Cranberry

• Vaccinium macrocarpon-cultivated in Washington

•Long history of use

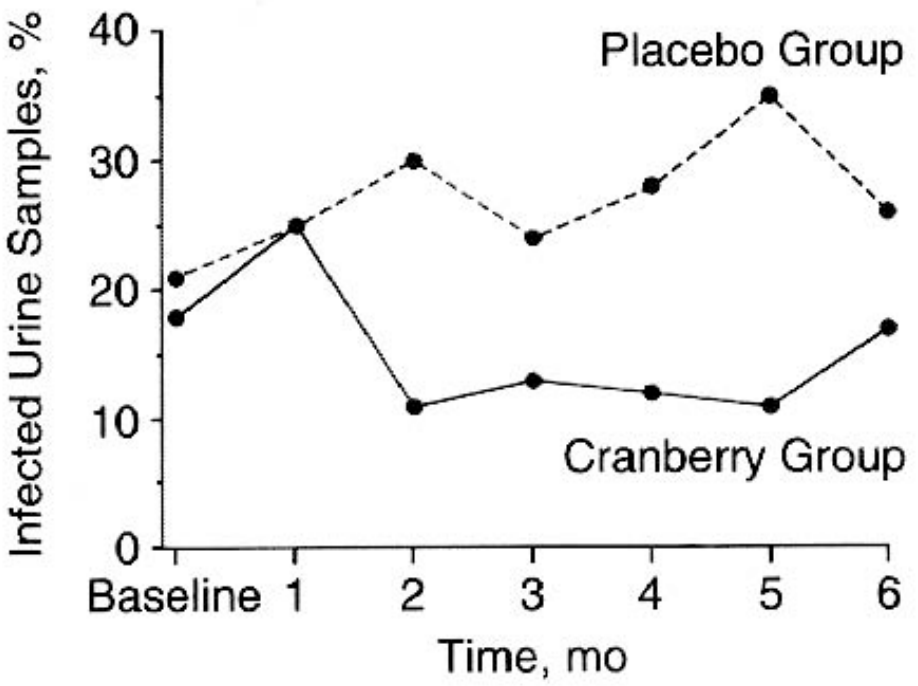
•The mechanism was thought to be urine acidification

•Now E. coli (other pathogens also) adhesion inhibitors are known to be present but not in other juices. An unidentified, high mol wt material may be responsible

•Need about 8-16 oz (240-480ml) of juice (not drink or cocktail)

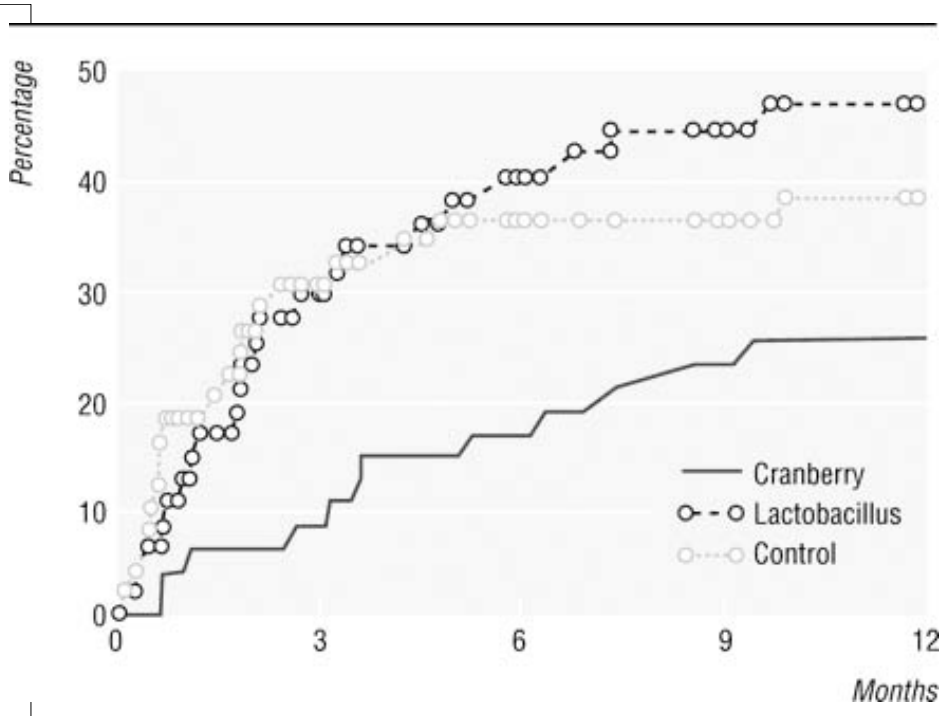
•Evidence for effectiveness in UTI **treatment** is weak

•Will acidify urine and contains high oxalic acid levels so that kidney stones could be a risk



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

First UTI in 12 months



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

Cranberry

- **Summary**
  - **Efficacy: reasonable evidence for benefit for PREVENTION of UTI.**
  - **Safety: good but could be risky for those that form kidney stones easily. Has salicylates.**
  - **Drug interactions: possible enhanced warfarin anticoagulant effect (case reports)**
  - **Product selection: need the juice; capsules work?**
  - **Questions remaining include**
    - ***Does cranberry juice help with Helicobacter pylori?***
    - ***Other infections?***
    - ***Help in dental caries?***

Soy-

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

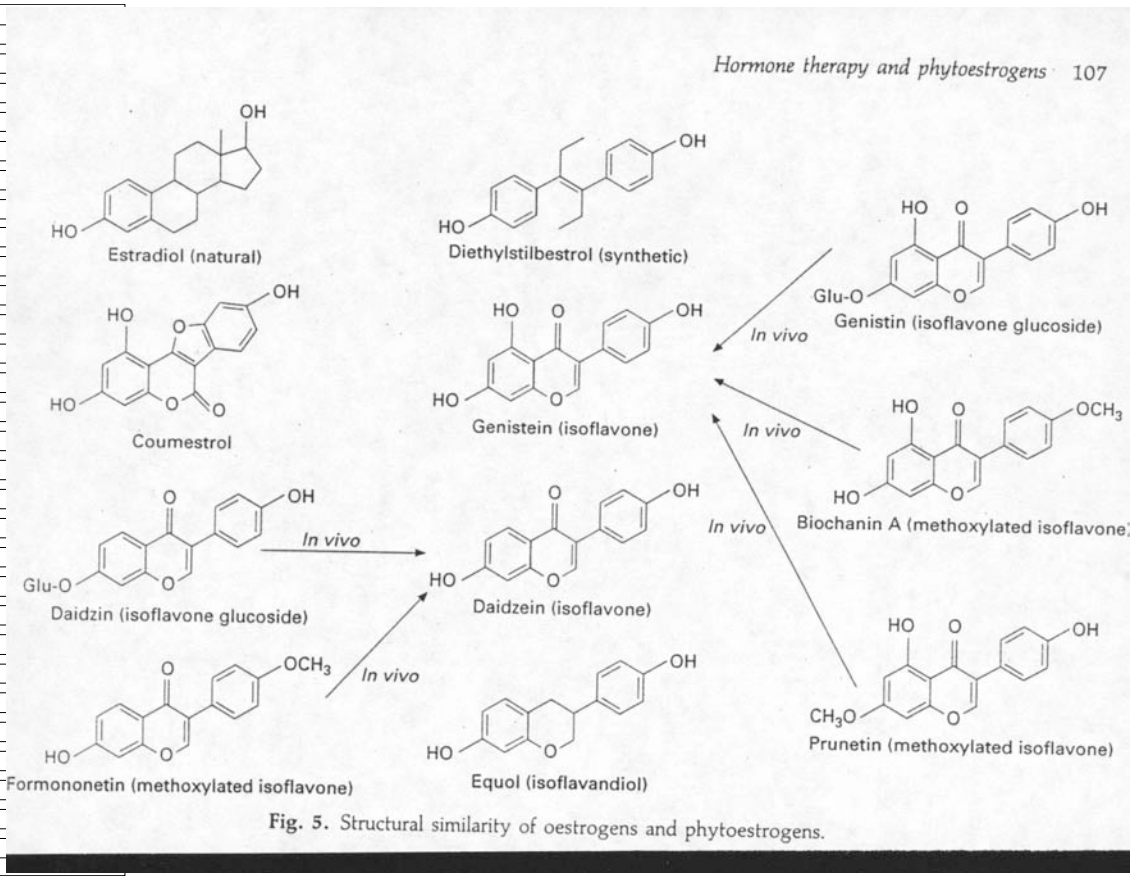
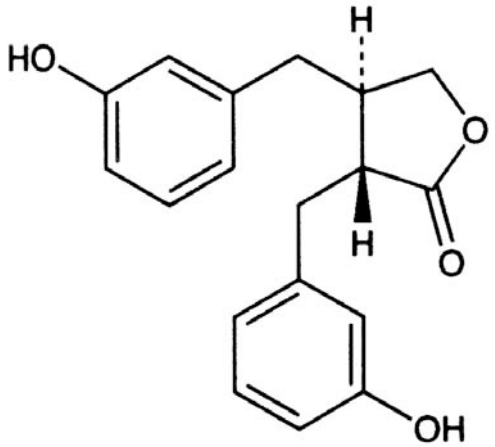


Fig. 5. Structural similarity of oestrogens and phytoestrogens.

