Herbal / Drug Interactions

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Table 1. Enrollees in CHS Study [a]

Total enrolled: 5849
White: 4925 (84)
Black: 924 (16)
Male: 2478 (42)
Female: 3371 (58)

Study period	1	2	3	4
Total users	4373	4351	3919	3561
Rx users	3994 (91)	3891 (89)	3533 (90)	3259 (92)
CAM users	278 (6)	295 (7)	504 (13)	533 (15)
Vitamin/mineral users	1713 (39)	1707 (39)	1678 (43)	2081 (58)
OTC users	2635 (60)	2720 (63)	2263 (58)	2219 (62)
Rx plus CAM	238 (5)	243 (6)	411 (11)	463 (13)
Rx, CAM, OTC	264 (6)	270 (6.2)	459 (11.7)	511 (14.4)

[a] The number in parentheses is t he percent of the enrolled

Elmer et al. Ann Pharmacother 2007,in press

Table 3 All users of the top 20 CAM products by race[a]

CAM Product	All (%)	Black (%)	White (%)
Garlic	5.86	7.76	5.48
Ginkgo	4.20	3.34	4.37
Glucosamine	2.45	0.48	2.85
Lecithin	1.92	0.36	2.23
Cod Liver Oil	1.82	4.30	1.33
Ginseng	1.11	1.67	1.00
CoQ10	0.97	0.24	1.12
Alfalfa	0.91	0.48	1.00
Antioxidant	0.91	0.72	0.95
Chromium picolinate	0.85	0.24	0.97
melatonin	0.65	0.48	0.69
Saw palmetto	0.63	0.36	0.69
Echinacea	0.61	0.84	0.57
Aloe	0.53	0.48	0.55
St. John's wort	0.51	0.24	0.57
Chromium	0.49	0.36	0.52
Bilberry	0.48	0.24	0.52
l-lysine	0.42	0.12	0.47
Bee pollen	0.36	0.36	0.36
Shark cartilage	0.32	0.36	0.31

[a] n=5052 for all participants; n=838 for blacks; n=4214 for whites

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?)
- Is the Rx drug one with a narrow therapeutic margin?

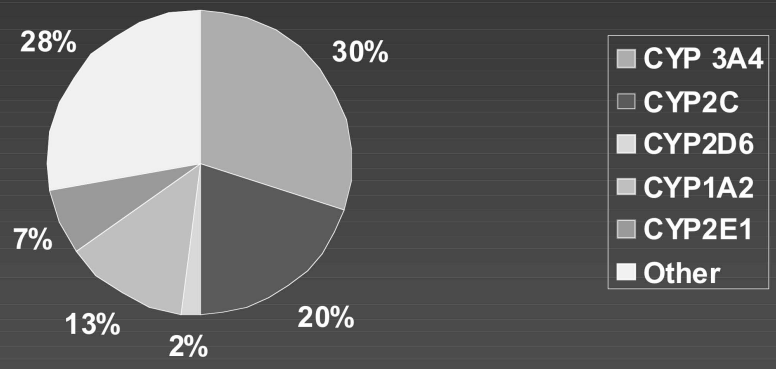
Evaluation of Herbal/Drug Interactions

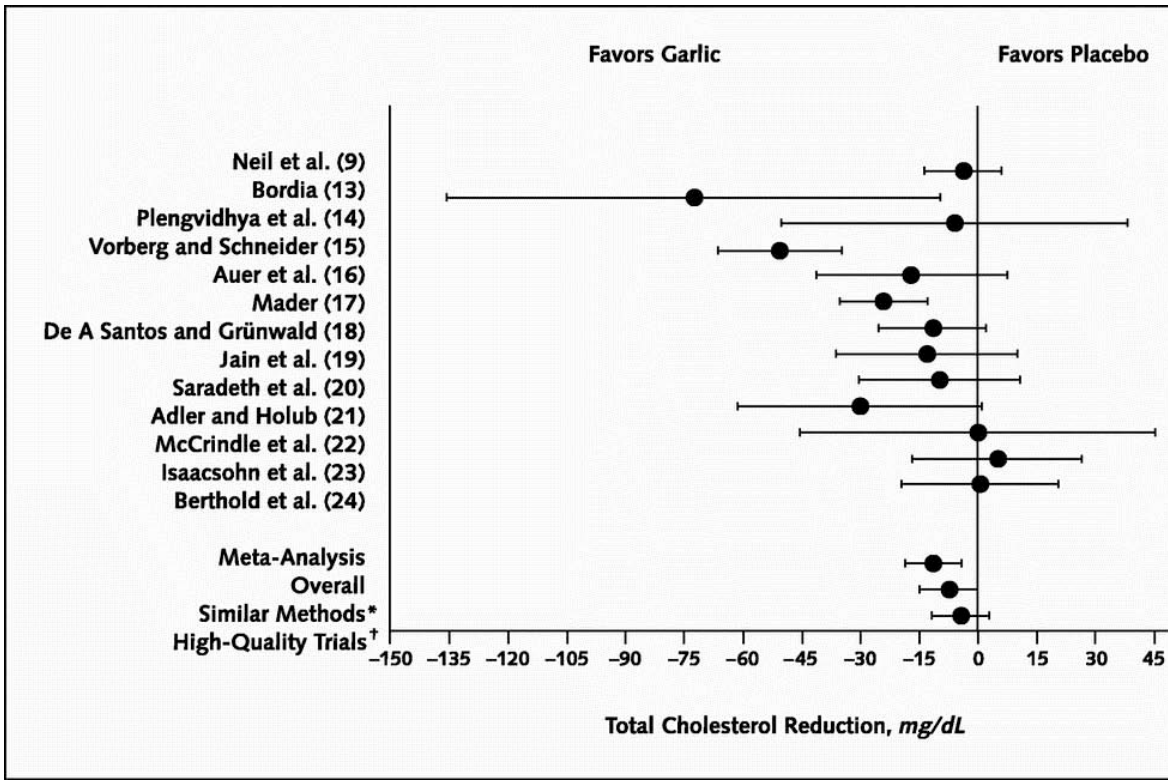
- Speculative or Theoretical
  - e.g. St. John's Wort and tyramine containing foods due to MAOI effects or evening primrose oil and risk for bleeds with warfarin
- In vitro effects
  - e.g. St. John's Wort and microsomal studies showing inhibition of CYP3A4
- In vivo - animal studies
  - e.g. Kava and 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

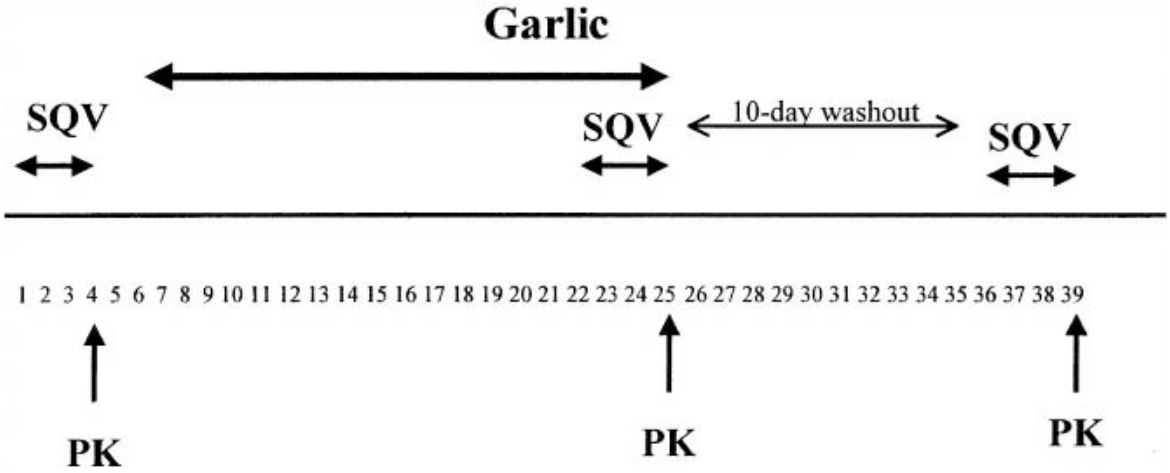
bleeding time of 11.5 min (normal = 3 min)

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

Other reports:

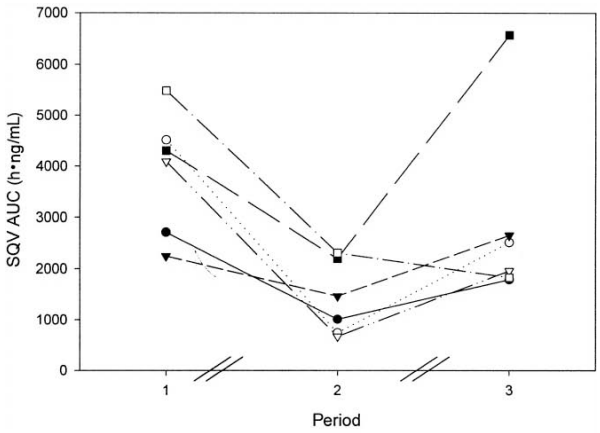
Garlic and TURP bleeding (German et al. Br J Urology 1995;76:518).

