



## •Garlic

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

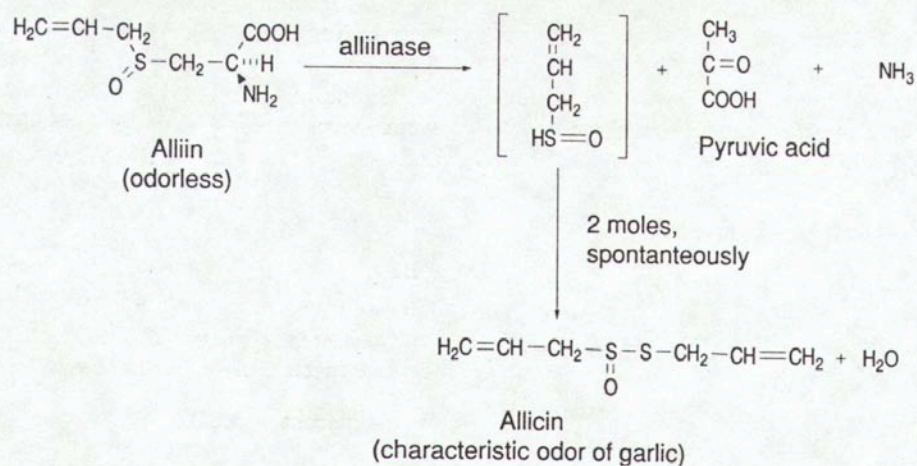


Fig. 4-6. Formation of allicin in *Allium* species.

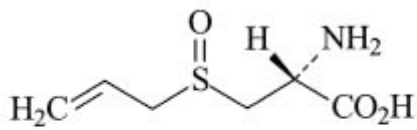
Alliin is a major component found in fresh and dried (carefully) garlic. Allicin is odiferous and pharmacologically active



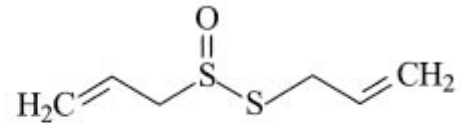
(Z)-Ajoene

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

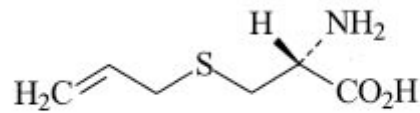
Ajoene and like allylsulfides are major components of garlic oil



**Alliin**



**Allicin**



**S-Allyl-L-Cysteine**

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

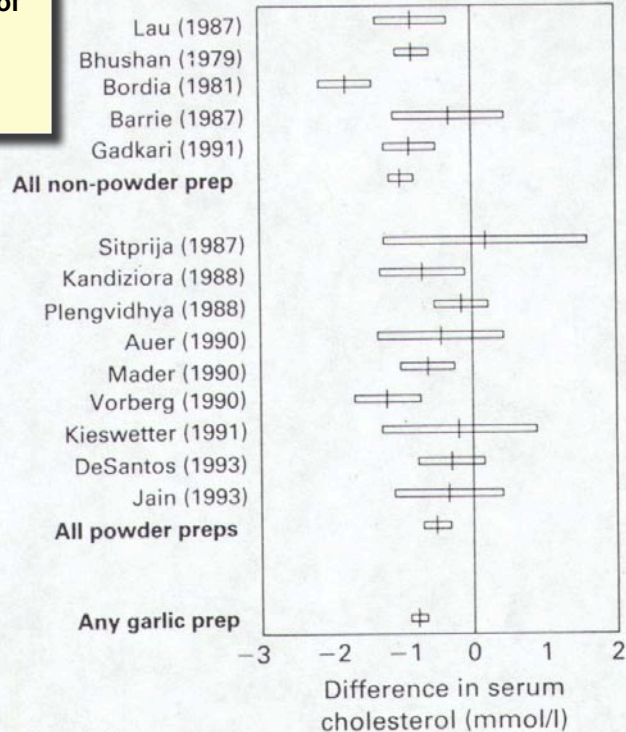
## •Pharmacology

- 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)

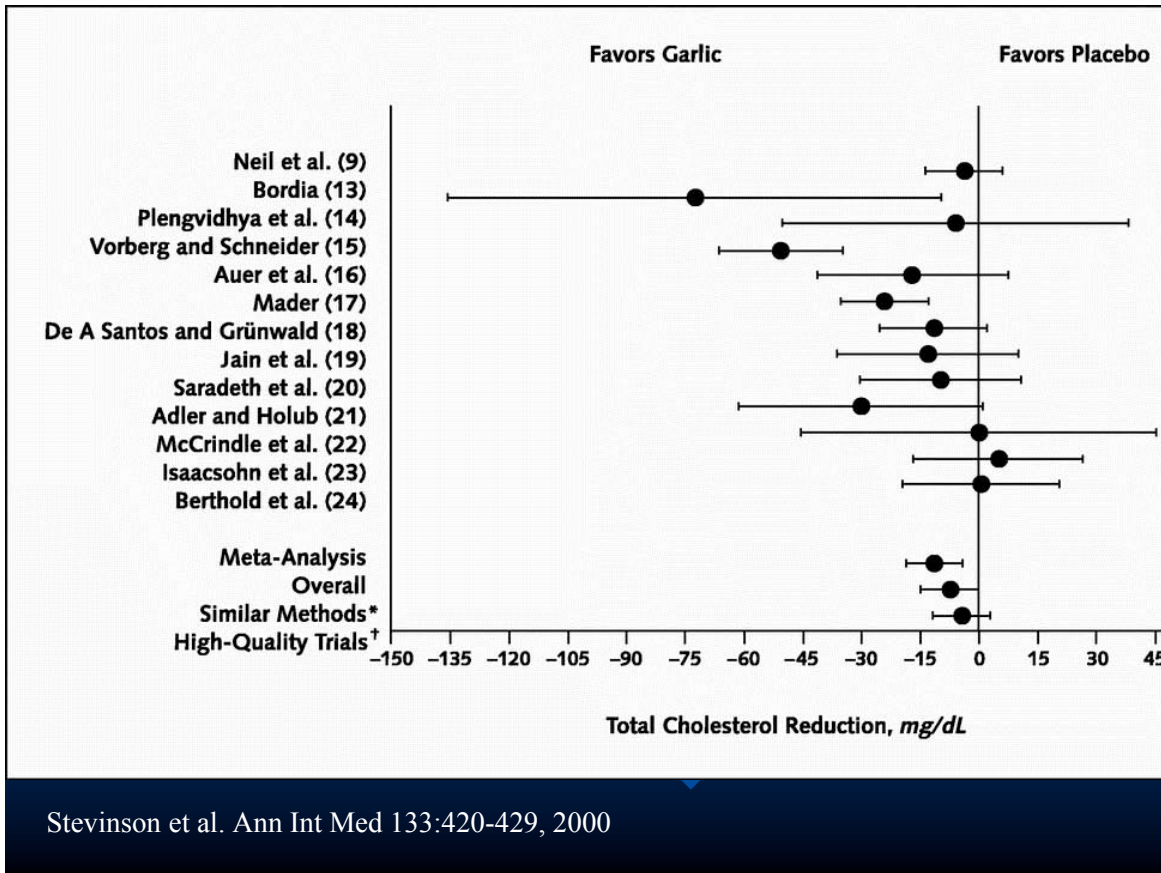
## In vivo evidence – cholesterol lowering

- most early studies (>40) show lowering effects but studies are often not of high quality
- Meta-analyses have shown a cholesterol lowering effect of 5-12% (**Ann Int Med 119:599-605,1993;J R Coll Physicians-London 28:39-45,1994, Ann Int Med 133:420-429, 2000**)