Soy

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



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

Enterolactone (example of a lignan)

Isoflavone Pharmacology

- Isoflavones (IF) act a weak estrogenic compounds. Are essentially SERMs
- IF are competitive inhibitors of estrogen. If estrogen is high (premenopause), then will displace; if low (postmenopause) then will be an estrogen agonist.
- Bind to estrogen receptor B (bone,vascular) better than ER-A (reproductive)
- Have effects other than receptor action. Decrease aromatase, 3 B and17B-hydroxysteroid dehydrogenase, enzymes that convert precursor steroids to potent estradiol.
- Are antioxidants
- Japanese consume 30-40mg isoflavones/d; USA consumes little.
- Japanese women have lower breast cancer and menopause problems

Isoflavones (continued)

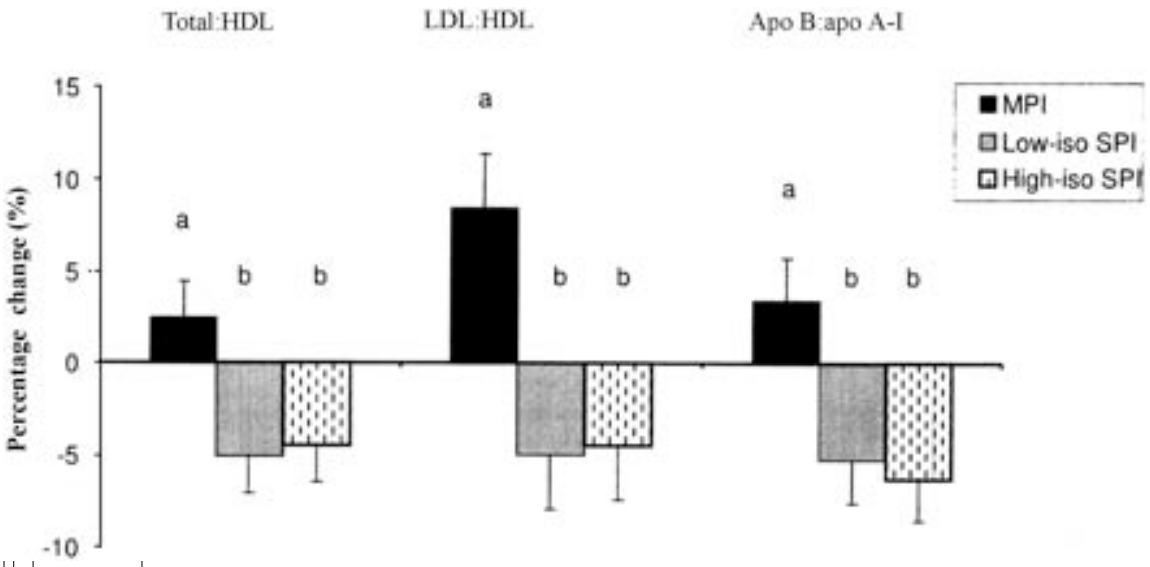
Product	mg isoflavones/100g
Raw soybeans	~100
Soy protein	100-300
Soy milk	10
Soy flour	199
Cooked soybeans	55
Tempeh	44
Tofu	31
Soy noodles	9

Soy Effects on Cancers

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

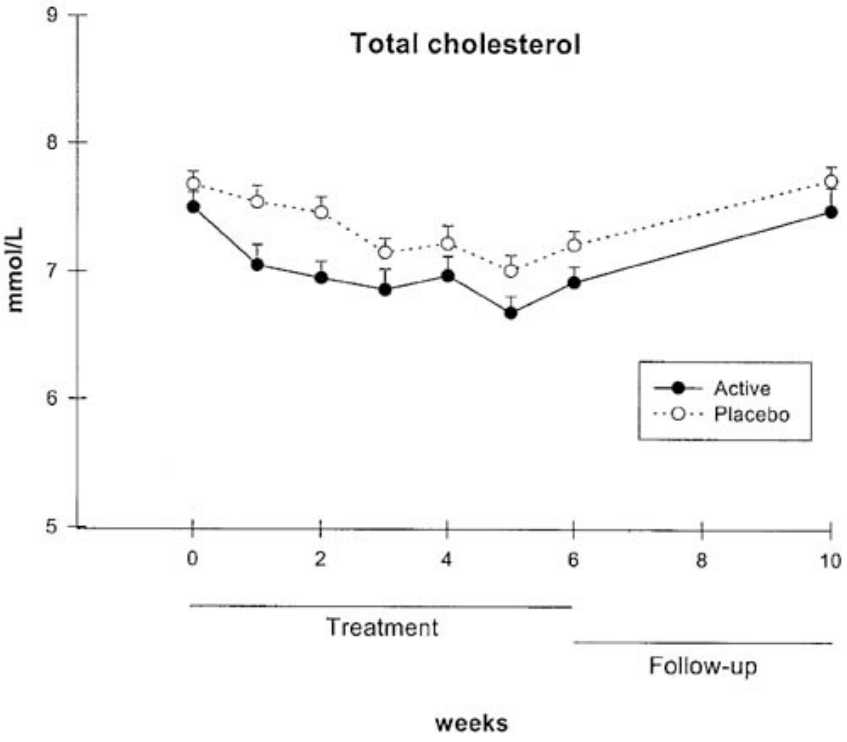
Soy Effects on Heart Disease Risks

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

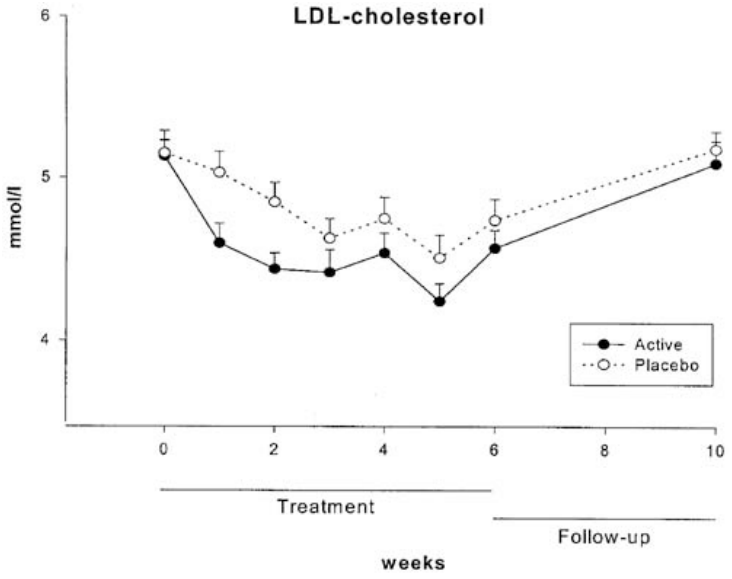


McVeigh et al. Am J Clin Nut 2006;83:244-251. n=35 cross-over study. Each treatment was 60d.

