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;40:1617-24.

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?

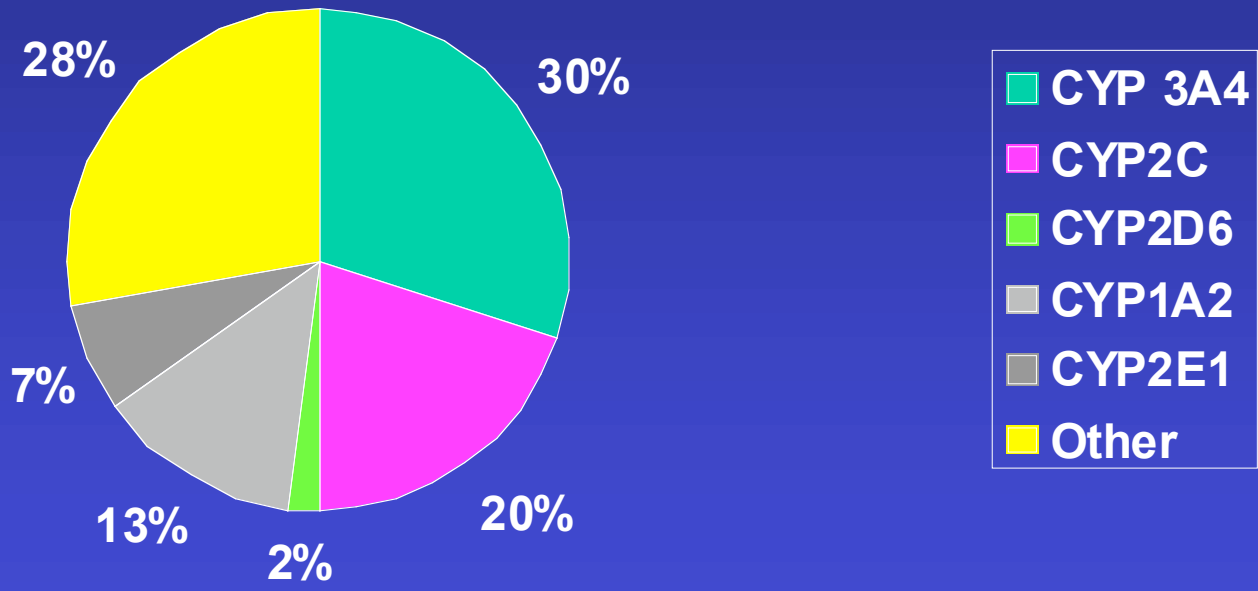
Evaluation of Herbal/Drug Interactions

- 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. ginkgo and microsomal studies showing inhibition of CYP2C9
- 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?
- Randomized, placebo controlled human volunteer study with appropriate n?

Relative Levels of P450 isozymes in human liver



Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	M $	% change	rank in 2006
1. soy	25	-17	1
2. cranberry	24	+24	3
3. garlic	20	-13	2
4. ginkgo	18	+12	5
5. saw palmetto	17	- 6	4
6. echinacea	16	- 9	6
7. black cohosh	09	-0.5	8
8. milk thistle	09	-0.4	7
9. ginseng	08	+ 3	10
10. St. John's wort	08	- 6	9
11. Green tea	05	- 7	11
12. Evening primrose oil	04	- 9	12
13. valerian	03	- 9	13
14. Horny goat weed	02	- 2	14

Red indicates risk for drug interactions

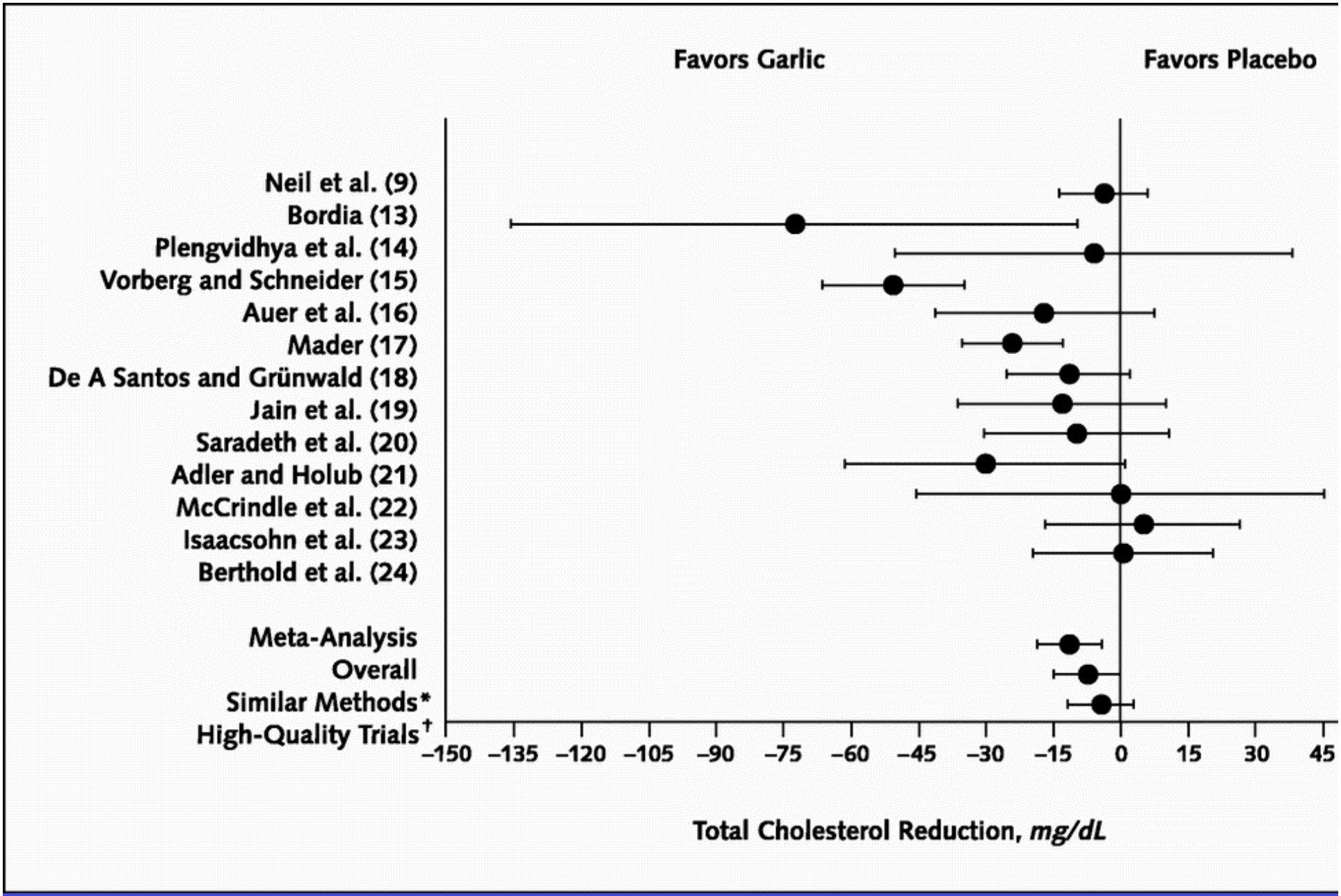
Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	M $	% change	rank in 2004
15. bilberry	02	- 9	15
16. grape seed	02	- 9	16
17. Yohimbe	01	-15	17
18. red clover	01	-13	18
19. Horse chestnut seed	01	-21	19
20. ginger	0.7	-20	20
Total (all herbs)	268	+7.6	

