

# Herbal / Drug Interactions

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Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005

HerbalGram 2005;66:63

<b>• Product</b>	<b>M \$</b>	<b>% change</b>	<b>rank in 2003</b>
- 1. garlic	27	-11	1
- 2. echinacea	24	-15	3
- 3. saw palmetto	20	-11	5
- 4. ginkgo	19	-13	2
- 5. soy	17	-27	4
- 6. cranberry	14	+7	9
- 7. ginseng	12	-10	6
- 8. black cohosh	12	-22	8
- 9. St. John's wort	9	-12	7
- 10. milk thistle	8	+1	11
- 11. evening primrose	6	-4	12
- 12. valerian	4	-9	10
- 13. green tea	3	+22	17
- 14. bilberry	2	-18	14

Red indicates risk for drug interactions

## Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005

HerbalGram 2003;58:71

<b>• Product</b>	<b>M \$</b>	<b>% change</b>	<b>rank in 2003</b>
- 15. grape seed	2	-12	15
- 16. horny goat weed	2	+12	-
- 17. yohimbe	2	-22	16
- 18. horse chestnut	2	+35	-
- 19. eleuthero	1	-63	13
- 20. ginger	0.8	-14	18
- multi-herbs	52	+29	na
- all other	12	-7.5	na
total	257		

Red indicates risk for drug interactions

Note: kava and pycnogenol fell off the top 20 list

Note: total herbal sales are estimated at \$4.2 billion

The above figures include sales from food stores, drug stores, and mass market retailers but with Wal-Mart figures not included. It does not include warehouse buying clubs, convenience stores, natural foods stores, multilevel marketers, health professional sales, mail order or internet sales.

## Steps for Detecting and Advising on Herbal/Drug Interactions

- Is the patient taking any herbal supplements?
- Does the herbal have efficacy for the intended use?
- Is the product reliable? (i.e., what are they REALLY taking?)

## Dietary Supplement Education Alliance Survey (Harris Interactive)

July 2001

- N=1022
- 59% take dietary supplements on a regular basis
- 46% take multivitamins
- 23% take herbal and specialty products (15% botanicals, 8% non botanical supplements)
- 95% indicate satisfaction; 75% very satisfied or extremely satisfied
- 25% wrong about expecting immediate results from herbals
- Only 49% consult with health care providers about taking supplements
- Most believe they have sufficient information on using supplements

### 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% hyperforin

# Consumerlab.com

- Manufacturers whose products “pass” are listed on consumerlab’s website ([www.consumerlab.com](http://www.consumerlab.com))
- A manufacturer whose product “passes” can (for a fee) include the consumerlab seal on their label
- Access is \$24/yr and allows access to The Natural Products Encyclopedia, an excellent database on dietary supplements.

## USP Dietary Supplement Verification Program

- Manufacturer must agree to meet standards set by USP and their monographs
- Must agree to inspections and random analyses of products
- USP analyzes the product and inspects the manufacturing facility
- Pharmavite is the first manufacturer to seek USP verification (Nature Made, Nature’s Resource) for their line of herbals and dietary supplements. The “USP” will appear on the labels.

## Some “Name Brand” Botanicals

Warner Lambert

Quanterra Mental<sup>®</sup> (ginkgo)

Quanterra Prostate<sup>®</sup> (saw palmetto)

Whitehall-Robins Healthcare

Centrum<sup>®</sup> botanicals line

Pharmaton (Boehringer Ingelheim)

Ginsana<sup>®</sup> (ginseng)

Ginkoba<sup>®</sup> (ginkgo)

Venastat<sup>®</sup> (horse chestnut)

Movana<sup>®</sup> (St. John’s wort)

SK-Beecham

Alluna<sup>®</sup> (valerian and hops)

Pharmavite

Nature Made<sup>®</sup>

Nature’s Resource<sup>®</sup>

Phyto-Phamica

Nature’s Way

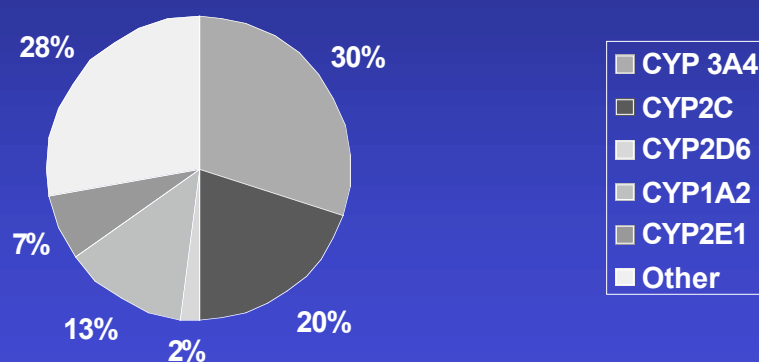
### **Evaluation of Herbal/Drug Interactions**

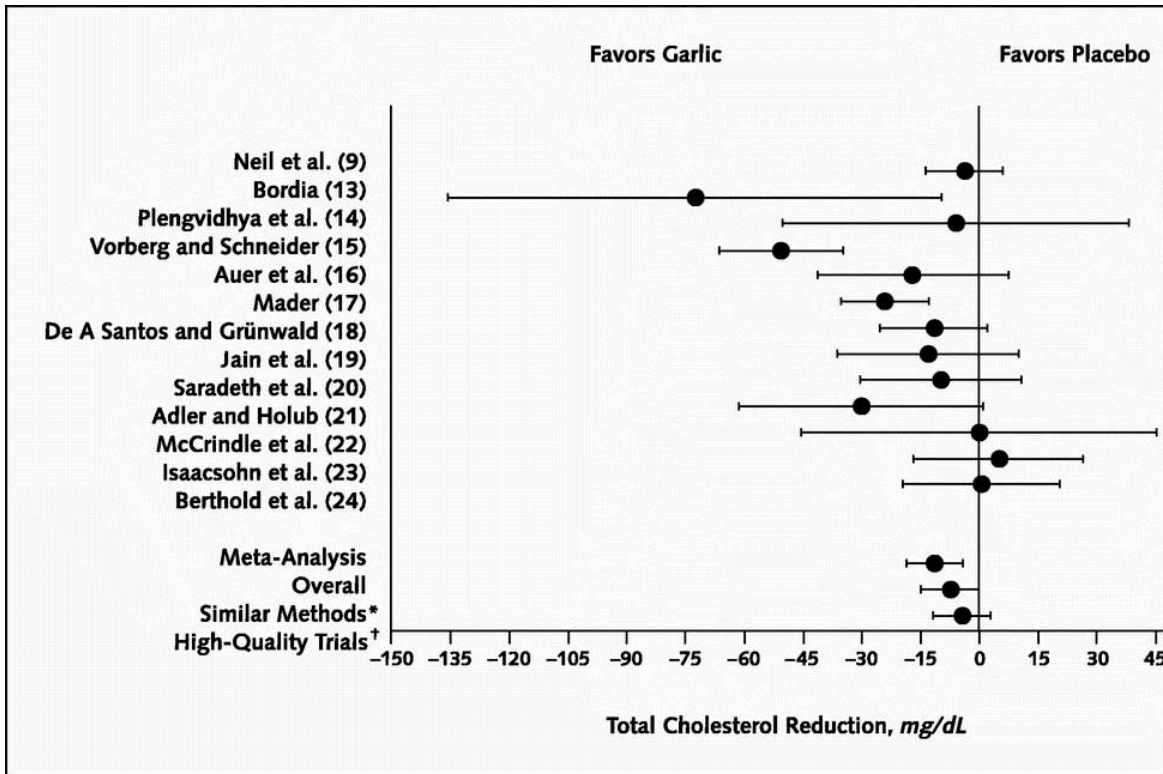
- Speculative
  - e.g. St. John’s Wort and tyramine containing foods due to MAOI effects
- In vitro effects
  - e.g. St. John’s Wort and microsomal studies showing inhibition of CYP3A4
- In vivo - animal studies
  - e.g. Kava and alcohol
- In vivo - human case reports
  - e.g. Ginkgo and warfarin bleeds
- In vivo - healthy human volunteer studies
  - e.g. indinivir and St. John’s Wort
- In vivo - clinical studies in patients

## Important Criteria for Evaluation of a Human Herbal/Drug Interaction Report

- Reputable standardized product used and carefully described?
- Product used analyzed for marker compounds?
- Same batch used throughout study?
- Doses appropriate?
- Steady state study to discern CYP induction?
- Is observation consistent with known mechanisms of action
- Is observation consistent with literature observations?
- Crossover, randomized, placebo controlled human volunteer study with appropriate n?

## Relative Levels of P450 isozymes in human liver





Stevinson et al. Ann Int Med 133:420-429, 2000

**Spontaneous spinal hemoatoma associated with garlic  
Rose et al. Neurosurgery 1990;26:880-882.**

**87 year old male**

**2g of garlic per day for “years”**

**presented with weakness and partial paralysis**

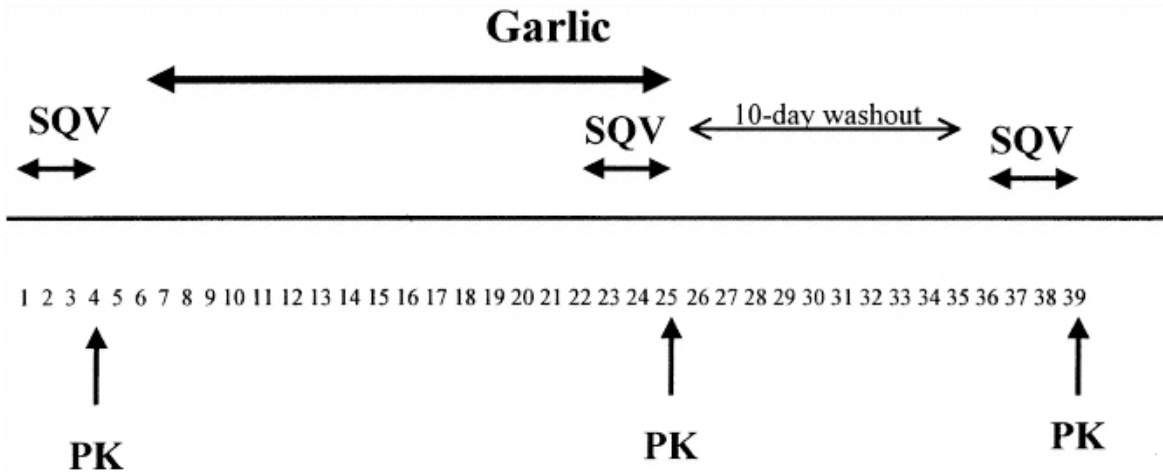
**bleeding time of 11.5 min (normal = 3 min)**