Puska et al.,Europ J Clin Nutr 2002;56:352-357.
N=60 note: placebo had cellulose fiber

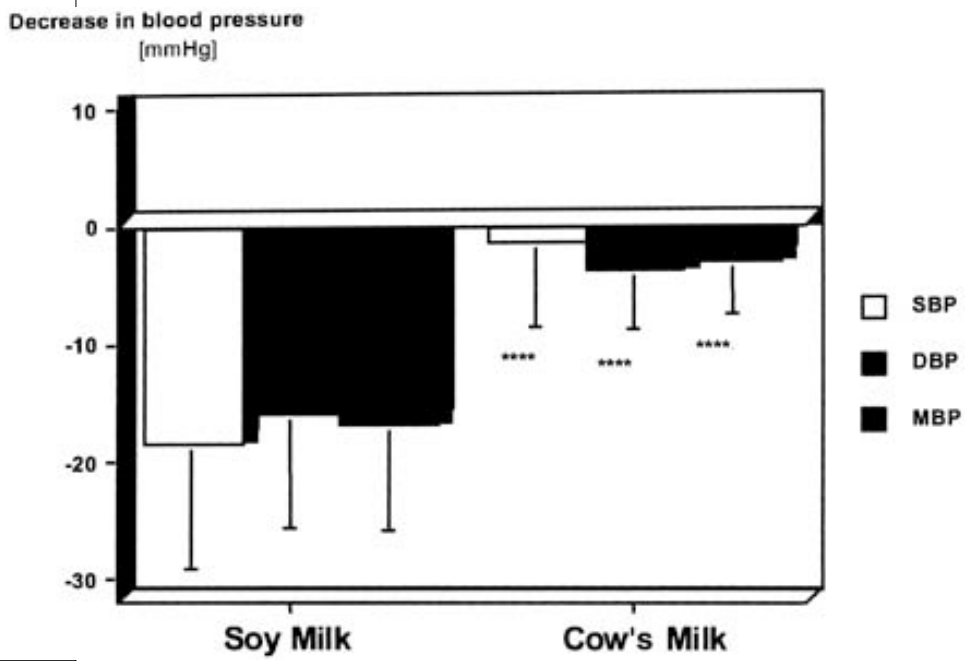


Puska et al.,Europ J Clin Nutr 2002;56:352-357.
N=60 note: placebo had cellulose fiber



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

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



Soy and Menopausal and Postmenopausal problems

- can soy replace HRT?
- Hot flashes and other symptoms: soy flour as well as higher doses of soy isoflavones (100mg/d) have been tested. The results are inconsistent. A big placebo effect is seen in the published studies.
- Osteoporosis- some studies using high isoflavone soy indicate decreased loss of bone mass in postmenopausal women

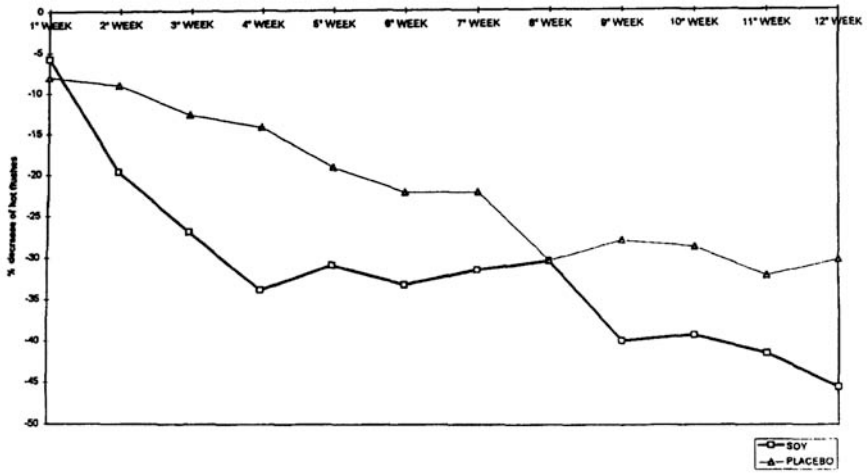
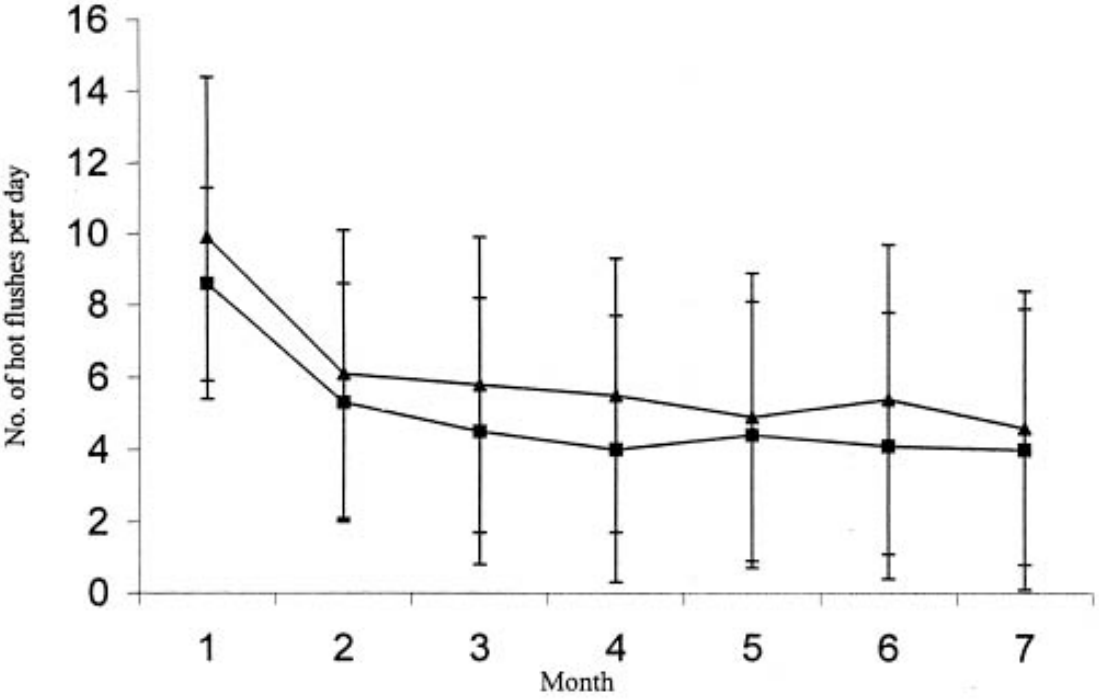


Figure 1. Weekly decrease in number of hot flushes; score expressed as percentage. The difference between soy and placebo was always significant after week 2, with the exception of week 8.

n = 104

Albertazzi et al. Obstet Gynecol 1998;9:6-11.

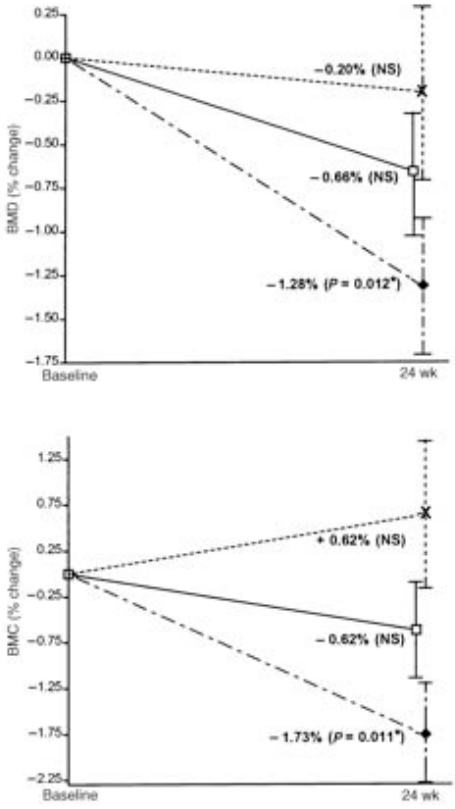


Penotti et al. Fertil Steril 2003;79:1112-7 n=62, 72mg soy isoflavones

N=88, 24 weeks of soy or whey protein; x=soy containing 80mg/d isoflavones, open square=soy containing 4.4mg/d isoflavones or diamond=whey

