



Milk Thistle

☛ Botany

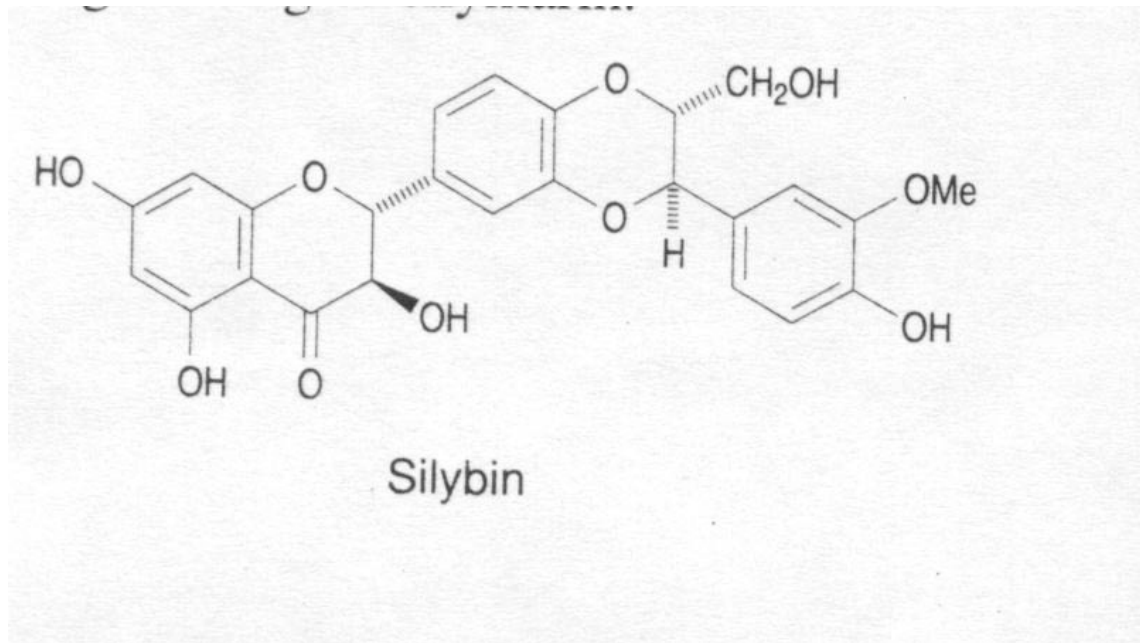
- *Silybum marianum*
- Asteraceae family (daisy, thistles, artichoke)

☛ History

- long used to treat “liver problems

☛ Chemistry

- fruits/seeds contain flavonolignans
- silymarin=crude mixture of flavonolignans; actually is mixture of several e.g. silybinin
- Seeds generally used



Milk Thistle

☛ Pharmacology

- silymarin has strong antioxidant properties
- has ability to block toxin entry through membranes
- stimulates liver regeneration; undergoes enterohepatic circulation
- increases glutathione
- stimulates ribosomal RNA polymerase
- has anti-carcinogenic activities in vitro and in animals

☛ Uses

- liver cirrhosis
- hepatitis A,B,C
- liver toxin poisoning (e.g. amanita mushroom)

Viral Hepatitis (A or B)

in several studies patients “normalized” hepatic function tests faster in the milk thistle group compared to placebo; shorter hospital stay

Hepatitis C – unknown efficacy; Tanamley et al. (Dig Liver Dis. 2004 Nov;36(11):752-9) were not able to show improvement compared to a multivitamin control at 1 yr (n=141).

A recent crossover study (placebo or milk thistle) for 12 weeks (n=17) showed no benefit (Gordon et al. J Gastroenterol Hepatol 2006;21:275-280).

