Garlic

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

Alliin is a major component found in fresh and dried (carefully) garlic. Allicin is odiferous and pharmacologically active
Ajoene and like allylsulfides are major components of garlic oil.

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

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

Evidence – cholesterol lowering

- Some recent well designed studies show no effect on cholesterol lowering
- 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)

N=140
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
Garlic

- **Evidence - atherosclerosis**
  - 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).

- **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 whereas antibiotic Rx did.

- **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.

- **Hypertension**
  - Some evidence for small reduction in systolic and diastolic but more study is needed before recommendations can be made

- **Insect Repellent**

**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 but mild benefit if excellent product is used
  - **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

Chicoric acid
(2) (2E)-N-isobutylundeca-2-ene-8,10-diyamide m/z = 231

(3) (2E,4Z)-N-isobutylundeca-2,4-diene-8,10-diyamide m/z = 243

(4) (3E,4Z,8Z)-N-isobutylundeca-2,4,10-triene-8-yamide m/z = 245

(5) (2E,4E,8Z,10Z)-N-isobutylundeca-2,4,8,10-tetraamide m/z = 247

(6) (2E,4E,8Z)-N-isobutylundeca-2,4,8-triename m/z = 249

(7) (2E,4E)-N-isobutylundeca-2,4-diename m/z = 251

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**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

  » 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
P-I 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.
• 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 part-based products showed benefit. The root extract did not.
No cure for the common cold


Previous 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.

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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 contained alkamides/chicoric acid/polysaccharides in a concentration of 0.25/2.5/25 5 mg/ml in 40% ethanol. Got benefit from treatment.


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

N=282 echinilin standardized; 10 stat then 1 qid
– Other immune stimulant uses?
  » Cancer
  » AIDS
  » bacterial and fungal infections
– Products
  » tablets 250mg
  » tincture
  » root extract or extract of tops or pressed juice

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**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
Saw palmetto

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

- **History**

- **Chemistry**
  - fatty acids
  - sitosterols
  - flavones, isoflavones, coumestans

- **Pharmacology**
  - lipid extracts of berry inhibit testosterone 5α-reductase and therefore conversion of testosterone to dihydrotestosterone
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.

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)#²

- Most other studies have showed benefit vs placebo, e.g. study by Gerber et al. (Urology 2001;58:960-5)
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

From 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**

- 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?

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**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. Urology 54:473-478, 1999.
- 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??
Ginkgo biloba

- Botanical Aspects
- History
- Chemistry
  - *bioflavonoid glycosides*
    - quercetin, kaempherol, 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.
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
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


6/7 acute studies show improvement in memory tests
7/9 long term studies show improvement in memory tests
A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGB 761® in a sample of cognitively intact older adults: neuropsychological findings

Joseph A. Min1,2 and W. David Crews, Jr.3,4

1University of Lynchburg, Lynchburg, Virginia, USA
2Virginia Neuropsychology Associates, Inc., Lynchburg, Virginia, USA
3Virginia Polytechnic Institute and State University, Blacksburg, Virginia, USA

N=262 Ginkgold 60mg BID x 6 weeks

This appears to be an absence of large-scale 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 predominately cognitively intact adults with claims of enhanced cognitive performance. The purpose of this research was to conduct the first known, large-scale clinical trial of the efficacy of Ginkgo biloba extract (EGB 761®) 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, placebo-controlled, parallel group, clinical trial. Participants were randomly assigned to receive either Ginkgo biloba extract (EGB 761® 135mg or placebo (135mg) 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 135mg of EGB 761® daily for 6 weeks exhibited significantly rare improvement on SRT tasks involving delayed (8min) free recall (p<0.01) and recognition (p<0.01) of noncontextual, auditory-verbal material, compared with the placebo controls. The EGB 761® group also demonstrated significantly greater improvement on the WMS-III FII subtest assessing delayed (8min) recognition (p<0.05) of visual material (i.e., human faces), compared with the placebo group. However, based on the significant differences (p<0.05) found between the two groups’ pretreatment/posture 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 and on the follow-up Self-report Questionnaire also revealed that significantly more participants in the EGB 761® group rated their overall abilities to remember by treatment and as “improved” compared with the placebo controls. Overall, the results from both objective, standardized, neuropsychological tests and a subjective, follow-up self-report questionnaire provide complementary evidence of the potential efficacy of Ginkgo biloba extract EGB 761® in enhancing cognitive functioning/memory processes of cognitively intact older adults, 60 years of age and over.
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).
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

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**

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<th>Patient age</th>
<th>Ginkgo use</th>
<th>Other therapy</th>
<th>Bleed</th>
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<td>Warfarin</td>
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1. NEJM 336:1108, 1997

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**Ginkgo biloba**

- **Summary**
  - Efficacy: good for dementia and poor peripheral circulatory problems
  - 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?