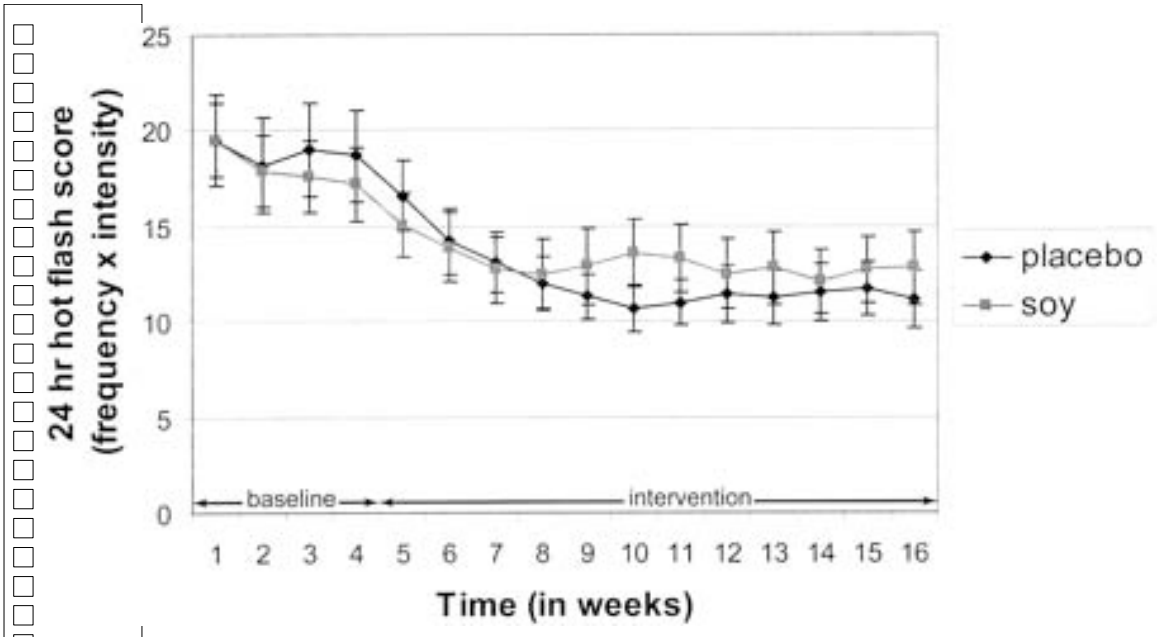
Alekel et al. Am J Clin Nutr 2000;72:844-852.

Measurements on lumbar spine



Risks and Interactions

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



Van Patten et al. J Clin Oncol 2002;20:1436-8 n=124, soy drink with 90mg isoflavones to breast cancer treated pts

Other Effects of Soy

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

Other herbals used for menopausal symptoms

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

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

Flaxseed and Flaxseed oil – some evidence for benefit

Evening primrose oil- not consistent evidence for benefit

Chasteberry- helps in PMS but ? for menopause

Dong quai- no observed benefit in one good study

Yam- is a scam

Topical progesterone- works but risks same as HRT?

Soy

- **Summary**
  - **Efficacy: increased soy ingestion may or may not decrease hot flashes and other postmenopausal symptoms; Soy has cardiovascular benefits.**
  - **Safety: good but use in breast cancer may be risky**
  - **Drug interactions: not with tamoxifen**
  - **Product selection: Soy is best. Isoflavones?**
  - **Dose: about 20-40g of soy protein has been used. This contains 30-50mg of isoflavones.**
  - **Questions remaining include**
    - ***How much benefit? Safety in breast cancer?***

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.

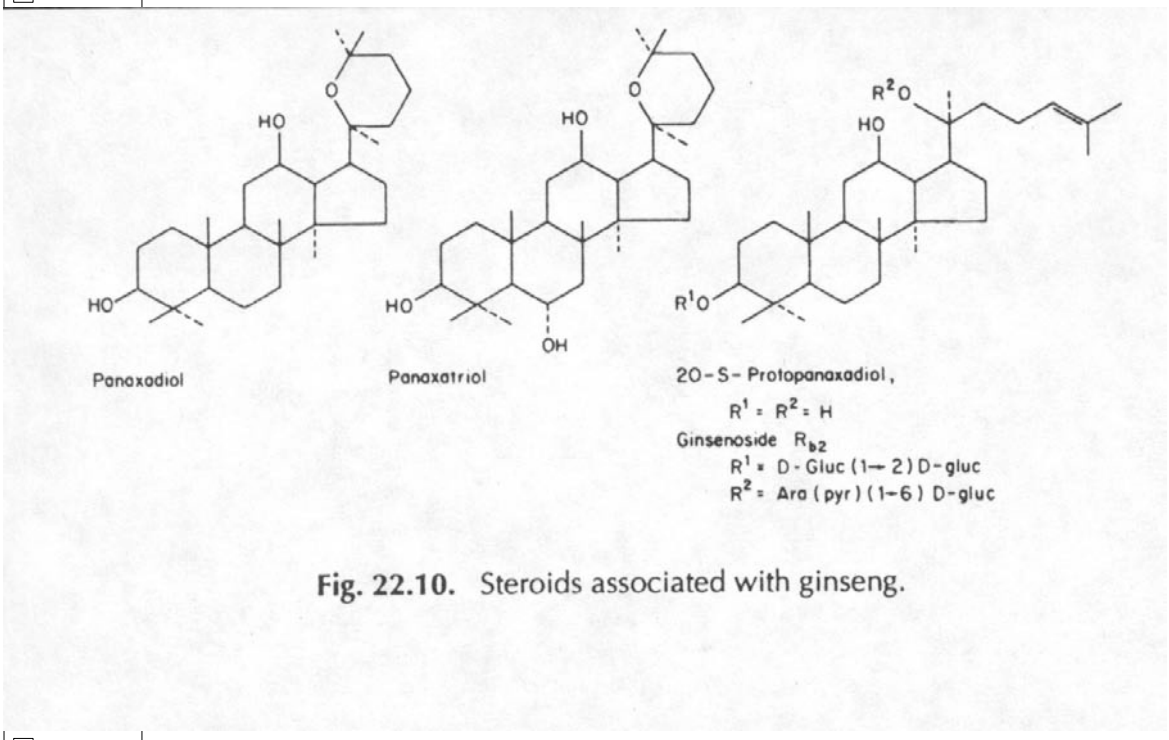


Fig. 22.10. Steroids associated with ginseng.

- 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
- mental functioning – mixed results but some intriguing results indicate promise for enhancing completion of mental tasks and (in combination with ginkgo) memory
- "improved quality of life" - several studies showed positive effects
- menopausal symptoms - no effect in one study but no hormonal effects either
- 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) with use of American ginseng
- Korean red ginseng in one recent study showed to be helpful in erectile dysfunction
- Common cold. One recent study (Predy et al. CMAJ 2005;173:1043-1048) showed preventative effects

- 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

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

Drug interactions: may precipitate hypoglycemia with insulin or oral hypoglycermics

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

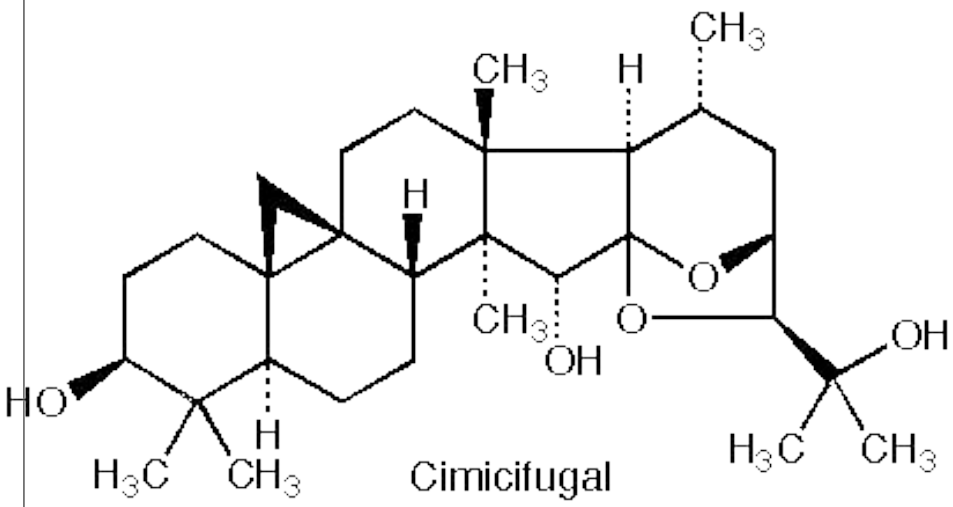
Dose: 200mg per day of extract

Questions remaining include:

- ***What, actually is this stuff good for!***

Black Cohosh

- Botany
  - Cimicifuga racemosa. A tall perennial shrub in NE 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 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



Cimicifugal

Pharmacology

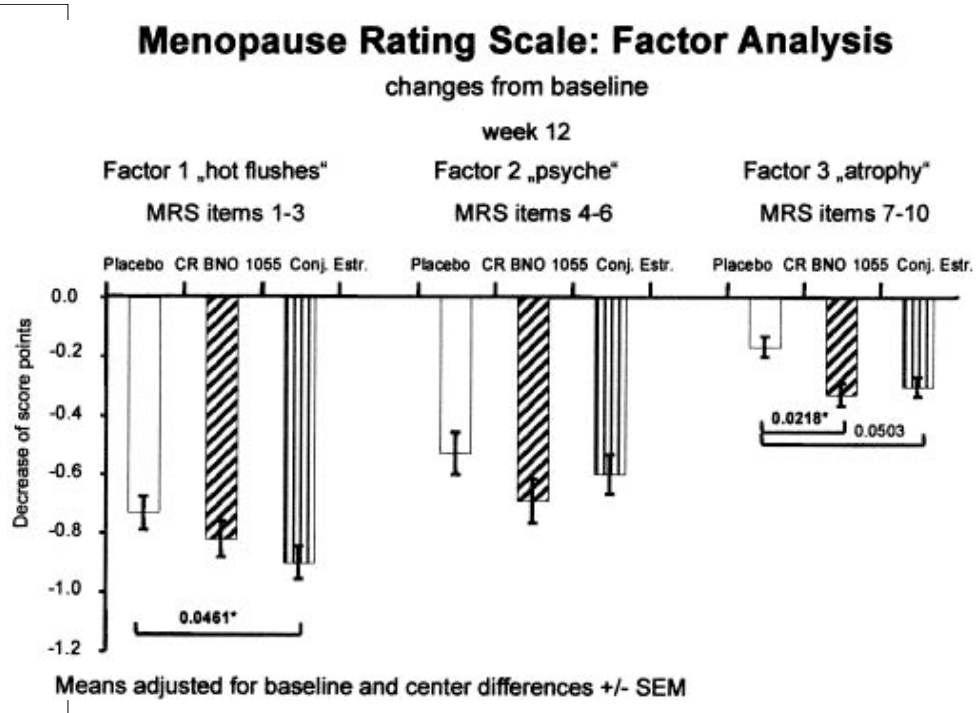
- black cohosh seems to lack estrogen activity in vivo; no effect on uterus (Liske et al. J Women's Health and Gender Based Med. 2002;11:163-174); SERM; mild stimulation of estrogen receptors B.
- May have central CNS effect on serotonin receptor
- Does not seem to stimulate estrogen receptor dependant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

Uses

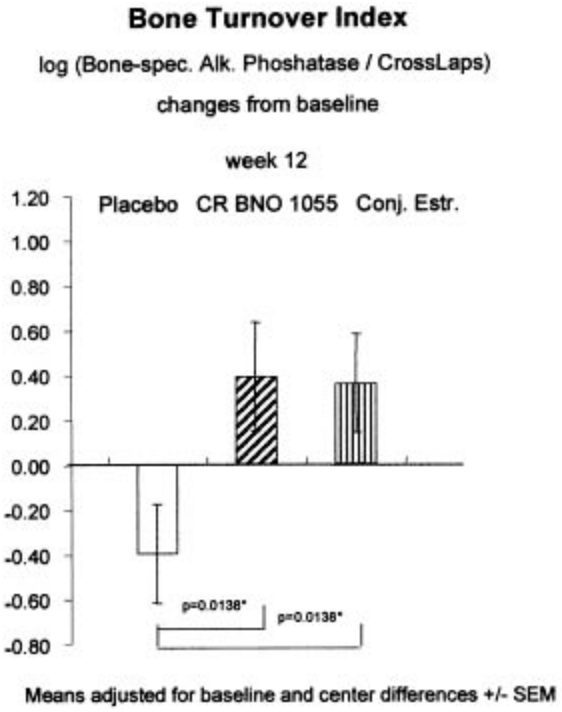
- •reduce symptoms associated with menopause
- •relieve symptoms of menopause associated with tamoxifen therapy
- •PMS
- •dysmenorrhea
- •hasten childbirthing

•Evidence for relief of menopausal symptoms

- •Early studies with Remifemin show support for reducing hot flashes, etc in menopause
- •well designed recent studies indicate benefit and SERM-like activity



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



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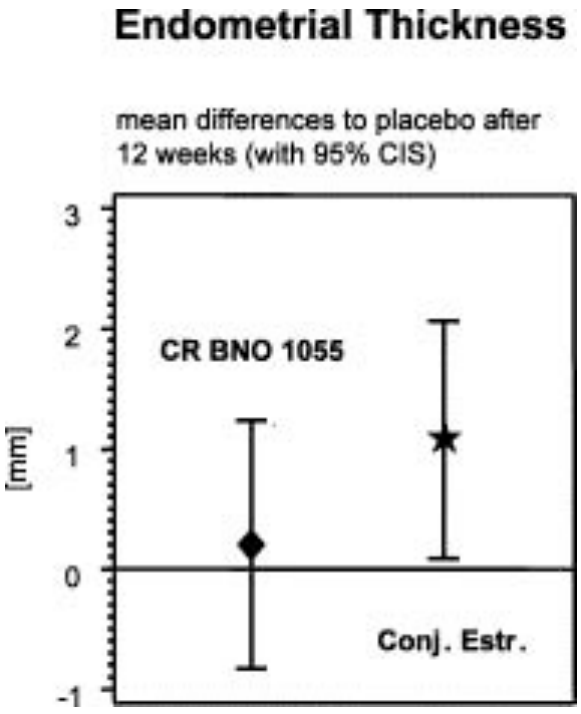

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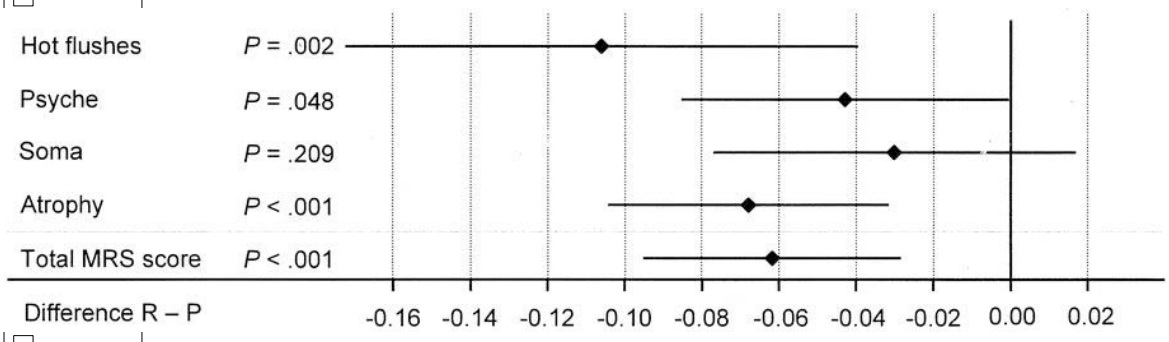
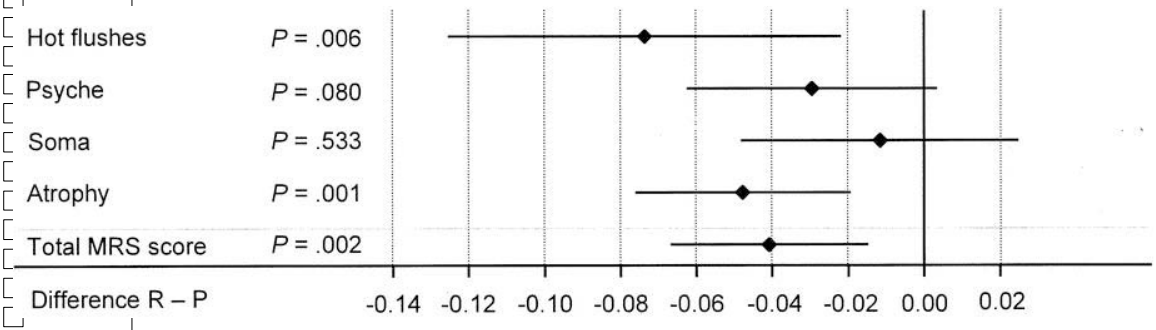