Toxin and Drug Induced Hepatitis

both animal and some small patient studies show protective effect of milk thistle or silymarin

A meta-analysis (Am J Med 2002;113:506-15) concluded no strong benefit but more studies needed; animal studies indicate considerable promise for beneficial activities

☛ Alcohol Related Liver Disease

- some improvement in liver function tests compared to placebo in limited studies
- cirrhosis: Pares et al. J. Hepatol 28:615-621, 1998; no effect on survival or clinical course of alcoholics; n=200; 2yr study
- cirrhosis: (Ferenci et al. J. Hepatol 9:105-113, 1989 showed 58% 4yr survival in treated vs 39% placebo (p=0.036); 4 yr study
- Lucena et al. (Int J Clin Pharmacol 2002;40:2-8) showed increase in glutathione and decreased liver peroxidation in patients with alcoholic cirrhosis but no change in routine liver tests in treated compared to placebo. N=60
- Alcoholic cirrhotic diabetics. Velussi et al. 1997;26:871-879. N=60. Open label. Improved

A Cochrane Database Review concluded that the quality of existing trials was low. For alcoholic and/or hepatitis B or C liver disease, there were trends for benefit on overall mortality and complications and a statistical reduction in liver-related mortality in all trials (RR 0.5, CI 0.29-0.88) but not in high quality trials (RR 0.57, CI 0.28-1.19). “high quality trials are needed”

Rambaldi et al. Cochrane Database Syst Rev 2005;2:CD003620.

Milk Thistle

☛ Cautions

- Nothing special

☛ Interactions

- None of significance reported as yet. Recently shown to not affect indinavir pharmacokinetics or CYP3A4 or P-glycoprotein.

☛ Products

- flavonolignans are not water soluble
- extract used
- extracts containing at least 70% silymarin are best
- A lipid complex of silibin has high bioavailability

New Potential Use in Diabetics

randomized, double –blind, placebo controlled trial (n=51) gave milk thistle extract or placebo for 4 months to diabetics. Glycosylated hemoglobin (HbA1c) and lipid profiles improved.

Huseini et al. *Phytother Res* 2006;20:1036-1039.

Milk Thistle

Summary

- **Efficacy: possibly helpful for liver injury due to hepatitis and drugs and alcohol but evidence is weak. Some promise for diabetics**
- **Safety: good**
- **Drug interactions: none noted so far. None of significance reported as yet.**
- **Product selection: extract containing 80% silymarin is best**
- **Dose: 200mg TID**
- **Questions remaining include**
 - *Does milk thistle really work for its hepatitis B or C and for alcoholic liver disease? Will it be useful for diabetic patients?*



Green Tea

Botany-Camillia sinensis leaves

black tea-fully fermented leaves that are roasted;40mg
caffeine/cup

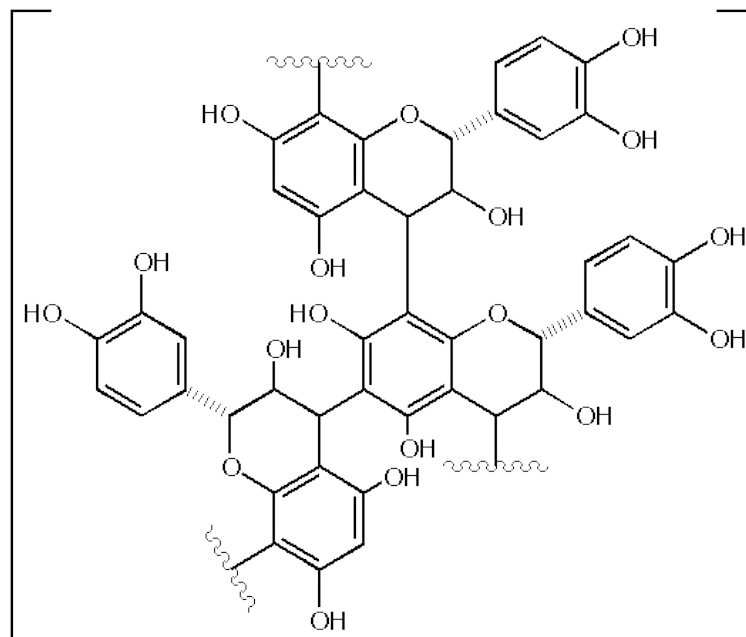
green tea-steamed, dried, nonfermented leaves;20mg/cup

oolong tea-partially fermented

white tea-steamed leaf buds;15mg/cup

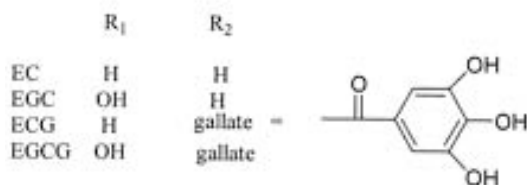
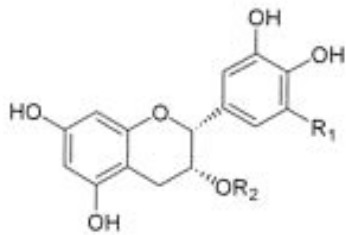
Chemistry-the hot water extract of the leaves contains oligomeric proanthocyanidins (OPCs) and other antioxidant/free radical scavenging compounds; green and white tea have mainly catechins and flavanols, black tea has theaflavins

Pharmacology-protective activity against experimental cancers in animals and some epidemiological evidence for protective effects for stomach, colon, pancreatic cancers and lower cardiovascular disease risk but these are observational not prospective, controlled trials. There are some new, very promising preliminary studies recently published, however.