Adapted from Silagy and Nei, JRCollge of Physicians London 28:39-45,1994



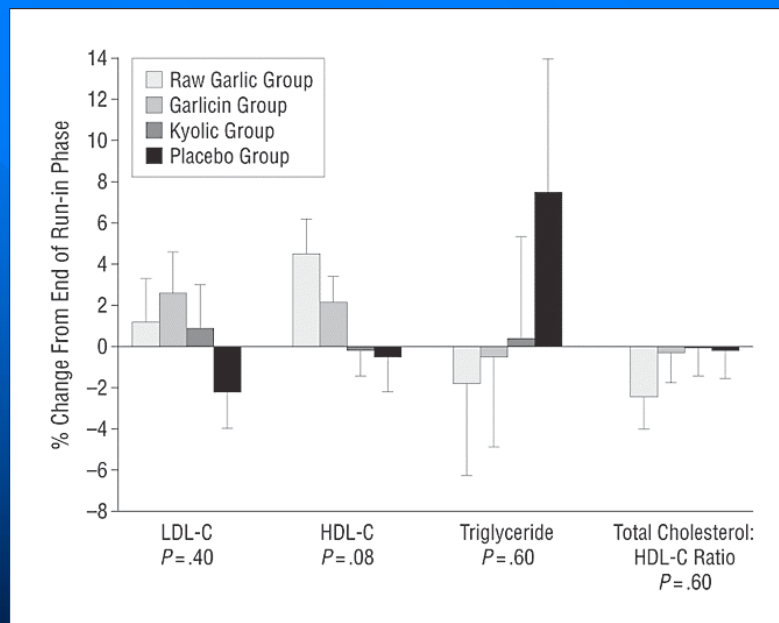




## Evidence – cholesterol lowering

- Some recent well designed studies show no effect on cholesterol lowering (see next slide)
- 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)

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.

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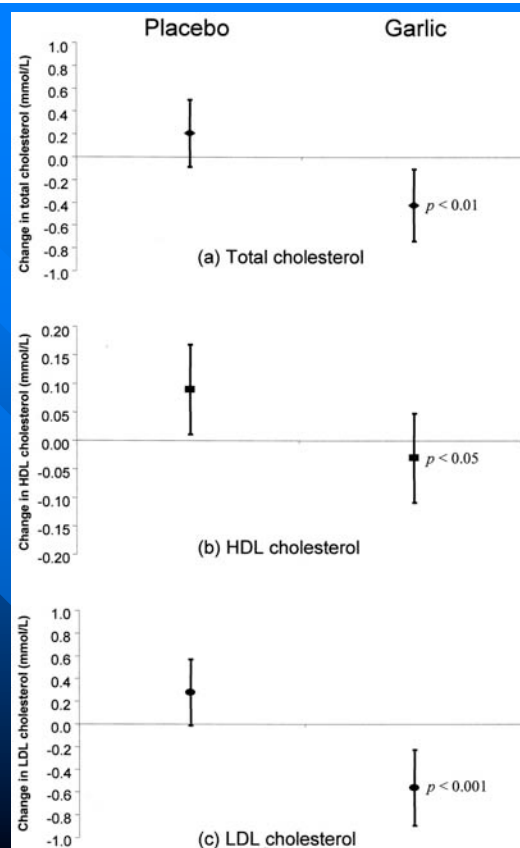
Kanner et al. J Am College Nutr 2001;20:225-231.

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



## What is the benefit of Garlic in general cardiovascular 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)
- Some evidence (Arch Intern Med. 2001 26;161:813-24) for small reduction in systolic and diastolic but more study is needed before recommendations can be made
- Garlic has modest platelet adhesion inhibition effects

## 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.
  - 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 use with anti HIV therapies

# Garlic

## ■ Summary

- **Efficacy:** the literature is conflicting for use in hyperlipidemia and hypertension maybe 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?*





# 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

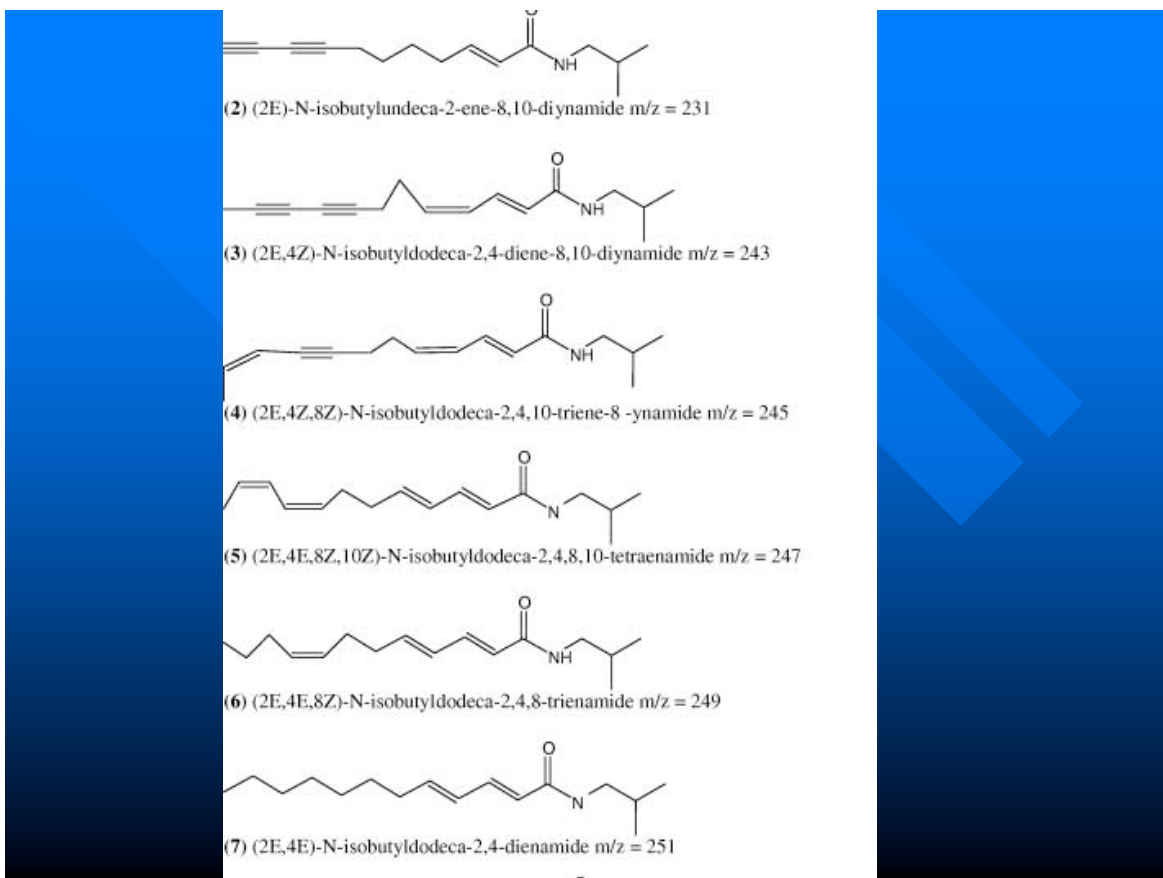
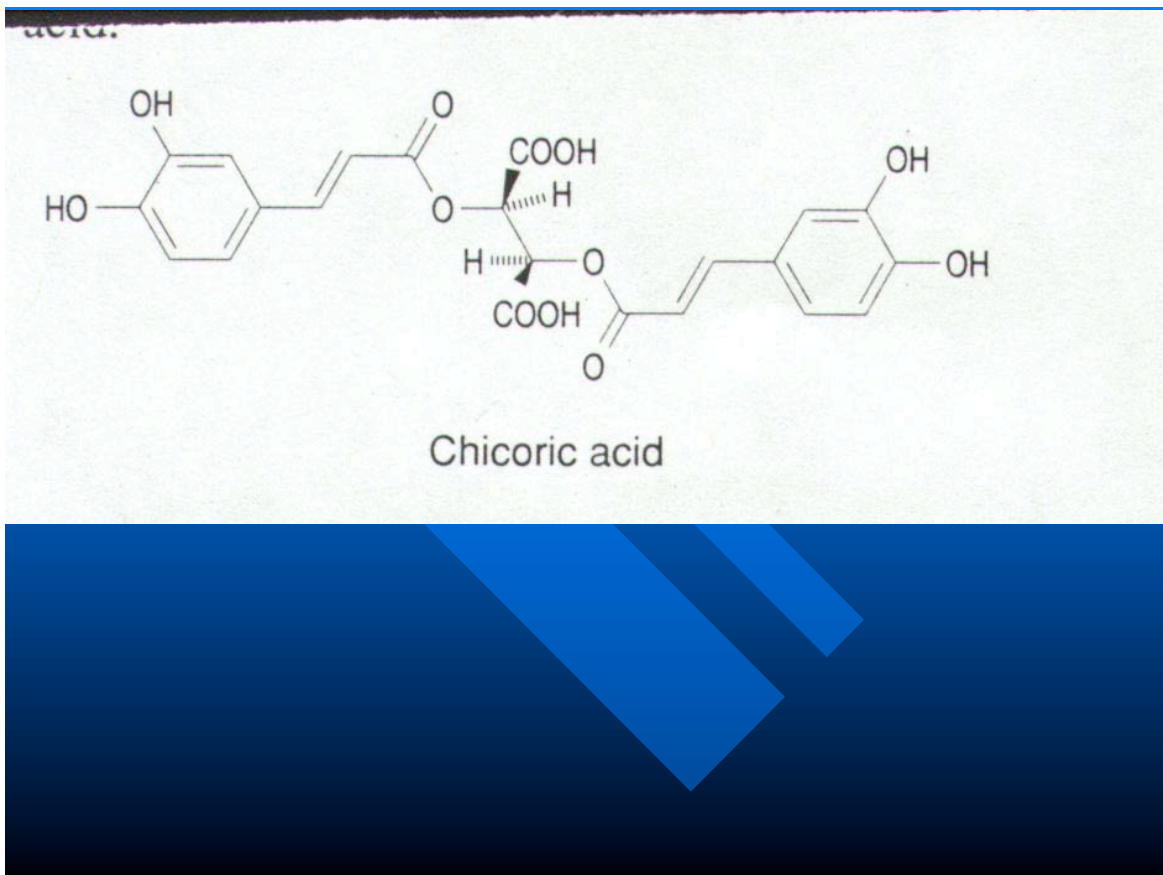
–release of TNF, interleukin-1 and B2