Osmers et al. Obstet Gynecol 2005;105:1074-83. N=304; 40mg extract for 12 weeks. (Remifemin)

Above are results in early climateric women



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

Above are results in late climateric women

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] ($n = 46$)	Intervention group[b] ($n = 90$)
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.
- •2 case reports of severe liver toxicity (causal?)

•Products

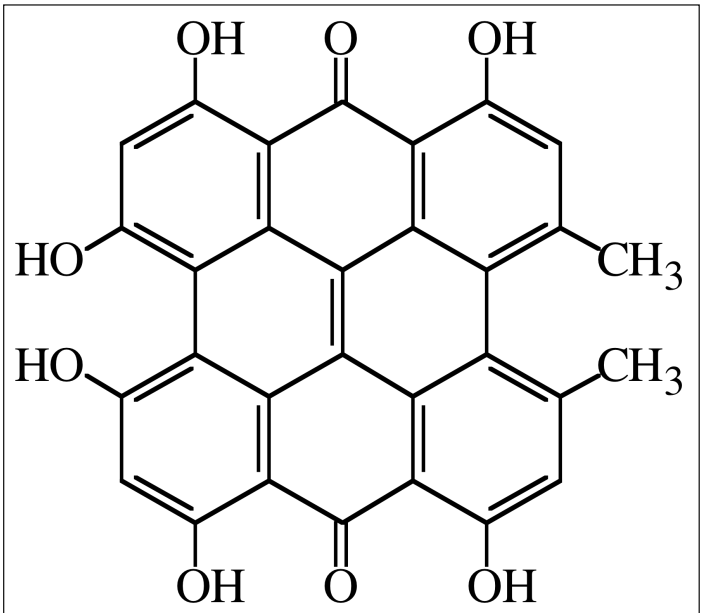
- •Remifemin (SK Beecham) is a good product that has been used successfully in controlled trials; it is standardized to contain 1mg of 27-deoxyacetin per 20mg tablet.
- •1 BID

Black Cohosh

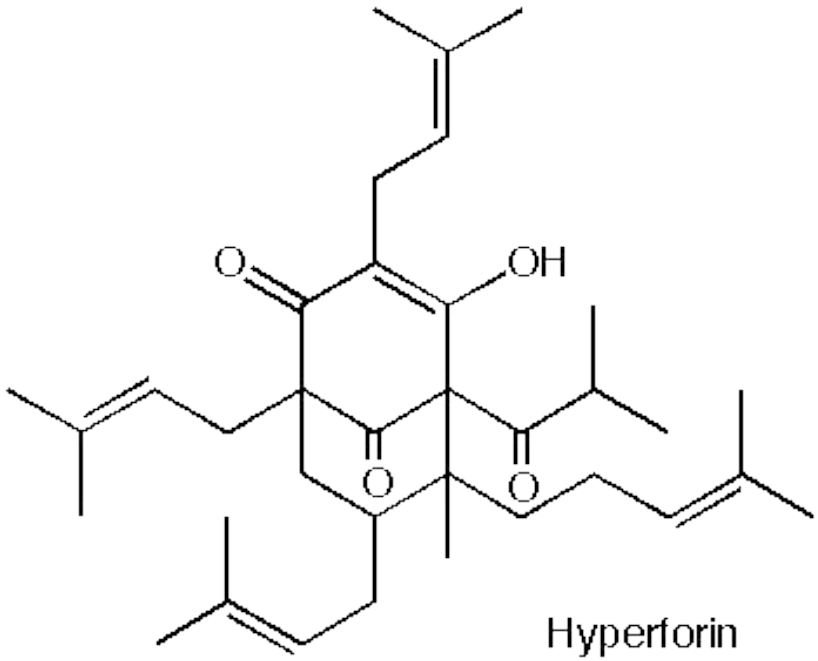
- **Summary**
  - **Efficacy: reasonable evidence for benefit for relief of menopausal symptoms. Mixed evidence for relief of tamoxifen adverse effects.**
  - **Safety: good but a few case reports of liver toxicity. Safety in women with existing breast cancer is uncertain.**
  - **Drug interactions: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

St. John's Wort

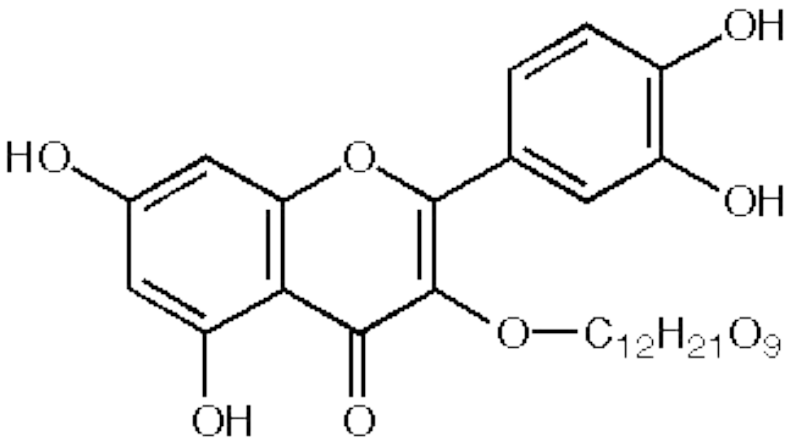
- Botany
  - Hypericum perforatum - grows here on campus*
- History
- Chemistry
  - Hypericin
  - hyperforin



hypericin



Hyperforin



Rutin
(flavonoid glycoside)

St. John's Wort

- Pharmacology
  - hypericin
    - antiviral acitivity
    - 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