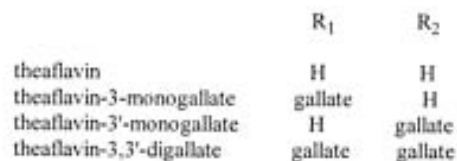
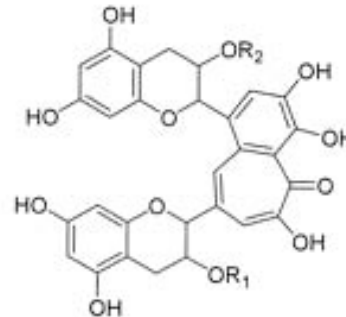
Proanthocyanidin oligomer

FLAVANOLS



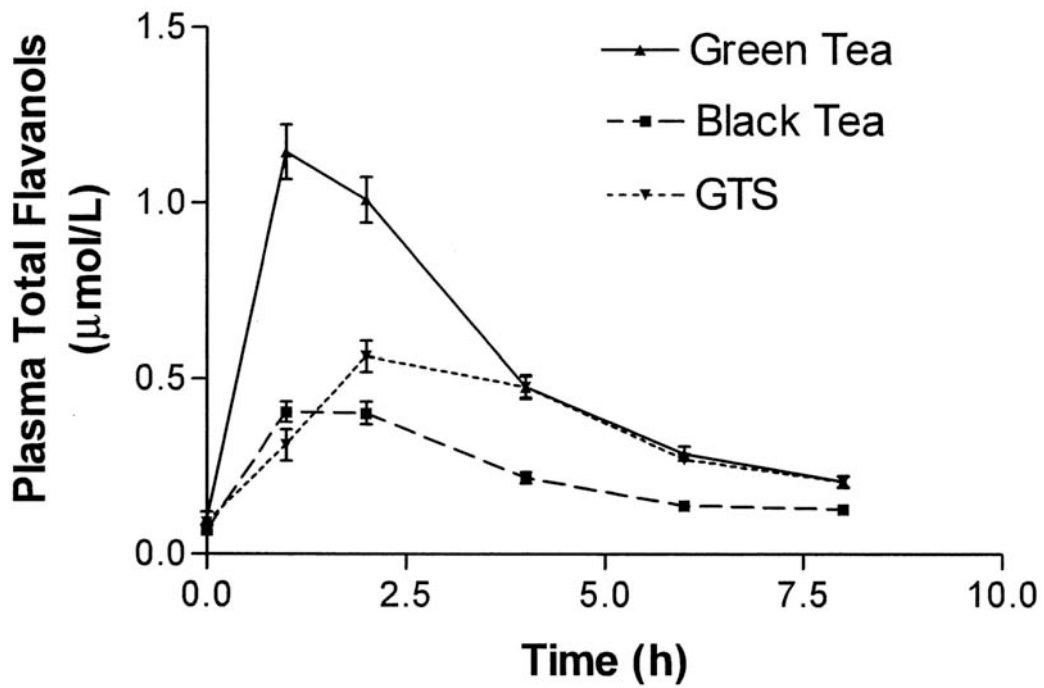
EGCG=epigallocatechin-3-gallate

THEAFLAVINS

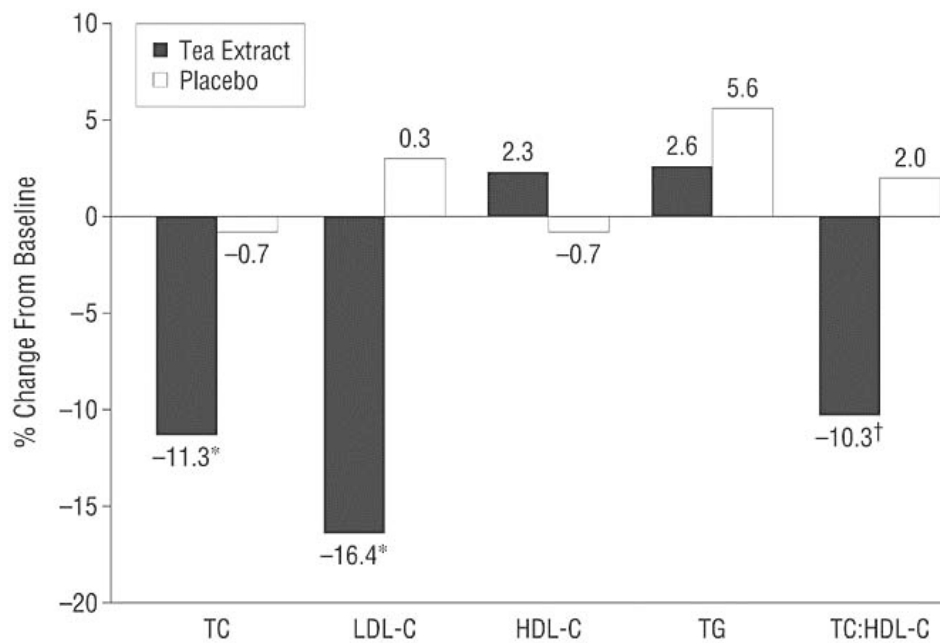


Uses and Evidence

- ☛ Topical use: some evidence for protection from UV light damage
- ☛ Cancer: some preliminary evidence for prostate cancer (Bettuzzi et al. *Cancer Res* 2006;66:1234-1240. n=64) and cervical dyplasia (Ahn et al. *Eur J Cancer Prev.* 2003;12:383-90).
- ☛ Also high consumption associated with lower risk for bladder, esophageal and pancreatic cancers.
- ☛ Heart Disease: some preliminary evidence for improved cholesterol levels (see slide)



Henning et al. Am J Clin Nutr 2004;80:1558-64. N=30
 GTS=Pharmanex; all had equal EGCG dose



Archiv Intern Med 2003;163:1448-1453 n=240 12 weeks used
 theaflavin enriched green tea extract in capsule form

Table 2. Prevalence of prostate cancer in placebo arm and GTC arm (12 months biopsy checkpoint)

Study arm	prevalence of cancer (%)
placbo	30
Green tea extract	3.3
P value	<0.01

Bettuzzi et al. Cancer Res 2006;66:1234-1240. n=64 with early signs of dysplasia; used capsules of a catechin enriched tea extract

June 30, 2005, FDA denied health claim for Green Tea

1. "Two studies do not show that drinking green tea reduces the risk of breast cancer in women, but one weaker, more limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of breast cancer."