Red indicates potential risk for drug interactions

Note: total herbal sales are estimated at $4.7 billion

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



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

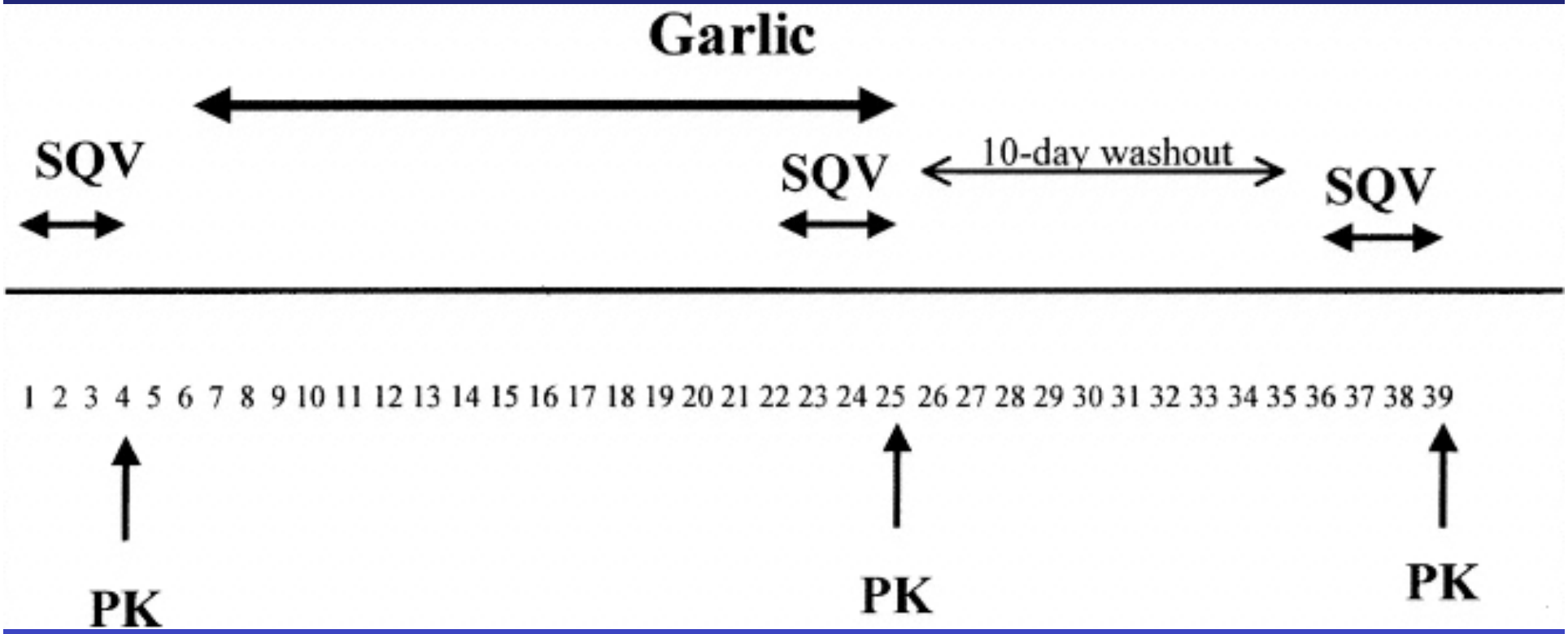
bleeding time of 11.5 min (normal = 3 min)

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

Other reports:

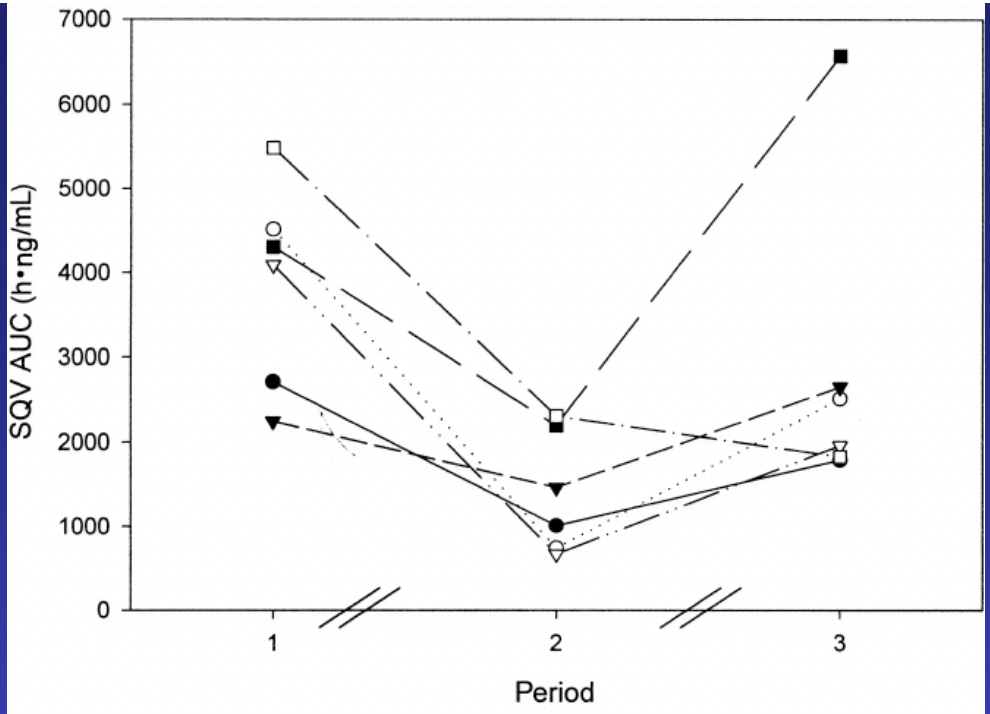
Garlic and TURP bleeding (German et al. Br J Urology 1995;76:518).