**day 3 post surgery bleed time of 5 min (after stopping garlic)**

**Other reports:**

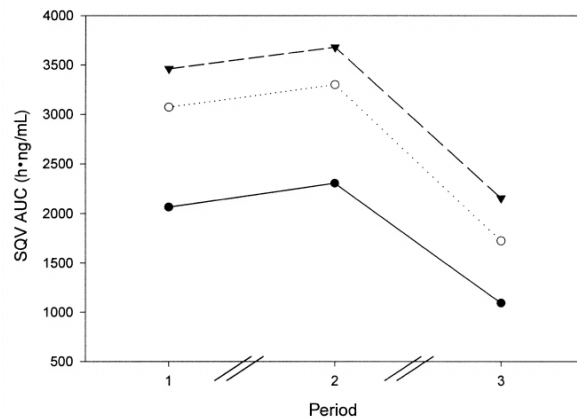
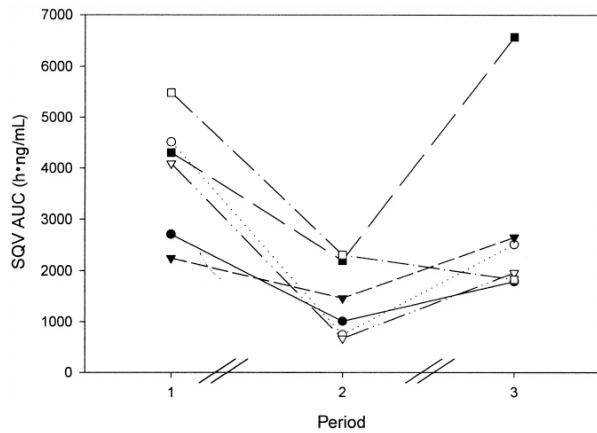
**Garlic and TURP bleeding (German et al. Br J Urology 1995;76:518).**

**Garlic and surgery bleeding (Burnham BE; Plastic Reconstr Surgery 1995;95:213).**

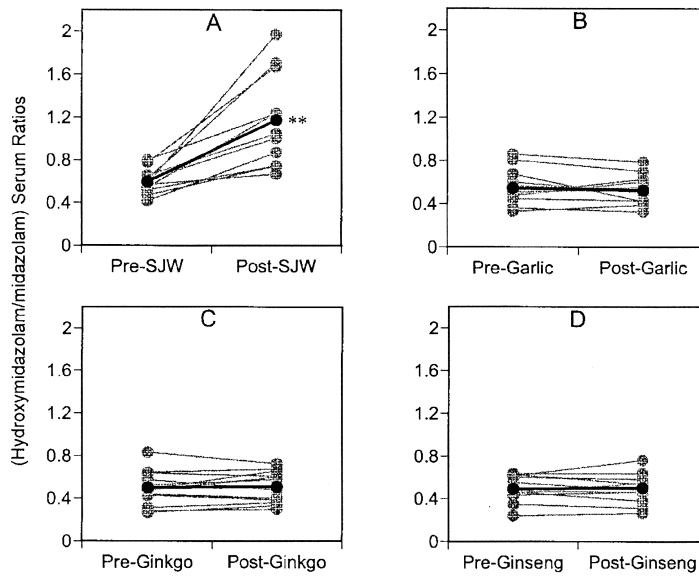


Piscitelli et al. Garlic and Saquinavir. Clin Infect Dis  
2002;34:234-238. N=10 Garlic=GarliPure (Natrol)(BID)

Piscitelli et al. Garlic and  
Saquinavir. Clin Infect Dis  
2002;34:234-238. N=9  
Garlic=GarliPure  
(Natrol)(BID)

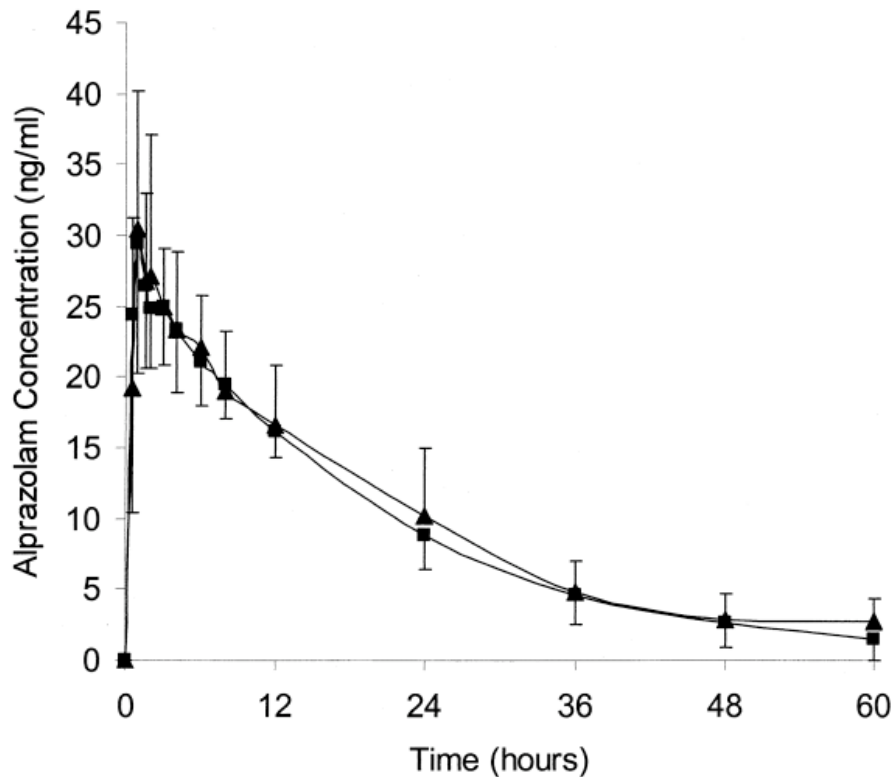






**Fig 2.** Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A**, St John's wort (SJW); **B**, garlic oil; **C**, *G biloba*; **D**, *P ginseng*. Gray circles, Individual values; black circles, group means. Asterisks, Statistically significant difference from baseline.

Gurley et al. Clin Pharmacol Ther 2002;72:276-287  
 n=12; note: used garlic oil prep (500mg TID)



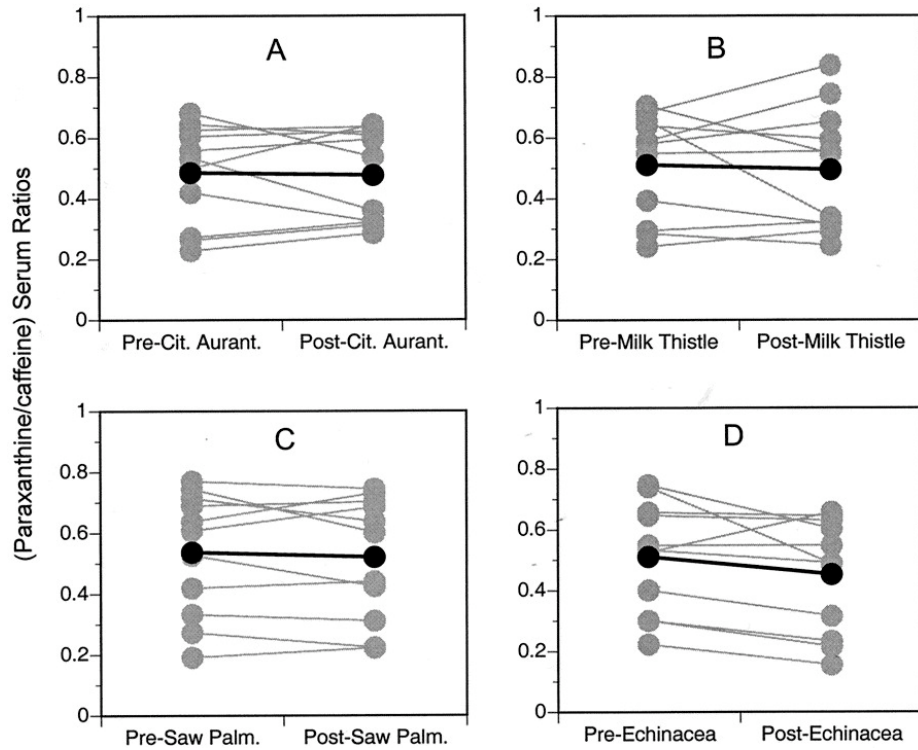
Markowitz et al. Clin Pharmacol Ther 2003;74:170, n=14, 3X600mg for 14d (Kwai)

## ***Garlic summary***

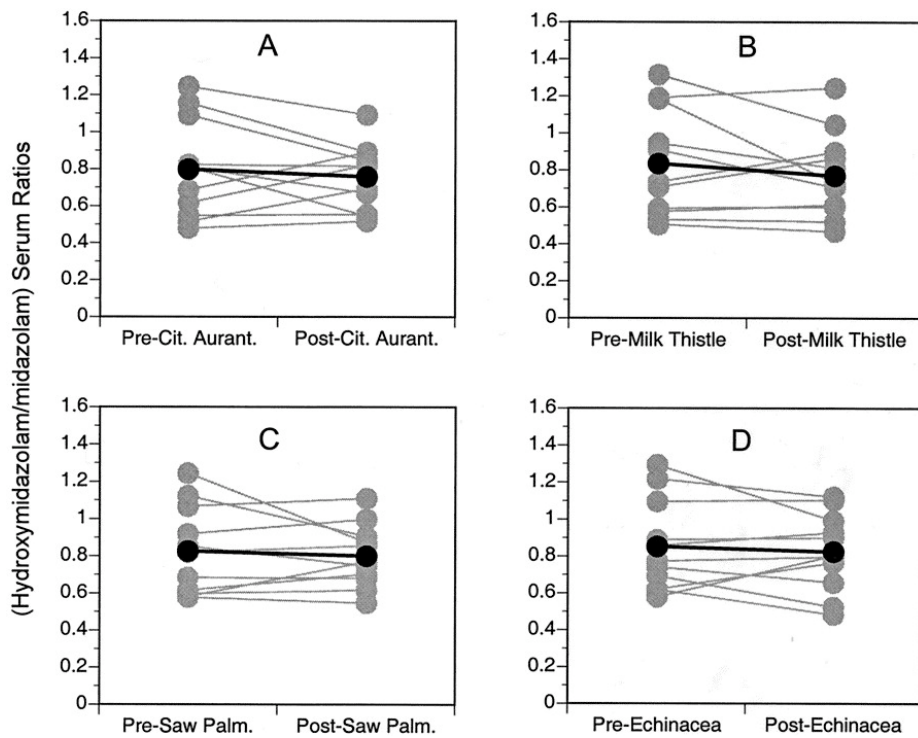
- **Efficacy:** the literature is conflicting for use in hyperlipidemia and hypertension
  - **Safety:** good
  - **Drug interactions:** warfarin; possibly aspirin and other antiplatelet adhesion drugs; not with HIV drugs (other 3A4 substrates?) but depends on product
  - **Product selection:** Suggest enteric coated tablets standardized to about 4mg allicin yield/tablet
  - **Dose:** equivalent of about 4g (2-3 cloves) of fresh garlic per day
- Questions remaining include**

- *Which product to recommend*
- *Who can benefit from use*
- *Other uses?*
- *Why the literature is conflicting*





Gurley et al. Clin Pharmacol Ther 2004;76:428-440.



