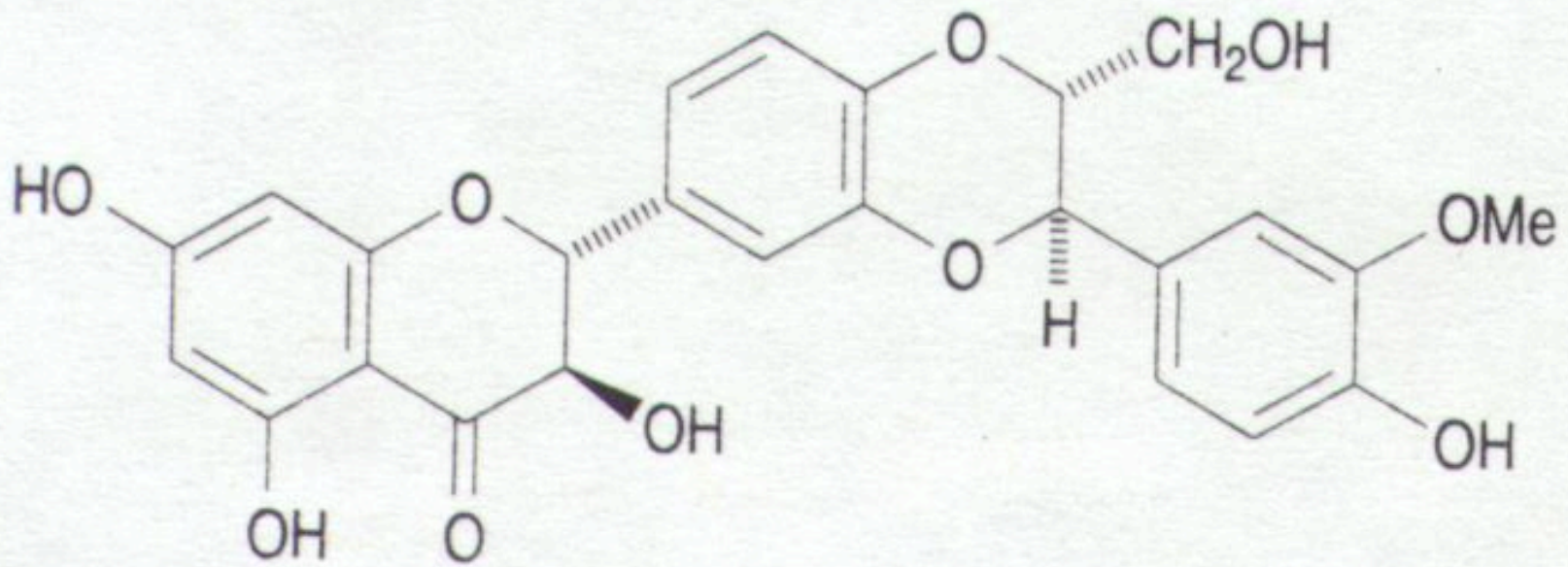


Milk Thistle

- 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



Silybin

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 phalloides 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 Inducted Hepatitis

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

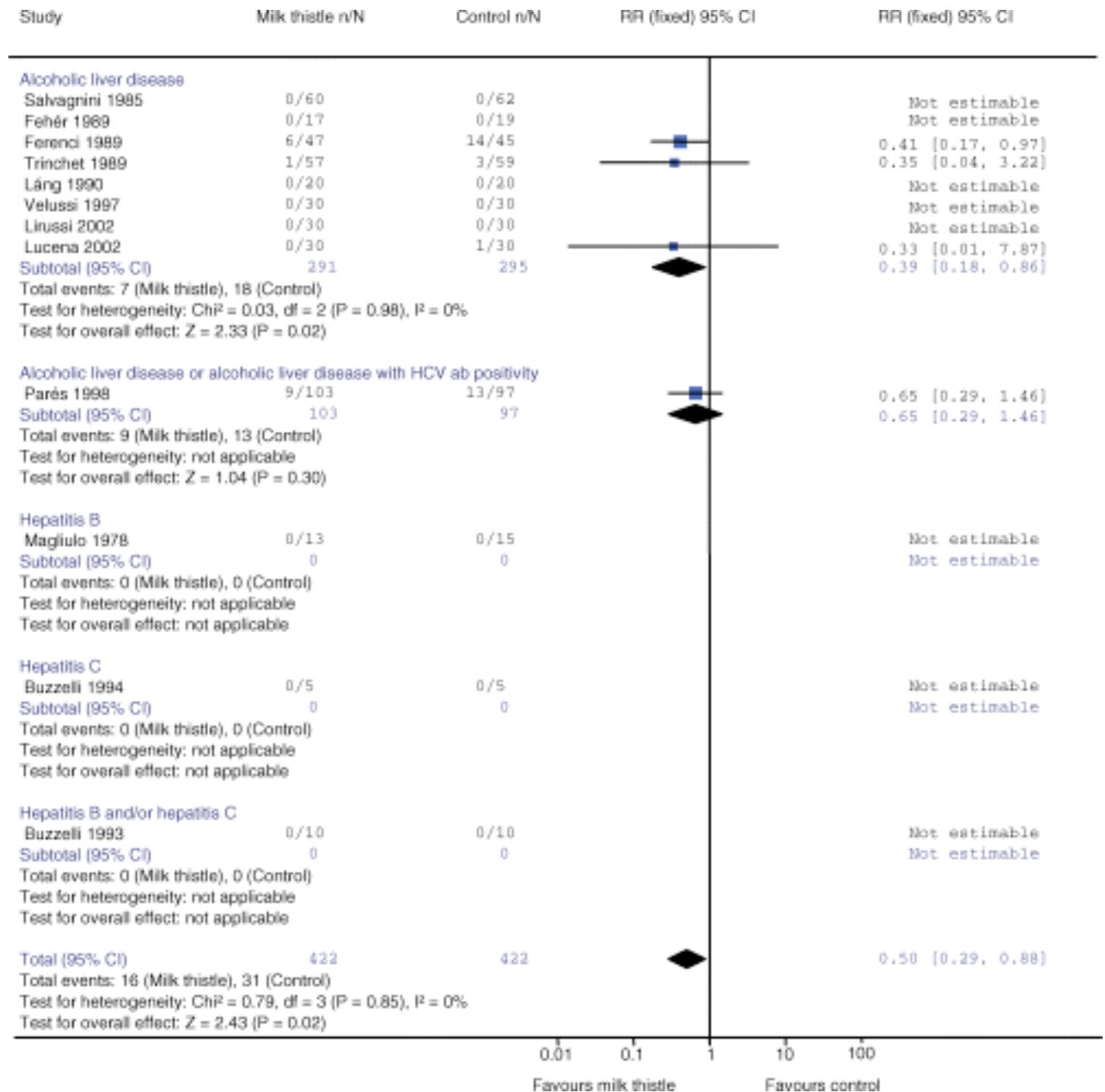
.
A meta-analysis (Am J Med 2002;113:506-15) concluded no strong benefit but more studies needed; animal studies indicate considerable promise for beneficial activities

- **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

Rambaldi et al. Cochrane Database Syst Rev 2007;4:CD003620. 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 (n=13) (RR 0.5, CI 0.29-0.88) but not in high quality trials (n=4)(RR 0.57, CI 0.28-1.19). Our results question the beneficial effects of milk thistle for patients with alcoholic and/or hepatitis B or C virus liver diseases and highlight the lack of high-quality evidence to support this intervention. Adequately conducted and reported randomised clinical trials on milk thistle versus placebo are needed

Rambaldi et al.
 Am J
 Gastroenterol
 2005;11:2583-2
 591



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

Other potential uses

- 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).
- Increased milk production in women (n=50) after delivery (*Acta Biomed* 2008;79:205-210)