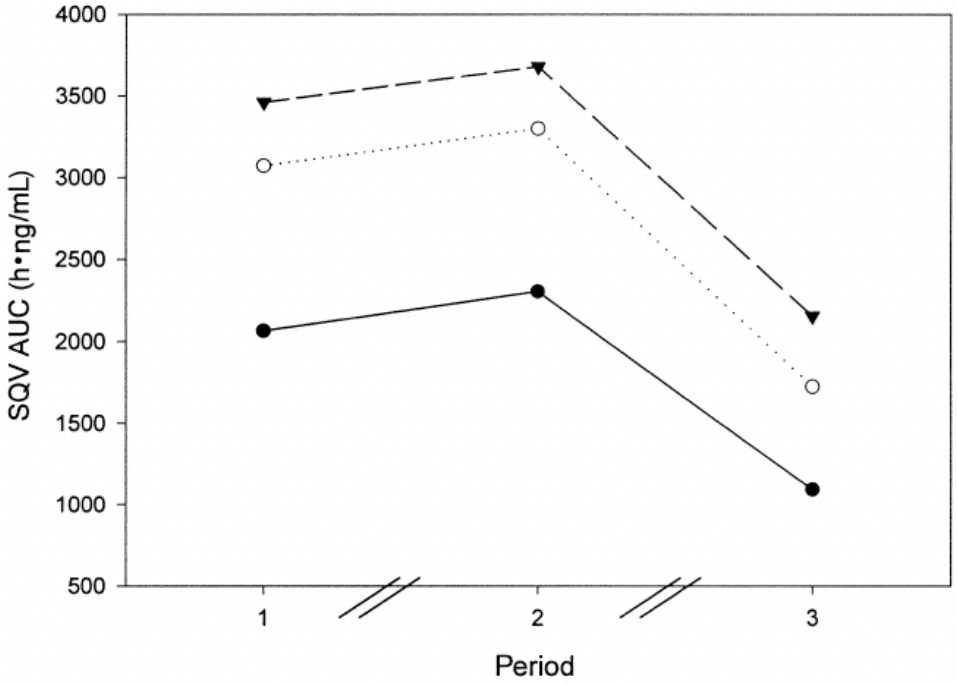
Garlic and surgery bleeding (Burnham BE; Plastic Reconstr Surgery 1995;95:213).



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)





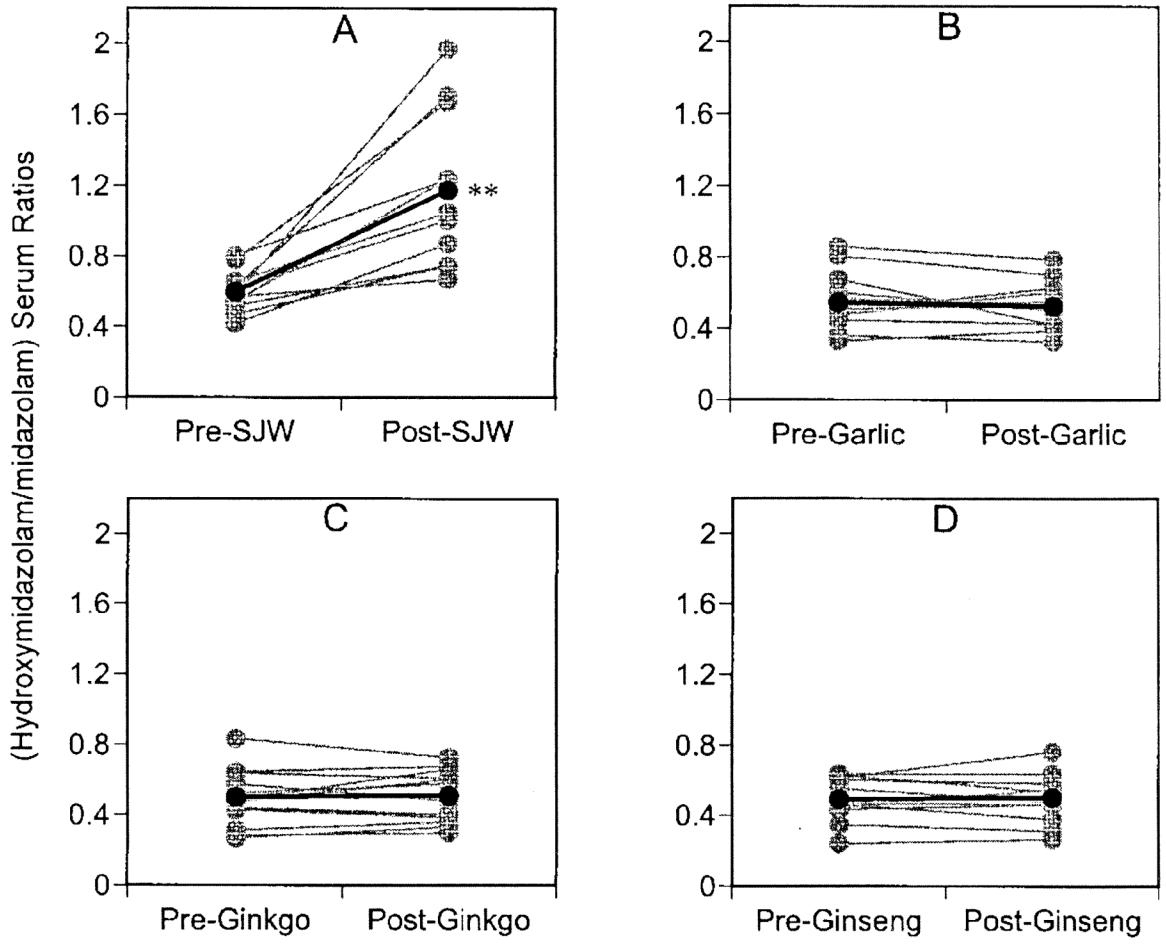
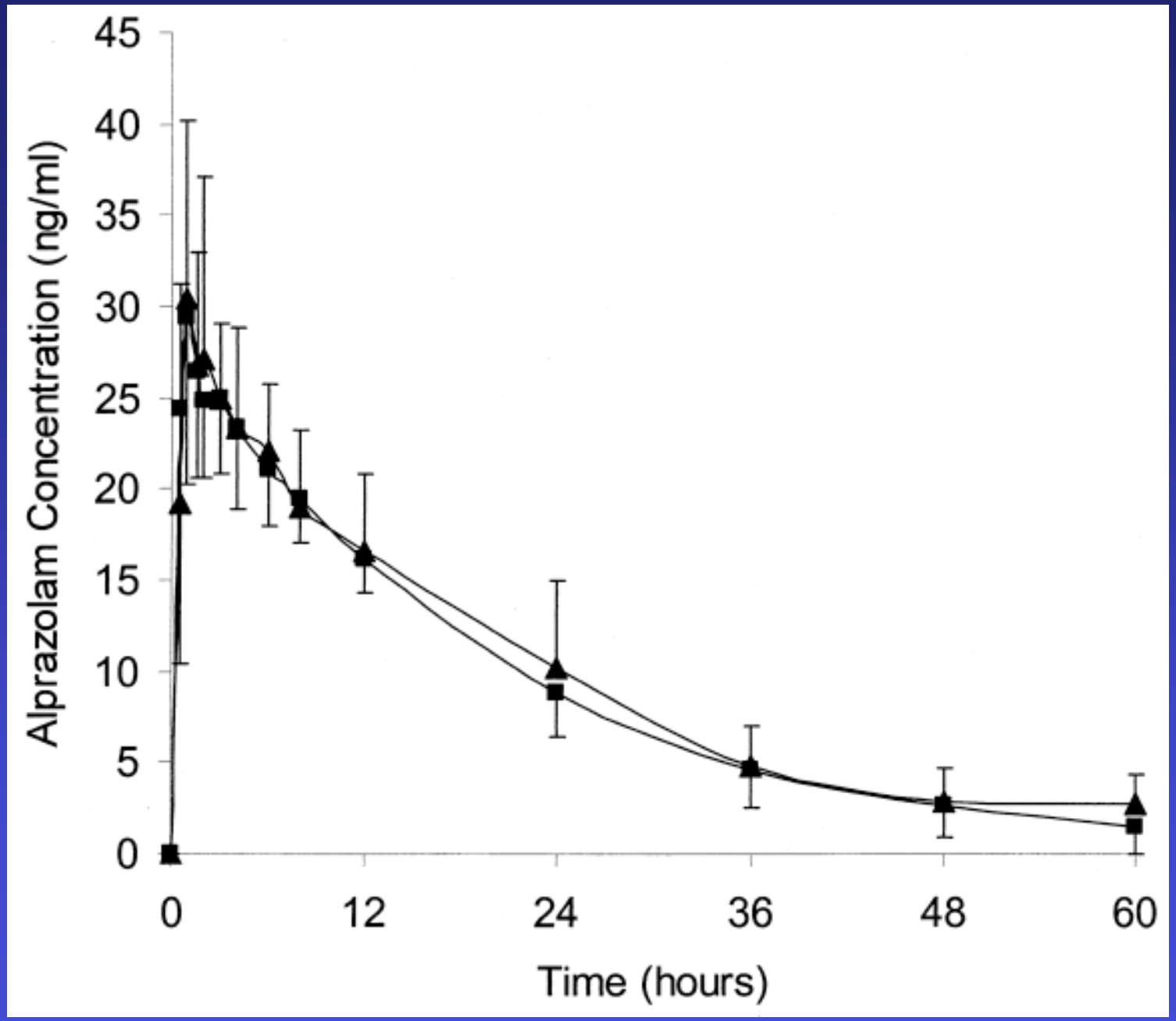