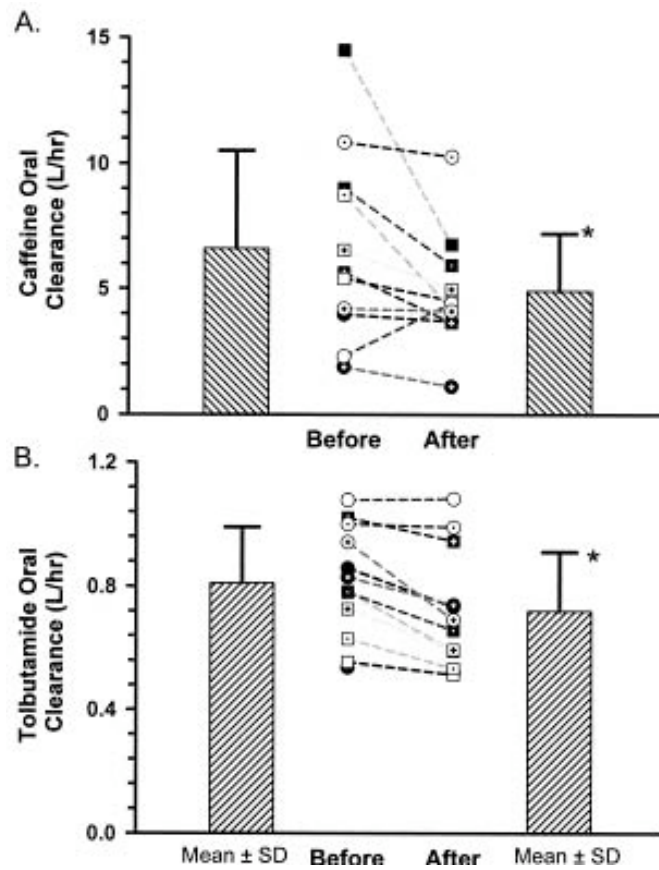
Gurley et al. Clin Pharmacol Ther 2004;76:428-440.

Gorski et al. Clin Pharmacol Ther 2004;75:89-100

N=12 crossover, before and after 400mg QID Echinacea purpurea root extract for 8d

A= Cl caffeine (CYP 1A2)

B= Cl tolbutamide (CYP 2C9)

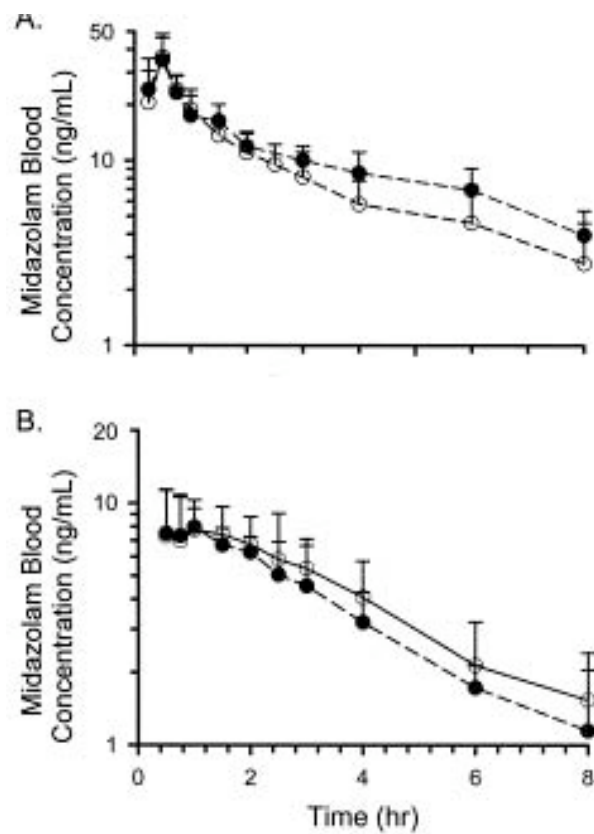


Gorski et al. Clin Pharmacol Ther 2004;75:89-100

N=12 crossover, before and after 400mg QID Echinacea purpurea root extract for 8d

A= midazolam IV (CYP 3A4)

B= midazolam PO (CYP 3A4)



# *Echinacea*

- **Summary**

**Efficacy: evidence for treatment not prevention**

**Safety: good; rare allergy**

**Drug interactions: Pharmacodynamic: don't give to patients taking immunosuppressive drugs**

**Pharmacokinetic: inhibits 1A2; may inhibit intestinal 3A4 but induce hepatic; clinical significance unclear**

**Product selection: want standardized extract containing about 4% phenolics**

**Dose: about 250mg QID for treatment**

**Questions remaining**

- ***Which product? Tincture? Tablets? Root extract? Flowering tops? Pressed juice? E. purpurea? E. augustifolia? E. pallida?***

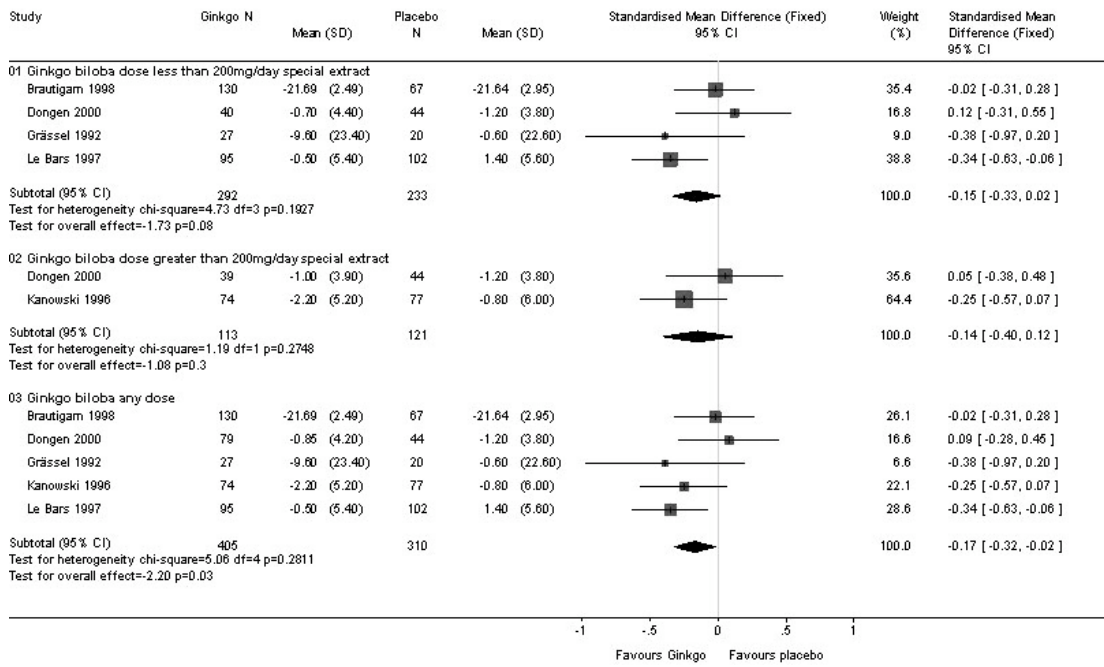
A new study in the  
Journal of the American  
Medical Association  
shows that Ginkgold helps  
with age-related  
mental function.\*\*

For the benefits of this breakthrough study choose the extract actually used, patented Ginkgold®. Other brands may claim to be similar, or perhaps cost 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.

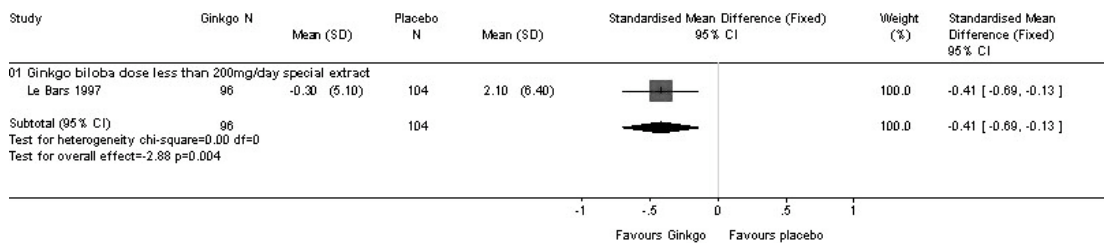
Trust The Leaf™ 

\*\*This statement has not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.  
© 2005 Nature's Way Products Inc., Springville, Utah. A Member, Nature's Way Company.  
†The Journal of the American Medical Association, November 19, 2004; 292(22):2811-2816.  
‡The Journal of the American Medical Association, 291(25):3207-3211, 2004.  
© 2004, T.B. and Associates 11700 Amphitheatre Parkway, Atlanta, GA 30339

Review: Ginkgo Biloba for Cognitive Impairment and Dementia  
 Comparison: 01 Ginkgo biloba vs placebo  
 Outcome: 11 Cognition (change from baseline after treatment of 24 weeks)



Review: Ginkgo Biloba for Cognitive Impairment and Dementia  
 Comparison: 01 Ginkgo biloba vs placebo  
 Outcome: 12 Cognition (change from baseline after treatment of 52 weeks)



# Bleeds associated with ginkgo use

PatientageGinkgo useOthertherapyBleedref701 weekAspirinIris1

— —

## Non-linear Regression

### Ki Values

Isoform	Type of Inhibition	Ki ( $\mu\text{g/ml}$ )	$\alpha$
CYP1A2	Mixed	11.2	0.6
	Competitive	2.1	---
CYP2A6	Mixed	21.2	2.1
CYP2C9	Competitive	9.1	---
CYP2D6	Competitive	133.1	---
CYP3A4	Mixed	17.0	2.5

## Tolbutamide Human Study

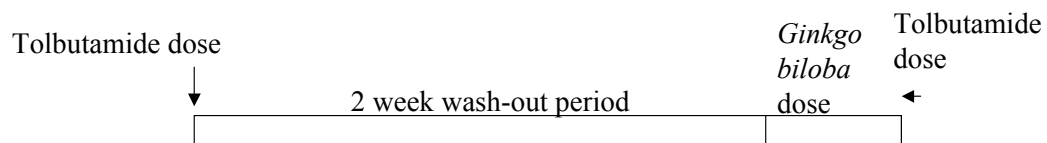
-6 Subjects (3 males, 3 females)

-Subjects ingested 500mg tolbutamide and collected 6-12 hour urine (Control phase)