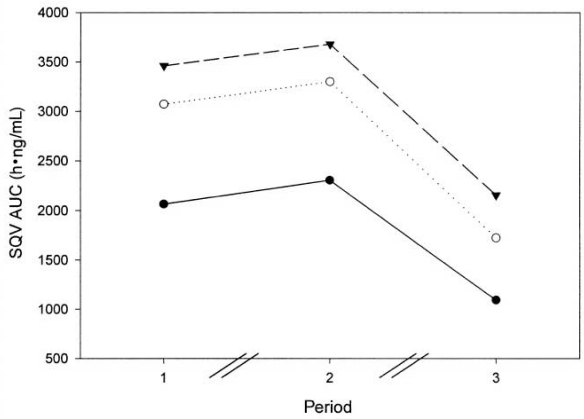
Garlic and surgery bleeding (Burnham BE; Plastic Reconstr Surgery 1995;95:213).



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)





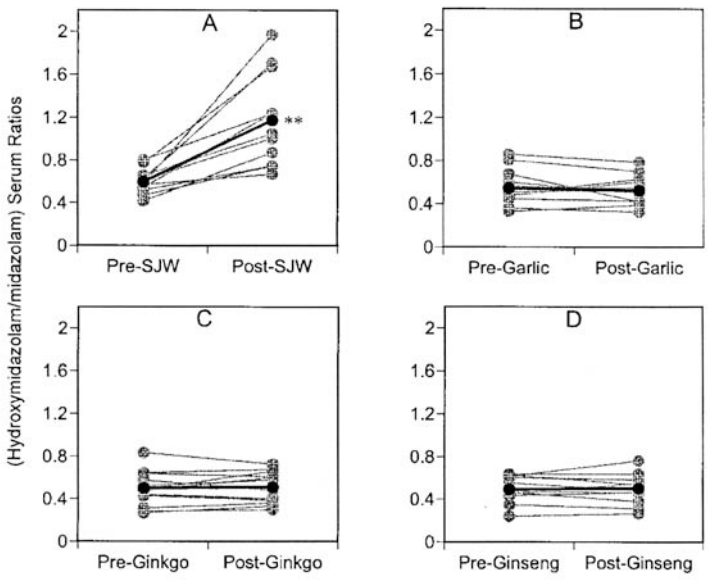
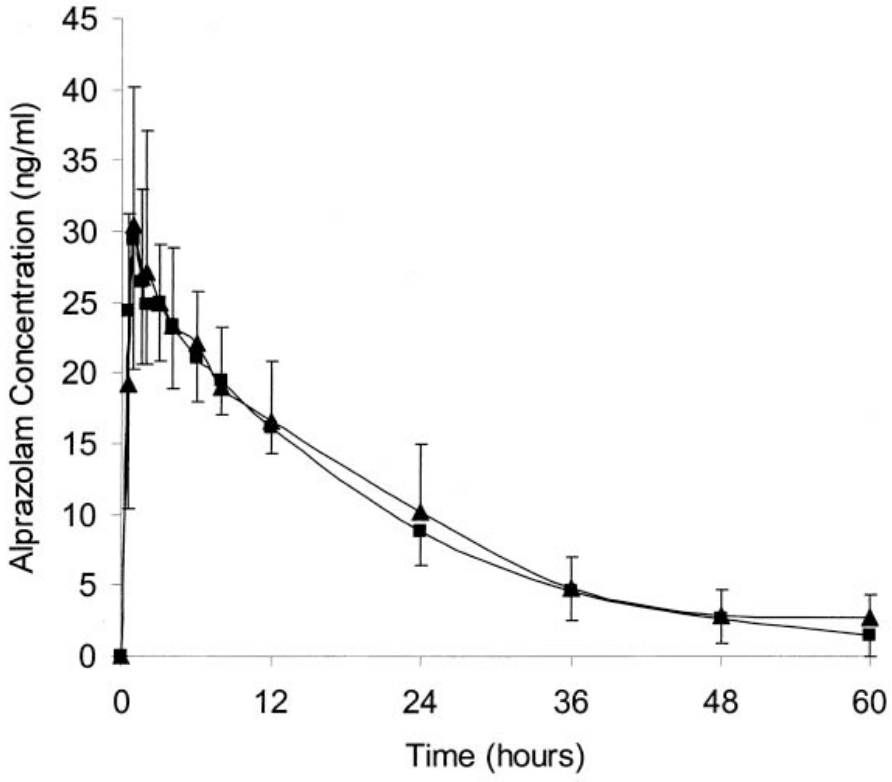


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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

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



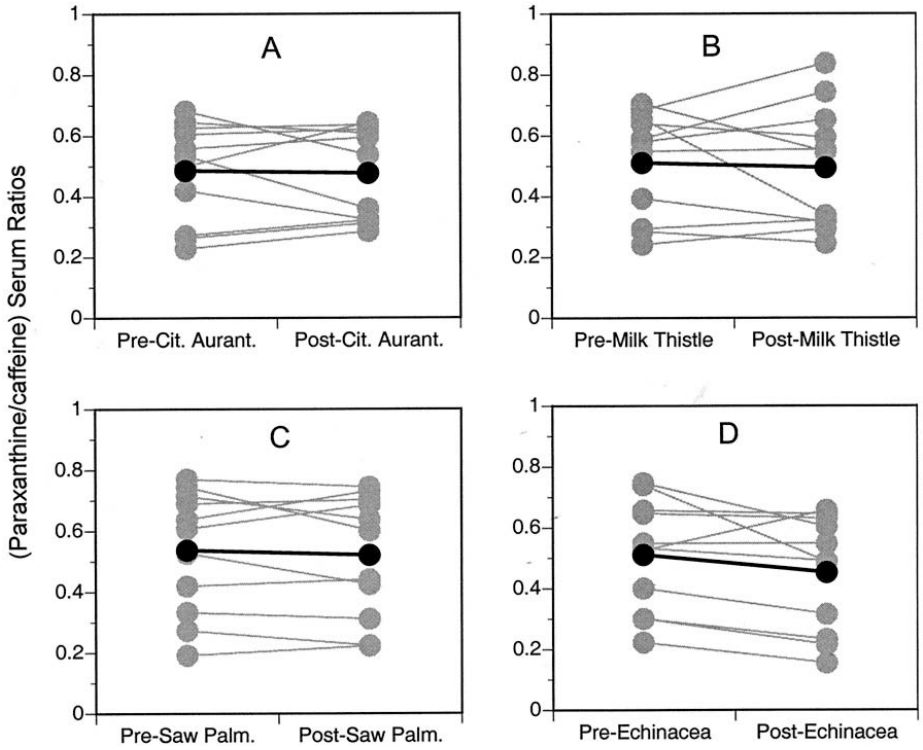
Markowitz et al. Clin Pharmacol Ther 2003;74:170, n=14, 3X600mg for 14d (Kwai)

Garlic and warfarin

- A new study showed no effect of aged garlic extract (Kyolic) on patients taking warfarin. HDL went up. No other changes
- Mecan et al. J. Nutr. 2006;136:793s-795s.

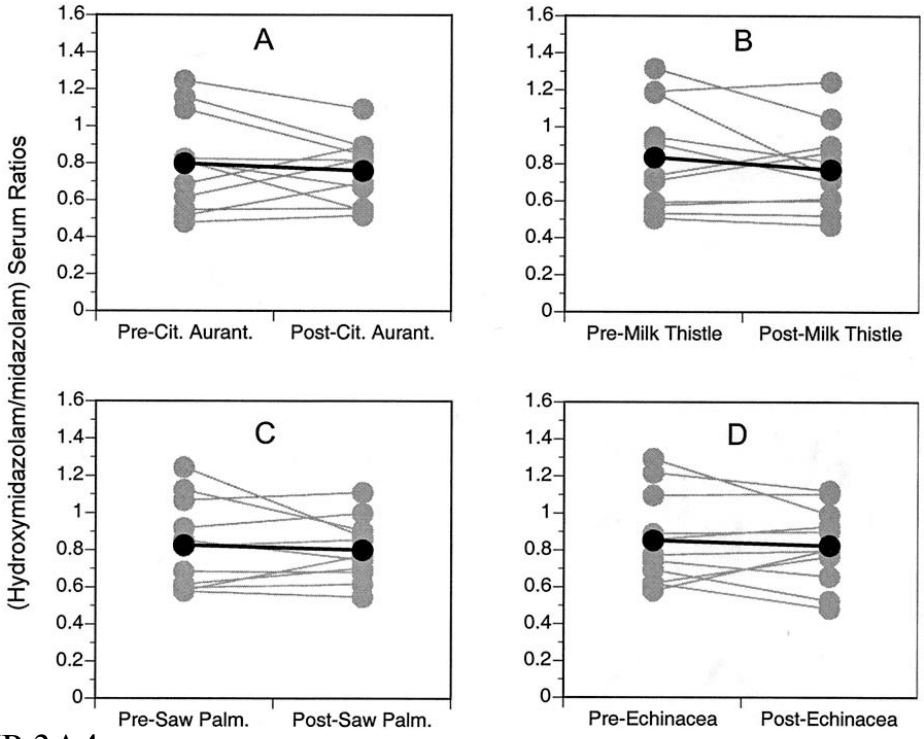
Garlic summary

- **Efficacy: ? benefit for use in hyperlipidemia. Possible other cardiovascular benefits.**
- **Safety: good**
- **Drug interactions: warfarin; possibly aspirin and other antiplatelet adhesion drugs (pharmacodynamic interaction); not with HIV drugs (other 3A4 substrates?) but depends on product (pharmacokinetic interaction)**
- **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 i.e. 8-12 mg allicin/d**