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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

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



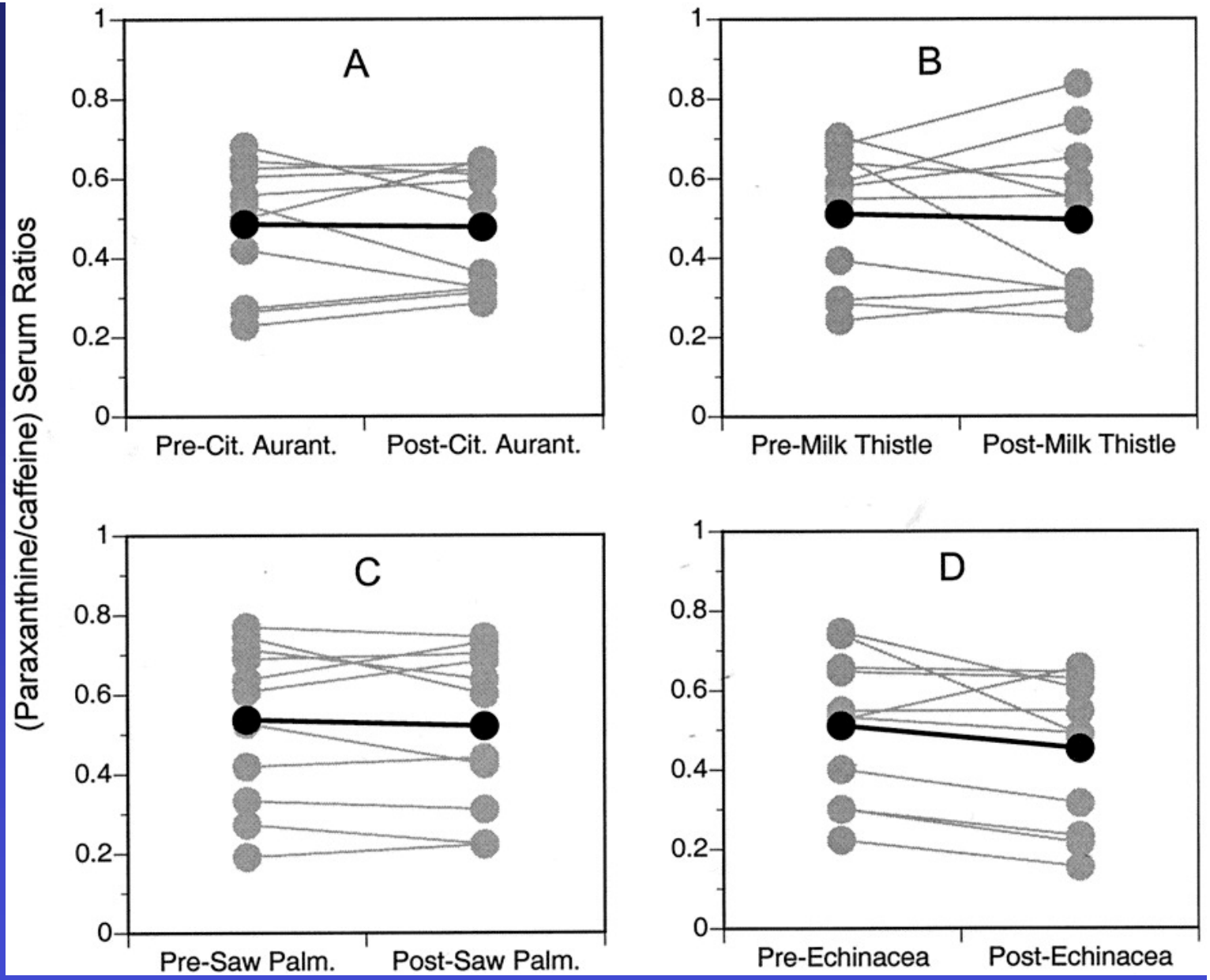
Markowitz et al. Clin Pharmacol Ther 2003;74:170, n=14, 3X600mg for 14d (Kwai)