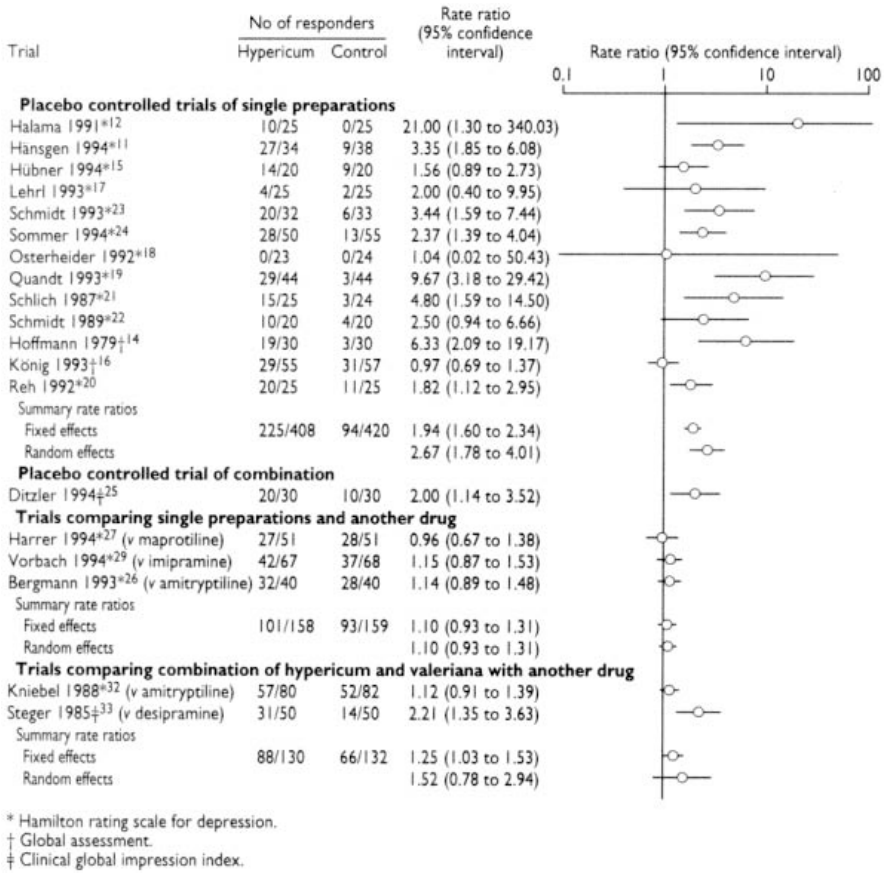
St. John's Wort

- 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,myalgi, burns

St. John's Wort

- Meta -analysis of 23 randomized trials, 1,757 pts, Linde et al BMJ 313:253,1996
  - 20 trials =double blind
  - 4-6 weeks in duration
  - doses used varied but in the range 0.5g-1g
  - Hamilton Depression Scale or Clinical Global Impressions index
  - results:
    - SJW, 51% improved vs 22.3% in placebo
    - SJW, 63.9% improved vs 58.5% in standard Rx
    - SJW+valerian, 67.7% improved vs 50% in standard Rx
    - SJW, 19.8% adverse effects vs 52.8% in standard Rx
    - SJW, 0.8% drop vs 3.0% in standard Rx

Linde et al. BMJ 313: 253-258, 1996



St. John's Wort

- **Linde et al conclusions: more effective than placebo, similar to standard drugs**
- **Medical Letter Oct 20, 1997**
  - **better, longer studies needed;doses unknown**
- **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 paroxitine with fewer adverse events. N=244**

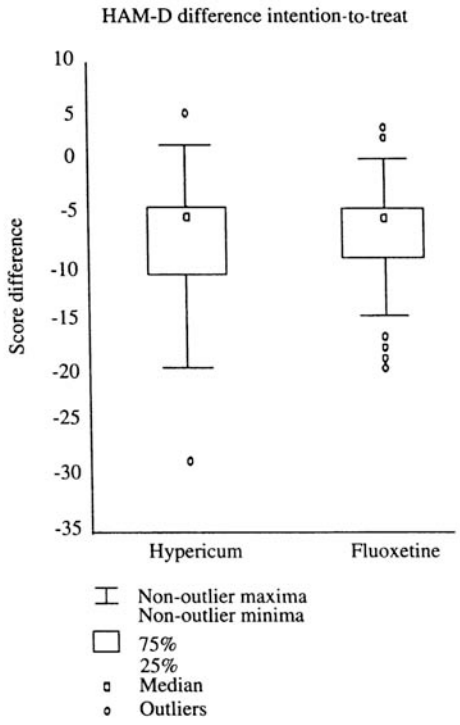


Figure 2. Improvement in HAM-D scores. ITT, intention-to-treat.

Schrader et al., Int J Clin Psychopharmacol 15:61-68,2000

Reuters Medical News
St. John's Wort Equivalent to Placebo For Treatment of Depression

CHICAGO, May 17 (Reuters Health) - Patients with depression respond equally well to St. John's wort and placebo, according to study results presented here during the annual meeting of the American Psychiatric Association.

Researchers from Vanderbilt University, Nashville, Tennessee, discussed the results of one of the first large, government-funded projects to look into the effectiveness of St. John's wort. The team, led by Dr. Richard Shelton, conducted an 8-week double-blind study of 200 patients with major depression from 11 university medical centers.

For at least 4 weeks, patients used 900 mg/day of St. John's wort or placebo. If response was inadequate, the dose of St. John's wort was increased to 1,200 mg/day. Few patients discontinued treatment due to side effects from St. John's wort, but the results of interim analysis showed that the herbal preparation was no more effective than placebo.

Time Magazine

Apr 30, 2001

St. John's What?

MEDICINE

The "natural" antidepressant may not work. Bummer

By FREDERIC GOLDEN

WHEN YOU squeeze the bright star-shaped yellow buds of the hardy perennial *Hypericum perforatum*, they yield a red juice that reminded medieval Europeans of the blood of John the Baptist. Valued for its magical healing powers, St. John's wort (a Middle English word for "plant"), as the shrub is commonly called, has been used since the time of ancient Greece for treating any number of ailments, from liver and bowel disorders to hysteria, obesity and insomnia.

But St. John's wort came into its own in 1984, when the German government classified it as an MAO inhibitor, on the basis of in-vitro studies, and approved its use as a mild, natural antidepressant. Sales took off both in Germany, where St. John's wort easily outsells prescription drugs like Prozac, and in the U.S., where concoctions of the herb, sold under such labels as Mood Support and Brighten Up, became flagships of the booming alternative- medicine industry. Before last year's warnings that St. John's wort could interfere with other medications--notably AIDS treatments, antibiotics, cardiac drugs and oral contraceptives--yearly sales had reached $310 million. Even today, some 1.5 million Americans take the extract regularly to treat their psychic pain.

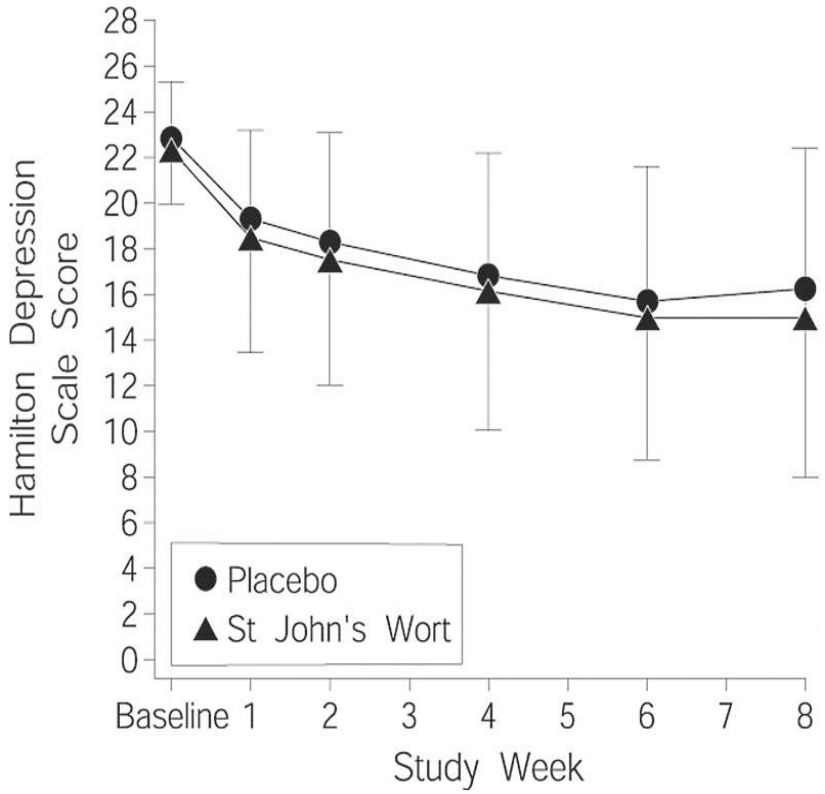
Let's hope they're doing something else to make themselves feel better, because the bloom may just have come off this flower. In what is by far the most definitive study yet of the efficacy of St. John's wort in treating major depression, doctors last week concluded that the extract is essentially useless. On the basis of these findings, published in the *Journal of the American Medical Association*, Dr. Richard Shelton, a psychiatrist at Vanderbilt University and the study's lead author, says flatly that he wouldn't recommend St. John's wort to any of his patients. As for the 30 or so earlier trials showing that the herb had some therapeutic value, he--like many other scientists--dismisses them as badly designed, inadequate or otherwise flawed.