Milk Thistle

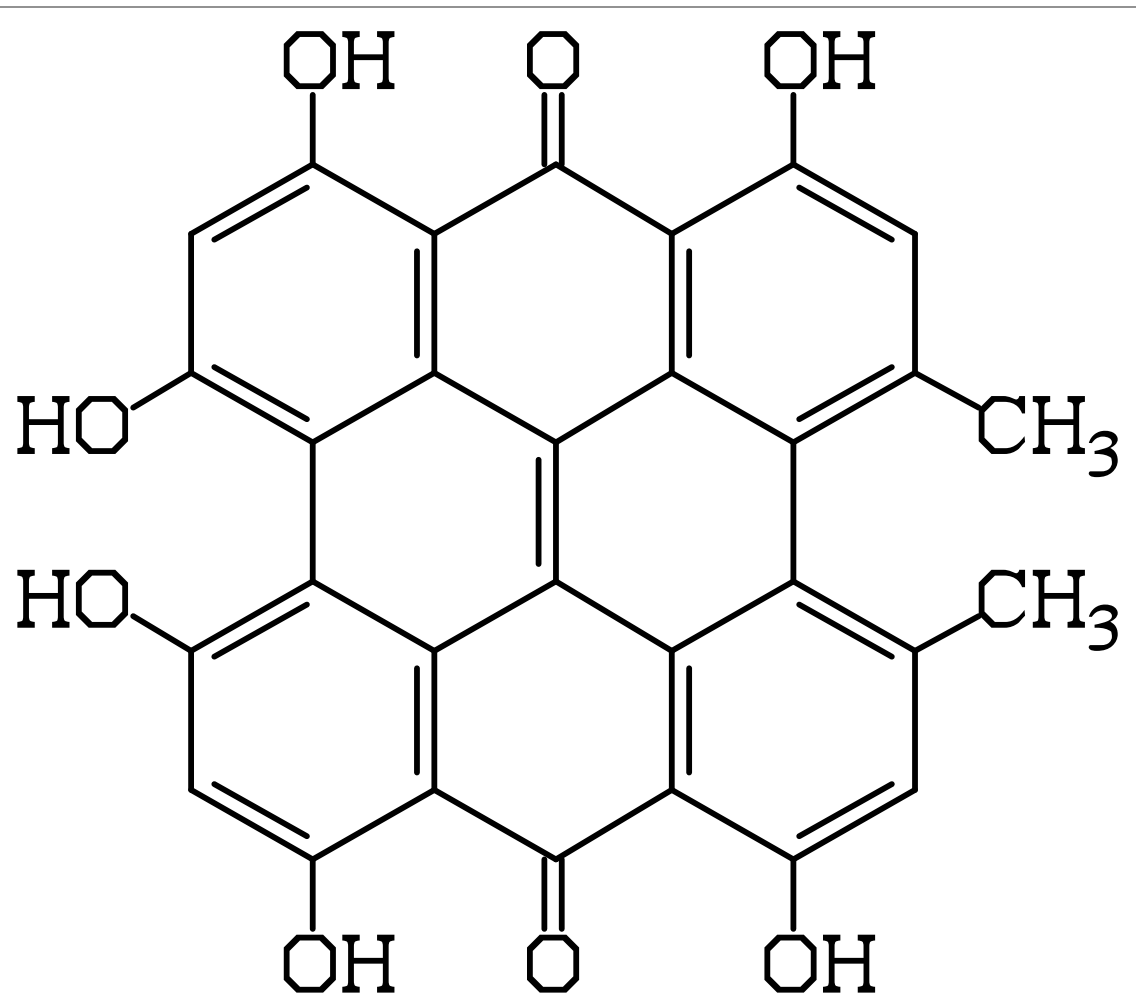
Summary: possibly helpful for liver injury due to hepatitis and drugs and alcohol but evidence is weak. Some promise for diabetics

- **Safety:** good
- **Drug interactions:** None 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?

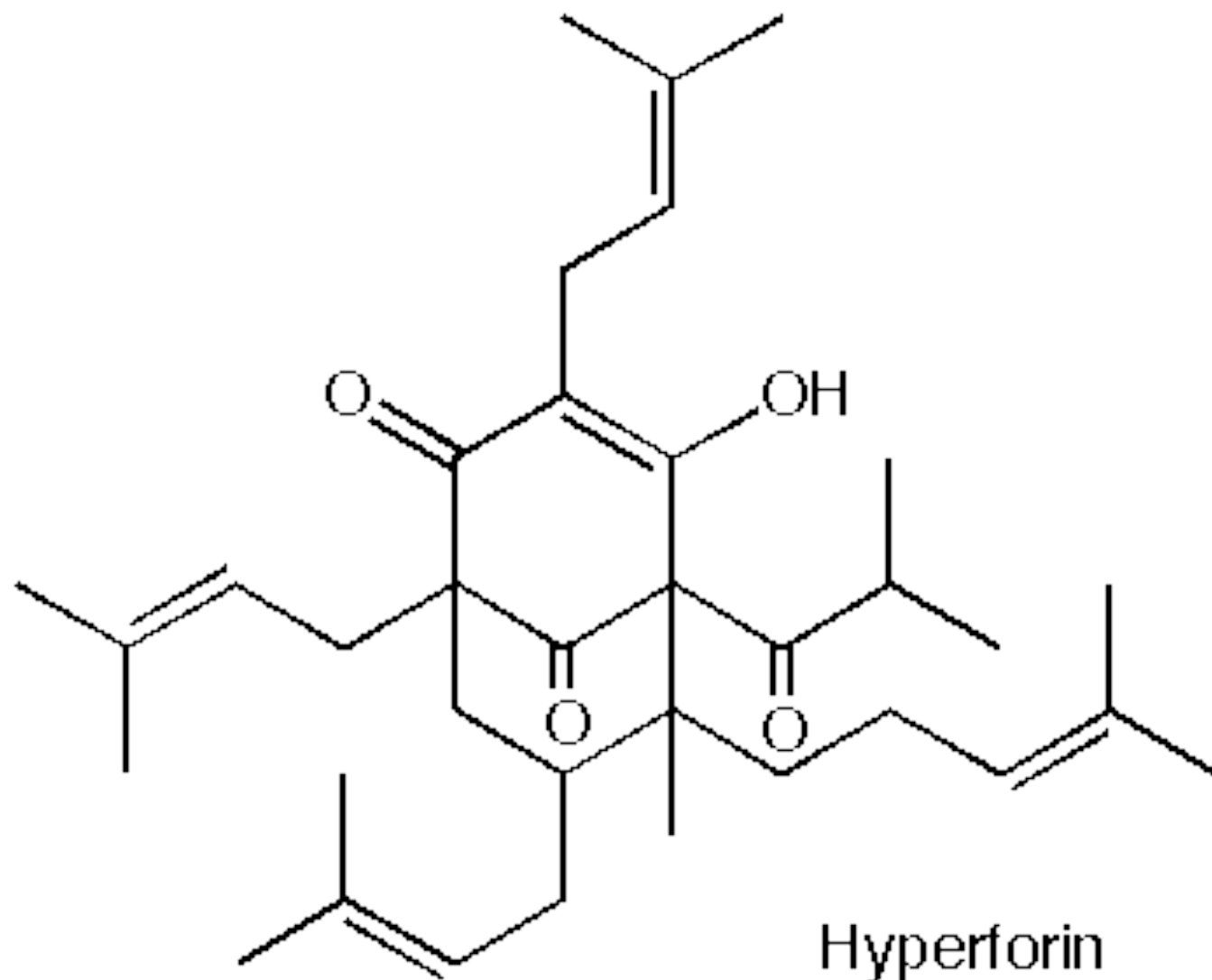
GWE – *For liver injury, milk thistle is worth a 3 month try coupled with monitoring progress with liver function tests*

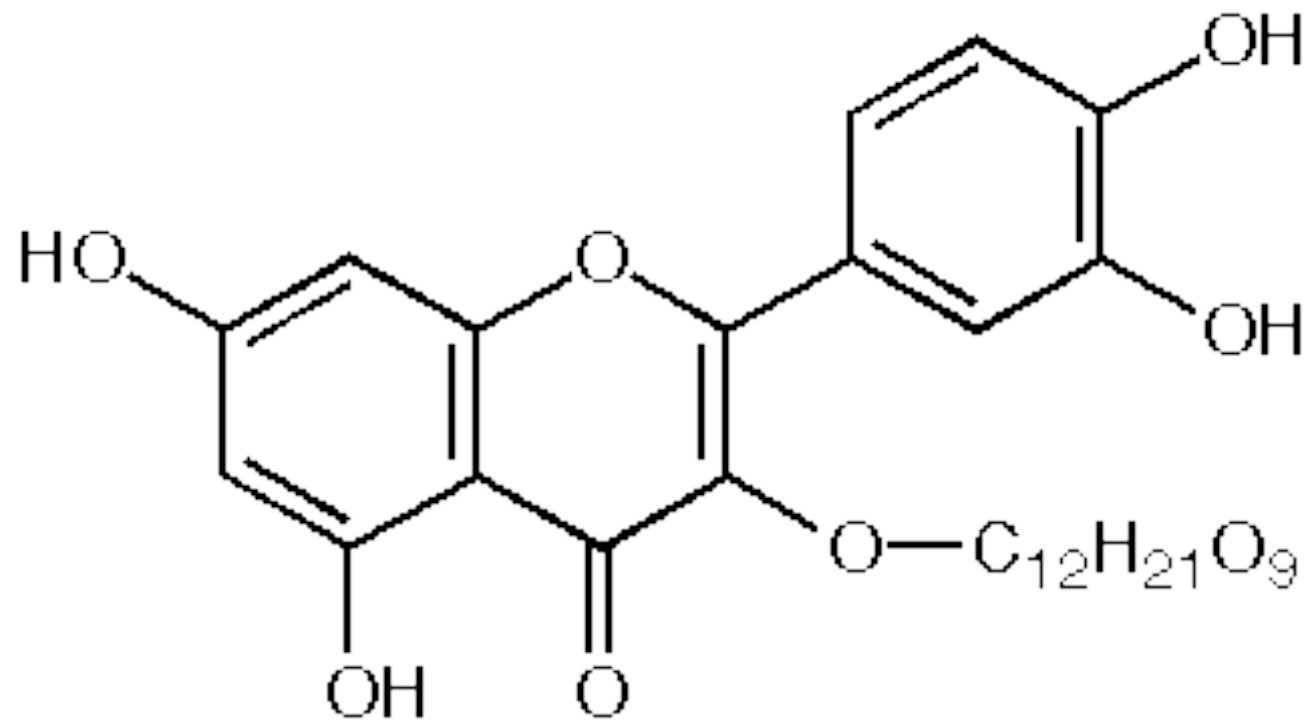
St. John's Wort

- **Botany**
 - **Hypericum perforatum**
- **History**
- **Chemistry**
 - **Hypericin**
 - **hyperforin**



hypericin





Rutin
(flavonoid glycoside)