Garlic and warfarin

- Another 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.

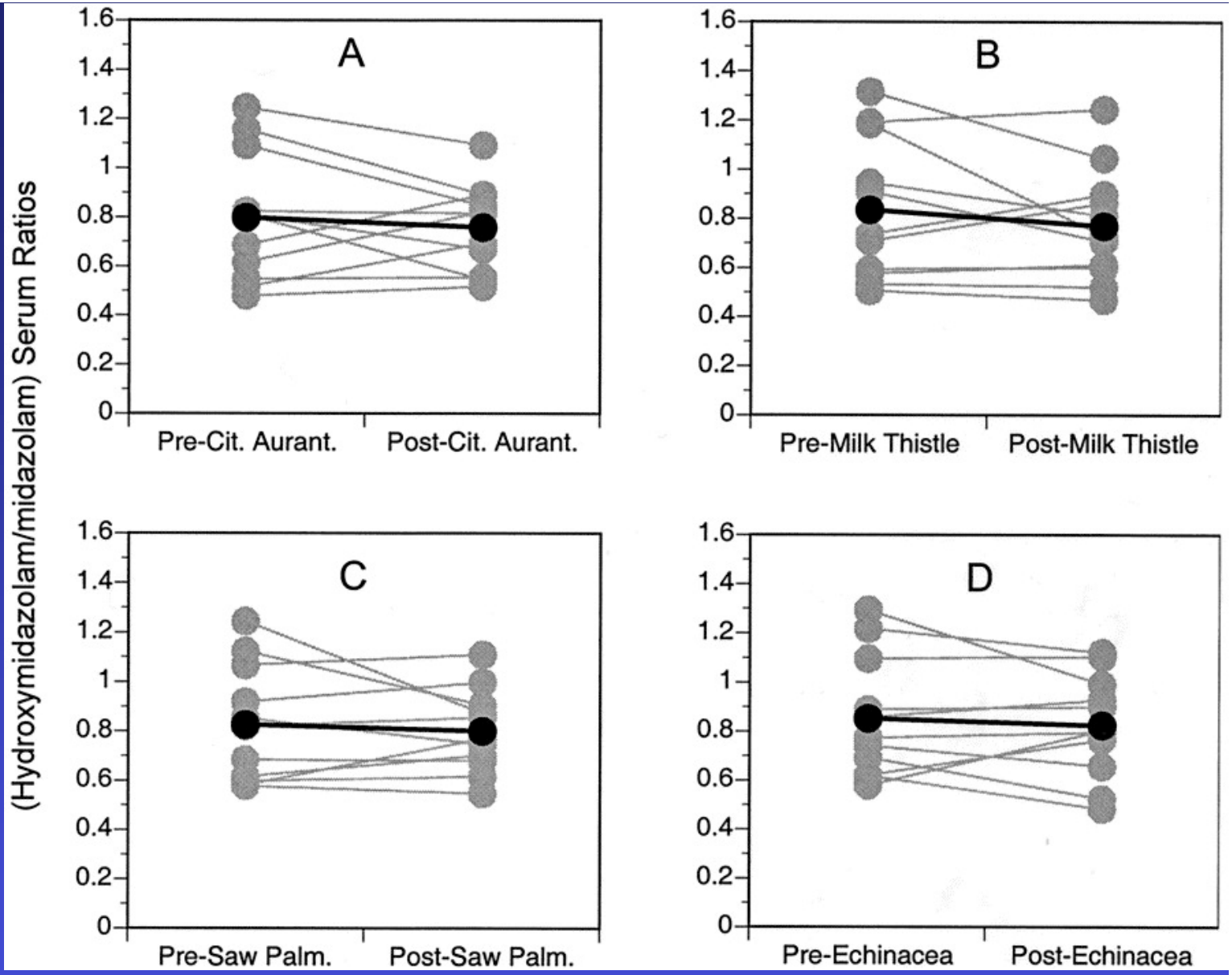
Garlic summary

- **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) (maybe raw garlic induces 3A4 but not extracts??)
- **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.