–increase immune response

–local anaesthesia

–antimicrobial

–antioxidant





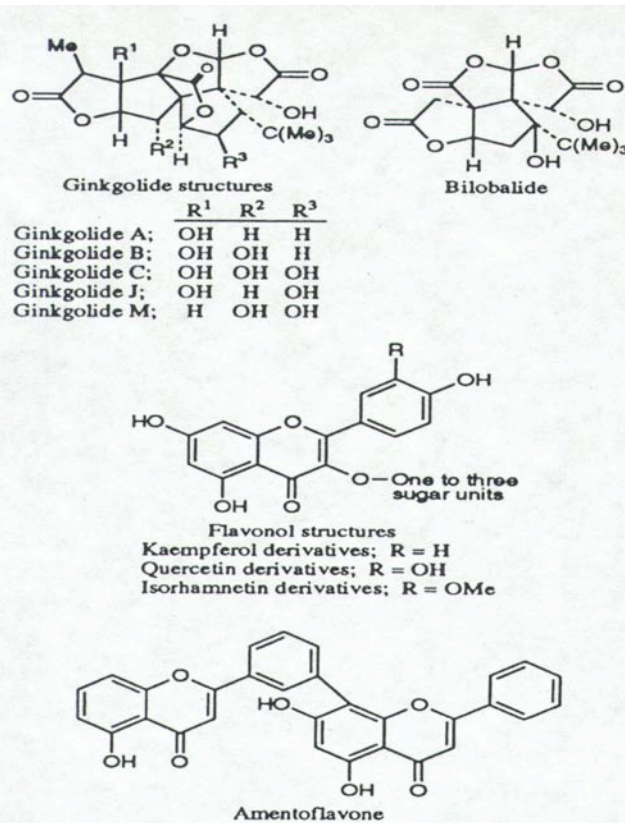


Fig. 23.5. Some constituents of *Ginkgo biloba* leaves

## 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

# Popular echinacea may make you sick

Study disputes herbal  
aid's preventive value

By **TOM PAULSON**  
PI REPORTER

A study done at one of the nation's leading research and teaching institutions for naturopathic medicine has shown that taking the popular herbal supplement echinacea as a preventive measure might make you sick.

## EDITORIALS

### Doubts about echinacea

**H**ERBAL hounds beware. Echinacea, the purported Holy Grail of cold cures, may actually cause more sickness than it prevents.

Preliminary findings by local researchers at Bastyr University indicate that echinacea users had more symptoms of respiratory infection than people who took placebos over a six-month study period. The results, which were presented at a medical conference in Seattle, have yet to be printed in a peer-reviewed medical journal. But they're similar to recently published studies on echinacea's lack of preventative powers.

A study published in the March issue of the American Journal of Medicine concluded that the world's most popular herbal supplement had no impact on the duration or severity of respiratory infections.

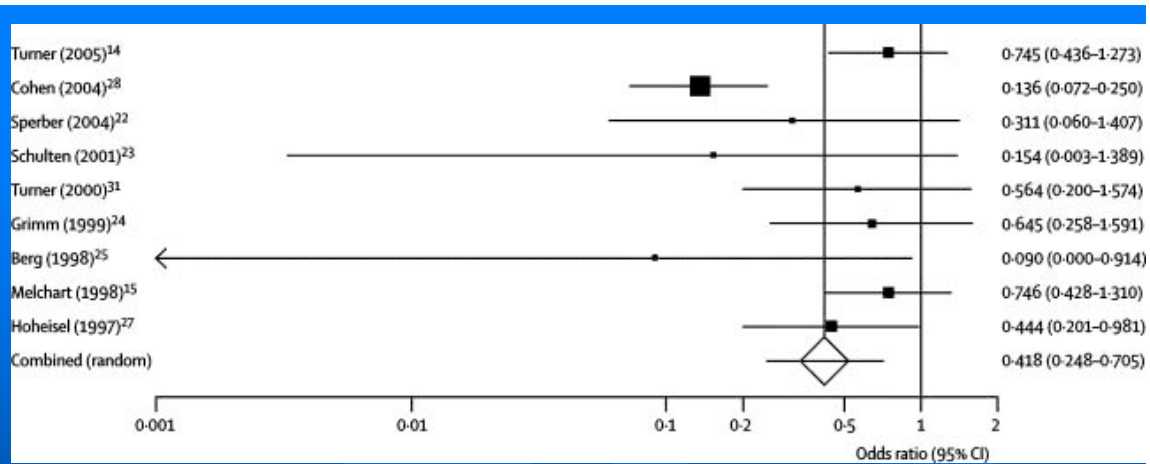
Serious scientific inquiry is demonstrating that echinacea use may be no better — or actually worse — than doing nothing at all.