CYP 1A2

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



CYP 3A4

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

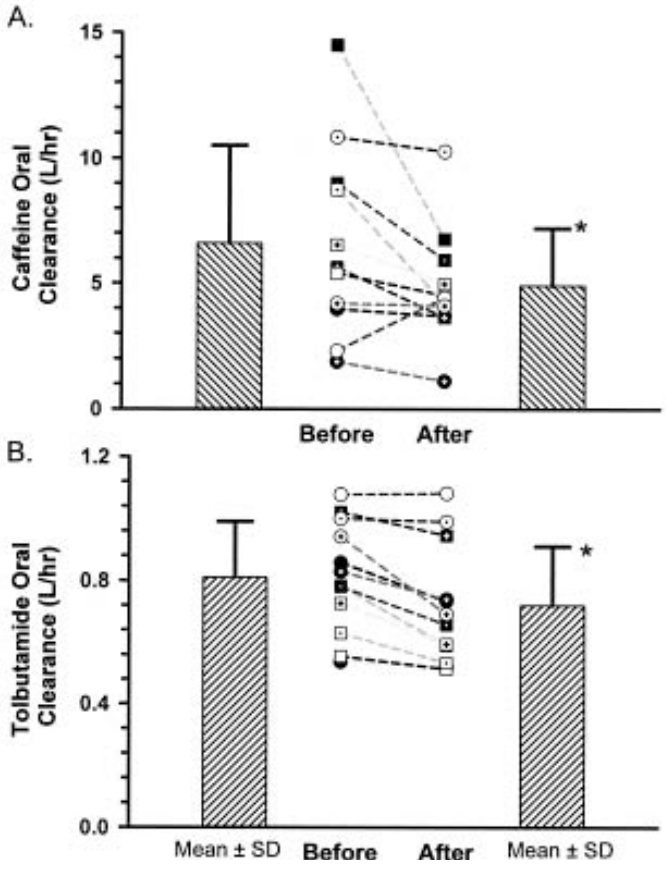
800mg BID for 30d (Wild Oats Market)(analyzed)

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)



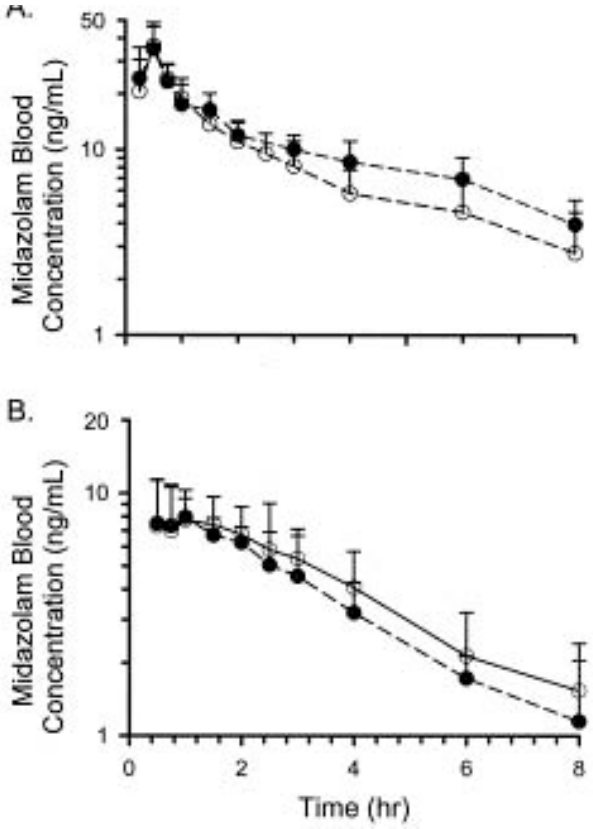
Gorski et al. Clin Pharmacol Ther 2004;75:89-100

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

Open circle is echinacea

A= midazolam IV (CYP 3A4)

B= midazolam PO (CYP 3A4)

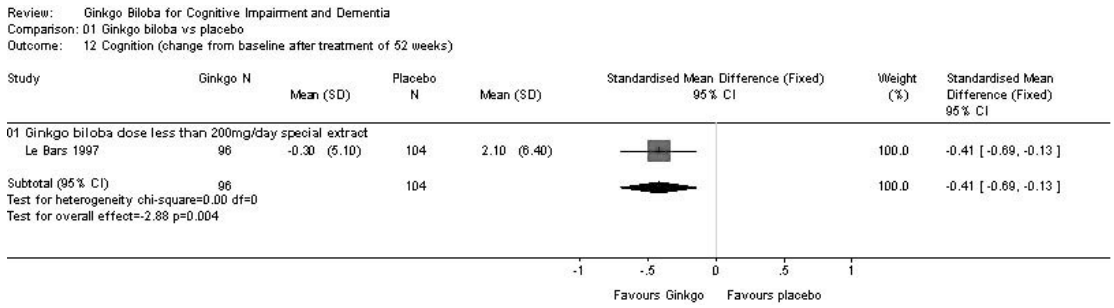


Echinacea

- **Summary**
  - **Efficacy: evidence for treatment <u>not</u> prevention**
  - **Safety: good; rare allergy**
  - **Drug interactions: Pharmacodynamic: don't give to patients taking immunosuppressive drugs**
  - **Pharmacokinetic: may inhibit 1A2; may inhibit intestinal 3A4 but induce hepatic; clinical significance unclear; effect on 2C9 is minor**
  - **Product selection: want standardized extract containing about 4% phenolics**
  - **Dose: about 250mg QID for treatment**
  - **Questions remaining**
    - ***Which product? Tincture? Tablets? Root extrract? Flowering tops? Pressed juice? E. purpurea? E. augusifolia? E. pallida?***

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)

Study	Ginkgo N	Mean (SD)	Placebo N	Mean (SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 Ginkgo biloba dose less than 200mg/day special extract							
Brautigam 1998	130	-21.69 (2.49)	67	-21.64 (2.95)		35.4	-0.02 [-0.31, 0.28]
Dongen 2000	40	-0.70 (4.40)	44	-1.20 (3.80)		16.8	0.12 [-0.31, 0.55]
Grässel 1992	27	-9.60 (23.40)	20	-0.60 (22.60)		9.0	-0.38 [-0.97, 0.20]
Le Bars 1997	95	-0.50 (5.40)	102	1.40 (5.60)		38.8	-0.34 [-0.63, -0.06]
Subtotal (95% CI)	292		233			100.0	-0.15 [-0.33, 0.02]
Test for heterogeneity chi-square=4.73 df=3 p=0.1927							
Test for overall effect=-1.73 p=0.08							
02 Ginkgo biloba dose greater than 200mg/day special extract							
Dongen 2000	39	-1.00 (3.90)	44	-1.20 (3.80)		35.6	0.05 [-0.38, 0.48]
Kanowski 1996	74	-2.20 (5.20)	77	-0.80 (6.00)		64.4	-0.25 [-0.57, 0.07]
Subtotal (95% CI)	113		121			100.0	-0.14 [-0.40, 0.12]
Test for heterogeneity chi-square=1.19 df=1 p=0.2748							
Test for overall effect=-1.08 p=0.3							
03 Ginkgo biloba any dose							
Brautigam 1998	130	-21.69 (2.49)	67	-21.64 (2.95)		26.1	-0.02 [-0.31, 0.28]
Dongen 2000	79	-0.85 (4.20)	44	-1.20 (3.80)		16.6	0.09 [-0.28, 0.45]
Grässel 1992	27	-9.60 (23.40)	20	-0.60 (22.60)		6.6	-0.38 [-0.97, 0.20]
Kanowski 1996	74	-2.20 (5.20)	77	-0.80 (6.00)		22.1	-0.25 [-0.57, 0.07]
Le Bars 1997	95	-0.50 (5.40)	102	1.40 (5.60)		28.6	-0.34 [-0.63, -0.06]
Subtotal (95% CI)	405		310			100.0	-0.17 [-0.32, -0.02]
Test for heterogeneity chi-square=5.06 df=4 p=0.2811							
Test for overall effect=-2.20 p=0.03							