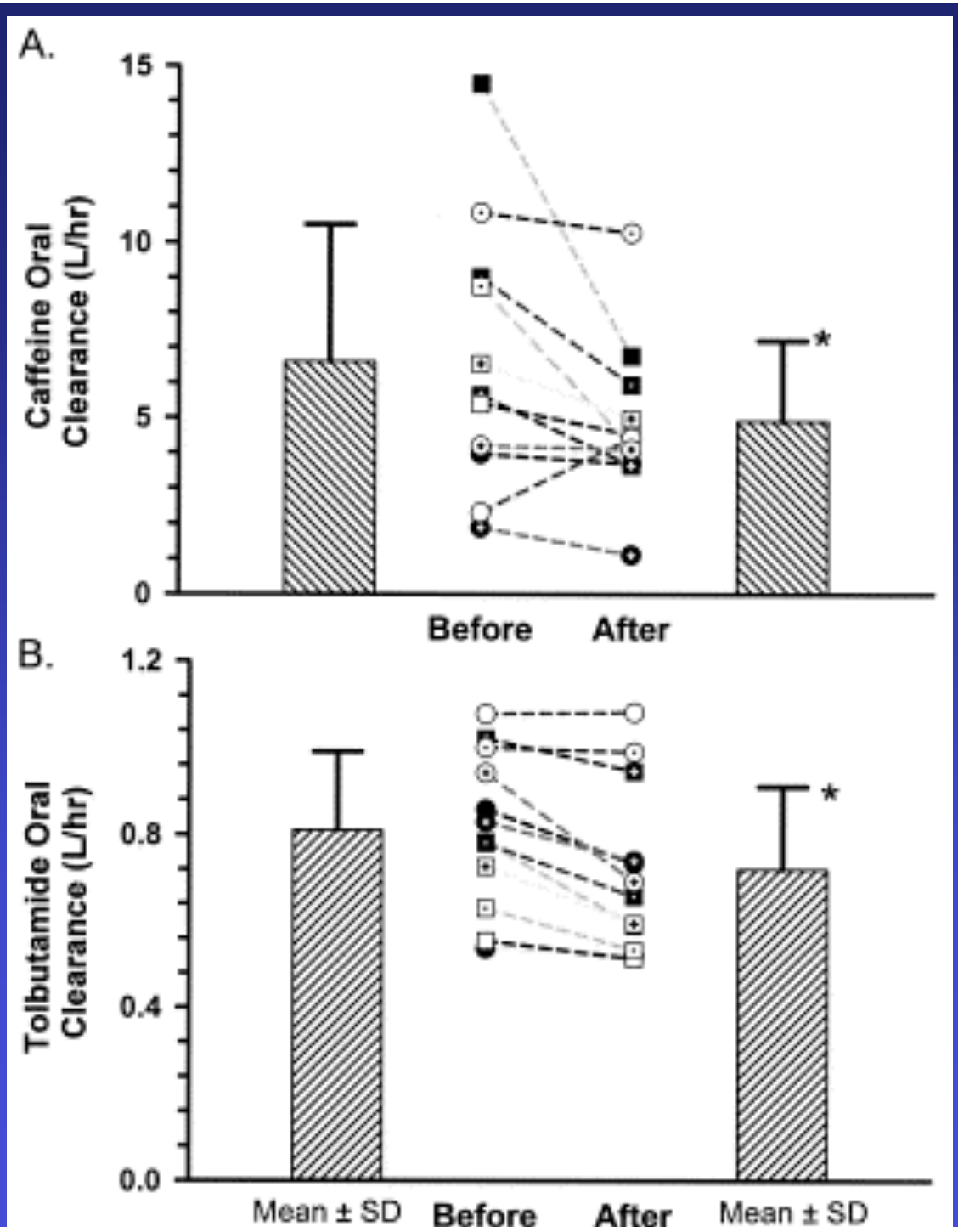
800mg BID for 30d (Wild Oats Market)(analyzed)

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)



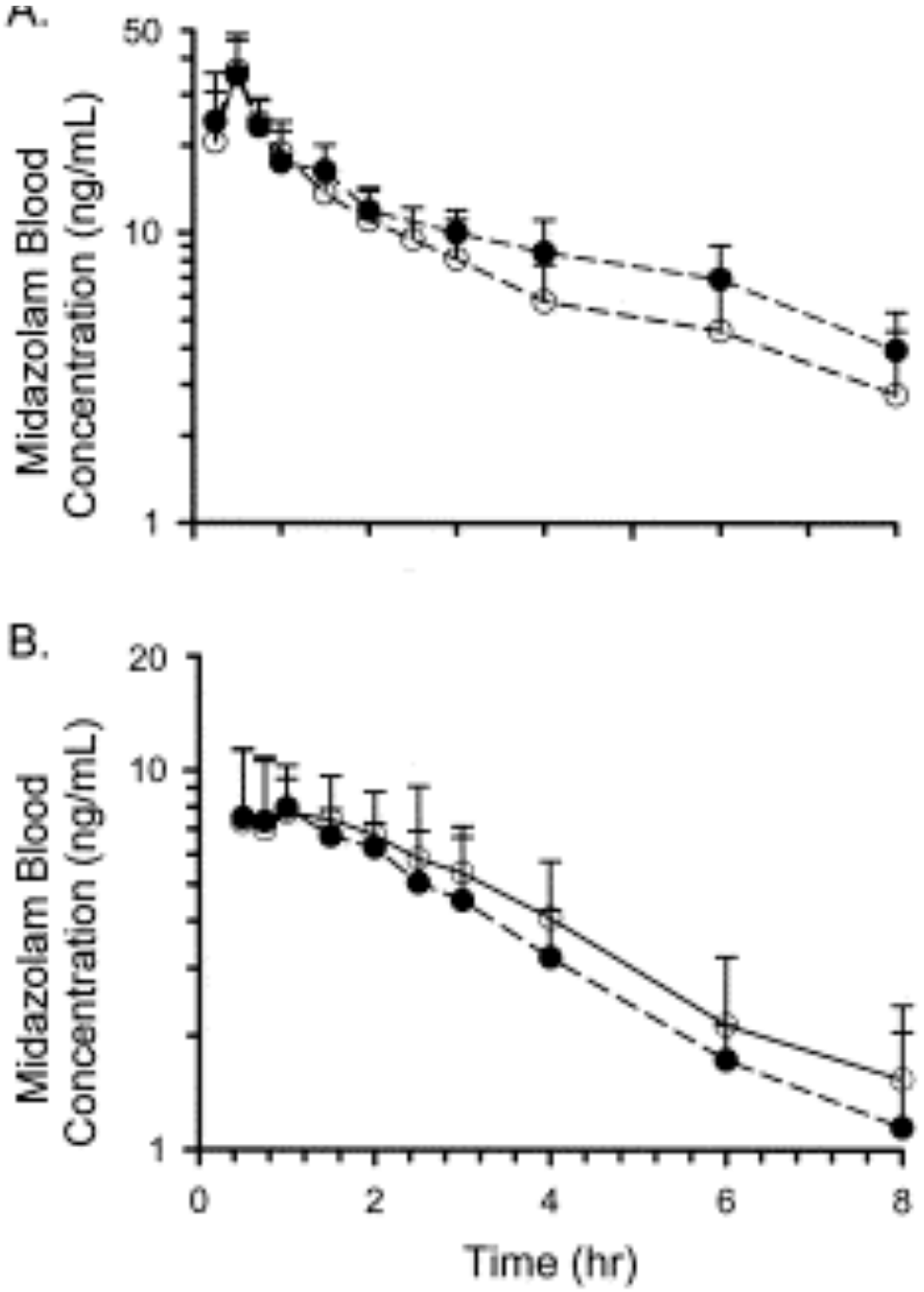
Gorski et al. Clin Pharmacol Ther 2004;75:89-100

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 not 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 so clinical significance unclear; effect on 2C9 is considered minor**
  - **Product selection: want standardized extract containing about 4% phenolics. *(GWE recommends Echinamide in 2008)***
  - **Dose: about 250mg QID for treatment**
  - **Questions remaining**
    - ***Which product? Tincture? Tablets? Root extract? Flowering tops? Pressed juice? E. purpurea? E. augusifolia? 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.