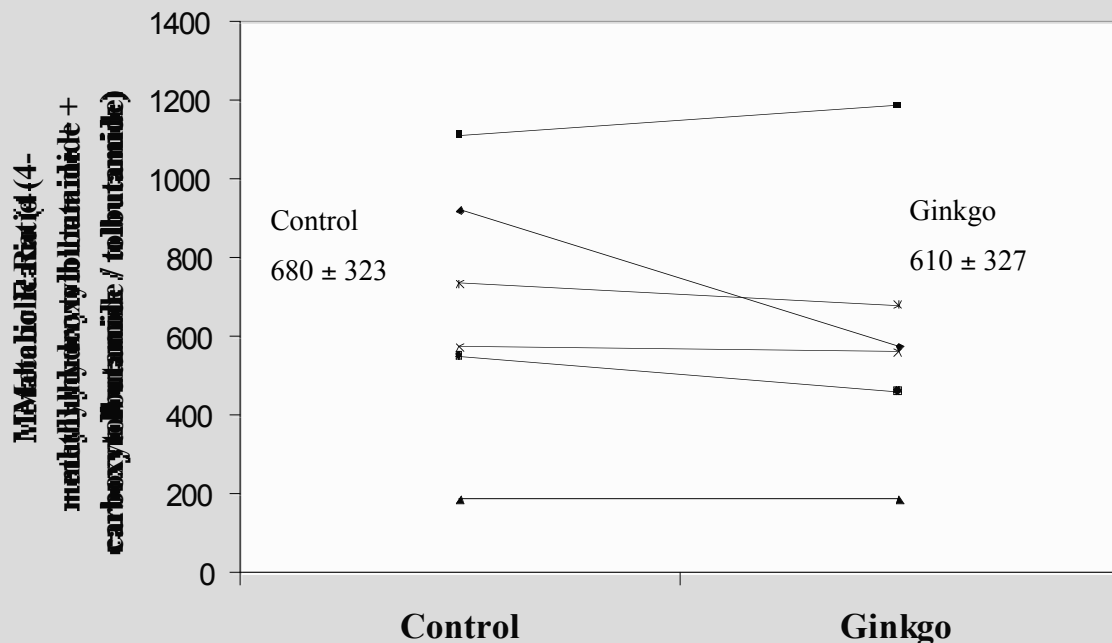
-Followed by a 2 week wash-out period

-Subjects then ingested two 60mg *Ginkgo biloba* extract tablets 2 times a day for 3 days

-The morning of day 4 patients received a 500mg dose of tolbutamide along with the ginkgo and collected 6-12 hour total urine (Ginkgo phase)



### Comparison of Tolbutamide Metabolic Ratios





## Diclofenac Ginkgo biloba Interaction Study

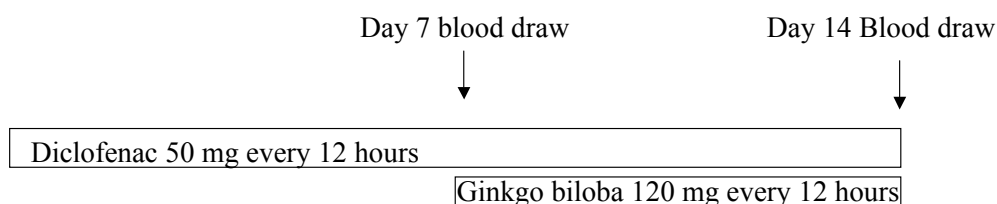
12 healthy non-smoking subjects were recruited (8 males 4 females)

50 mg diclofenac potassium (immediate release) was administered every 12 hours for 14 days

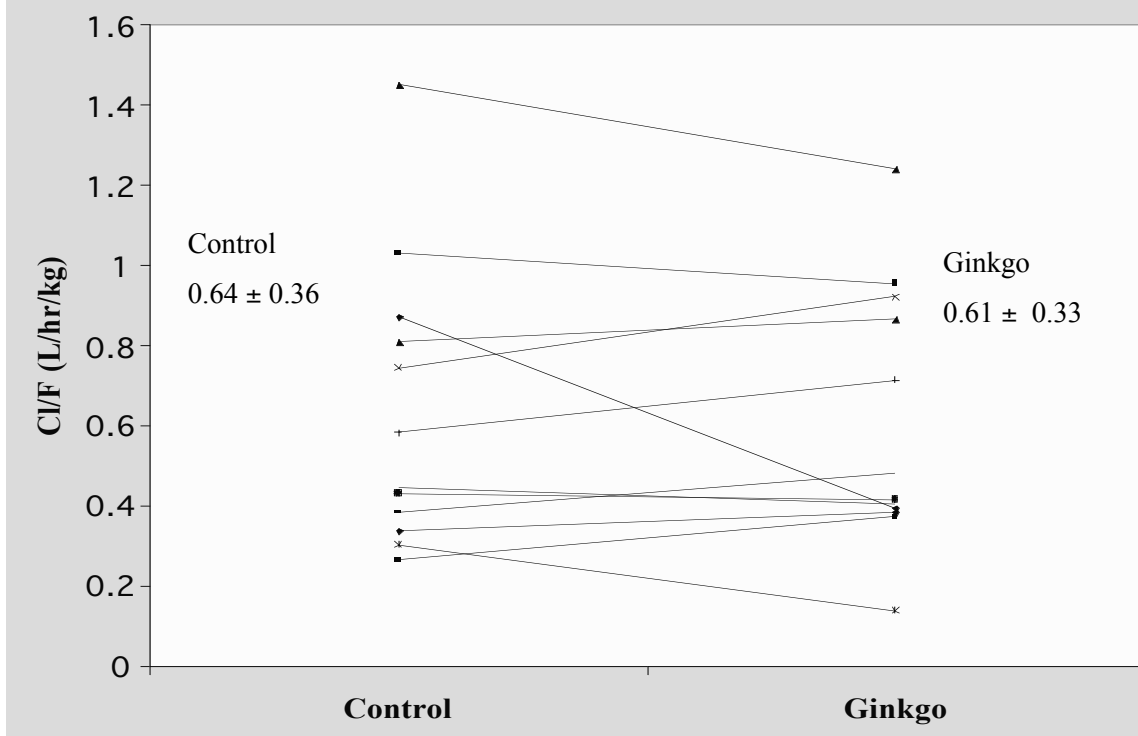
On day 8, 120 mg of *Ginkgo biloba* extract was added to the diclofenac regimen.

On days 7 and 14 plasma collected at times (0, 0.5, 1,2,4,6,8,10, and 12 hrs)

12 hour urine collected

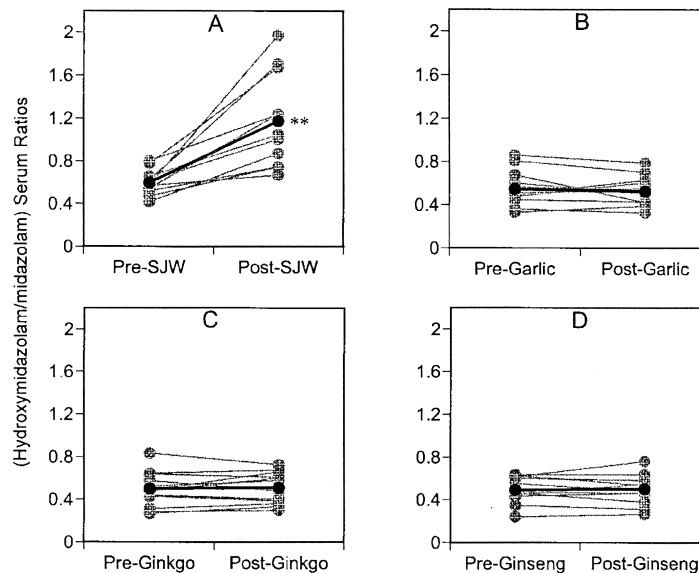


### Comparison of Diclofenac Clearances from Plasma



## Ginkgo biloba - Diclofenac Tolbutamide Human Studies Conclusions

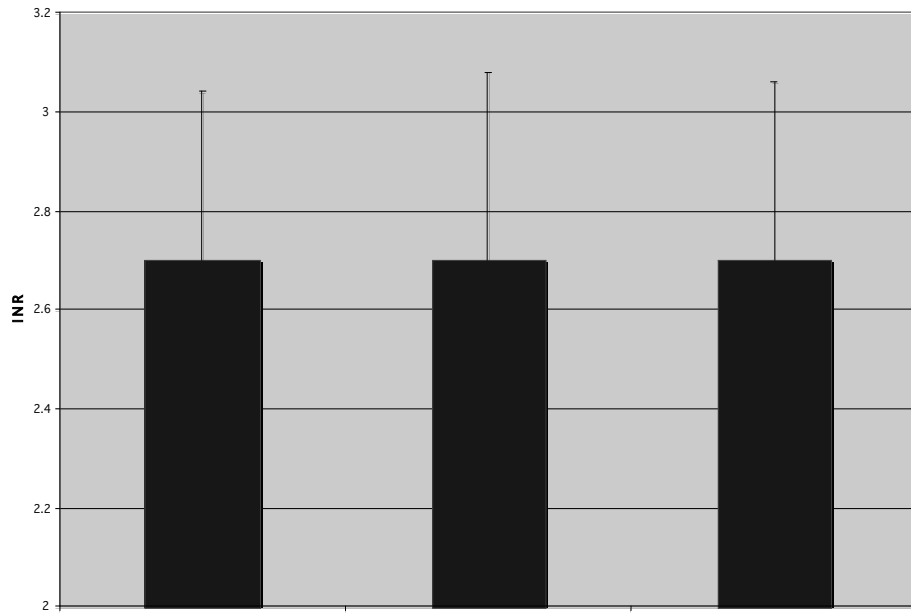
- **No difference was observed in the metabolic ratio between the two arms of the study (tolbutamide alone and tolbutamide + Ginkgo)**
- **No difference was seen between the clearances of the two arms of the study ( diclofenac alone and diclofenac + Ginkgo)**
- **Ginkgo extract does not appear to interact with CYP2C9 substrates in humans**



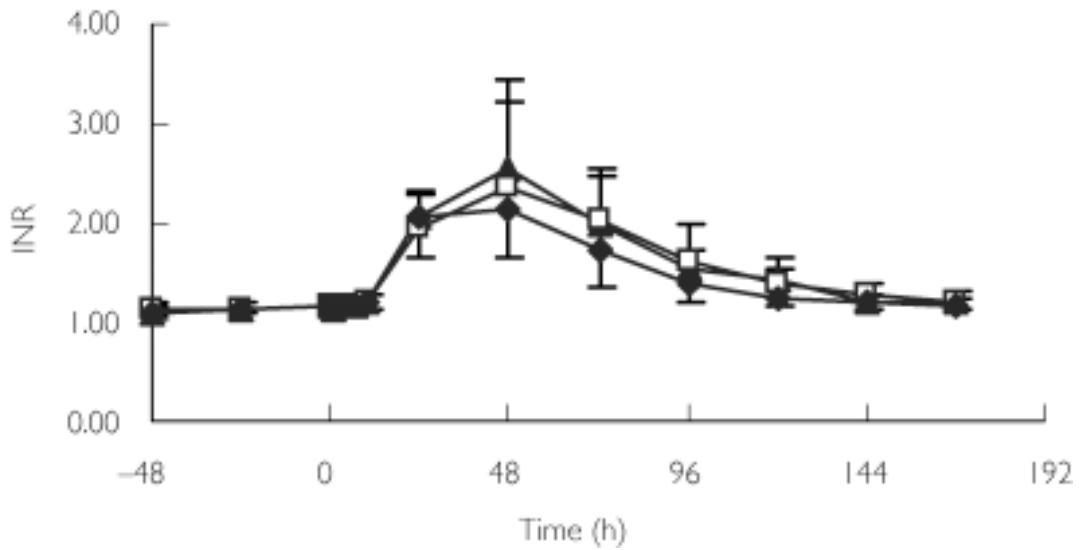
**Fig 2.** Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A**, St John's wort (SJW); **B**, garlic oil; **C**, *G biloba*; **D**, *P ginseng*. Gray circles, Individual values; black circles, group means. Asterisks, Statistically significant difference from baseline.