The snuffle-prone should be free, of course, to gobble down eye of newt or root of purple coneflower if they believe it clears their stuffy noses. They should be free to hang garlic around their necks, on their earlobes, or from their window sills if they think it will ward off germs. They should even be free to undergo strange procedures such as "sham surgery," outlined in gruesome detail in The New York Times this week, if they are fully informed of the risks, benefits and incomplete scientific evidence of bona fide effectiveness.

The freedom to heal — whether physically, psychologically or psychosomatically — is only truly free when patients are fully informed.

Bastyr University earns kudos for subjecting alternative therapies to rigorous scientific research and publicizing the results regardless of special-interest opposition. Proponents as well as skeptics of alternative medicine must agree on age-old principles: Methodical testing and full disclosure are the best antidotes to health quackery.





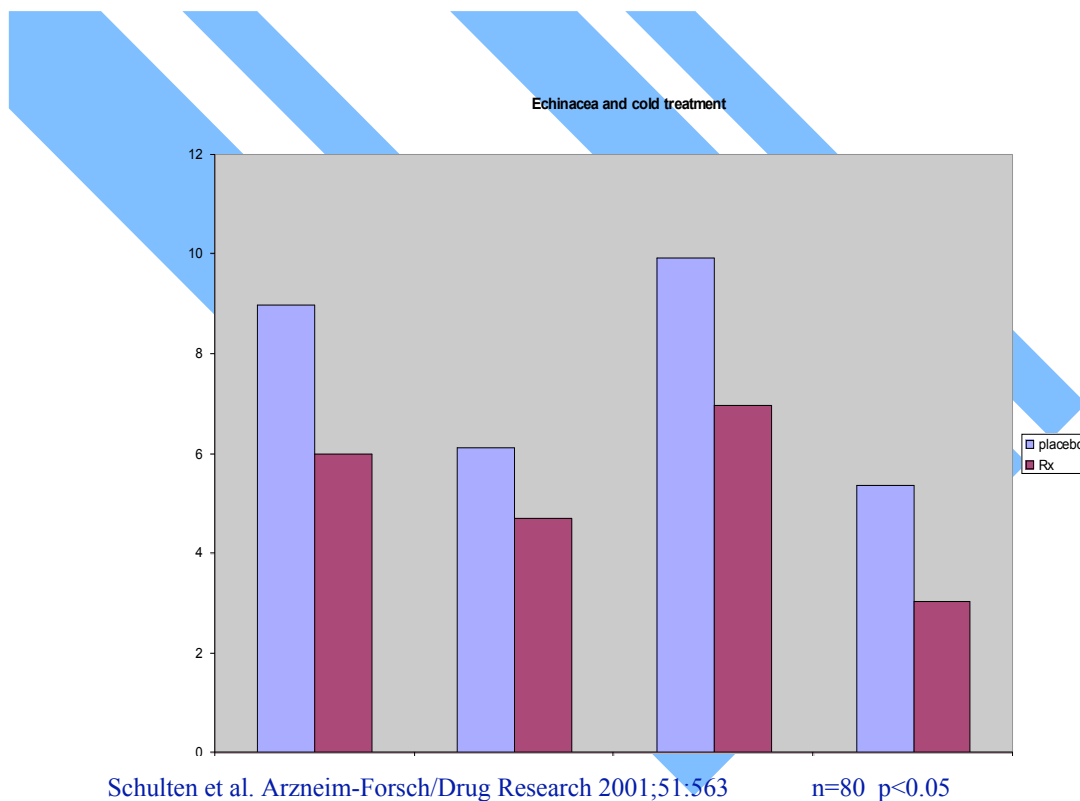
Shah et al. Lancet Infect Dis 2007;7:473-80.

Note: Cohen study used a mix of ginkgo, vitamin C and propolis (500mg of each/day)

## •Echinacea

### ■ Evidence for Efficacy for treatment of cold/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.



## LUNG ALERT .....

### No cure for the common cold

▲ Barrett BP, Brown RL, Locken K, *et al.* Treatment of the common cold with unrefined Echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002;137:939-46

**P**revious studies of Echinacea have reported success varying from 10% to 50% in the treatment of colds. A few randomised trials have reported only a small effect in preventing colds.

In this randomised, double blind, placebo controlled study the authors report on the effect of 10 days of treatment with dried, encapsulated, whole plant Echinacea starting within 36 hours of onset of symptoms in 142 students reporting common colds (69 Echinacea, 73 placebo). Their primary objective was to measure the severity and duration of reported upper respiratory tract infections. They concluded that there was no statistical difference between the two groups. They do, however, believe this should not be the last word on the use of Echinacea in the treatment of colds because (1) they used whole plant mixture rather than extracts as reported in previous trials, (2) they studied a healthy population of students in whom the clinical effect would be small, and (3) the trial was of modest size and would have missed an effect of 5-10%. Furthermore, they did not confirm infection by serological testing or inflammatory markers and simply based it on reported symptoms. This raises doubt about the exact aetiology of the illness.

This is a well designed study which clearly shows that whole plant Echinacea has no significant clinical effect on the course and severity of the common cold, although it is unlikely that this will end discussion on this subject.

**K Hattotuwa**

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## 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 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.

**The Seattle Times**  
seattletimes.com

Thursday, July 28, 2005 - 12:00 AM

### 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.

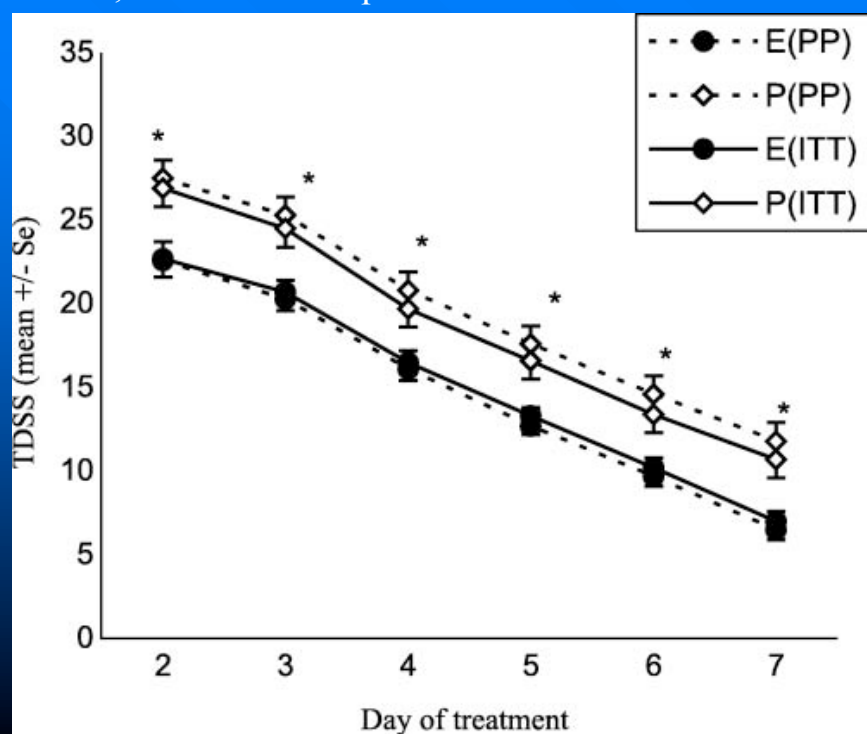
"We find no evidence that it actually does anything to common cold symptoms," said Dr. Ronald Turner, a professor of pediatrics at the University of Virginia School of Medicine and the study's lead author. "If that's the reason you're buying it, then you're wasting your money."