2. "One weak and limited study does not show that drinking green tea reduces the risk of prostate cancer, but another weak and limited study suggests that drinking green tea may reduce this risk. Based on these studies, FDA concludes that it is highly unlikely that green tea reduces the risk of prostate cancer."

Green Tea

☛ Summary

- **Efficacy:** Increased consumption *may* be somewhat protective against certain cancers and heart disease.
- **Safety:** good; caffeine content is significant; several reports of hepatotoxicity associated with green tea extracts. Causal?
- **Drug interactions:** antihypertensives? (caffeine); does contain vitamin K so large amounts might counteract warfarin.
- **Product selection:** Most are not standardized to OPCs
- **Dose:** tea? Maybe 3 cups/d; extracts? Maybe 200mg TID.
- **Questions remaining:**
 - *How much benefit and how much tea consumption? Black tea? Do capsules act the same as the tea? What to standardize on?*



Evening Primrose Oil

Botany

Oenothera biennis., a wildflower/weed on the East USA coast

The seed is pressed to yield an oil

History

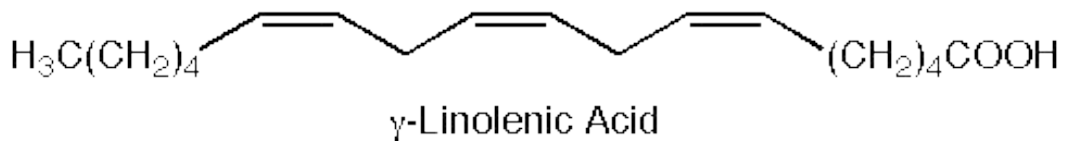
Many native American uses for the plant

Recent years have focused on the uses of the seed oil



Chemistry

- Seed contains about 14% oil of which half is gamma linolenic acid (GLA); this is a omega -6 essential fatty acid;
- note: omega -3 fatty acids are present in fish oils and flaxseed oils and have different uses (e.g. lower cholesterol and risk of cancer)
- GLA is a precursor to prostaglandin E1 which modulates (reduce) inflammation
- Other rich sources of GLA are borage seed oil (20%GLA) and black current oil (15% GLA)