Gurley et al. Clin Pharmacol Ther 2002;72:276-287  
n=12

### CoQ10 and Ginkgo on Warfarin



Engelsen et al, Thromb Haemost 2002;87:1075-6. N=21, double blind, crossover. Rx=1 month with 2 week washout. Dose of warfarin did not change.



Jiang et al. Br J Clin Pharmacol 2005;59:425-432.

N=12 ginkgo for 7d; warfarin alone or in combination with ginkgo or ginger

Table 1. The median inhibitory concentration (IC<sub>50</sub>) values for commercial plant extracts and tinctures against cytochrome P450 3A4.

Commercial Extract/Tincture	IC <sub>50</sub> Relative Concentration (% Full Strength)	Regression Line:					Ranked Inhibition
		Slope	Constant	N	R <sup>2</sup>	p (1 tail)	
<i>Arctium lappa</i>	> 100	18.88 (14.66, 23.10)	9.53 (42.5, 14.81)	21	0.822	0.000	16
<i>Echinacea angustifolia/purpurea</i> (1:1)	6.73 <sup>a</sup> (10.09, 4.75)	35.15 (32.40, 37.90)	20.91 (17.47, 24.34)	21	0.974	0.000	10
<i>Echinacea angustifolia</i> roots	1.05 <sup>b</sup> (2.19, 0.64)	24.85 (20.17, 29.52)	49.43 (43.12, 55.73)	18	0.888	0.000	4
<i>Echinacea purpurea</i> roots	3.99 <sup>a</sup> (7.74, 2.39)	34.81 (30.34, 39.29)	29.07 (23.04, 35.11)	18	0.944	0.000	7
<i>Echinacea purpurea</i> tops	8.56 <sup>a</sup> (13.05, 5.95)	43.75 (40.40, 47.10)	9.218 (4.93, 13.51)	20	0.977	0.000	14
<i>Eleutherococcus senticosus</i>	NI	7.78 (-2.25, 17.81)	5.74 (-7.77, 19.24)	17	0.154	0.060	NI
<i>Ginkgo biloba</i>	4.75 <sup>a</sup> (12.82, 2.57)	69.38 (53.09, 85.68)	3.04 (-8.82, 14.90)	12	0.900	0.000	8
<i>Glycyrrhiza glabra</i>	1.83 (4.29, 1.11)	43.95 (32.68, 55.22)	38.45 (29.33, 47.57)	12	0.883	0.000	6
<i>Harpagophytum procumbens</i>	NI	0.14 (-3.71, 3.99)	25.23 (20.41, 30.05)	21	0.000	0.470	NI
<i>Hydrastis canadensis</i>	0.03 <sup>b</sup> (0.02, 0.04)	15.02 (11.05, 18.99)	72.80 (68.80, 76.80)	16	0.824	0.000	1
<i>Hypericum perforatum</i>	0.04 <sup>b</sup> (0.03, 0.05)	17.33 (12.38, 22.27)	74.01 (69.78, 78.25)	14	0.829	0.000	2
<i>Matricaria chamomilla</i>	1.48 <sup>a</sup> (1.97, 1.16)	21.64 (19.90, 23.32)	46.32 (44.13, 48.51)	21	0.972	0.000	5
<i>Panax quinquefolius</i>	NI	-3.96 (-12.12, 4.20)	20.53 (9.54, 31.52)	17	0.067	0.842	NI
<i>Prunus serotina</i>	6.90 <sup>a</sup> (10.45, 4.89)	77.47 (70.20, 84.74)	-14.97 (-21.53, -8.41)	15	0.976	0.000	12
<i>Sambucus canadensis</i>	6.82 <sup>a</sup> (24.41, 2.97)	26.24 (20.73, 31.75)	28.12 (21.23, 35.01)	21	0.840	0.000	11
<i>Serenoa repens</i>	7.41 <sup>a</sup> (14.39, 4.41)	38.93 (34.17, 43.68)	16.15 (10.43, 21.87)	20	0.943	0.000	13
<i>Silybum marianum</i>	5.22 <sup>a</sup> (7.94, 3.67)	38.45 (35.20, 41.69)	22.39 (18.33, 26.45)	21	0.970	0.000	9
<i>Tanacetum parthenium</i>	> 100	22.14 (13.82, 28.46)	-6.19 (-14.57, 2.18)	18	0.775	0.000	16
<i>Trifolium pratense</i>	1.05 <sup>b</sup> (1.80, 0.72)	29.38 (24.00, 34.76)	49.42 (43.89, 54.96)	17	0.900	0.000	4
<i>Uncaria tomentosa</i>	0.79 <sup>b</sup> (1.56, 0.66)	80.28 (31.81, 128.75)	58.37 (43.88, 72.86)	4	0.962	0.010	3
<i>Valeriana officinalis</i>	9.56 <sup>a</sup> (70.49, 3.09)	19.08 (13.79, 24.37)	31.30 (24.52, 38.08)	20	0.761	0.000	15

Note: Numbers in brackets correspond to the lower and upper 95% confidence limits of the particular value respectively.

<sup>a</sup> value was achieved within the tested range.

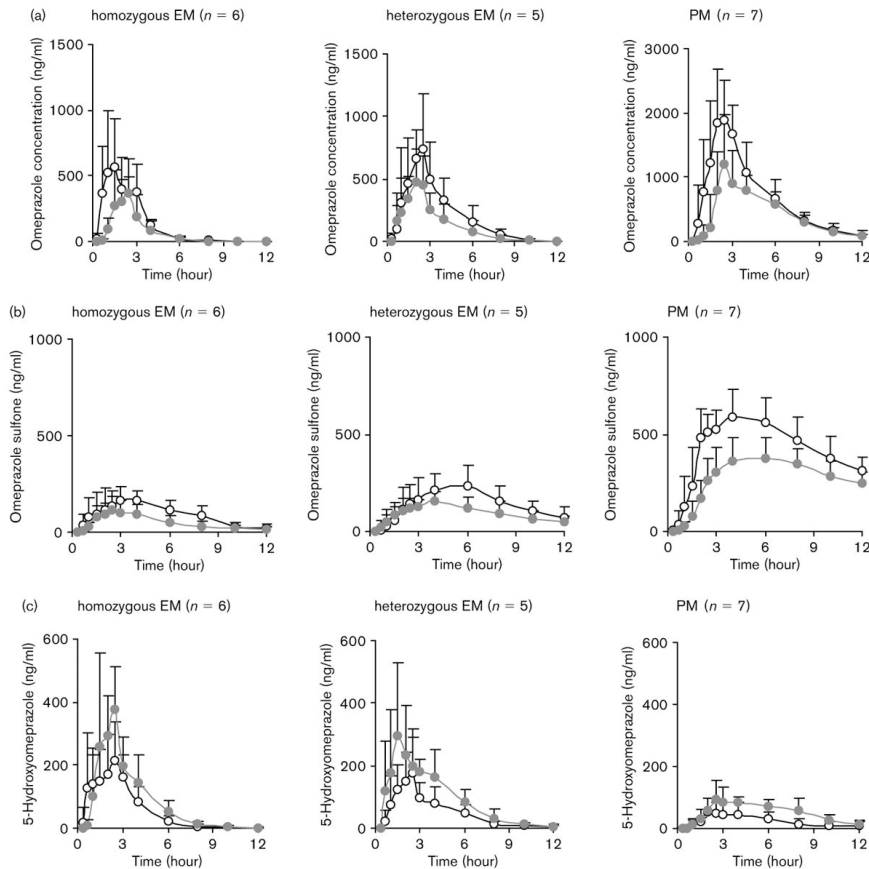
<sup>b</sup> value was achieved by extrapolating the regression line beyond the tested range.

NI – non inhibitory within the tested range.

## Ginkgo/Drug Interactions new studies

- Markowitz et al. J Clin Psychopharmacol 2003;23:576-581. No effect of multiple dosing of ginkgo on dextromethorphan (2D6) or alprozolam (3A4) pharmacokinetics. n=12
- Mauro et al. Am J Ther 2003;10:247-251. No effect of multiple dosing of ginkgo on digoxin (Pgp) pharmacokinetics. N=8 crossover
- Mohutsky et al. Am J Ther in press. No effect of multiple dosing of ginkgo on diclofenac (2C9) or tolbutamide (2C9). N=12 crossover
- Yin et al. Pharmacogenetics 2004;14:841-850. Induction of 2C19 mediated hydroxylation of omeprazole.

Yin et al.  
Pharmacogenetics  
2004;14:841-850. Induction of 2C19 mediated hydroxylation of omeprazole



## ***Ginkgo biloba* summary**

- **Efficacy:** good for dementia and poor peripheral circulatory problems
- **Safety:** good; rare bleeding episodes
- **Drug interactions:** no effect on 3A4,2C9 or 2D6 but may induce 2C19; inhibits platelet adhesion; possible pharmacodynamic interaction with “blood thinners” but not common
- **Product selection:** look for EGb761 extract
- **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?*

## **Soy and Menopausal and Postmenopausal problems**

- Hot flashes and other symptoms: soy flour as well as higher doses of soy isoflavones (100mg/d) will reduce**
- Osteoporosis- studies using high isoflavone soy indicate decreased loss of bone mass in postmenopausal women**

## **Soy Effects on Cancers**

- Long consumption of soy associated with lower rates of breast, endometrial and prostate cancers (Asian cultures)**
- Soy and some soy isoflavones decrease prostate cancer and breast cancer growth in animal studies**
- Genistein enhances effect of adriamycin on breast cancer cells but blocks inhibitory effect of tamoxifen**

## **•Soy-Cardiovascular Benefits**

- Favorable effects on cholesterol balance; “heart healthy”**

## **Other herbals used for menopausal symptoms**

**Red clover- contains lignans and isoflavones; some studies show benefit**

**Black cohosh- does not affect endometrium but may relieve hot flashes 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?**

**6 $\beta$ -hydroxycortisol/cortisol ratio  
(CYP 3A4)**

herbal	Baseline Week 1	Treatment Week 2	Treatment Week 3	Washout Week 4	Statistics
Ginseng	4.4 $\pm$ 2.4	3.7 $\pm$ 2.2	3.6 $\pm$ 1.8	3.7 $\pm$ 1.6	NS
Soy isoflavones	4.9 $\pm$ 2.5	5.0 $\pm$ 2.0	4.6 $\pm$ 2.2	-----	NS

From: Anderson and Elmer, Clinical Pharmacology and Therapeutics 43:643-648 (2003).