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.

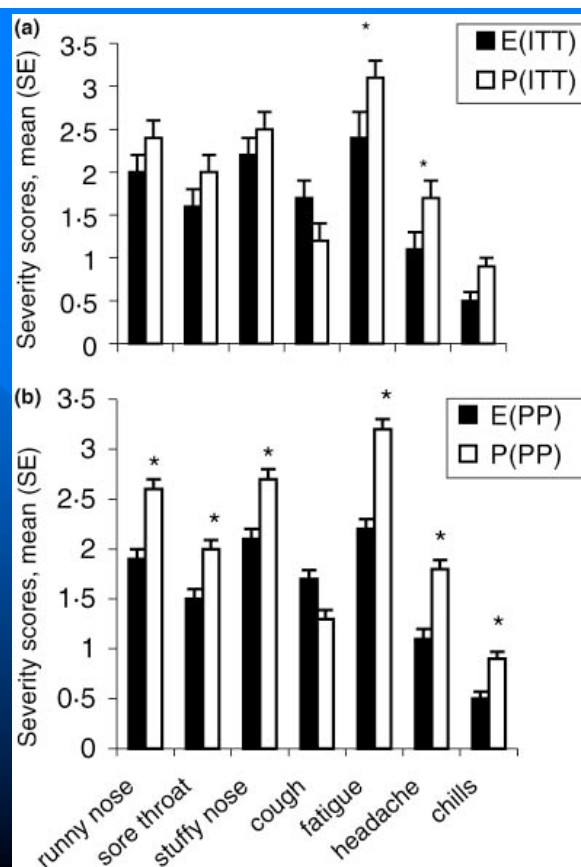
Americans spent \$153 million on echinacea products last year, making it one of the five best-selling herbs in the country, according to the Nutrition Business Journal, an industry publication.

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-  
83

N=282  
echinilin  
standardized;  
10 stat then 1  
qid



- 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 extract? Flowering tops? Pressed juice? *E. purpurea*? *E. augustifolia*? *E. pallida*? (GWE recommends Echinamide in 2007)





*Serenoa repens*  
Saw Palmetto  
Photo: John Egbert



# 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

- 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)
  - » 6 months Rx of Permixon 160mg BID or finasteride 5mg am (placebo pm)<sup>#2</sup>
- 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)

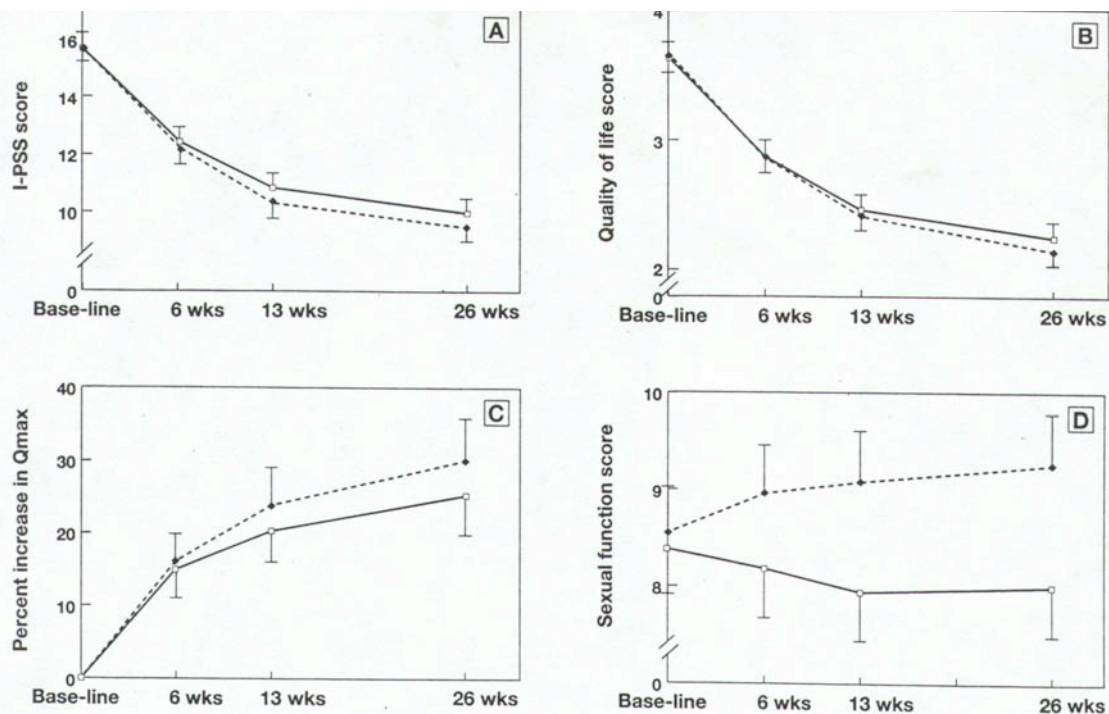
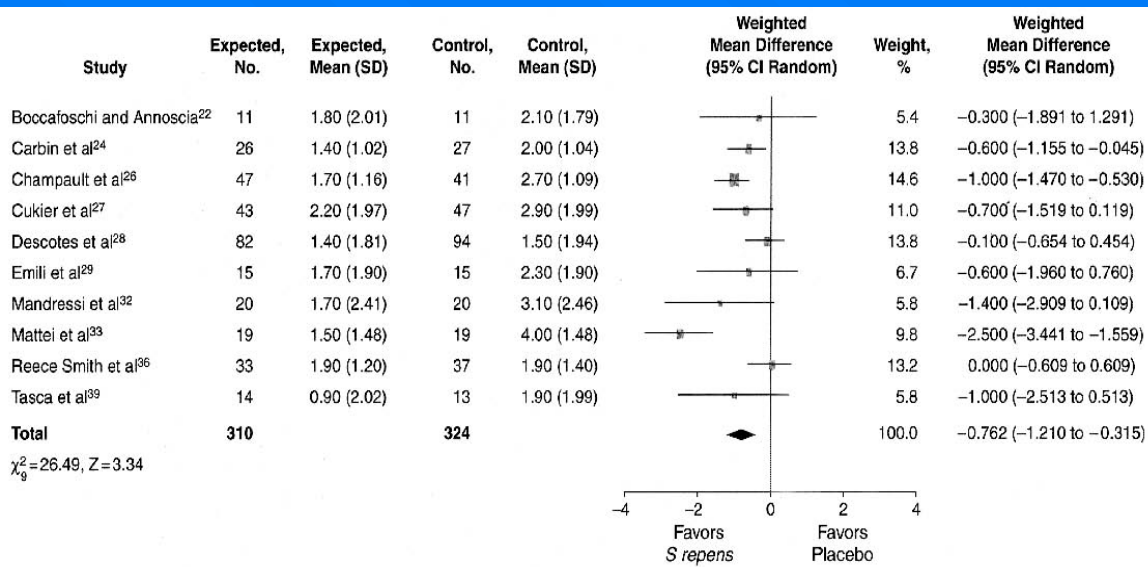
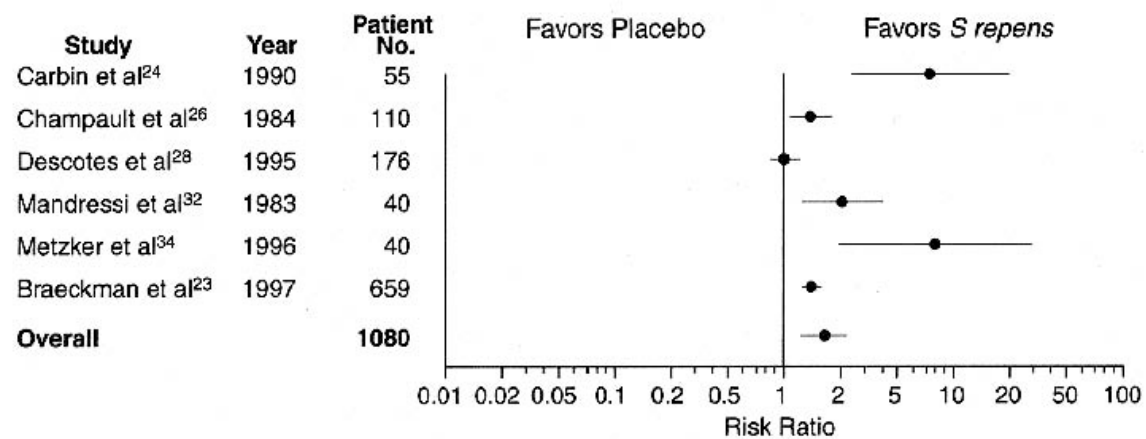