St. John's Wort

- Pharmacology
 - hypericin
 - antiviral activity
 - MAOI ? 1984 study found activity but 3 more recent studies say no
 - hyperforin
 - more important
 - Flavonoids
 - antioxidant
 - MAOI ? But maybe not in vivo
 - Other? MAOI, SSRI

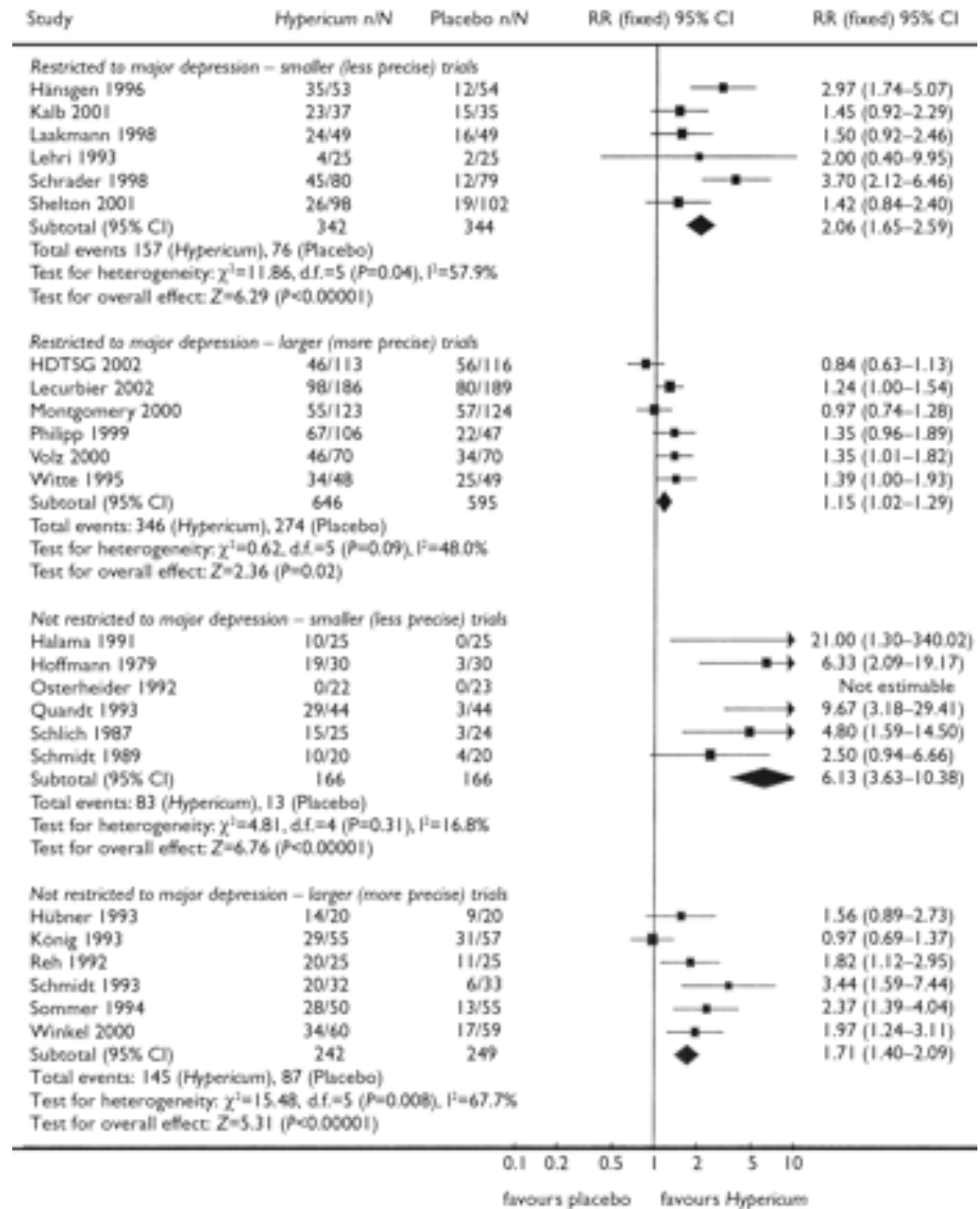
St. John's Wort

- Evidence -Depression
 - widely prescribed in Europe for depression
 - Commission E “approved” for this use
 - Commission E- psychological disturbances, depression, anxiety,nervous unrest; topically the oil for bruises,myalgia, burns

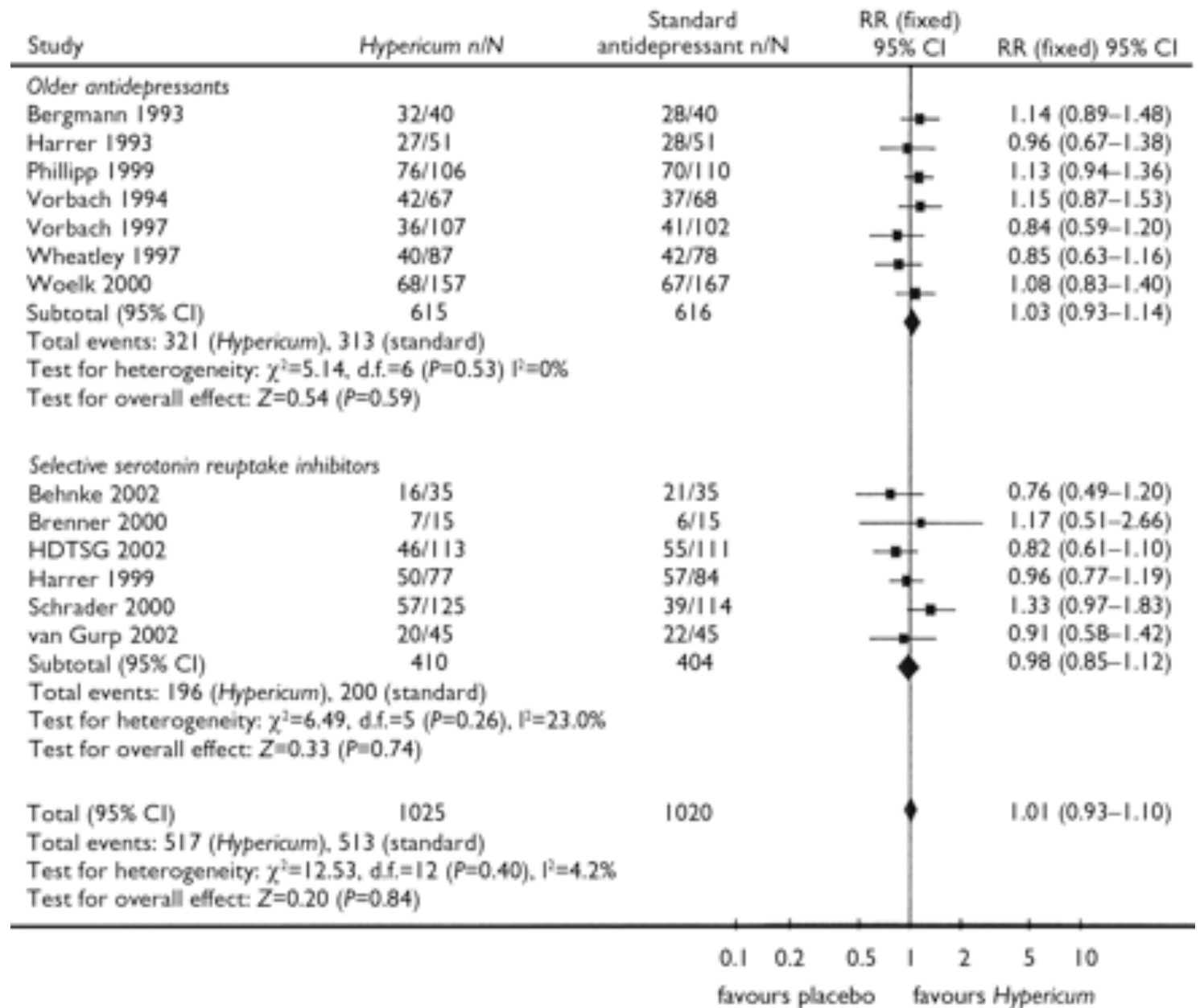
St. John's Wort

- Meta -analysis of 40 randomized trials (Linde et al. Br J Psychiatry. 2005;186:99-107)
 - 26 trials =double blind, placebo controlled; 3320 patients
 - 14 trials = double blind, compared to standard treatment; 2283 patients