## Soy

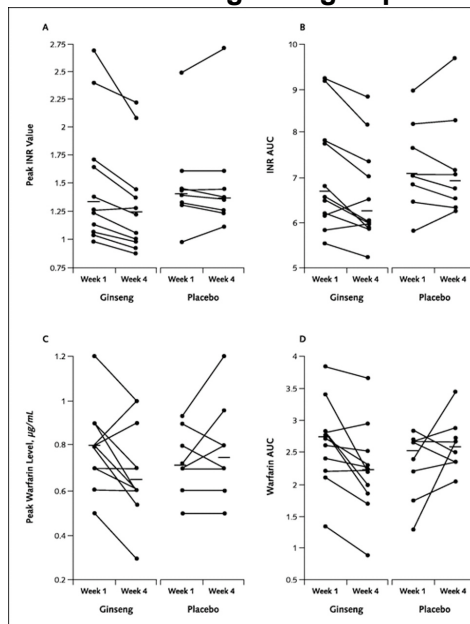
- **Efficacy: increased soy ingestion may decrease hot flashes and other postmenopausal symptoms; cardiovascular benefits as well.**
- **Safety: good but use in breast cancer may be risky**
- **Drug interactions: not with with tamoxifen but effect on CYP3A4 is unlikely**
- **Product selection: soy or 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?*

# “Probable Interaction Between Warfarin and Ginseng”

Janetzky and Morreale, Am J. Health-Syst Pharmacy 54:692-693,1997

- 47 yr old male
- on warfarin for 10 years with an INR of 3-4
- started ginseng (INR= 3.1, 4 weeks prev)
- INR declined to 1.5 after 3 weeks on ginseng
- INR increased to 3.3 after stopping ginseng
- ginseng causing CYP induction?

Changes in individual peak international normalized ratio (INR), INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC in weeks 1 and 4 in American ginseng or placebo groups

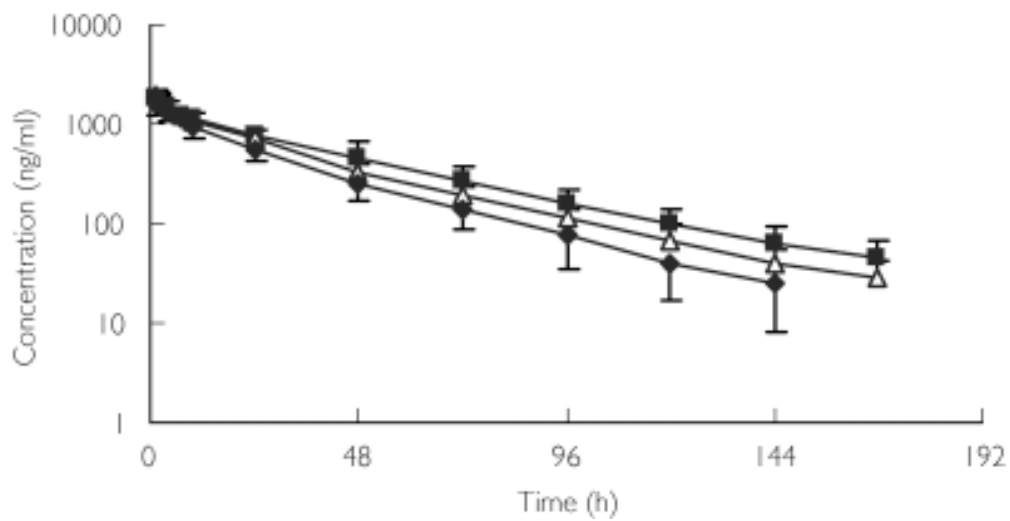


Yuan, C.-S. et. al. Ann Intern Med 2004;141:23-27

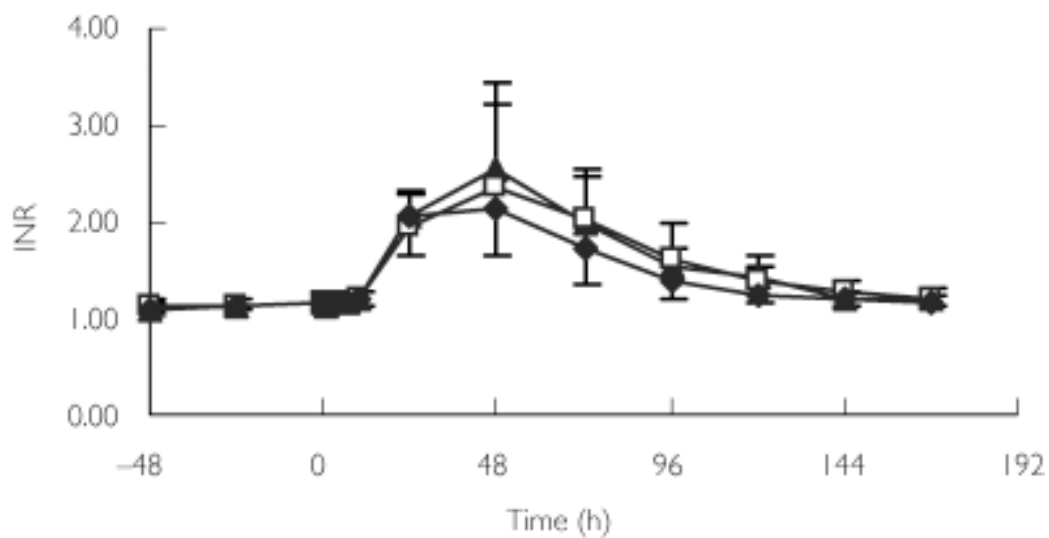
5mg warfarin for 3d before and after 1g/d ginseng (50mg/d ginsenosides) American ginseng (*Panax quinquefolius*) n=20

Annals of Internal Medicine





Jiang et al. Br J Clin Pharmacol 2004;57:592-599. SJW, ginseng and placebo in triple crossover study. N=12 single dose 25mg warfarin following 7d (ginseng) or 14d (sjw) of herbal; ginseng dose=54mg/d ginsenosides; Korean ginseng (Panax ginseng)

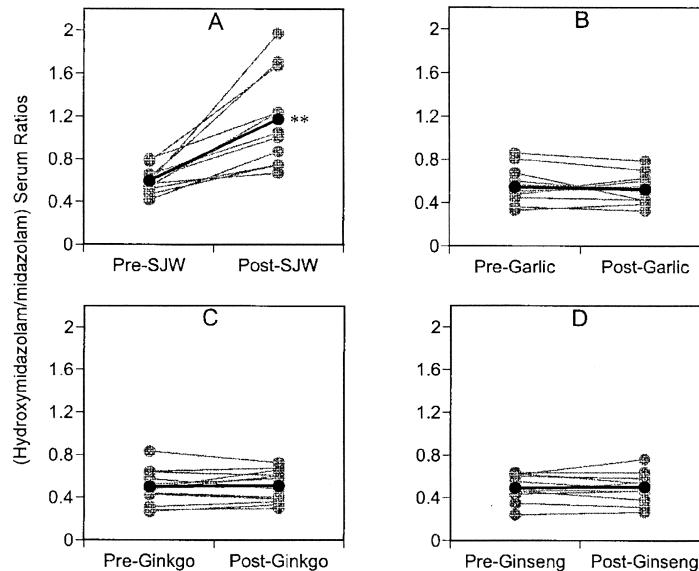


Jiang et al. Br J Clin Pharmacol 2004;57:592-599. SJW, ginseng and placebo in triple crossover study. N=12 single dose 25mg warfarin following 7d (ginseng) or 14d (sjw) of herbal; ginseng dose=54mg/d ginsenosides; Korean ginseng (Panax ginseng)

## 6 $\beta$ -hydroxycortisol/cortisol ratio (CYP 3A4)

herbal	Baseline Week 1	Treatment Week 2	Treatment Week 3	Washout Week 4	Statistics
Ginseng	4.4 $\pm$ 2.4	3.7 $\pm$ 2.2	3.6 $\pm$ 1.8	3.7 $\pm$ 1.6	NS
Soy isoflavones	4.9 $\pm$ 2.5	5.0 $\pm$ 2.0	4.6 $\pm$ 2.2	-----	NS

From: Anderson and Elmer, Clinical Pharmacology and Therapeutics 43:643-648 (2003).



**Fig 2.** Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A**, St John's wort (SJW); **B**, garlic oil; **C**, *G biloba*; **D**, *P ginseng*. Gray circles, Individual values; black circles, group means. Asterisks, Statistically significant difference from baseline.

Gurley et al. Clin Pharmacol Ther 2002;72:276-287  
n=12; Panax ginseng

## ***Ginseng***

**Efficacy: some evidence for applications in geriatric patients (improved “quality of life”) and in diabetes**

**Safety: good;**

**Drug interactions: no apparent induction of CYP 3A4 but induction of 2C9 (warfarin) with Am ginseng (*Panax quinquefolius*) but maybe not Korean (*Panax ginseng*). May precipitate hypoglycemia with insulin or oral hypoglycemics.**

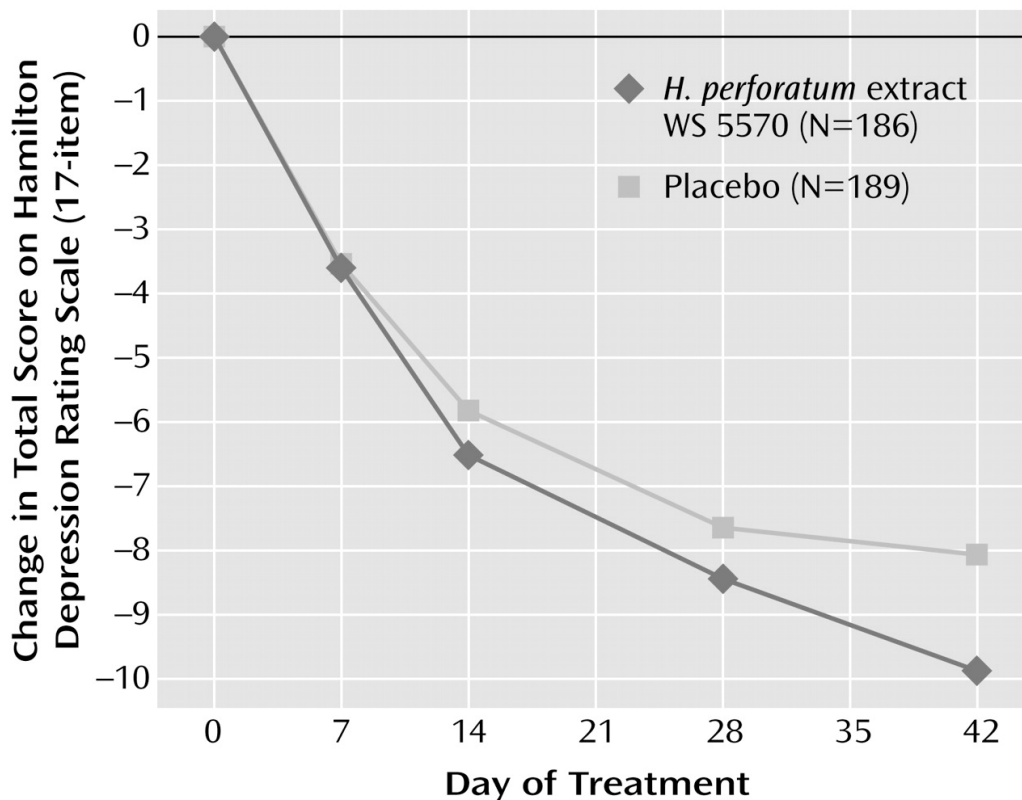
**Product selection: product should be standardized so dose is 4-7% ginsenosides/d**