Fig. 1. Mean total IPSS (A), mean quality of life score (B), percentage of increase in mean peak urinary flow (C), and mean sexual function score (D), in men with BPH receiving either 320 mg Permixon® (open squares) or 5 mg finasteride (solid diamonds) ( $\pm 0.95$  confidence intervals).

Carraro et al., Prostate 29:231-240, 1996



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



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

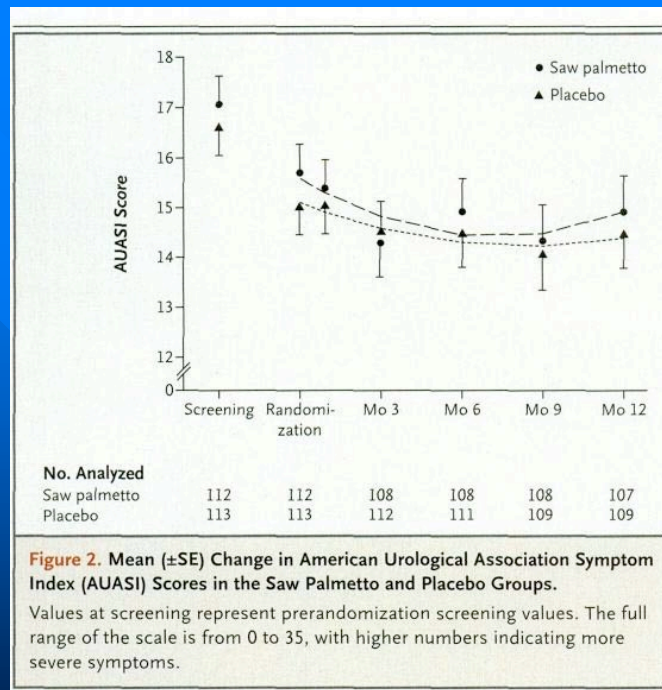
**TABLE I. Changes in International Prostate Symptom Score and quality-of-life score in men treated with saw palmetto and placebo for 6 months**

	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

## *Saw Palmetto*

### ■ Summary

- **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 CO<sub>2</sub> extract?

## *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*

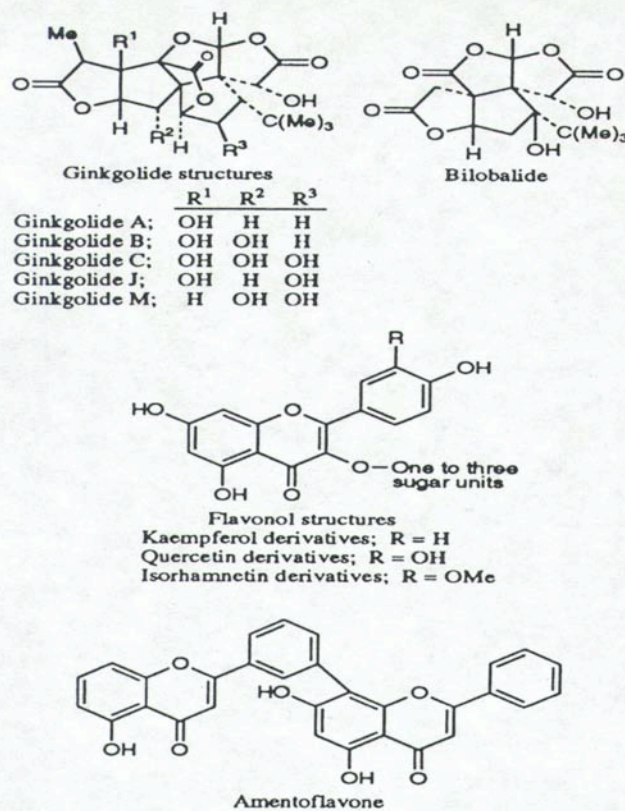


Fig. 23.5. Some constituents of *Ginkgo biloba* leaves

## • *Ginkgo biloba*

### ■ Pharmacology

- Antioxidant/antiinflammatory
- Free radical scavenger
- Anti PAF (ginkgolide B)- but may not occur in vivo in humans
  - »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
- Stimulation of endothelium-derived relaxing factor
- Inhibition of endothelial nitric oxide synthesis
- Neuroprotective effects and neurotransmitter modulations (animal and in vitro studies)

### Common Uses

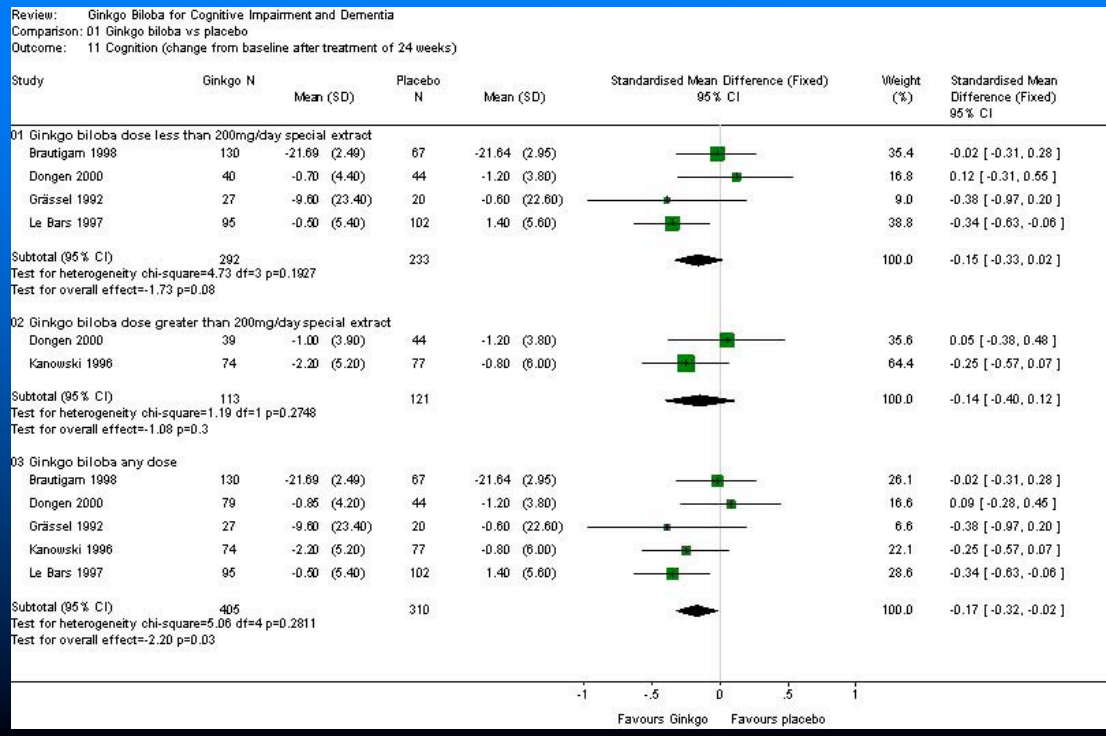
- Claudication (peripheral vascular disease)
- Dementia treatment (multi-infarct and Alzheimer's)
- Cerebral insufficiency
- Age-associated memory impairment
- Memory enhancement (in healthy patients)
- Tinnitus
- Altitude (mountain) sickness
- Vertigo
- Macular degeneration
- Premenstrual syndrome (PMS)
- 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 show ginkgo to be better than placebo. The benefits have been modest, however.