6,9,12 octadecatrienoic acid

Linoleic is 9,12 octa decadienoic acid-plentiful in diet

Pharmacology of GLA

- GLA is precursor to several prostaglandins and leukotrienes that influence pain and inflammation
- The idea is to “flood the system” with precursor to enhance synthesis.
- Linoleic acid is an essential amino acid widespread in our diet
- GLA is formed from linoleic acid and is not found in common foods

Uses of GLA and Evening Primrose Oil

- Cyclic mastalgia
- PMS
- Diabetic neuropathy
- Eczema
- Arthritis, fatigue, digestive, asthma, weight loss, and many others

Evidence

- The evidence is surprisingly weak for most uses
- Several placebo controlled trials in the 1980s showing improvement in breast pain associated with menses; a recent study showed no effect (Am J Obstet Gynecol. 2002 Nov;187(5):1389-94).
- No strong evidence to show improvement of other symptoms of PMS or post menopausal symptoms
- Eczema use has been not effective in recent studies
- Use in diabetic neuropathy and rheumatoid arthritis looks promising based on a small number of older controlled studies
- More evidence is needed to support use of EPO in Raynauds syndrome, ADD, osteoporosis, as an adjunct treatment for breast cancer, for obesity, and hyperlipidemias

Safety

No special concerns at present

Dose: 2-6g of EPO/d or even higher

Evening Primrose Oil

☛ Summary

- **Efficacy: uneven evidence for most uses; best for diabetic neuropathy, cyclic breast pain, and possibly rheumatoid arthritis. May have application in helping treat breast cancer.**
- **Safety: good**
- **Drug interactions: none noted so far but increased blood clotting time has been noted. Caution with warfarin.**
- **Product selection: Efamol is the best studied; has 1g/capsule**
- **Dose: 2-6g/d**
- **Questions remaining include**
 - *Does EPO really work for its many suggested uses?*