**Questions remaining include:**

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

## **St. John's Wort**

- **Linde et al conclusions: more effective than placebo, similar to standard drugs**
- **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**

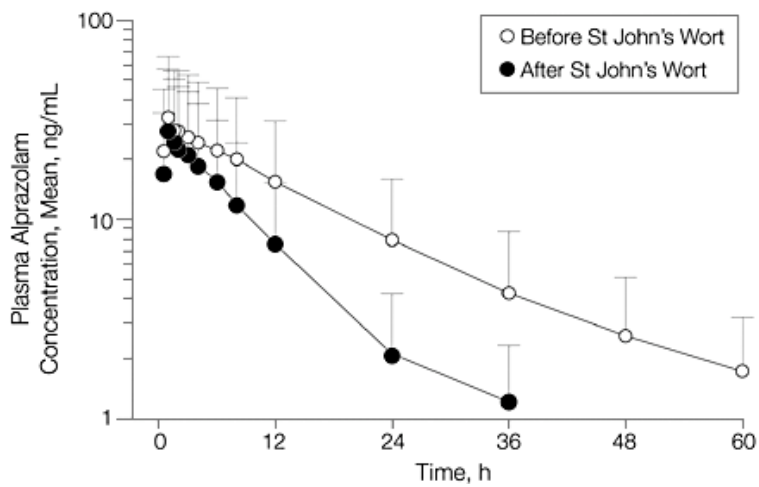
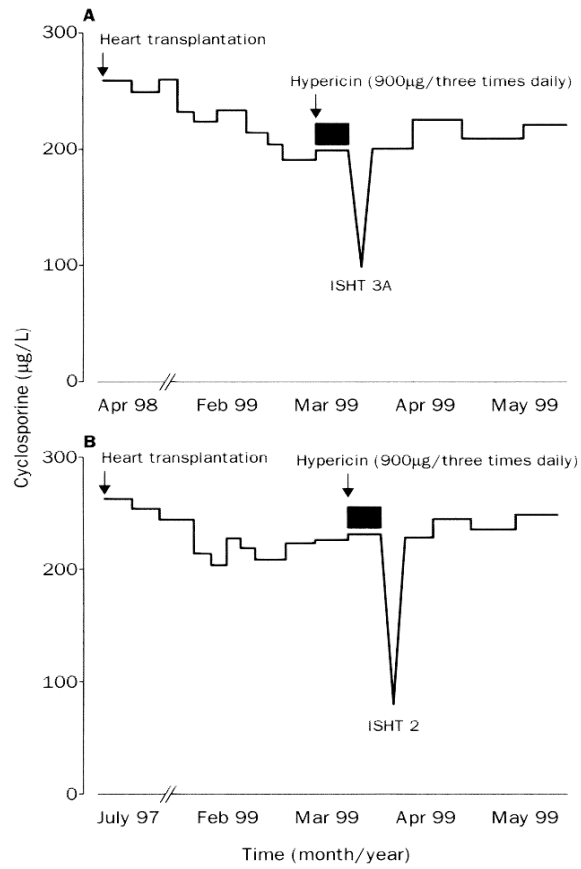


Lecrubier et al. Am J Psychiatry 2002;159:1361 n=375

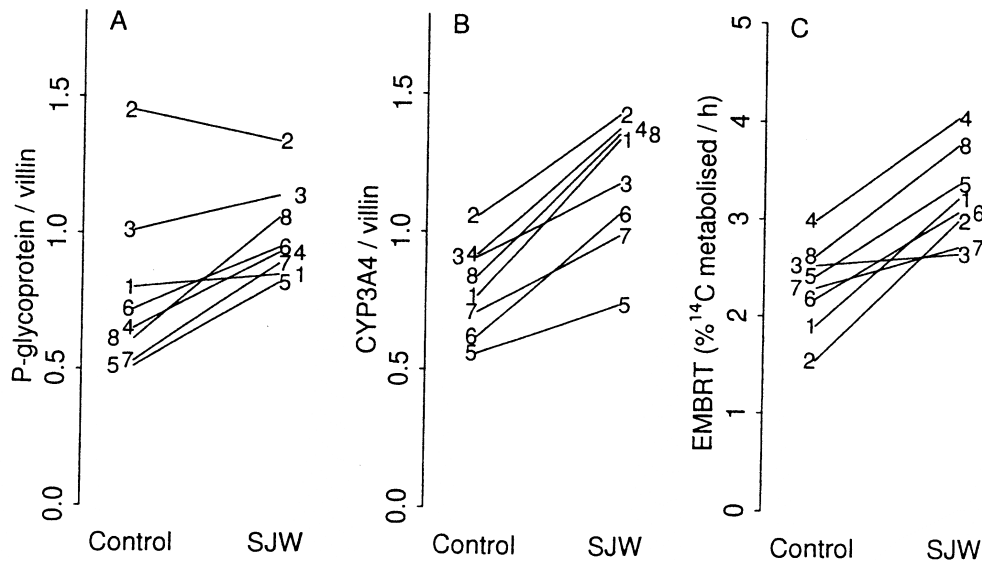
## Interactions with St. John's Wort -cyclosporin-

- Study: 2 case reports
  - case 1: 61yr had transplant 11mos earlier; cyclosporin, azathioprine, steroids for 11 mos. Unexplained heart failure noted after SJW started.
  - case 2: 63yr had transplant 20mos earlier: same scenario as case 1.

Ref: Ruschitzka et al. Lancet 355:548-549,2000



Markowitz et al. JAMA 290:1500,2003 n=12 14d of SJW



**Fig 3.** Comparison of intestinal P-glycoprotein/MDR1 and CYP3A4/villin expression ratios and erythromycin breath tests in humans. Eight healthy male volunteers were treated with St John's wort extract for 14 days. Duodenal biopsy specimens (A, B) and <sup>14</sup>C-erythromycin breath tests (EMBRT; C) were performed before treatment (control) and after treatment (SJW). Intestinal P-glycoprotein (A) and CYP3A4/villin (B) expression ratios were determined by densitometric analysis of Western blots and are given as the geometric means of 3 individual biopsy specimens obtained before and after treatment with St John's wort.

Durr et al. Clin Pharmacol Ther 2000;68:598-604.

### Summary of SJW Interactions

(adapted from Henderson et al. Br J Clin Pharmacol 2002;54:349-346)

Drug	CYP	Effect	Management
HIV protease inhibitors (nelfinavir,ritonavor,saquinavir)	Induce 3A4	/	Stop and measure viral load
HIV non-nucleoside RTI (efavirenz,nevirapine)	Induce 3A4	/	Stop and measure viral load
warfarin	Induce 2C9	/	Stop and adjust warfarin dose
cyclosporin	Induce P-glycoprotein	/	Stop and adjust cyclosporine dose
oral contraceptives	Induce 3A4	/	Stop and use alternate birth control
anticonvulsants	Induce 3A4	/	Stop and adjust anticonvulsant dose
digoxin	Induce P-glycoprotein	/	Stop and adjust digoxin dose
theophylline	Induce 1A2	/	Stop and adjust theophylline dose
Triptans (sumatriptan)	Increase serotonin	-	Stop
SSRI (fluoxetine,sertraline, etc)	Increase serotonin	-	Stop

## ***St. John's Wort***

- **Summary**
  - **Efficacy:** good evidence for 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 and 1% hyperforin
  - **Dose:** about 300mg TID for treatment
  - **Questions remaining include**
    - *How best to use this herbal given that there are drug interaction problems*



## Kava (Kava Kava)

- Uses
  - mild tranquilizer
- Precautions
  - additive effect with alcohol
  - don't take with other CNS depressants (documented problem when combined with alprazolam, Zoloft)
  - long use may result in rash and discolored skin or allergy
  - not for use in pregnancy or depression
  - is a local anesthetic
  - 32 reports in USA of liver toxicity including some with liver failure

### “Coma from the health food store: interaction between kava and alprazolam”

Ann Int Med 125:940-941, 1996

- 54 yr old male hospitalized in a “lethargic and disoriented state”
- on alprazolam, cimetidine, terazosin
- took kava for 3 days
- alpha pyrones in kava known to bind to GABA receptors (benzodiazepines)
- apparent additive effect ⇒ oversedation

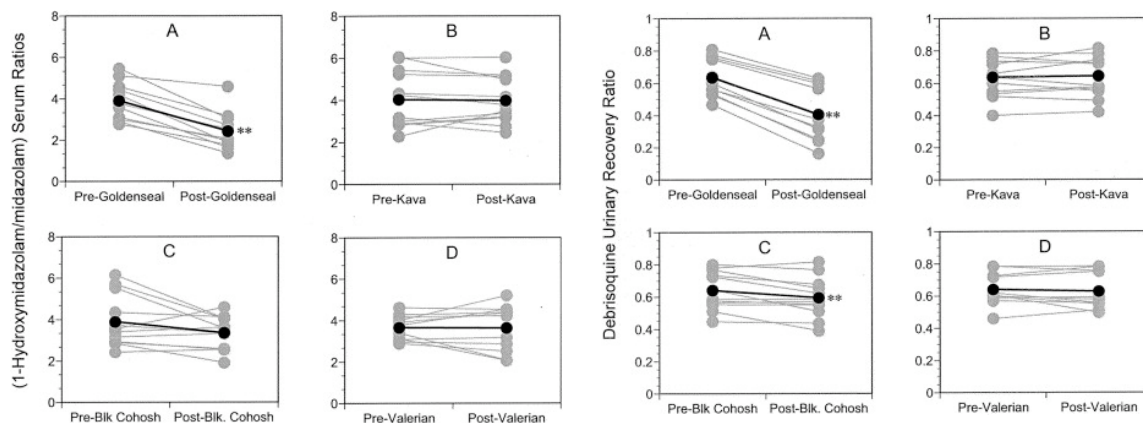


## ***Kava-Summary***

- **Summary**
  - **Efficacy:** long historical use; reasonable evidence for efficacy for mild to moderate anxiety.
  - **Safety:** hepatotoxicity, rash with long use,
  - **Drug interactions:** not with other anxiolytics or sedatives or liver toxic drugs (acetaminophen)
  - **Advice:** don't take Kava!
  
