supported by large-scale clinical studies.*

### THE ROLE OF THE PHARMACIST

#### Education

Pharmacists field many questions regarding the common cold and its associated problems. Since each patient may experience one or more possible symptoms, pharmacists should first determine which symptoms are most troublesome. If questions about the patient's medical history or medication use do not reveal exclusions for self-treatment, pharmacists may recommend a product that targets the specific symptoms. The patient should also be asked about self-treatment of current and previous colds and the effectiveness of these treatments.

#### Counseling

The patient who suffers from the common cold may require dedicated counseling by pharmacists. In order to make the appropriate recommendations, pharmacists need to keep in mind the symptoms related to the common cold. Pharmacists must ask enough questions to ensure that the symptoms are not related to a more serious medical condition. If there is any doubt, referral to a physician is warranted. Nonpharmaceutical measures may be effective in relieving the discomfort associated with common cold symp-

- Other immune stimulant uses?
  - Cancer
  - AIDS
  - bacterial and fungal infections
- Products (which is best??)
  - tablets 250mg
  - tincture
  - root extract or extract of tops or pressed juice

# *Echinacea*

## ■ Summary

- **Efficacy:** evidence for treatment not prevention; take at first sign of cold/flu; reduce severity and duration about 25%
- **Safety:** good; rare allergy; not where immunostimulation would be undesirable (e.g. lupus, rheumatoid arthritis); outcomes in 206 pregnant women taking echinacea were OK but-----
- **Drug interactions:** not documented but don't give to patients taking immunosuppressive drugs
- **Product selection:** standardized extracts usually contain about 4% phenolics
- **Dose:** use loading dose (2x) then 1 QID
- **Questions remaining** include
  - *Which product? Tincture? Tablets? Root ? Flowering tops? Pressed juice?*
  - *E. purpurea? E. angustifolia? E. pallida?*
- *GWE: I recommend Echinamide taken at the first sign of a cold*