Bleeds associated with ginkgo use

Patient age	Ginkgo use	Other therapy	Bleed	ref
70	1 week	Aspirin	Iris	1
78	2 mos	Warfarin	Intracerebral	2
33	2 years	None	Subdural	3
61	6 mos	None	Subarachnoid	4

1. NEJM 336:1108,1997
2. Neurology 50:1933-1934,1998
3. Lancet 352:36-37,1998
4. Neurology 46:1775-1776,1996

Non-linear Regression

K_i Values

Isoform	Type of Inhibition	Ki (μg/ml)	α
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**

Mohutsky et al. Am J Ther 2006;13:24-31

Tolbutamide Human Study (CYP 2C9 probe)

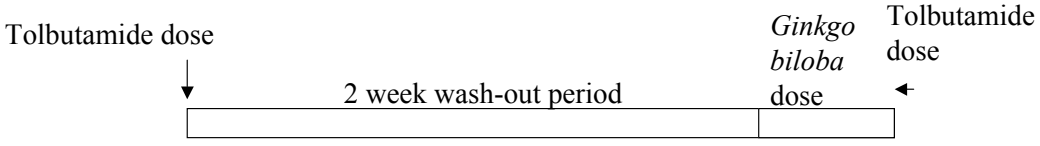
-6 Subjects (3 males, 3 females)

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

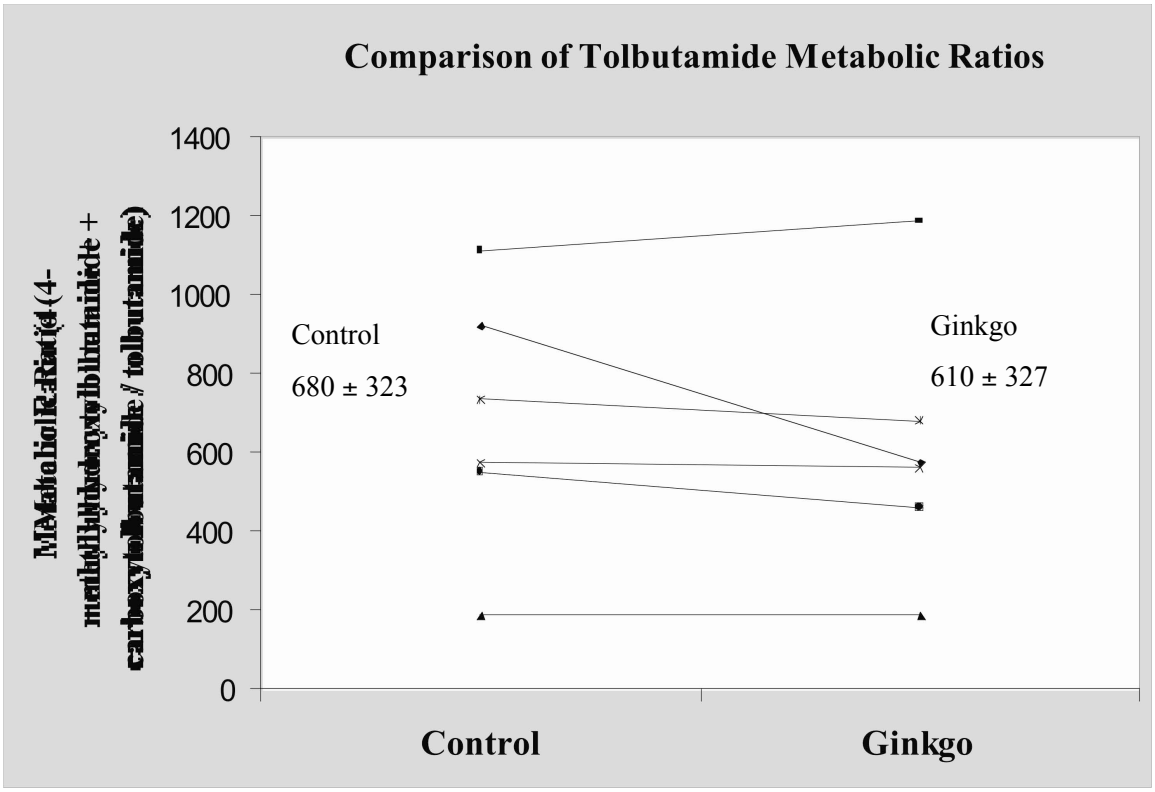
-Followed by a 2 week wash-out period

-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)



Mohutsky et al. Am J Ther 2006;13:24-31



Mohutsky et al. Am J Ther 2006;13:24-31

Diclofenac-Ginkgo Interaction (CYP 2C9 probe)

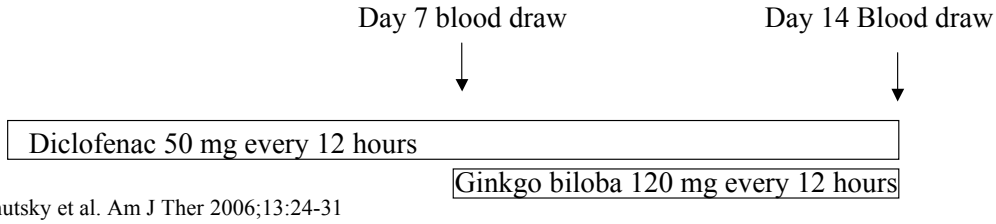
12 healthy non-smoking subjects were recruited (8 males 4 females)

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

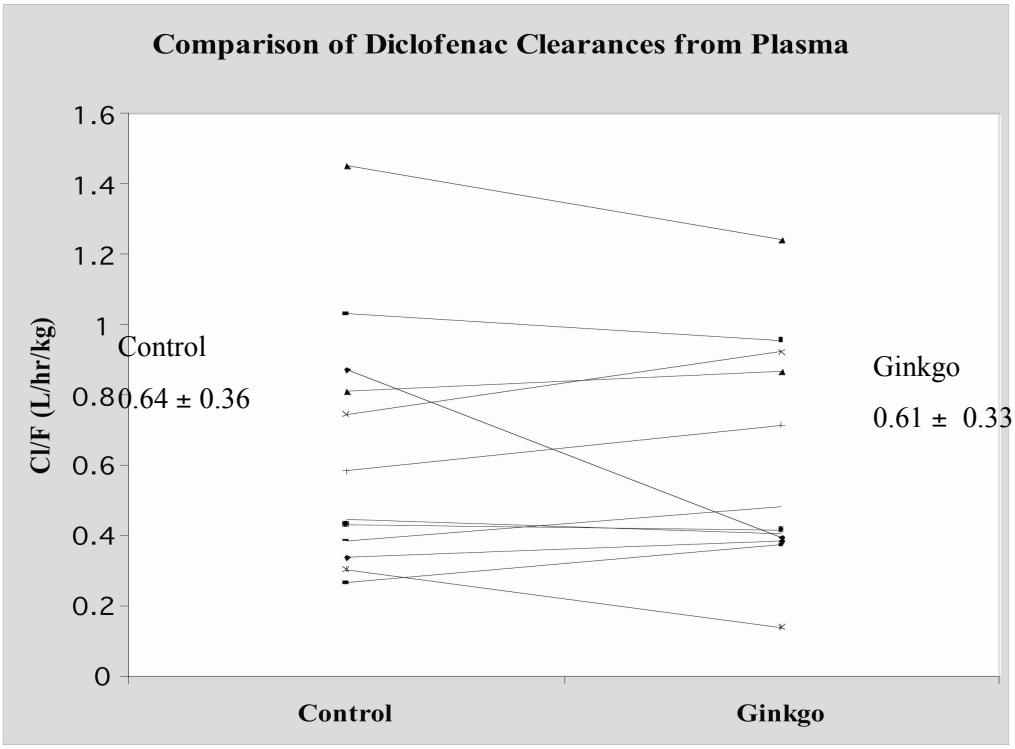
On day 8, 120 mg of *Ginkgo biloba* extract was added to the diclofenac regimen.