Linde et al. Br J
Psychiatry. 2005 Feb;
186:99-107

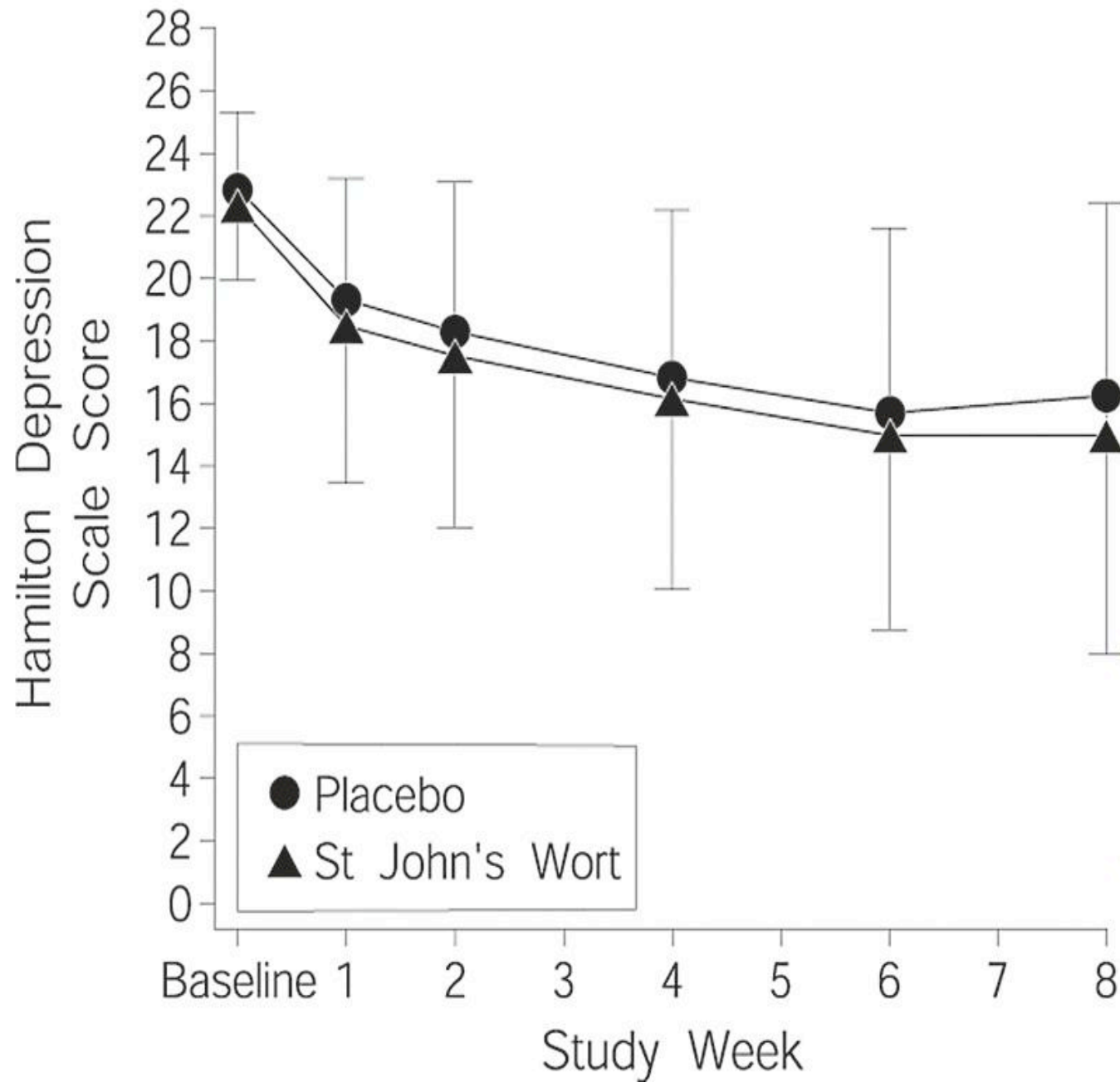


Linde et al.
 Br J
 Psychiatry.
 2005 Feb;
 186:99-107



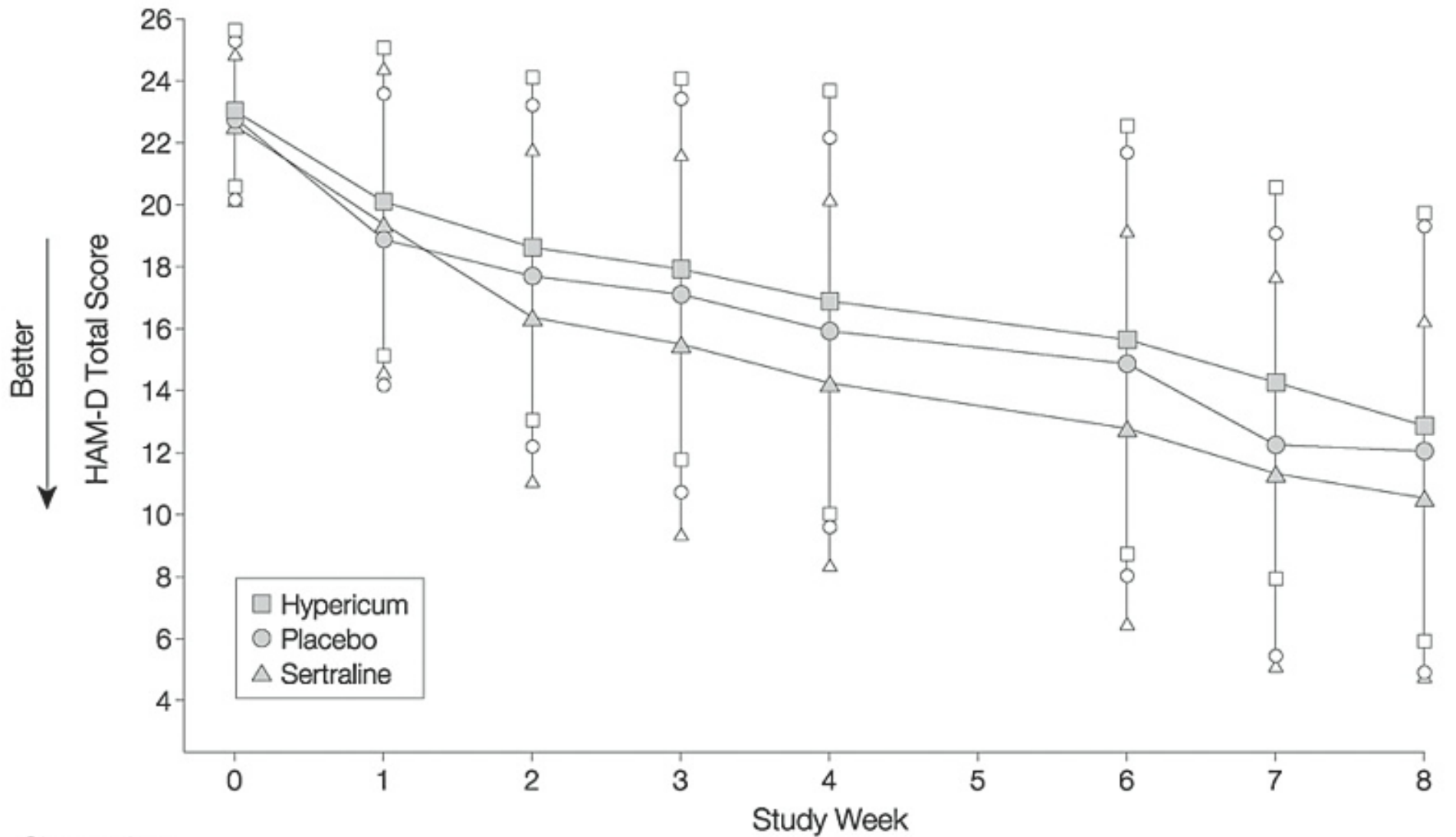
St. John's Wort

- **Linde et al conclusions: more effective than placebo, similar to standard drugs but not for major depression**
- **Woelk et al. BMJ 321:536-539, 2000. SJW same as imipramine with fewer adverse effects in multicentered German study (n=324) in patients with mild to moderate depression**
- **Brenner et al. Clin Ther 22:411-419, 2000. SJW same as sertraline in double blind, randomized study (n=30) with mild to moderate depression**
- **Schrader et al. Int Clin Psychopharmacol 15:61-68,2000. SJW same as fluoxetine with fewer adverse effects in multicentered German study (n=240) in patients with mild to moderate depression**
- **Szegedi, A et al. BMJ 2005;330:503. SJW same as paroxetine with fewer adverse events. N=244**