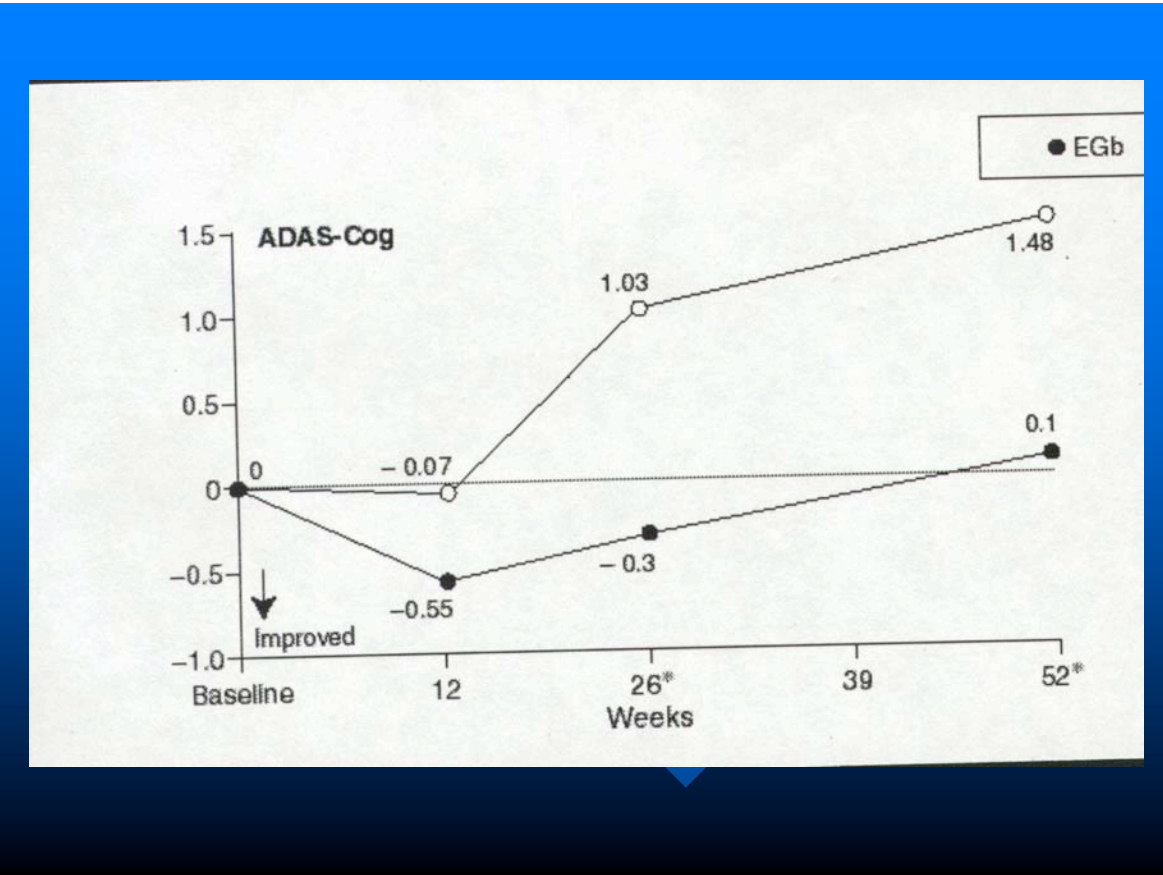
Pittler MH, Ernst E. Ginkgo biloba extract for the treatment of cognitive impairment and dementia: a meta-analysis of randomized trials. Am J Med 2000;108(4):276-281.



## 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
- conclusions: modest improvement, improvement recognized by caregivers



A new study in the  
Journal of the American  
Medical Association  
shows that Ginkgold helps  
with age-related  
mental function.\*

For the benefits of this breakthrough study choose the extract actually used, patented Ginkgold®. Other brands may claim to be similar, or perhaps even less. But don't be fooled. In head-to-head research, only the Ginkgold® extract was shown to increase activity in all areas of the brain\*\*\*. So, for better mental sharpness, choose the better ginkgo extract—Ginkgold® from Nature's Way.

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\*This statement has been evaluated by the Food & Drug Administration. This statement is not intended to diagnose, treat, cure or prevent any disease.

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The Name of "Ginkgold" is a Registered Trademark of Nature's Way Products, Inc. All other names are trademarks of their respective owners.  
\*\*Journal of the American Medical Association (JAMA) 279:1212-1219, 1998  
\*\*\*JAMA 279:1212-1219, 1998



- 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.

## Ginkgo and Memory Enhancement in Healthy Adults

Crews et al. *HerbalGram* 2005;67:43-62

6/7 acute studies show improvement in memory tests

7/9 long term studies show improvement in memory tests

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

# ORIGINAL CONTRIBUTION

## Ginkgo for Memory Enhancement A Randomized Controlled Trial

Paul R. Solomon, PhD  
Felicity Adams, BA  
Amanda Silver, BA  
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Richard DeVaux, 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.

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**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.

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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

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N=262  
Ginkgold  
60mg BID  
x 6 weeks