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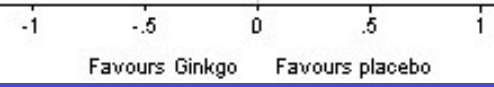
*This statement has not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

†Le Bars et al "A Placebo-Controlled, Double-blind, Randomized Trial of an Extract of Ginkgo Biloba for Dementia" Journal of the American Medical Association 278 (16) 1327-1332. 1997

††Itil, T.M. and Martorano, D. Psychopharmacology Bulletin 31:147-158. 1995

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)

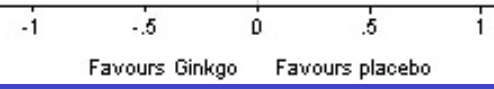
Study	Ginkgo N	Mean (SD)	Placebo N	Mean (SD)	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 Ginkgo biloba dose less than 200mg/day special extract						
Brautigam 1998	130	-21.69 (2.49)	67	-21.64 (2.95)	35.4	-0.02 [-0.31, 0.28]
Dongen 2000	40	-0.70 (4.40)	44	-1.20 (3.80)	16.8	0.12 [-0.31, 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						



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)

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							
Le Bars 1997	96	-0.30 (5.10)	104	2.10 (6.40)		100.0	-0.41 [-0.69, -0.13]
Subtotal (95% CI)	96		104			100.0	-0.41 [-0.69, -0.13]

Test for heterogeneity chi-square=0.00 df=0
Test for overall effect=-2.88 p=0.004



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

Ginkgo-warfarin interactions?

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)

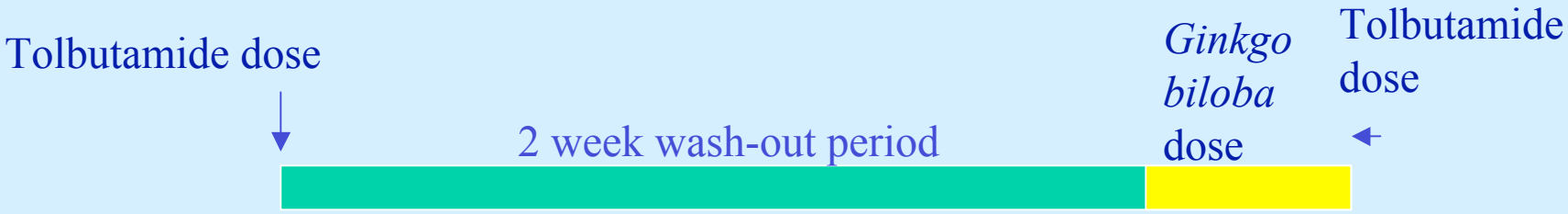
- **6 Subjects (3 males, 3 females)**

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

-Followed by a 2 week wash-out period

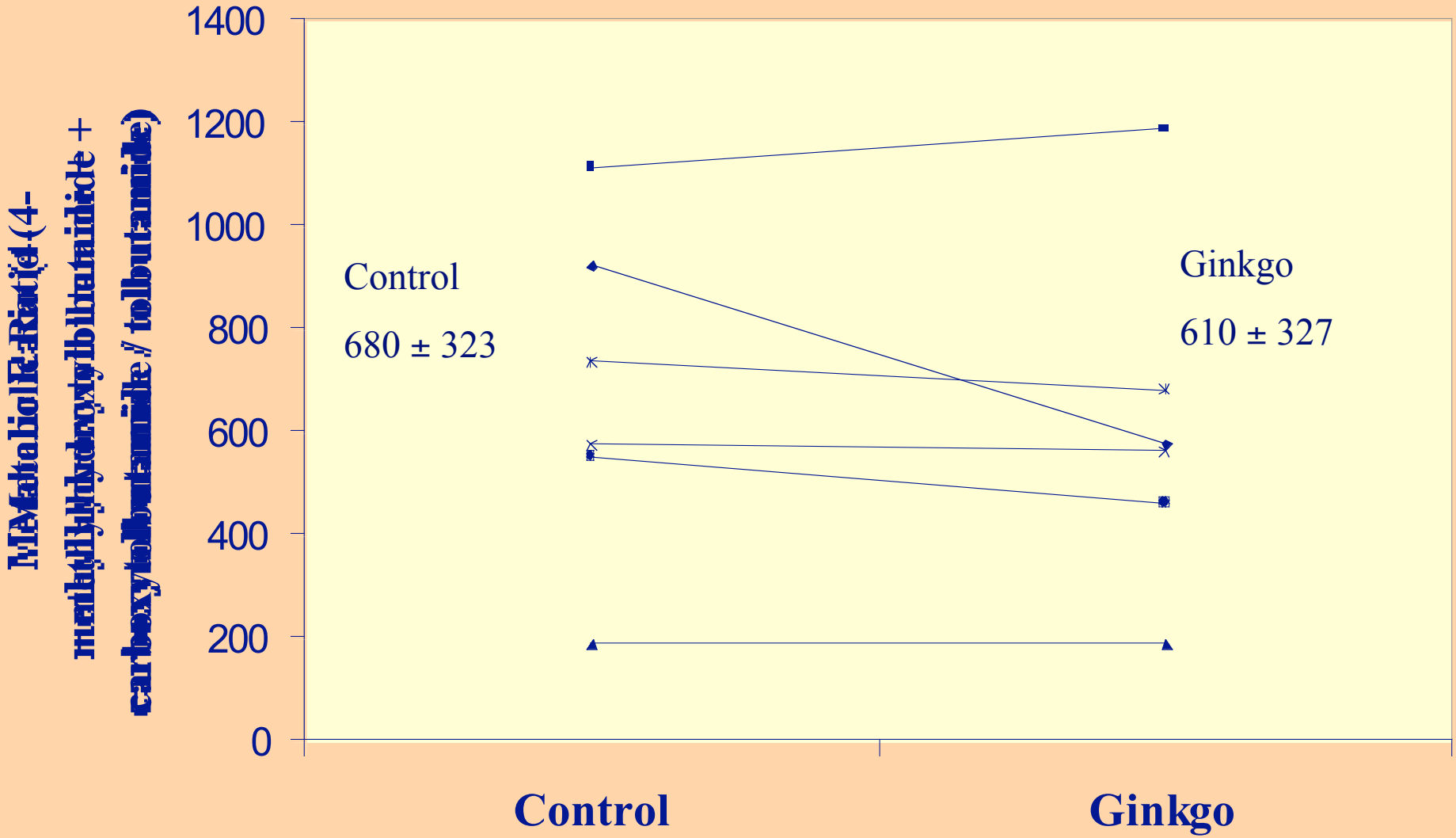
-Subjects then ingested two 60mg *Ginkgo biloba* extract tablets 2 times a day for 3 days