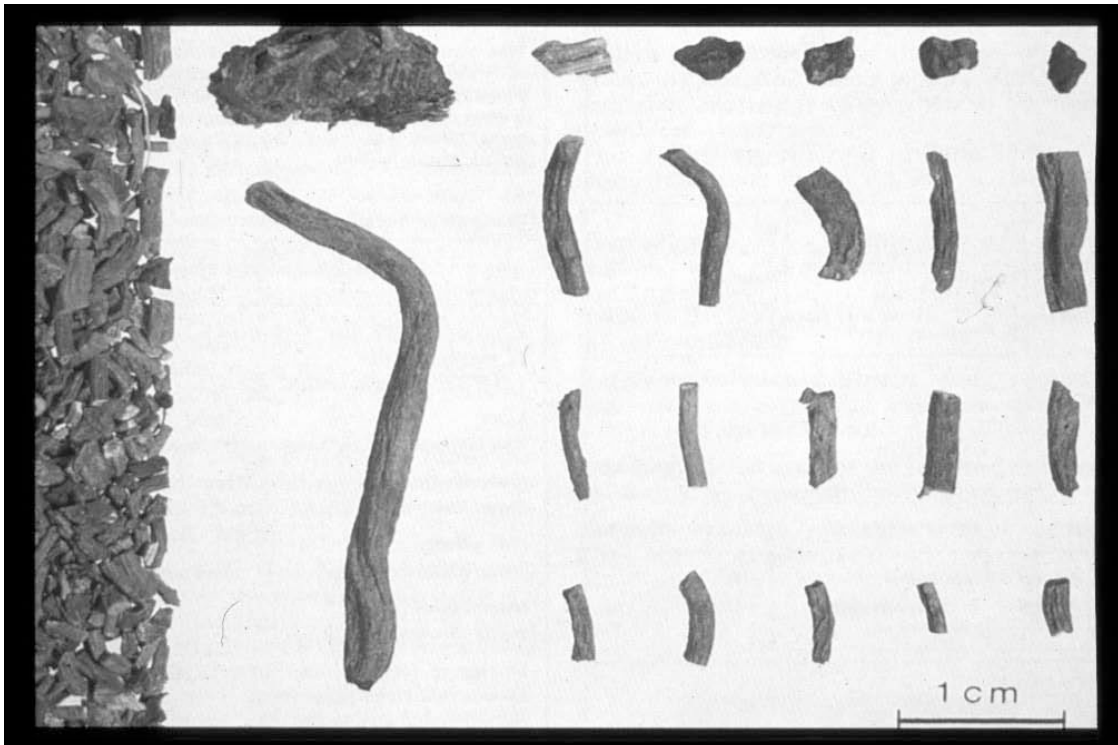
Valerian

☛ Botany

- *Valeriana officinalis*, garden heliotrope
- roots and rhizomes used
 - powder
 - tincture

☛ History

- roots long used as tranquilizer and sedative



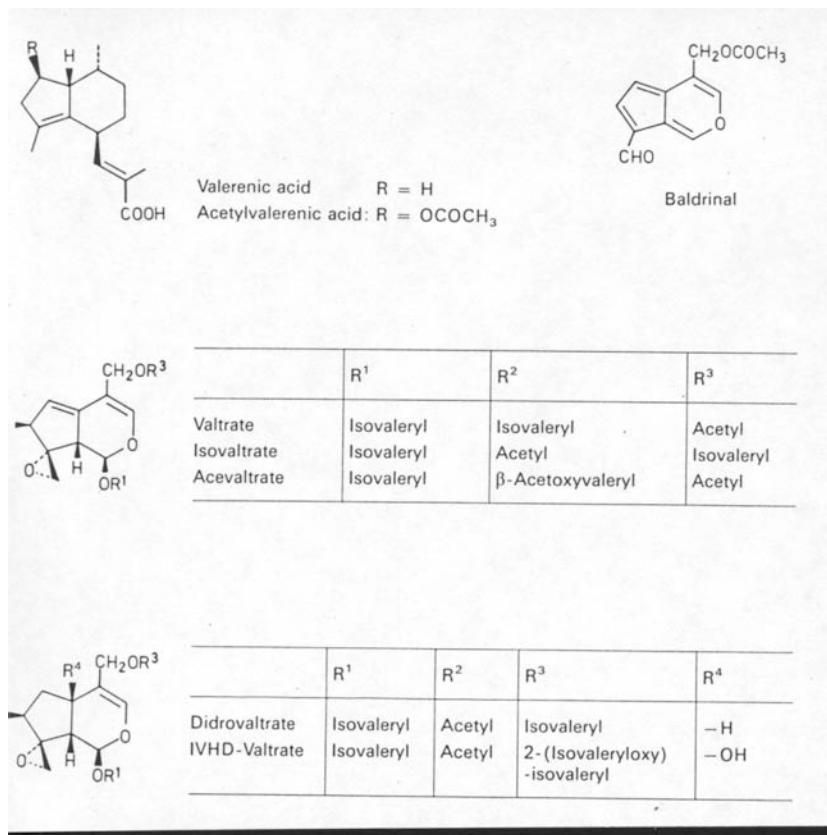
Valerian

☞ Chemistry

- 0.1%-0.3% volatile oil in roots
- contains sesquiterpenes e.g. valerenic acid
- contains valepotriates
- contains baldrinal and other decomposition products

☞ Pharmacology

- volatile oil is sedative in animals
- valepotriates have tranquilizer activity
- water extract is sedative and has neither!
- ? Active components
- in vitro-
 - aqueous extracts causes release of GABA (similar to benzodiazepines)
 - inhibit GABA breakdown
- mechanism unknown, active components unknown!