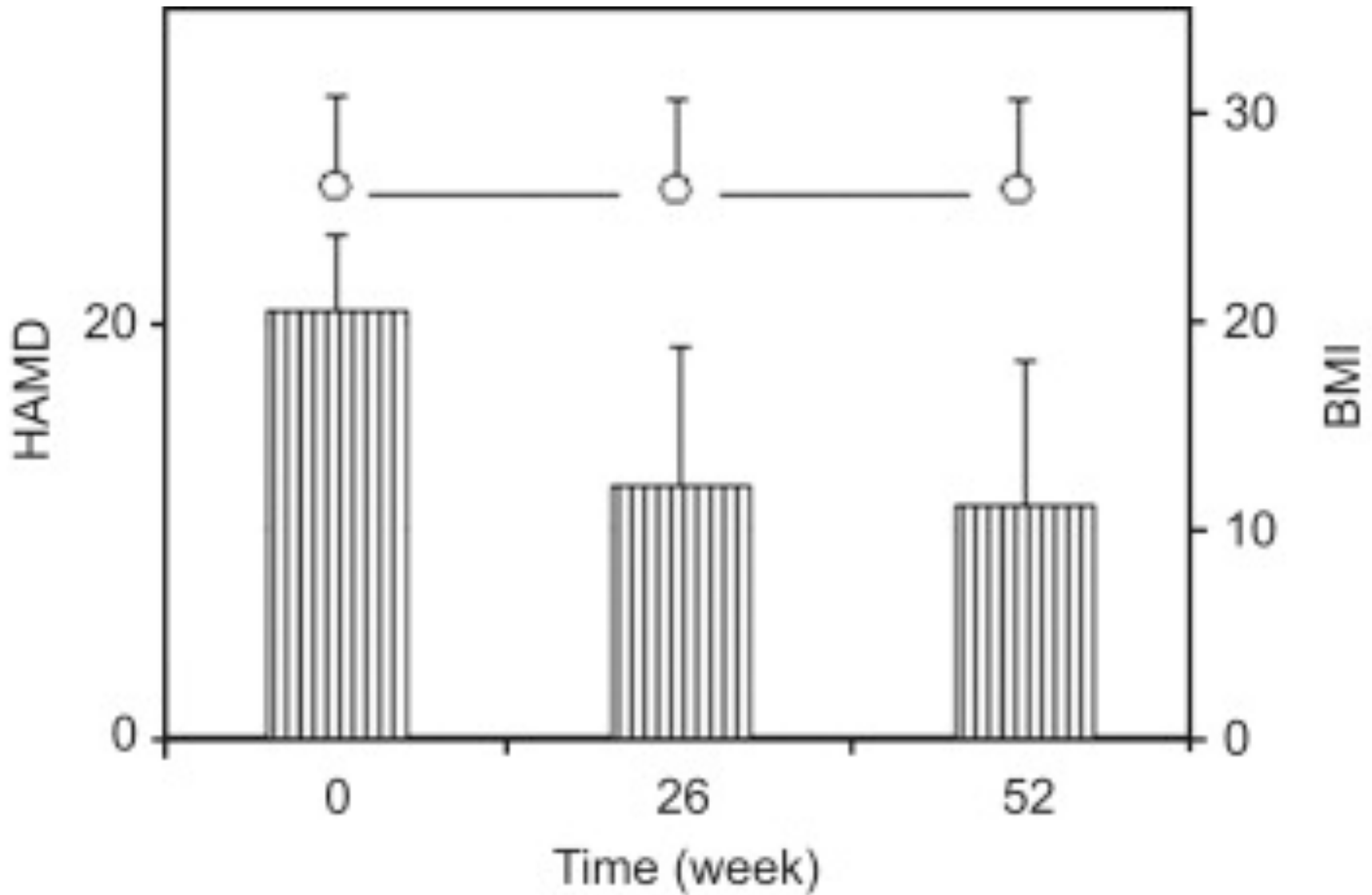
Shelton et al. JAMA 2001, 285:1978-1986

- NIH funded study
 - Duke Univ.
 - N=336 with **major** depression
 - 1/3 SJW 1/3 SSRI 1/3 placebo
 - 3 years



Observations

Hypericum	113	101	102	100	97	91	82	82
Placebo	116	111	107	94	99	93	84	84
Sertraline	109	99	88	88	87	80	77	77



Brattstrom A Phytomedicine.
 2009;16(4):277-83. n=440 mild to
 moderate depression;.

St. John's Wort

- Other Uses: less well documented
 - Seasonal Affective Disorders
 - n=20 SAD patients
 - same decrease in Hamilton depression scale with SJW ± light
 - Hypericin antiviral studies
 - hypericin activity against glioma cells
 - SJW long used to heal wounds
 - plant oil has antimicrobial activity

St. John's Wort

- **adverse**
 - **photosensitivity-animals**
 - **photosensitivity- humans- in high doses is a risk**
 - 1800mg/d + UVA; not at usual doses
 - **SSRI drugs contraindicated. Additive effects with imipramine**
 - **Open study of 3250, Wolk et al 1994**
 - 0.5% allergic rxns, 0.6% GI, 0.4% fatigue
 - **SJW is a CYP inducer with herbal/drug interactions documented.**
 - **SJW is a PGP inducer with documented interactions**

St. John's Wort

- **Summary**

- **Efficacy**: good evidence in mild to moderate depression
- **Safety**: don't combine with other medications unless under close monitoring; possible photosensitivity
- **Drug interactions**: a problem. Is a P450 inducer and a p-glycoprotein inducer
- **Product selection**: want standardized extract containing about 0.3% hypericin or 2-3% hyperforin; 300mg TID for treatment; LI160 and WS1172 extracts are the best studied
- **Questions remaining** include
 - *How best to use this herbal given that there are drug interaction problems*

Hypericin and Hyperforin in Eight Brands of St. John's Wort

De Los Reyes and Koda, Am J Health-syst Pharm 59:545-547.2002

<u>Product-</u>	<u>hypericin (%)</u>	<u>hyperforin (%)*</u>
• Hyperifin	0.29	1.89
• PNC	0.12	0.20
• Brite-Life	0.22	1.16
• ShopKo	0.26	0.05
• Shurfine	0.17	0.29
• YourLife	0.28	0.19
• Nature's Balance	0.03	0.01
• Natrol	0.25	0.48

* Usually want 0.3% hypericin and 1-2% hyperforin

Ginseng

•Botany

- Panax ginseng (Korean or Asian ginseng),
- Panax quinquefolius (American ginseng)
- note: Siberian ginseng is different (Eleutherococcus senticosus)
- steamed and dried product is “red” ginseng vs “white” ginseng which is dried only

•History

- Chemistry-ginsenosides, a series of steroid glycosides. The ratio of these differ between Panax sp.

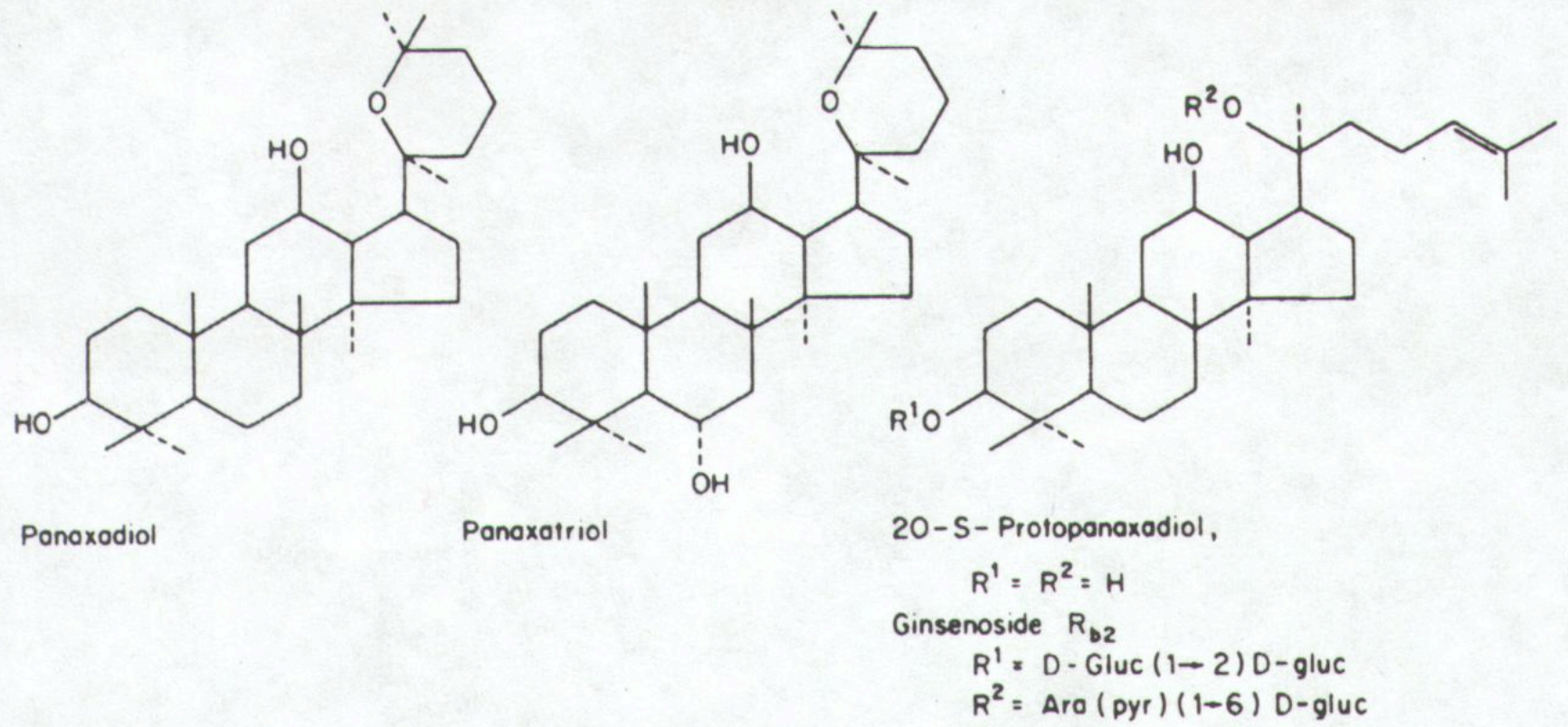


Fig. 22.10. Steroids associated with ginseng.

• **Pharmacology** – “adaptogen” is the term that perhaps best describes what ginseng is supposed to accomplish.

• **Uses**

- immune stimulant - animal and human studies (with flu vaccine) indicate that it may enhance the immune response
- sports performance - mixed results but generally negative
- mental functioning – mixed results but some intriguing results indicate promise for enhancing completion of mental tasks and (in combination with ginkgo) memory and a recent study gave suggestive evidence of improvement in Alzheimer’s Disease
- “improved quality of life” – results of small studies are inconsistent
- cancer prevention - one controversial study in Korea showed preventative effects
- hypoglycemic effects in diabetic patients (e.g. Vuksan et al., Diabetes Care 23:1221-1226,2000, Vuksan et al. Nutr Metab Cardiovasc Dis. 2008;18:46-56.) with use of American ginseng and Panax ginseng (Reay et al. J Psychopharmacol. 2006;20:771-81)
- Korean red ginseng in one recent study showed to be helpful in erectile dysfunction
- Common cold. Several studies indicate that a special extract (Cold-FX) shows preventative and treatment benefits

Predy et al. CMAJ
2005;173:1043-1048

Note: special extract of ginseng used that contains polyfuranosyl-pyranosyl-saccharides. Product (Cold-FX) available in Canada and USA. An earlier, smaller study showed activity in preventing flu in older adults (McElhaney et al. *Am Geriatr Soc.* 2004;52:13-19.)