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



Mohutsky et al. Am J Ther 2006;13:24-31



Mohutsky et al. Am J Ther 2006;13:24-31

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**

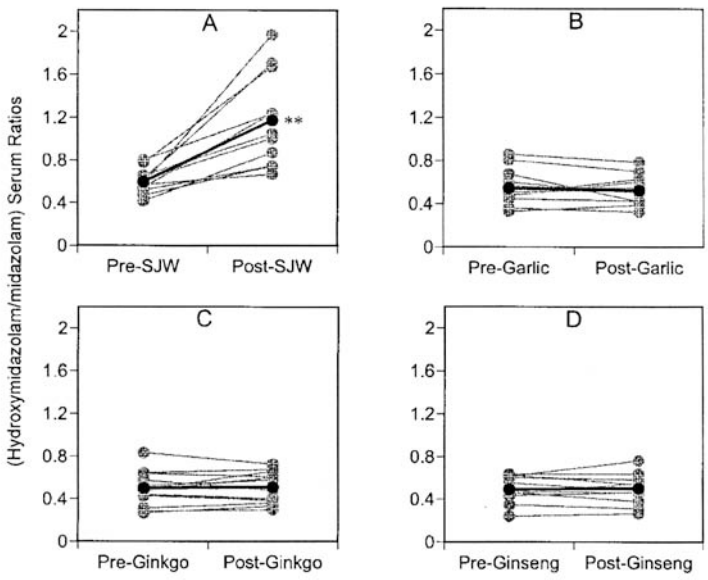
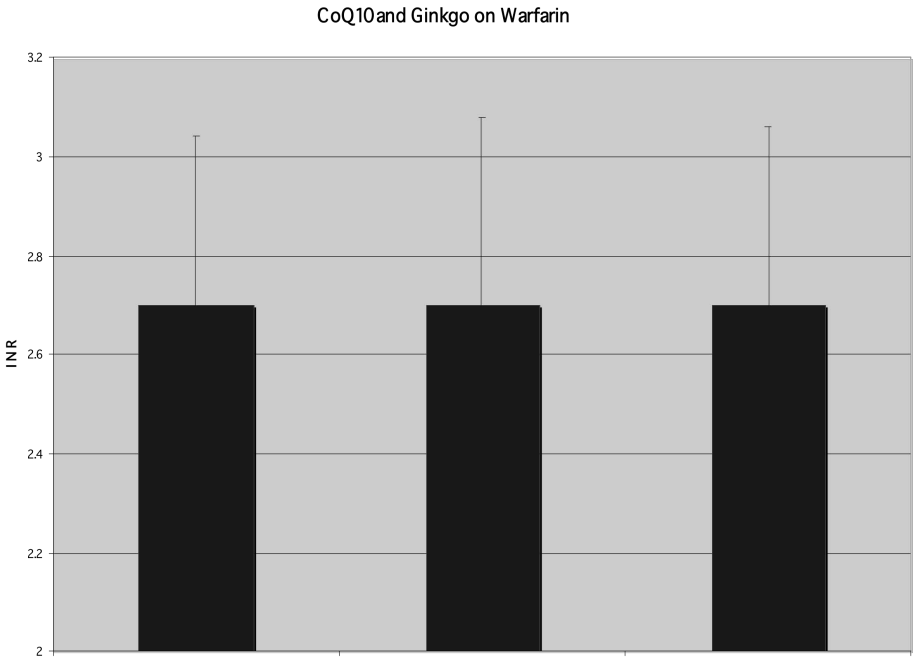
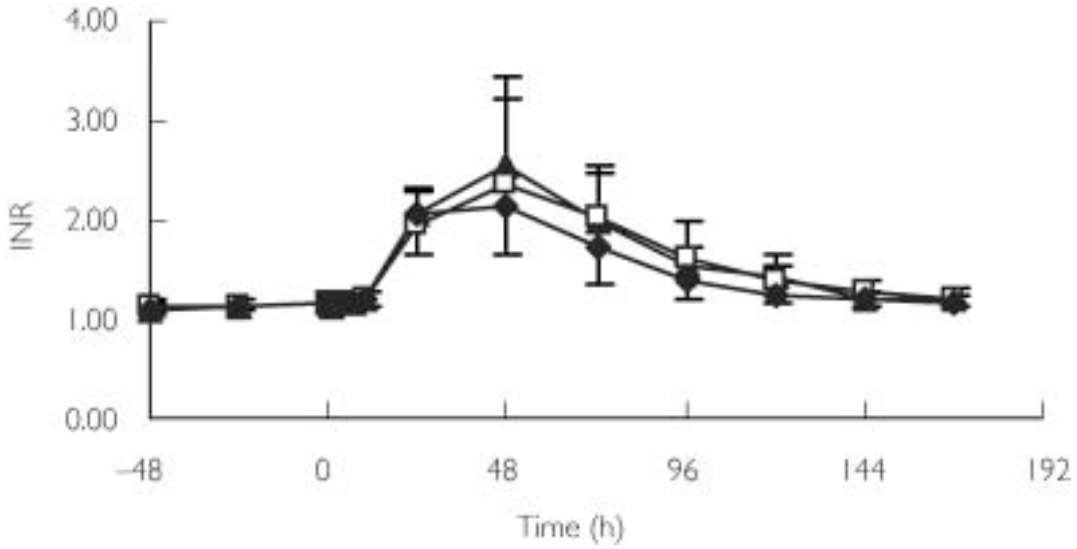


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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

Gurley et al. Clin Pharmacol Ther 2002;72:276-287 n=12 (CYP 3A4) ginkgo-Wild Oats Markets (24% flavone glycosides, 6% ginkgolides)(analyzed)



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_{50}) values for commercial plant extracts and tinctures against cytochrom P450 3A4.

Commercial Extract/Tincture	IC_{50} Relative Concentration (% Full Strength)	Regression Line: Slope	Constant	N	R^2	p (1 tail)	Ranked Inhibition
Arctium lappa	> 100	18.88 (14.66, 23.10)	9.53 (425, 14.81)	21	0.822	0.000	16
Echinacea angustifolia/purpurea (1:1)	6.73[a] (10.09, 4.75)	35.15 (32.40, 37.90)	20.91 (17.47, 24.34)	21	0.974	0.000	10
Echinacea angustifolia roots	1.05[b] (2.19, 0.64)	24.85 (20.17, 29.52)	49.43 (43.12, 55.73)	18	0.888	0.000	4
Echinacea purpurea roots	3.99[a] (7.74, 2.39)	34.81 (30.34, 39.29)	29.07 (23.04, 35.11)	18	0.944	0.000	7
Echinacea purpurea tops	8.56[a] (13.05, 5.95)	43.75 (40.40, 47.10)	9.218 (4.93, 13.51)	20	0.977	0.000	14
Eleutherococcus senticosus	NI	7.78 (–2.25, 17.81)	5.74 (–7.77, 19.24)	17	0.154	0.060	NI
Ginkgo biloba	4.75[a] (12.82, 2.57)	69.38 (53.09, 85.68)	3.04 (–8.82, 14.90)	12	0.900	0.000	8
Glycyrrhiza glabra	1.83 (4.29, 1.11)	43.95 (32.68, 55.22)	38.45 (29.33, 47.57)	12	0.883	0.000	6
Harpagophytum procumbens	NI	0.14 (–3.71, 3.99)	25.23 (20.41, 30.05)	21	0.000	0.470	NI
Hydrastis canadensis	0.03[b] (0.02, 0.04)	15.02 (11.05, 18.99)	72.80 (68.80, 76.80)	16	0.824	0.000	1
Hypericum perforatum	0.04[b] (0.03, 0.05)	17.33 (12.38, 22.27)	74.01 (69.78, 78.25)	14	0.829	0.000	2
Matricaria chamomilla	1.48[a] (1.97, 1.16)	21.64 (19.90, 23.32)	46.32 (44.13, 48.51)	21	0.972	0.000	5
Panax quinquefolius	NI	–3.96 (–12.12, 4.20)	20.53 (9.54, 31.52)	17	0.067	0.842	NI
Prunus serotina	6.90[a] (10.45, 4.89)	77.47 (7020, 84.74)	–14.97 (–21.53, –8.41)	15	0.976	0.000	12
Sambucus canadensis	6.82[a] (24.41, 2.97)	26.24 (20.73, 31.75)	28.12 (21.23, 35.01)	21	0.840	0.000	11
Serenoa repens	7.41[a] (14.39, 4.41)	38.93 (34.17, 43.68)	16.15 (10.43, 21.87)	20	0.943	0.000	13
Silybum marianum	5.22[a] (7,94, 3.67)	38.45 (35.20, 41.69)	22.39 (18.33, 26.45)	21	0.970	0.000	9
Tanacetum parthenium	> 100	22.14 (15.82, 28.46)	–6.19 (–14.57, 2.18)	18	0.775	0.000	16
Trifolium pratense	1.05[b] (1.80, 0.72)	29.38 (24.00, 34.76)	49.42 (43.89, 54.96)	17	0.900	0.000	4
Uncaria tomentosa	0.79[b] (1.56, 0.66)	80.28 (31.81, 128.75)	58.37 (43.88, 72.86)	4	0.962	0.010	3
Valeriana officinalis	9.56[a] (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.
[a] value was achieved within the tested range.
[b] value was achieved by extrapolating the regression line beyond the tested range.
NI – non inhibitory within the tested range.