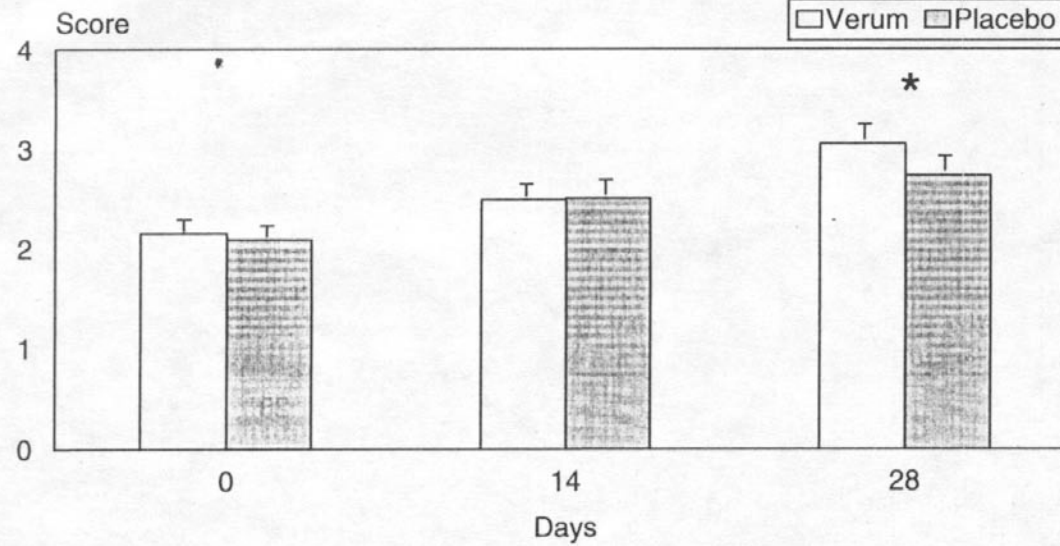


Fig. 2.16. Effect of 4 week's treatment with an ethanol valerian extract (600 mg/day) compared with a placebo. The results were assessed by the Görtelmeyer sleep questionnaire (SF-B) and statistically evaluated. A significant difference between valerian and placebo is seen only after a 4-week course of treatment (Vorbach et al., 1996).

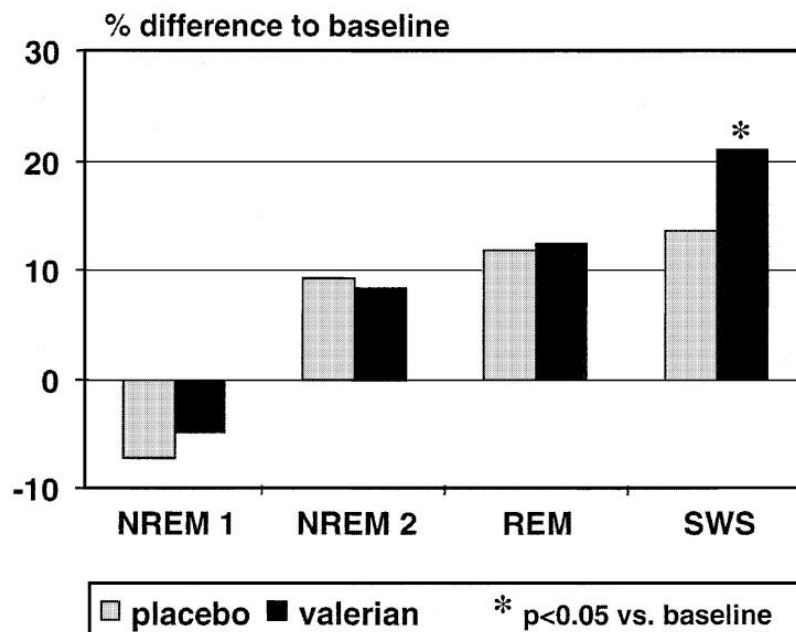


Fig. 2 Differences in sleep stages: NREM 1, NREM 2, REM, and slow-wave sleep (SWS) between baseline and long-term treatment under placebo and valerian.

Donath et al. Pharmacopsychiatry 2000;33:47-53. N=16; valerian for 14d; crossover study