Table 2: Number of colds over the 4-month intervention period*

Outcome	Group; no. (%)†		Difference (95% CI)
	Placebo n = 149	Ginseng extract n = 130	
Jackson+ colds‡			
No. per person, mean (SD)	0.93 (0.91)	0.68 (0.82)	0.25 (0.04 to 0.45)
1 cold	95 (63.8)	71 (54.6)	9.1 (-2.4 to 20.7)
≥ 2 colds	34 (22.8)	13 (10.0)	12.8 (4.3 to 21.3)
Colds§			
No. per person, mean (SD)	0.99 (1.00)	0.71 (0.83)	0.29 (0.07 to 0.50)
1 cold	96 (64.4)	73 (56.2)	8.3 (-3.2 to 19.8)
≥ 2 colds	37 (24.8)	13 (10.0)	14.8 (6.2 to 23.5)

Note: SD = standard deviation, CI = confidence interval.

*Unless stated otherwise.

†Subjects providing baseline data only (placebo n = 21, ginseng extract n = 23) were excluded from the data analysis.

‡Total symptom score over 2 days > 14.

§Daily total symptom score > 4.

Table 3: Severity, number of days of symptoms and duration of all colds* over the 4-month intervention period per subject reporting cold symptoms

Outcome	Group; mean (SD)		Difference† (95% CI)
	Placebo n = 96	Ginseng extract n = 73	
Total symptom score	112.3 (102.5)	77.5 (84.6)	1.5 (1.2-2.0)
Total symptom score per cold	75.9 (68.3)	64.2 (75.1)	1.3 (1.1-1.6)
Total days with cold symptoms, no.	16.5 (13.8)	10.8 (9.7)	1.6 (1.3-2.0)
Duration of each cold, d	11.1 (8.1)	8.7 (7.2)	1.3 (1.0-1.7)

Note: SD = standard deviation, CI = confidence interval.

*Daily total symptom score > 4.

†Statistical analyses were performed on the log-transformed data; differences and confidence intervals were obtained by transforming back to the original scale using antilogs.

COLD-FX™

COLD-FX™

**Strengthens the
Immune System***

CVT-E002 • Patented

30 CAPSULES



200mg

cbp
DendroPlus

A Dietary
Supplement

•Dose

- 1-2g/d of dried root
- 200mg/d of a standardized extract of the root containing 4-7% ginsenosides; it is recommended to take for 4 weeks then stop for 1-2 weeks.

•Adverse Effects

- much listed but close evaluation indicates wide safety; reports of problems may be associated with poor products and adulterated products

•Drug Interactions

- may be CYP inducer (more later)

•Bottom Line

- pick a good product
- maybe useful in diabetes and in geriatric populations
- watch for drug interactions with narrow therapeutic index drugs

Ginseng

Efficacy: huge literature of small, uncontrolled studies; some evidence for applications in geriatric patients (improved “quality of life”) and in diabetes and common cold and flu (Cold-FX)

Safety: good; reported problems may be due to poor quality product

Drug interactions: may precipitate hypoglycemia with insulin or oral hypoglycemics; may decrease wafarin effect (decrease INR)

Product selection: product should be standardized to deliver about 25mg/dose ginsenosides or about 50mg/d

Dose: 200mg per day of extract

Questions remaining include:

- *What, actually is this stuff good for!*
- **GWE:** *I don't usually recommend ginseng use except COLD-FX; for use in diabetics and the elderly, I await the results of further studies*

Black Cohosh

- Botany
 - *Actaea (Cimicifuga) racemosa*. A tall perennial shrub native to Eastern USA; roots and rhizomes used
- History
 - Used by Native Americans for women's health problems and a variety of other uses; A component of Lydia Pinkham's elixir,
 - In Europe a special black cohosh extract (Remifemin) has been used since the 1950s for symptoms of menopause and PMS
- Chemistry
 - Contains phytosterin, salicylic acid, tannins, and triterpine glycosides that may be important for activity
 - The triterpine glycosides include acetin, 27-deoxyacetin, and cimicifugoside

Pharmacology

- black cohosh seems to have no effect on uterus or hormone levels(Liske et al. J Women's Health and Gender Based Med. 2002;11:163-174)
- May have central CNS effect on serotonin receptor
- Does not seem to stimulate estrogen receptor dependant tumors in animals or in vitro tumor cell growth. Humans?

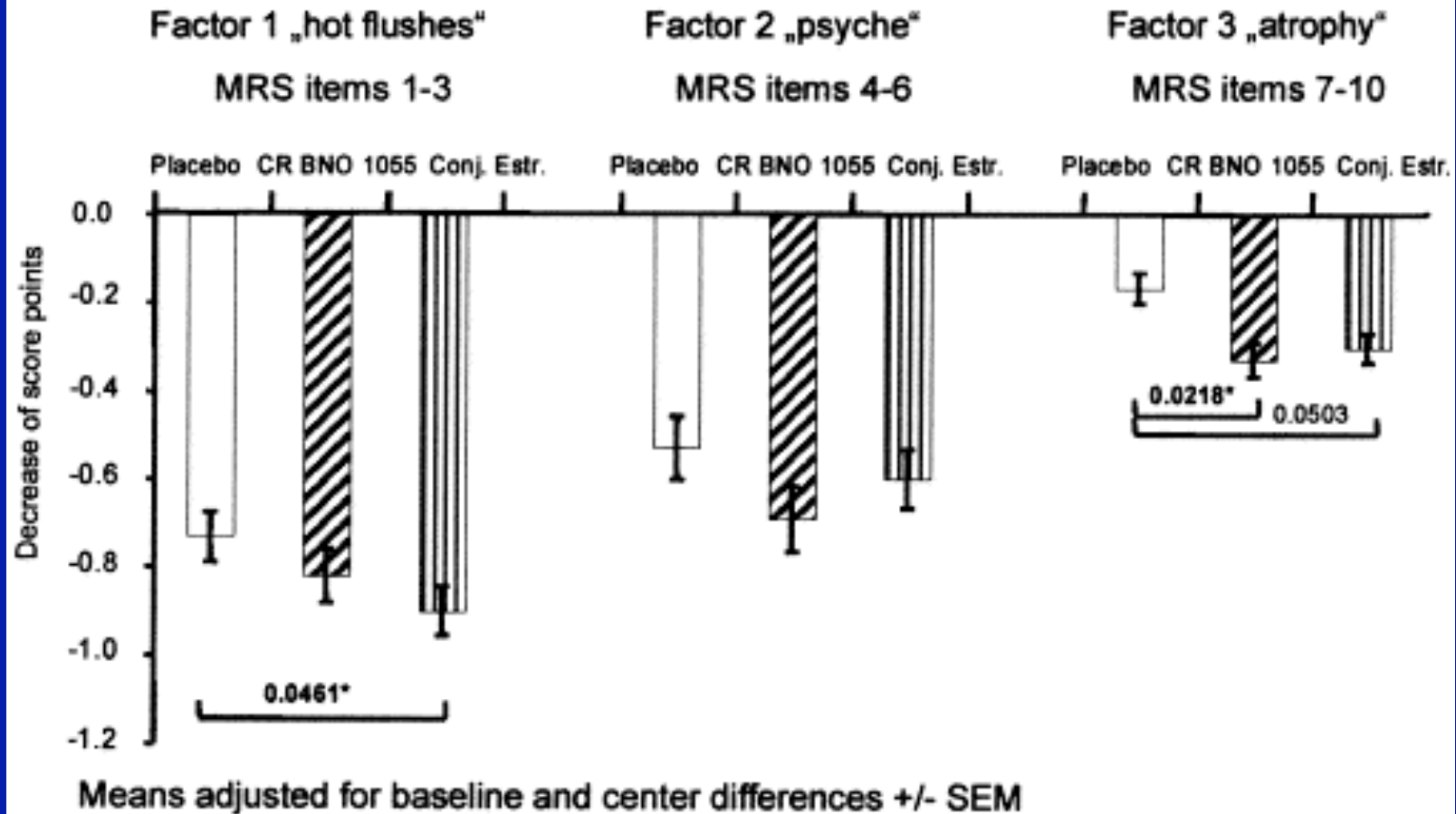
Uses

- reduce symptoms associated with menopause
 - relieve symptoms of menopause associated with tamoxifen therapy
 - PMS
 - dysmenorrhea
 - hasten childbirthing
- Evidence for relief of menopausal symptoms**
- Early studies with Remifemin show support for reducing hot flashes, etc in menopause
 - well designed studies indicate benefit
 - However, a recent well designed study done here (see slide) showed no effect but Remifemin was not the product tested