GOLDEN DUD: It won't ward off the doldrums

Coming as it did amid reports that federal regulators are about to call for tighter controls on dietary supplements, including the memory pill Ginkgo biloba (which has been found to cause excessive bleeding and, in rare cases, stroke), the study's conclusions touched a raw nerve among those who see herbal medicine as a gentler, more natural route to healing. The nonprofit American Botanical Council issued a stinging press release criticizing the research as inconclusive, and the supplement industry's Council for Responsible Nutrition said there was nothing in the study that showed St. John's wort wouldn't work in cases of mild to moderate depression. Says the group's president, John Cordaro: "Consumers wouldn't use a throat lozenge for strep throat, but that same lozenge might be just right for a scratchy throat."

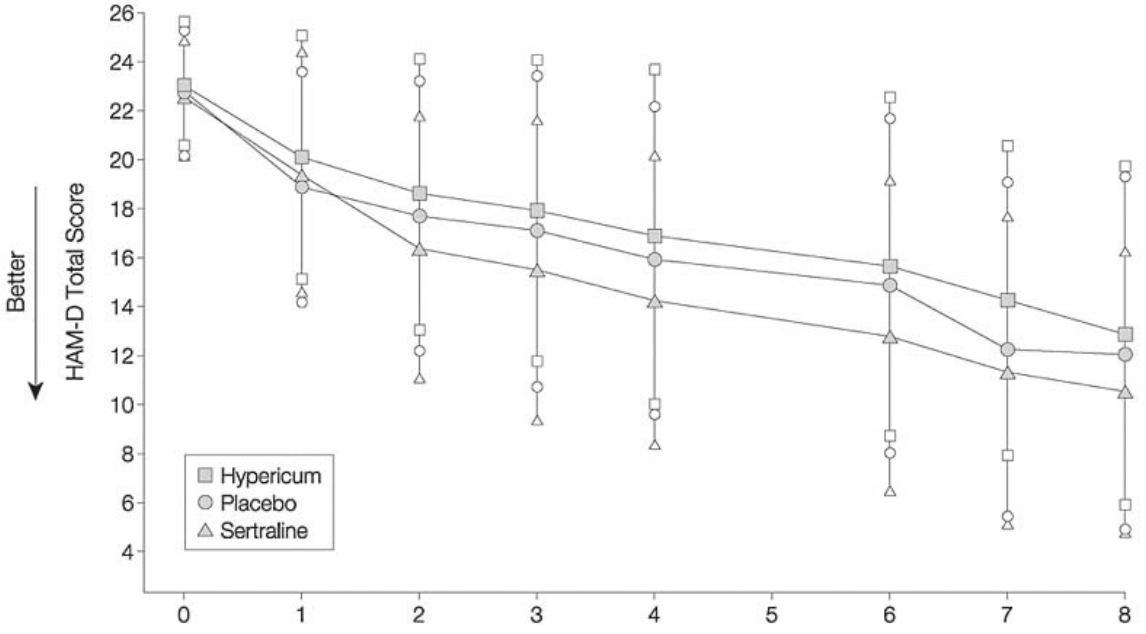
Shelton, however, stood his ground. He organized the study after seriously depressed patients, who had taken St. John's wort but hadn't been helped by it, began

HIGH-TECH HEART



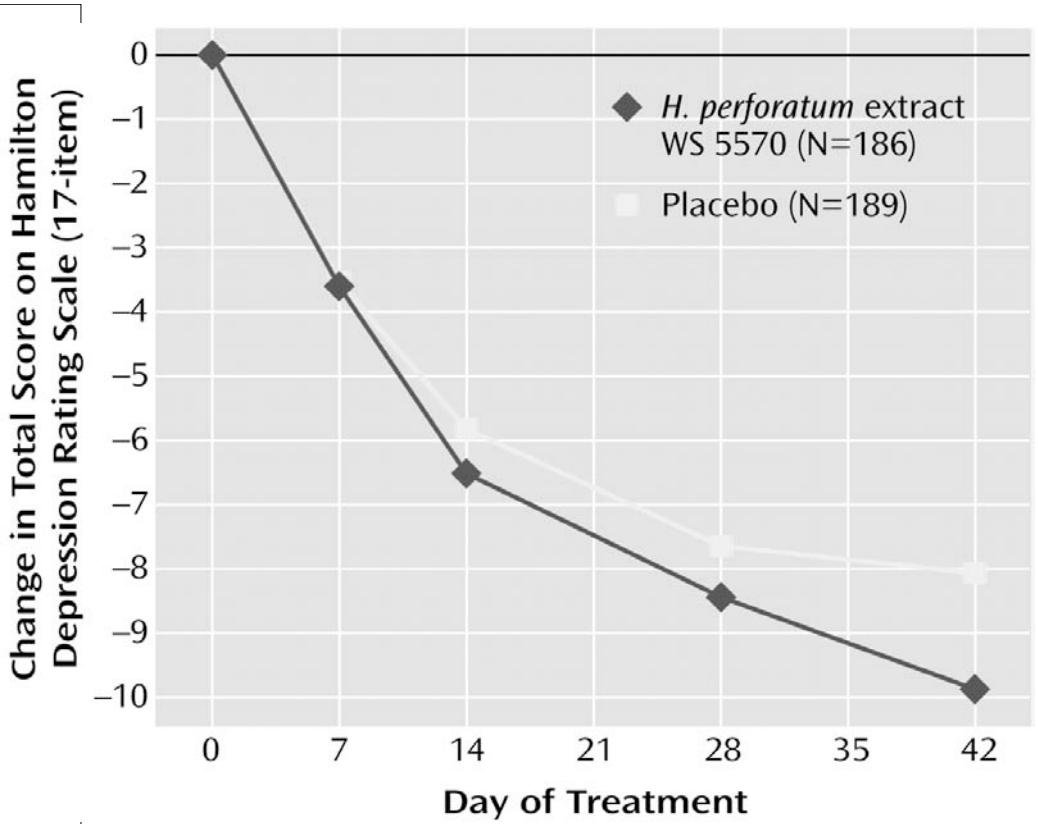
Shelton et al. JAMA 2001, 285:1978-1986

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



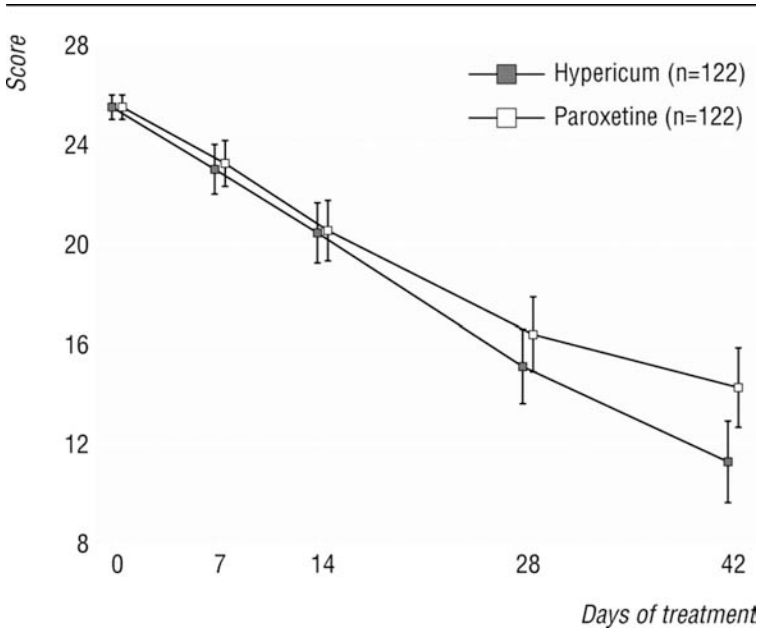
Observations								
Hypericum	113	101	102	100	97	91	82	82
Placebo	116	111	107	94	99	93	84	84
Sertraline	109	99	88	88	87	80	77	77

Davidson et al. JAMA 2002;287:1807-1814



Lecrubier et al. Am J Psychiatry 2002;159:1361 n=375

Fig 2 Total Hamilton depression scores over time (intention to treat analysis, means and 95% confidence intervals)



Szegedi, A et al. BMJ 2005;330:503

Used WS552 containing 5.2% hyperforin

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 5% 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

Product-	hypericin (%)	hyperforin (%)*
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% hyperforin