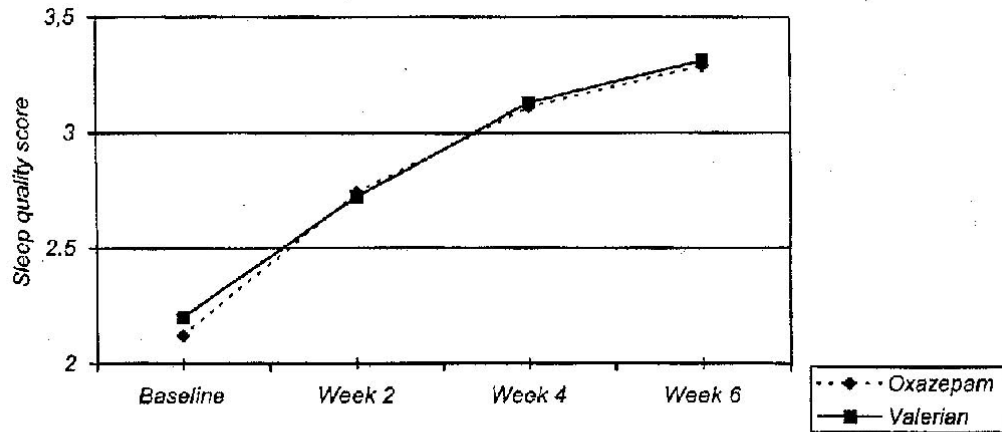
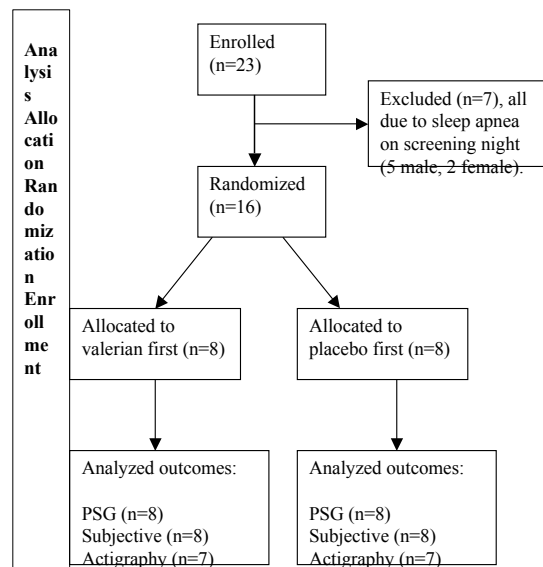


Fig. 2. Mean Sleep quality (SQ) at baseline and after 2, 4 and 6 weeks of treatment (PP analysis).

Ziegler et al. European J Med Res 2002;7:480-486. N=202

A Randomized Clinical Trial of Valerian Fails to Improve SUBJECTIVE AND OBJECTIVE Sleep Quality of Older Women with INSOMNIA. Taibi et al. Sleep (submitted 2007)



Results: no difference between placebo and valerian in subjective and objective sleep in this UW study

Valerian

☛ Precautions

- drowsiness, avoid alcohol
- restlessness, nausea
- worry over valepotriate epoxide (liver damage) but commercial products have little
- not pregnancy, not infants, not nursing
- limit use to 2 weeks, withdrawal signs have been reported but these reports are suspect
- acute overdose (20x) gave only mild effects

☛ Dose

- 400mg –600mg of an extract at hs
- 2-3g of powder to make tea
- 1-3ml of tincture

☛ Products

- valerenic acid as marker

Valerian

☛ Summary

- **Efficacy: long historical use; limited number of controlled studies but all show some efficacy. Acute use may be ineffective.**
- **Safety: good but be careful as with any sedative**
- **Drug interactions: none noted so far**
- **Product selection: many products failed consumerlab.com's testing**
- **Dose: about 600mg of a root extract at HS**
- **Questions remaining include**
 - *How effective is this for occasional use?*
 - *How effective is this for chronic insomnia?*



Horny Goat Weed (really!!)

- Botany Epimedium species, usually *E. grandiflorum*;
 leaves or root used
- History long used in traditional Chinese medicine
 (TCM) and called Ying Yang Huo
- Chemistry flavonoids, icariin (a flavonol glycoside),
 polysaccharides; active components are unknown
- Pharmacology animal studies show some effects in
 increasing semen, increasing growth of
 prostate and testicular tissue, lowering
 blood pressure and decreasing platelet
 adhesion. In vitro inhibitory effects on
 cancer cells
- Use impotence, aphrodisiac, tonic and a variety of
 other uses in TCM including for heart disease

Horny Goat Weed

- Evidence: animal studies support some hormonal effects and hypotensive action
- Safety: a report of tachyarrhythmia and hypomania with use in a patient with CHD.
- Drug Interactions: caution with anti-platelet adhesion drugs, anticoagulants and antihypertensives
- Products: no recommendations; most contain 500mg crude plant; some are extracts
- Summary: avoid this unproven and poorly studied product