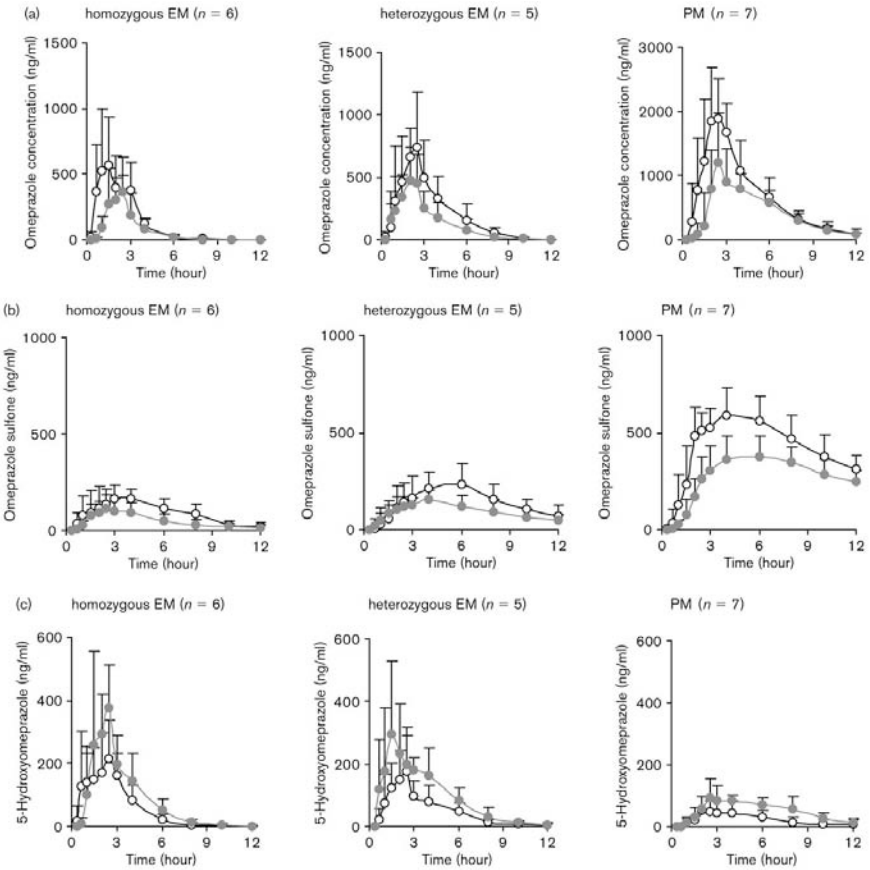
Ginkgo/Drug Interactions
other studies

- Markowitz et al. J Clin Psycopharmacol 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 2006;13:24-31. 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

(shaded circle is ginkgo, open circle is baseline)

140mg BID x 12d



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Aruna, D. & Naidu, M. U. R.
Pharmacodynamic interaction studies of *Ginkgo biloba* with cilostazol and clopidogrel in healthy human subjects.
British Journal of Clinical Pharmacology **63** (3), 333-338.
doi: 10.1111/j.1365-2125.2006.02759.x

Table 3
Bleeding time (s)

	Mean	SD	SE	95% CI (lower)	95% CI (upper)
Baseline, *n* = 80	107	33	4	99	115
Cilostazol 100 mg (*n* = 10)	150*	42	14	118	182
Cilostazol 200 mg (*n* = 10)	138**	30	10	115	161
Ginkgo 120 mg (*n* = 10)	144*	28	9	124	164
Ginkgo 240 mg (*n* = 10)	133*	30	10	110	157
Clopidogrel 75 mg (*n* = 10)	141	59	21	91	190
Clopidogrel 150 mg (*n* = 10)	159*	56	20	113	206
Clopidogrel + Ginkgo (*n* = 10)	148*	78	28	83	213
Cilostazol + Ginkgo (*n* = 10)	211*†	70	25	153	270

*P < 0.05 compared with baseline. **P < 0.001 compared with baseline. †P < 0.05 compared with 150 mg of clopidogrel.

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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; pharmacodynamic interaction with "blood thinners" so avoid or close monitoring needed**
- **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- maybe helps**
- **Osteoposis-some evidence for help**
- **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 have unknown effects on estrogen receptor positive breast cancer but may stimulate growth**
- **Soy may slightly inhibit protate cancer growth**
- **Soy-Cardiovascular Benefits Favorable effects on cholesterol balance; "heart healthy"**
- **Isoflavones inhibit CYP3A4 in vitro**

6β-hydroxycortisol/cortisol ratio (CYP 3A4)

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

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

Soy

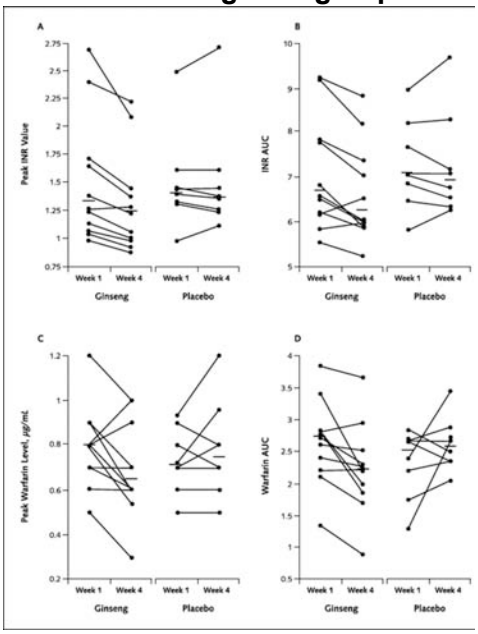
- **Efficacy: increased soy ingestion may decrease hot flashes and other postmenopausal symptoms; cardiovascular benefits as well.**
- **Safety: good but use in breast cancer may be risky**
- **Drug interactions: not with with tamoxifen but effect on CYP3A4 is unlikely**
- **Product selection: soy or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

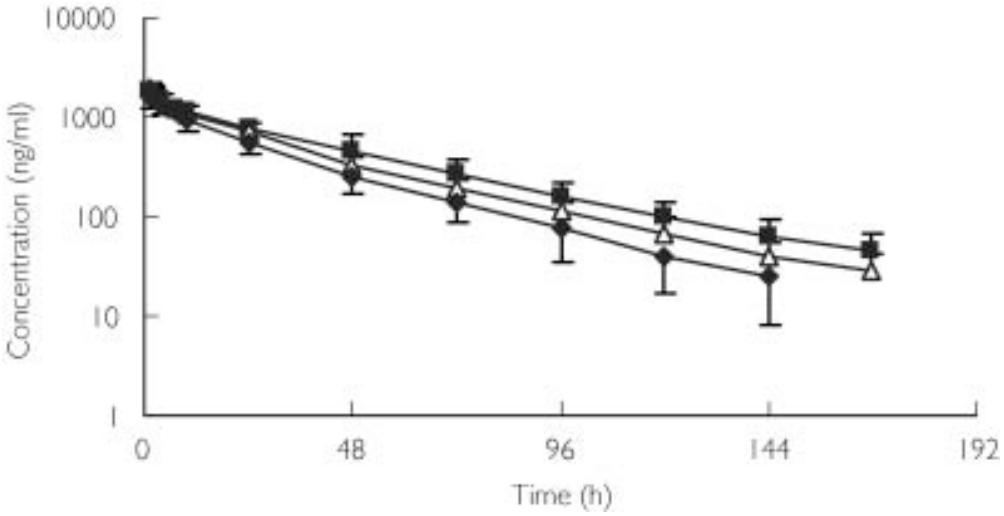
Changes in individual peak international normalized ratio (INR), INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC in weeks 1 and 4 in American ginseng or placebo groups



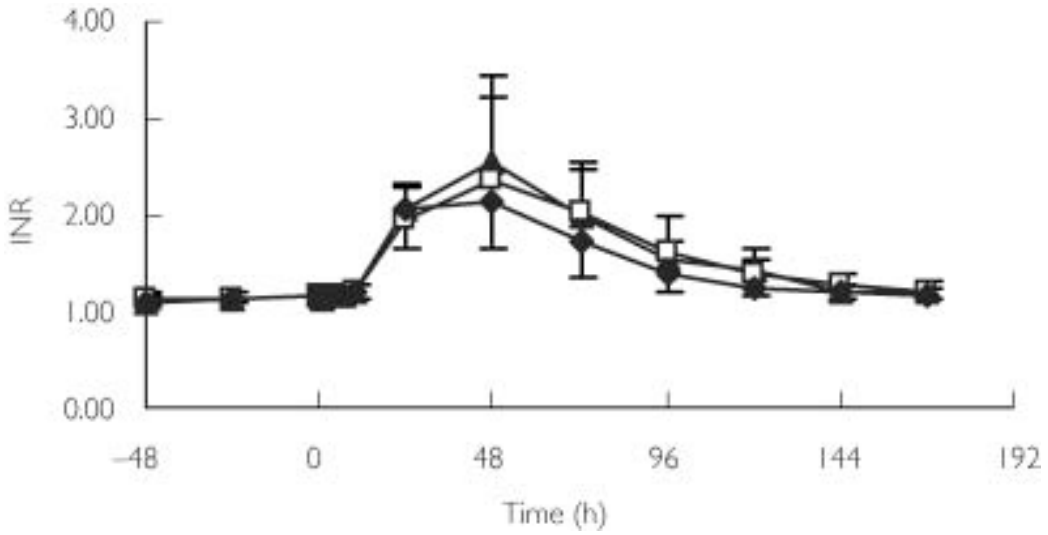
Yuan, C.-S. et. al. Ann Intern Med 2004;141:23-27