### HUMAN PSYCHOPHARMACOLOGY

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## 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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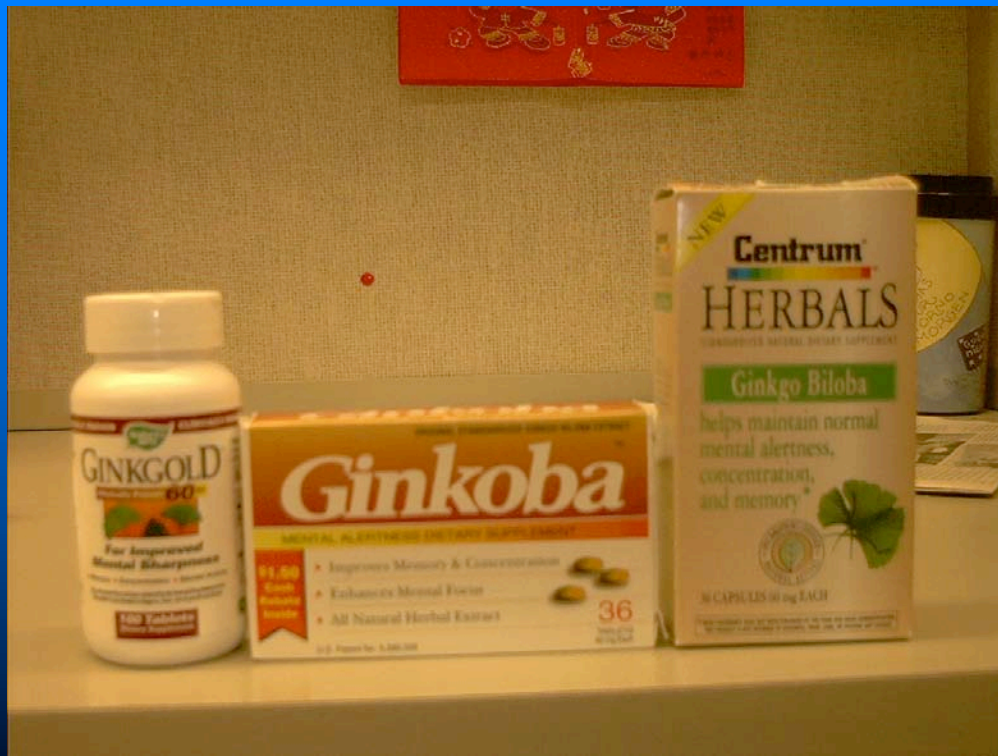
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There appears to be an absence of large-scaled clinical trials that have examined the efficacy of *Ginkgo biloba* extract on the neuropsychological functioning of cognitively intact older adults. The importance of such clinical research appears paramount 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





***Ginkgo biloba – peripheral circulation***



Adapted from Vasa 27:106-110,1998

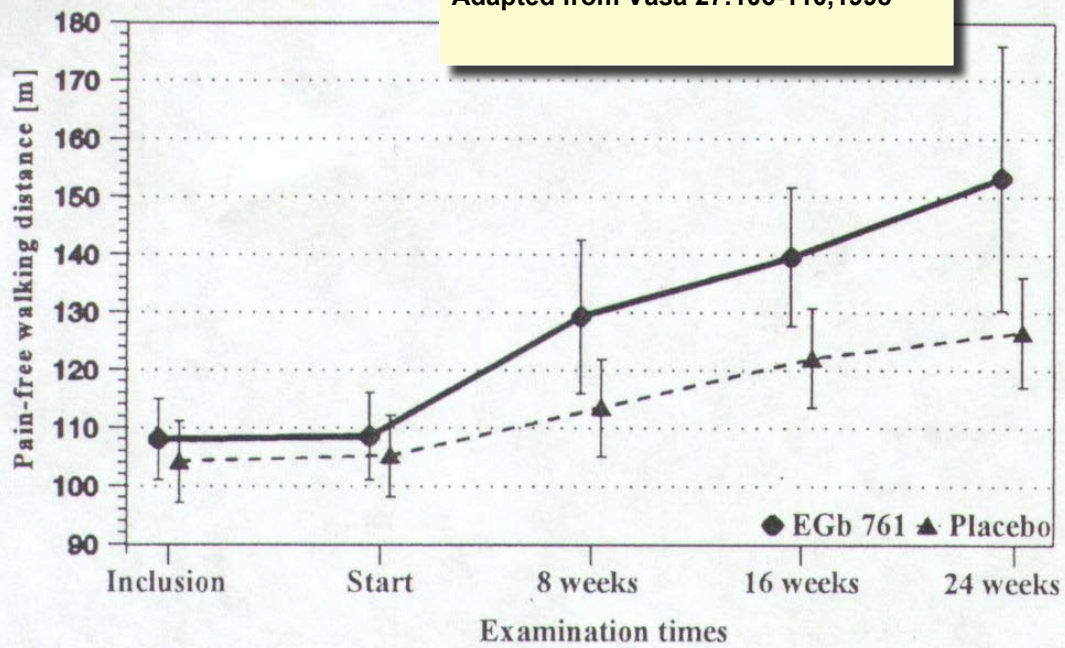
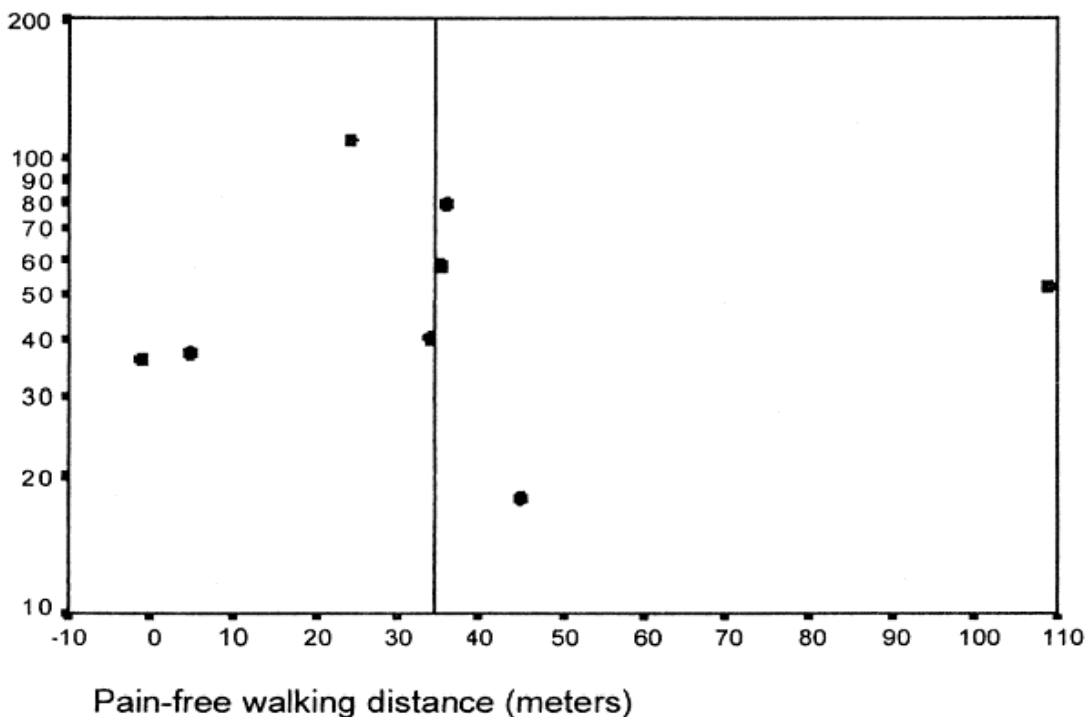


Fig. 1: Course of pain-free walking distance (m) at baseline, after 2 weeks placebo treatment and after 8, 16, and 24 weeks treatment with EGb 761 or placebo (arithmetic means with 95% confidence intervals)

### Sample size



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

## • *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- (studies show promise; start 1-5d before trip but recent large (n=487) study showed effect of acetazolamide but not ginkgo)
- 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

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)

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:** evidence for benefit in dementia, poor memory and poor peripheral circulation
- **Safety:** good but watch for rare bleeding episodes, seizures?
- **Drug interactions:** warfarin; possibly aspirin and other antiplatelet adhesion drugs (ticlopidine)
- **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
- **Questions remaining include**
  - » *Extent of memory improvement in younger patients?*
  - » *Delay Alzheimer's and dementia?*
  - » *Help in other circulatory disorders?*
  - » *Synergistic with other drugs and treatments?*
  - » *Optimum dose and treatment time?*