Menopause Rating Scale: Factor Analysis

changes from baseline

week 12

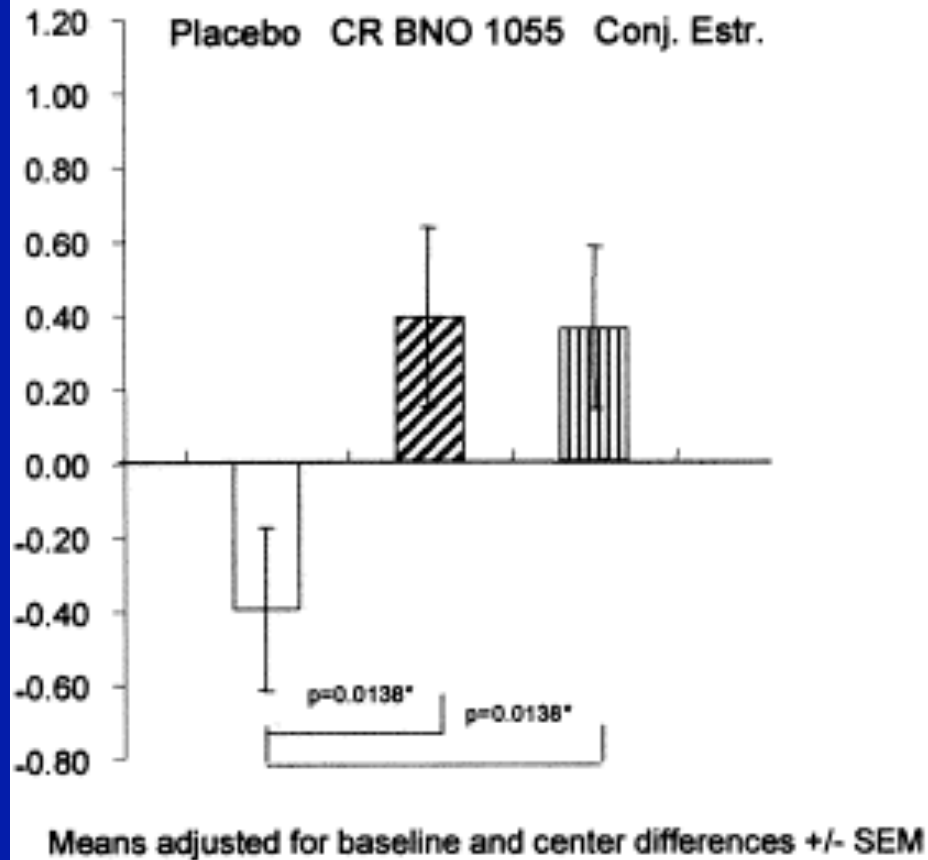


Wuttke et al. Maturitas 2003;44:S67-S77; n=62; 40mg/d for 3 months.

Bone Turnover Index

log (Bone-spec. Alk. Phosphatase / CrossLaps)
changes from baseline

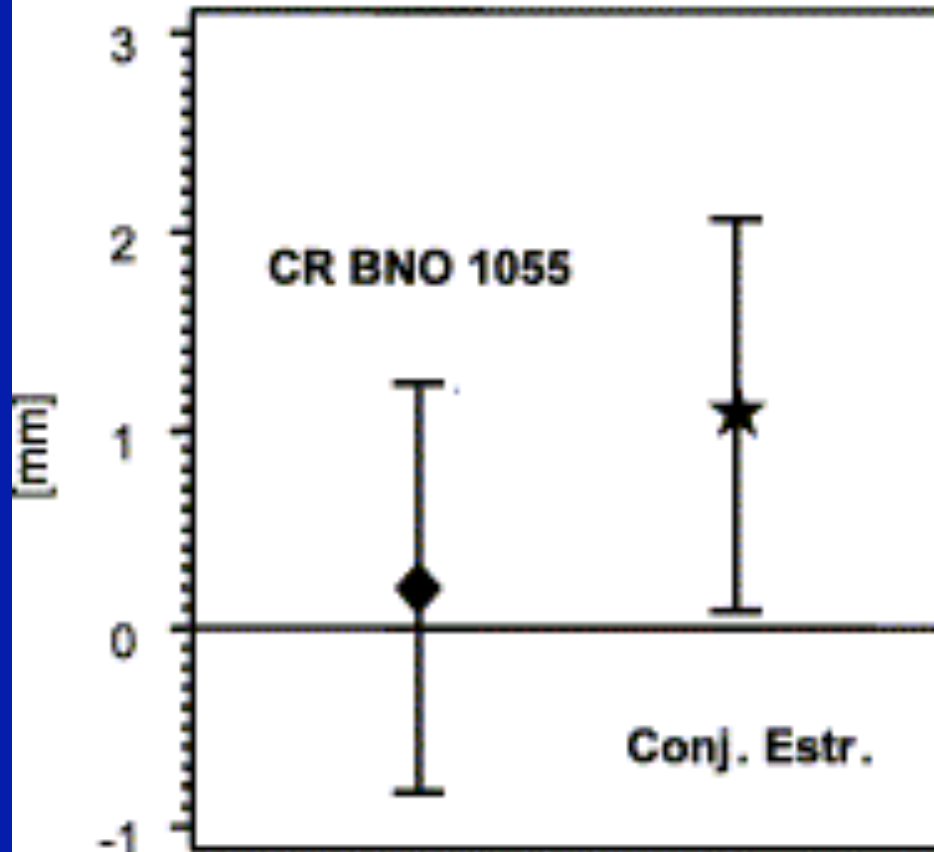
week 12



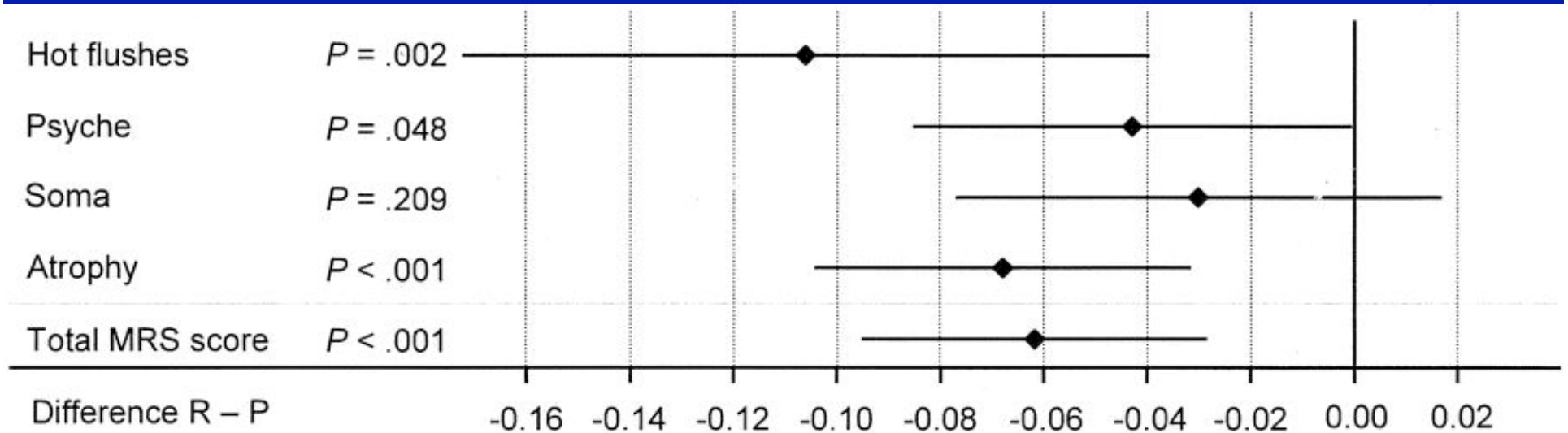
Wuttke et al. Maturitas 2003;44:S67-S77; n=62; 40mg/d for 3 months.

Endometrial Thickness

mean differences to placebo after
12 weeks (with 95% CIS)

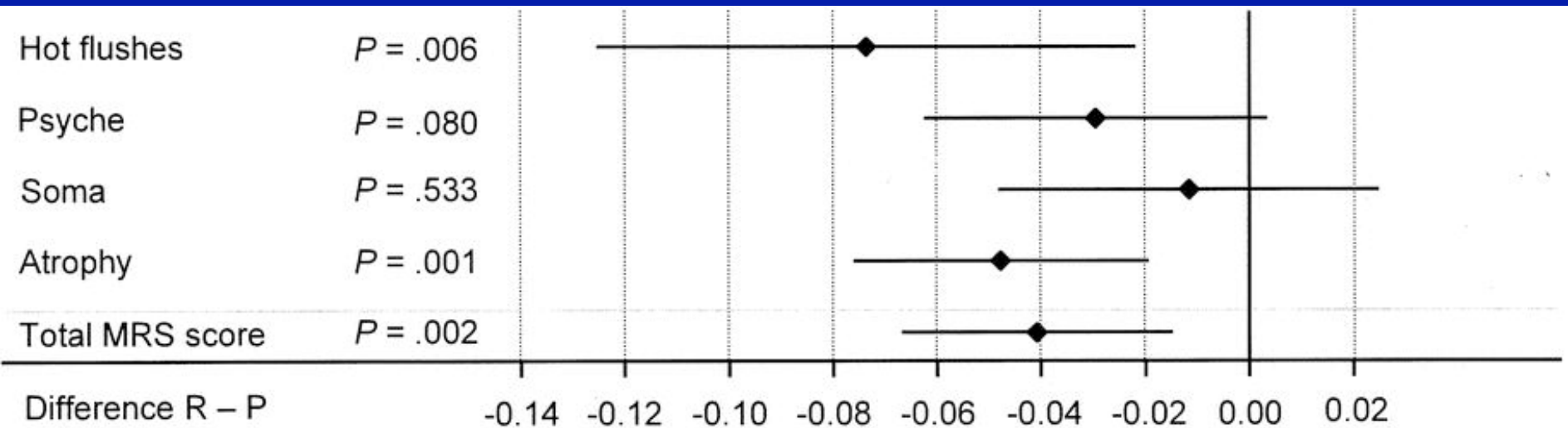


Wuttke et al. *Maturitas* 2003;44:S67-S77; n=62; 40mg/d for 3 months.