5mg warfarin for 3d before and after 1g/d ginseng (50mg/d ginsenosides) American ginseng (Panax quinquifolius) 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)

6β-hydroxycortisol/cortisol ratio (CYP 3A4)

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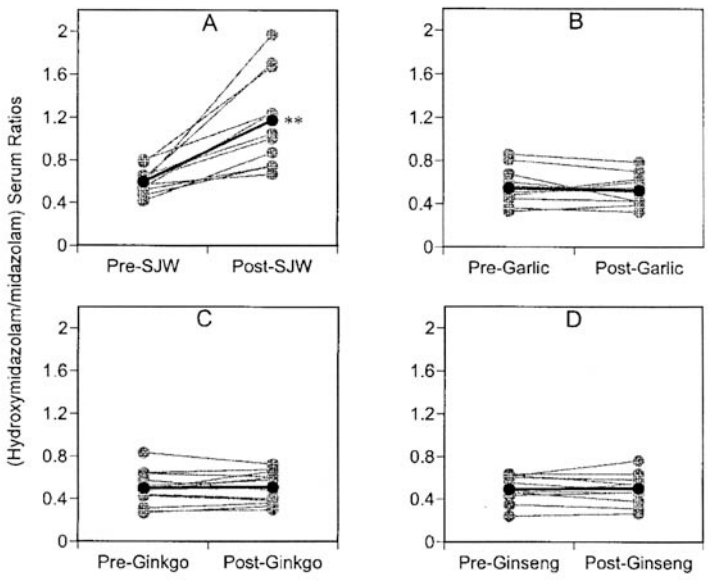


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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

Gurley et al. Clin Phamcol 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;

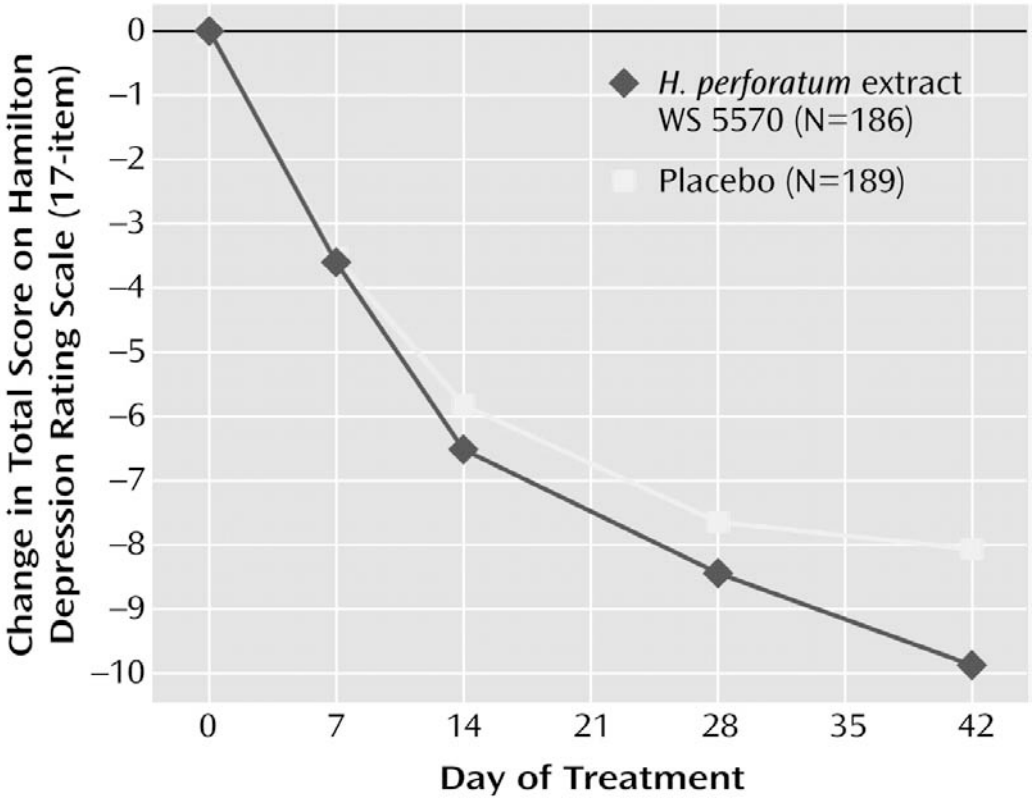
Drug interactions: no apparent induction of CYP 3A4 but induction of 2C9 (warfarin) with Am ginseng (Panax quinquifolius) but maybe not Panax ginseng. May precipitate hypoglycemia with insulin or oral hypoglycermics.

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

Questions remaining include:

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

300mg; 1 TID

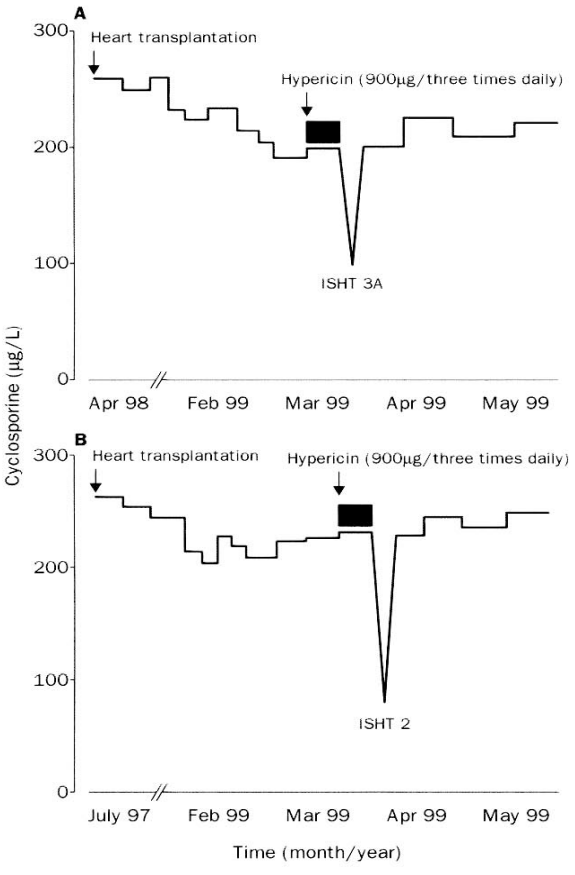


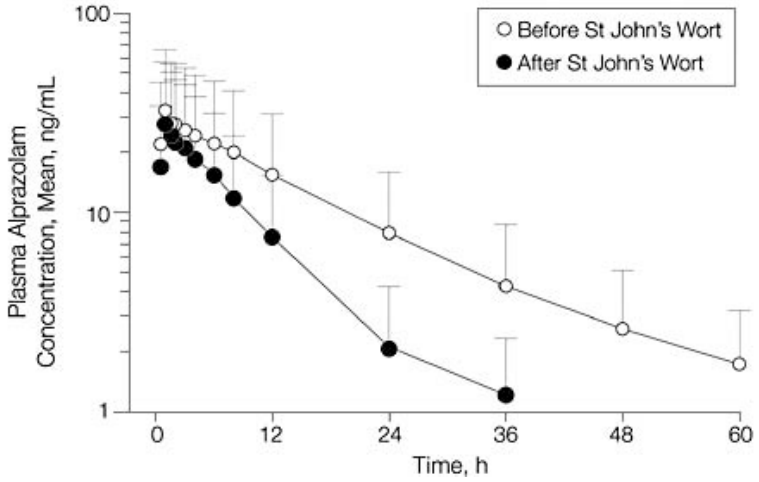
Lecrubier et al. Am J Psychiatry 2002;159:1361 n=375

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 senario as case 1.