- **Questions remaining include**
  - *How effective is this for occasional use?*
  - *How prevalent is hepatotoxicity?*



## Potential Interactions of Goldenseal with CYP2D6 and CYP 3A4 substrates



Gurley et al. Clin Pharmacol Ther 2005;77:415-426. N=12

## Herbals affecting clotting

adapted from Natural Medicine Comprehensive Database and Norred and Brinker, Alt Ther Health Med 2001;7:58-67.

Andrographis paniculata	Bogbean	Devil' claw	ginseng	Pau d'arco
angelica	Boldo	Dong quai	green tea	meadow sweet
anise	capsicum	Erigeron	hawthorn	prickly ash
arnica	celery	Evening primrose oil	horse chestnut bark	passionflower
Asafoeta	chamomile	feverfew	Huang qi	popular
Baikal skullcap	clove oil	fish oil	horseradish	quassia
Bilberry	coleus root	fenugreek	kava	red clover
Black current seed	danshen	garlic	licorice	reishi mushroom
Bladderwrack	dandelion root	ginger	onion	Sha shen
Bomelain	Danshen	ginkgo	papain	Shinpi bark
Sweet birch oil	Tonka bean	tumeric	vitamin E	wintergreen oil
wild carrot	wild lettuce	willow	wood ear mushroom	woodruff

## Herbs with clotting problems reported in humans

Ginkgo -	case reports of bleeds alone and in combination with aspirin or warfarin but human studies show no effect on CYP or INR
Garlic -	case reports of increased surgical blood loss
St. John's wort -	induces P450 enzymes leading to reduced drug action
Evening primrose oil -	human study showed 40% increase in bleed time
Borage seed oil -	same as evening primrose oil
Vitamin E -	doses >1200 i.u./d can increase bleed time
Cranberry juice	reports of increased INR
Kava -	liver toxicity could increase warfarin effect
Lycium barbarum	report of increased INR
Danshen -	case reports of increased INR with warfarin
Dong quai -	case reports of increased INR with warfarin
Ginseng -	decreased INR with warfarin (Panax quinquefolius)
Green tea -	case report of decreased INR with warfarin
CoQ10 -	case reports of decreased INR with warfarin but human study showed no effect on INR

Seem to have low  
pharmacokinetic drug interaction  
potential based on recent studies

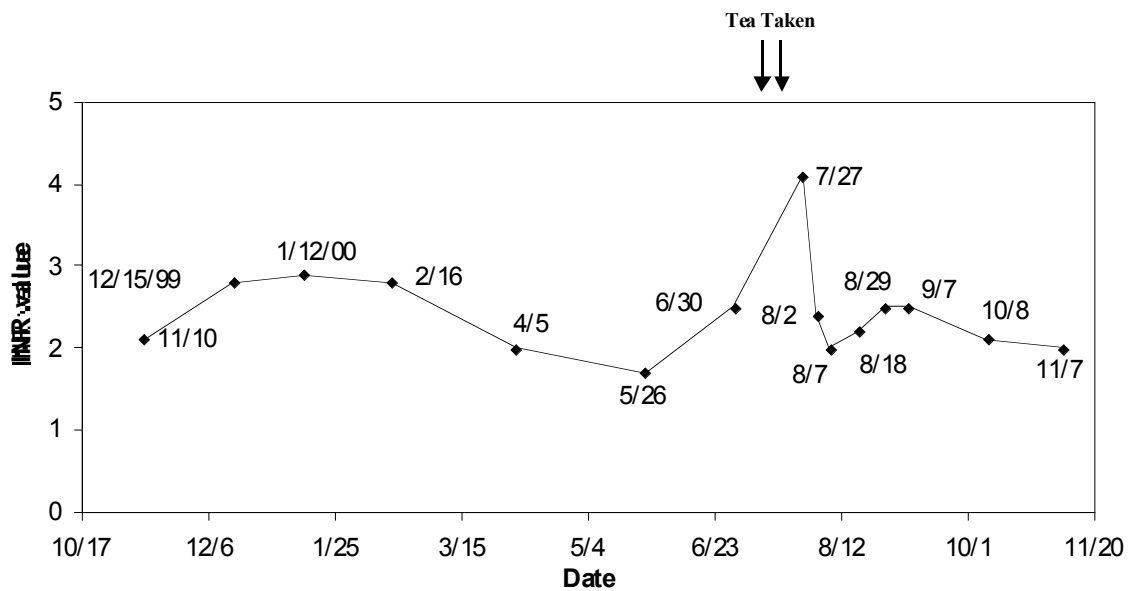
- Ginger
- Valerian
- Milk thistle
- Saw palmetto
- Kava

## Herbals affecting drug management (i.e., herbal/drug interactions)

**literature analysis (Fugh-Berman and Ernst, Herbal Drug  
“Interactions and Assessment of Reliability” Br J Clin Pharmacol  
2001;52:587-595)**

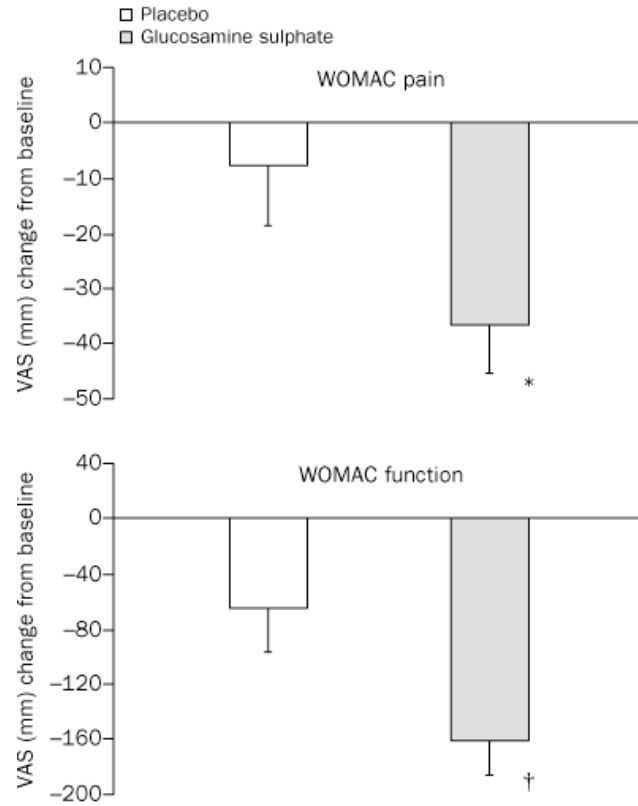
- **108 reported cases of suspected interactions**
- **69% “unable to be evaluated”**
- **19% possible interactions**
- **13% (14) well documented**
- **11/14 involved warfarin**
- **7/14 involved St. John’s wort**

**Fig. 1 Patient INR Values**



From: Lam AY, Mohutsky MA and Elmer GW. Probable herbal/drug interaction between warfarin and a common Chinese herb, Lycium barbarum. Ann Pharmacother 2001;35:1199-1201

Reginster et al. Lancet 2001;357:251-256. N=212 all over 50 with osteoarthritis of the knee; 1500mg/d x 3 yr;



## Glucosamine and type 2 diabetics

- Recent study examined the effect of 90d of Cosamin DS or placebo on glycosylated hemoglobin levels in type 2 diabetics. N=38 result: no effect
- Arch Intern Med 2003;163:1587-90

Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005  
HerbalGram 2005;66:63

- **Product**

- |                        |   |
|------------------------|---|
| – 1. garlic            | product dependent Inhibition of 3A4;<br>enhance warfarin effect |
| – 2. echinacea         | may inhibit CYP 1A2   |
| – 3. saw palmetto      |   |
| – 4. ginkgo            | may induce 2C19   |
| – 5. soy               | may block action of tamoxifen                                   |
| – 6. cranberry         |   |
| – 7. ginseng           | Panax quiquifolius may induce 2C9                               |
| – 8. black cohosh      | may have weak 2D6 induction action                              |
| – 9. St. John's wort   | definitive interactions; induce 3A4 and Pgp                     |
| – 10. milk thistle     |   |
| – 11. evening primrose | may enhance warfarin effect                                     |
| – 12. valerian         |   |
| – 13. green tea        |   |
| – 14. bilberry         |   |

Red indicates risk for drug interactions

## Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005

HerbalGram 2003;58:71

### • **Product**

- 15. grape seed				
- 16. horny goat weed	enhance warfarin effect and increase BP			
- 17. yohimbe	affect BP medications			
- 18. horse chestnut	might enhance warfarin effect			
- 19. eleuthero	might enhance warfarin effect			
- 20. ginger				
- multi-herbs		52	+29	na
- all other		12	-7.5	na
total		257		

Red indicates risk for drug interactions

Note: kava and pycnogenol fell off the top 20 list

Note: total herbal sales are estimated at \$4.2 billion

The above figures include sales from food stores, drug stores, and mass market retailers but with Wal-Mart figures not included. It does not include warehouse buying clubs, convenience stores, natural foods stores, multilevel marketers, health professional sales, mail order or internet sales.

## References with Good Herbal/Drug Interactions Discussion

– **“Top 100 Drug Interactions”** Hansten PD and Horn JD. H&H Publications 2005

– **Natural Medicines Comprehensive Database.**

Online version updated “daily”. UW Healthlinks  
<http://www.naturaldatabase.com/>; \$92

– **The Natural Medicines Encyclopedia.**

free with access subscription (\$24/yr) to  
consumerlab.com [www.consumerlab.com](http://www.consumerlab.com)

# Recent Reviews

- Scott GN and Elmer GW. Update on natural product-drug interactions. *Am J Health-Syst Pharm* 2002;59:339-347
- Ernst E. The risk-benefit profile of commonly used herbal therapies: ginkgo, St. John's wort, ginseng, echinacea, saw palmetto and kava. *Ann Intern Med* 2002;136:42-53
- Izzo AA. Herb-drug interactions: an overview of the clinical evidence. *Fundam Clin Pharmacol.* 2005 Feb;19(1):1-16.
- Ernst E. Prescribing herbal medications appropriately. *J Fam Pract.* 2004 Dec;53(12):985-8.

## What can we do?

- **dialog with NDs and other prescribers**
- **recommend the best products**
- **ask patients about herbals they may be taking**
- **herbals should not usually be recommended for acute or serious illnesses**
- **avoid herbal use with drugs with narrow therapeutic window, esp. warfarin, cyclosporin, digoxin, HIV protease inhibitors, theophylline, carbamazepine**
- **stay informed**