Osmer et al. *Obstet Gynecol* 2005;105:1074-83. N=304; 40mg extract for 12 weeks. (Remifemin)

Above are results in early climateric women



Osmer et al. *Obstet Gynecol* 2005;105:1074-83. N=304; 40mg extract for 12 weeks.

Above are results in late climateric women

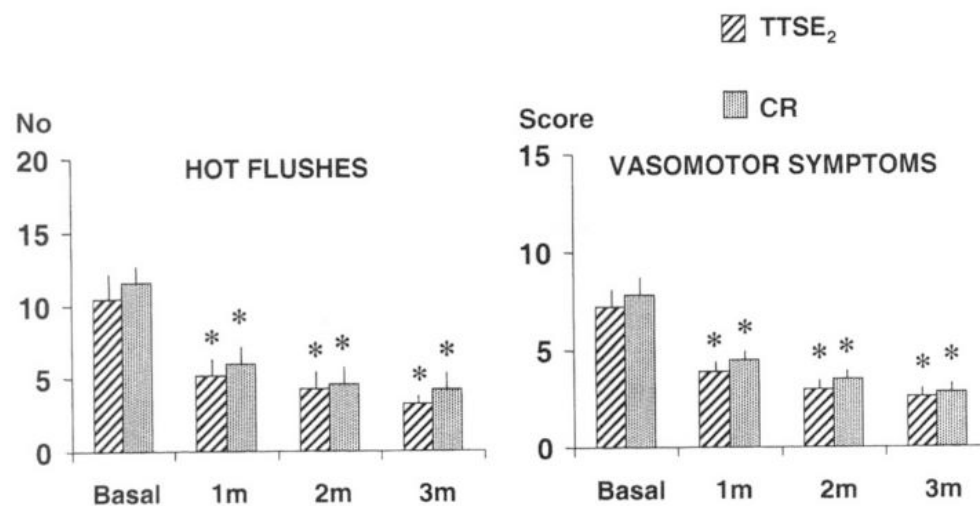


Figure 1. Mean (\pm standard deviation) number of hot flushes per day recorded in a diary throughout the 3 months of treatment and mean Greene score for vasomotor symptoms recorded monthly in postmenopausal women treated with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE₂). Significance (*) is reported in the text.

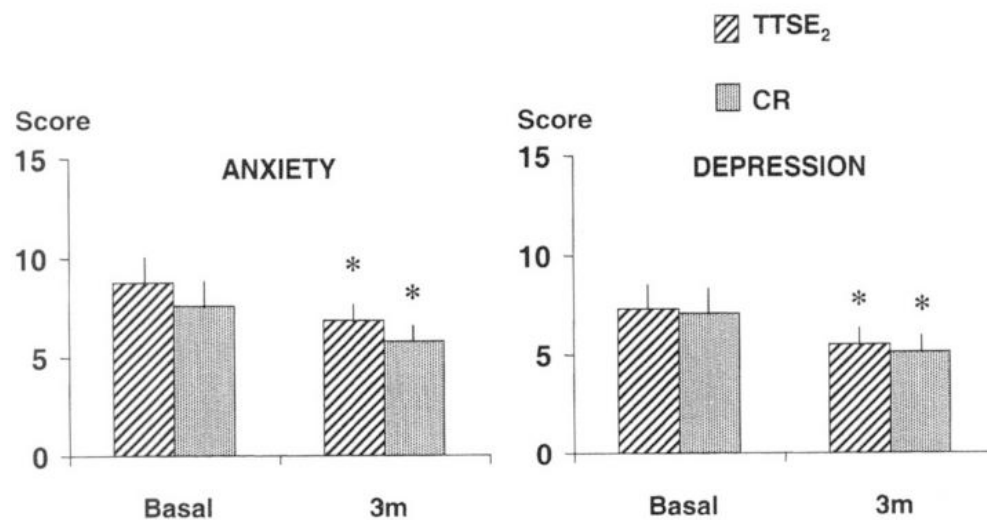
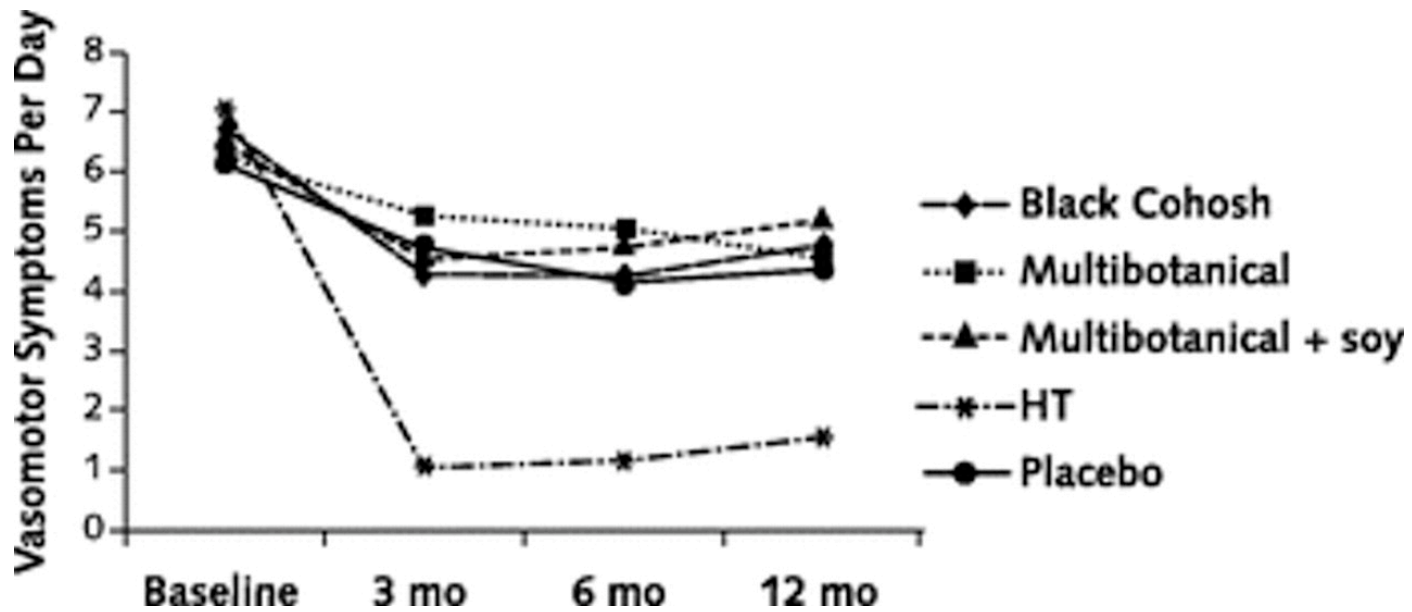


Figure 2. Mean (\pm standard deviation) Symptom Rating Test score for anxiety and depression recorded before and after 3 months of treatment with either *Cimicifuga racemosa* (CR) or low-dose transdermal estradiol (TTSE₂). Significance (*) is reported in the text.

Adjusted mean number of vasomotor symptoms per day, by study group
Newton, K. M. et. al. Ann Intern Med 2006;145:869-879

N=351 for 1 yr



Evidence for help in tamoxifen therapy:

- Results are mixed. One study showed no benefit
 - Jacobson et al. J Clin Oncol 2001;19:2739-2745 n=85; cohosh product NOT DESCRIBED
 - Munoz and Pluchino. Maturitas 2003;44:S59-S65. N=136; cohosh 20mg/d Menofem[®] for 12 months.
 - Table 4

Table 4

Hot flushes reduction by CR BNO 1055

Hot flushes	Usual-care group ^a (<i>n</i> = 46)	Intervention group ^b (<i>n</i> = 90)
Severe	34 (73.9%)	22 (24.4%)
Moderate	12 (26.1%)	26 (28.9%)
None	–	42 (46.7%)

^a Tamoxifen adjuvant therapy.

^b Combined therapy: tamoxifen + CR BNO 1055.

Munoz and Pluchino *Maturitas* 2003;44:S59-S65. N=136; 12 mos

Safety

- GI upset, headache, dizziness possible
- due to possible estrogenic effects, use with caution pregnancy
- in vitro does not stimulate breast cancer cells (in contrast to soy isoflavones) but in vivo the risk is uncertain.
- several reports of severe liver toxicity (causal?)

•Products

- Remifemin (SK Beecham) is a good product that has been used successfully in controlled trials; it is standardized to contain 1mg of 27-deoxyacetin per 20mg tablet.
- 1 BID

Black Cohosh

- **Summary**
 - **Efficacy**: conflicting evidence for benefit for relief of menopausal symptoms using products other than Remifemin. Mixed evidence for relief of tamoxifen adverse effects.
 - **Safety**: good but a few case reports of liver toxicity. Safety in women with existing breast cancer is uncertain.
 - **Drug interactions**: weak 2D6 induction?
 - **Product selection**: standardized root extract; 20mg BID; Remifemin seems to work.
 - **Questions remaining** include
 - *What is the risk in breast cancer?*
 - *What is the risk for hepatotoxicity?*