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





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

CYP 3A4

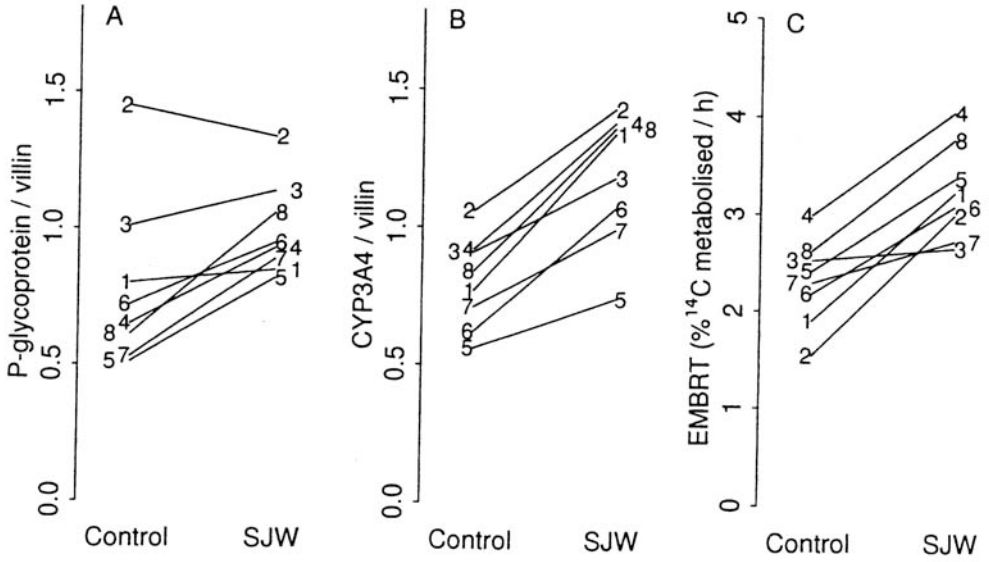


Fig 3. Comparison of intestinal P-glycoprotein/MDR1 and CYP3A4/villin expression ratios and erythromycin breath tests in humans. Eight healthy male volunteers were treated with St John's wort extract for 14 days. Duodenal biopsy specimens (**A, B**) and ^{14}C-erythromycin breath tests (EMBRT; **C**) 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 or 1-2% 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) (pharmacodynamic effect)
  - 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"

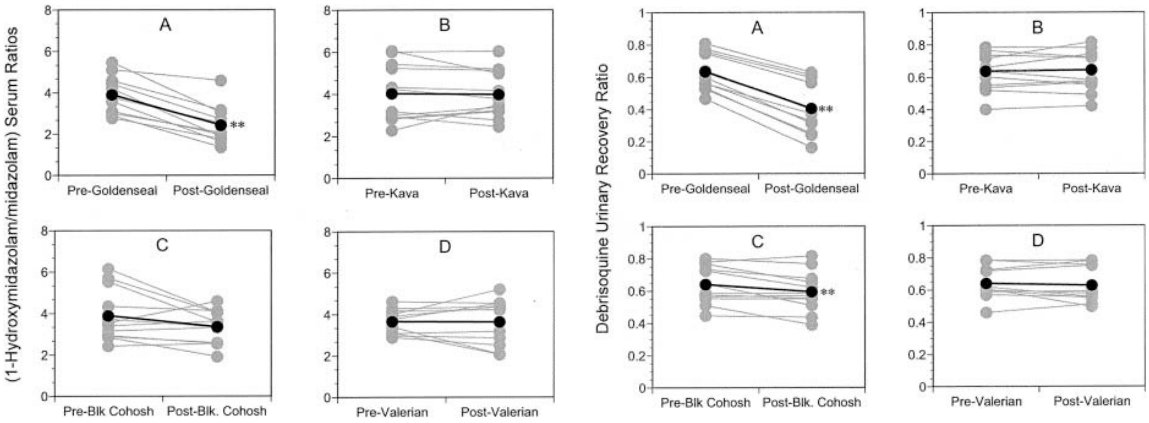
Ann Int Med 125:940-941,1996

- 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 of AQUEOUS extract; reasonable evidence for efficacy for mild to moderate anxiety.**
  - **Safety: hepatotoxicity associated with alcoholic extracts, rash with long use,**
  - **Drug interactions: not with other anxiolytics or sedatives or liver toxic drugs (acetaminophen)**
  - **Advice: don't take Kava until hepatotoxicity risk is sorted out!**
  - **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 panucula	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
Garlic -	case reports of increased surgical blood loss
St. John's wort -	induces P450 enzymes and Pgp leading to reduced drug action
Evening primrose oil -	human study showed 40% increase in bleed time but no other reports
Borage seed oil -	same as evening primrose oil
Vitamin E -	doses >1200 i.u./d can increase bleed time
Cranberry juice	case reports of increased INR (salicylic acid? CYP 2C9 inhibition?) but in vivo study showed no change in flurbiprofen (CYP 2C9 substrate) in vivo
Kava -	liver toxicity could increase warfarin effect
Lycium barbarum	case 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 quinquifolius)
Green tea -	case report of decreased INR with warfarin but huge amount

Table 4a Significant Risk of CAM-drug Adverse Interaction

Potential Event	Mechanism[a]	Number[b]	Occurrences[c]
n=294 with CAM plus conventional med combinations with significant risk			
Risk of bleeds			
Aspirin			
Garlic[23;25-27]	PD	147	214
Ginkgo[24;28]	PD	102	127
Warfarin			
Garlic[25-27]	PD	13	16
Ginkgo[29]	PD	7	7
Ginseng[32;33]	PK[d]	3	3
Ticlopidine			
Garlic[23;25-27]	PD	4	6
Ginkgo[24;30;31;54]	PD	2	3
Pentoxifylline			
Ginkgo[24;30;31]	PD	3	3
Total	281 (5.6%)		380

Table 4b
Significant Risk of CAM-drug Adverse Interaction

Potential Event	Mechanism[a]	Number[b]	Occurrences[c]
Decreased drug benefit			
Digoxin			
St. John's wort[21;34]	PK[e]	2	2
Felodipine			
St. John's wort[21;52]	PK[f]	2	2
Tamoxifen			
Garlic[41]	PK[f]	4	5
Other			
Furosemide/Aloe[55]	PD	3	3
Thyroid/Kelp[56]	PD	2	2
Grand Total		294	393
Garlic interactions:		168	241
Ginkgo interactions:		114	140
Garlic plus ginkgo:		282 (96%)	381 (97%)

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

- Ginger
- Valerian
- Milk thistle
- Saw palmetto
- Black cohosh
- CoQ10
- glucosamine

Glucosamine and type 2 diabetics

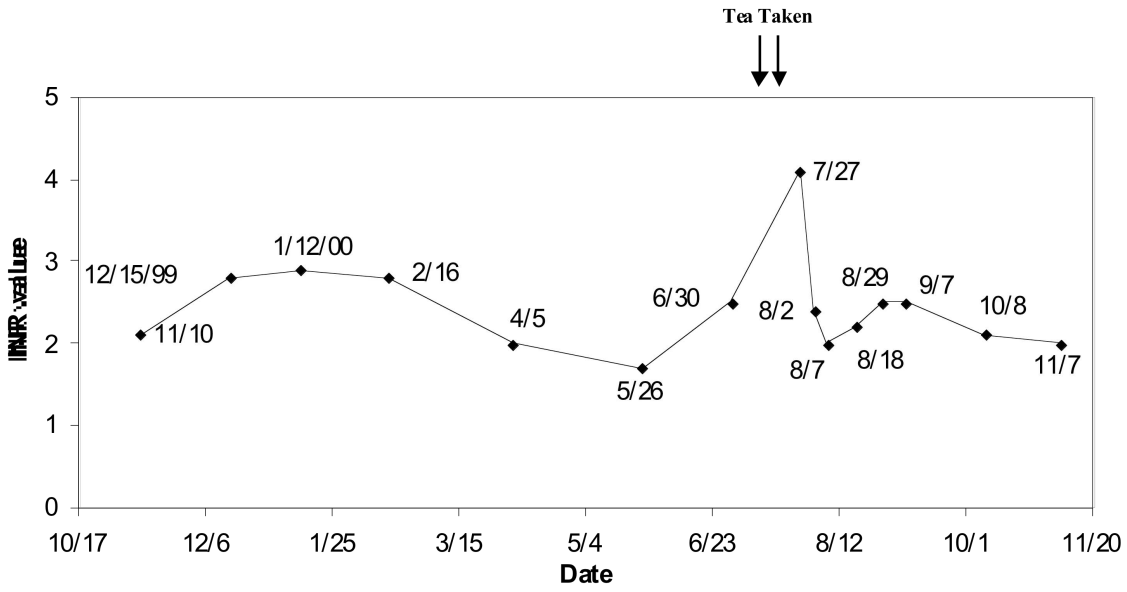
- Recent study examined the effect of 90d of Cosamin DS or placebo on glycosylated hemoglobin levels in type 2 diabetics. N=38 result: no effect
- Arch Intern Med 2003;163:1587-90

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

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

HerbalGram 2005;66:63

- **Product**
  - 1. garlic — product dependent Inhibition of 3A4; 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.

Gary Elmer's assessment of herbal/drug interaction potential (in rank order of significance)(11/13/06)

1. St. John's wort – induces CYP and Pgp; don't take with other drugs unless the drugs have a large therapeutic range and are not "life saving" drugs
2. American ginseng (Panax quinquefolius) – induces CYP2C9; not with warfarin, tolbutamide and other 2C9 substrates
3. Goldenseal – induces CYP3A4 and 2D6. This herbal is not recommended due to lack of efficacy proof and potential interactions
4. Garlic and ginkgo – don't take with antiplatelet adhesion drugs or aspirin or with warfarin (risk of bleeds); this is a pharmacodynamic effect
5. Ginkgo may induce CYP2C19 so may lower 2C9 substrate
6. Echinacea may induce CYP1A2 so may lower 1A2 substrates

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

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**