-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

Comparison of Tolbutamide Metabolic Ratios



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

Diclofenac-Ginkgo Interaction (CYP 2C9 probe)

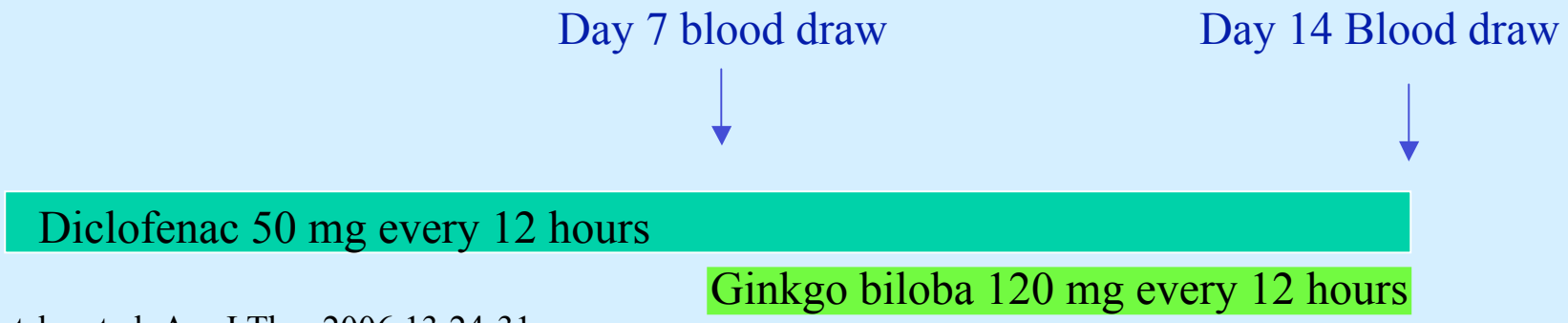
12 healthy non-smoking subjects were recruited (8 males 4 females)

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.

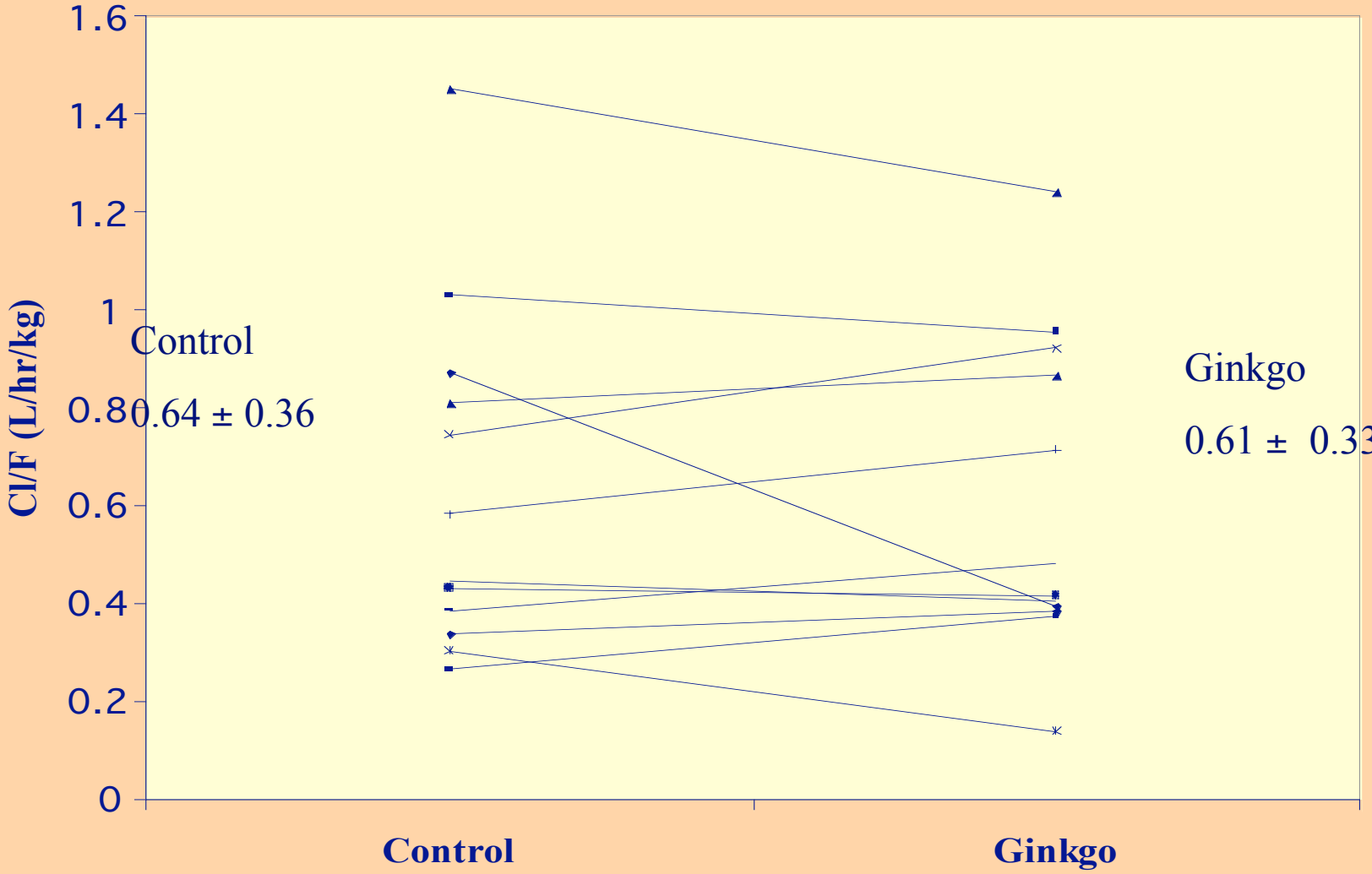
On days 7 and 14 plasma collected at times (0, 0.5, 1,2,4,6,8,10, and 12 hrs)

12 hour urine collected



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

Comparison of Diclofenac Clearances from Plasma



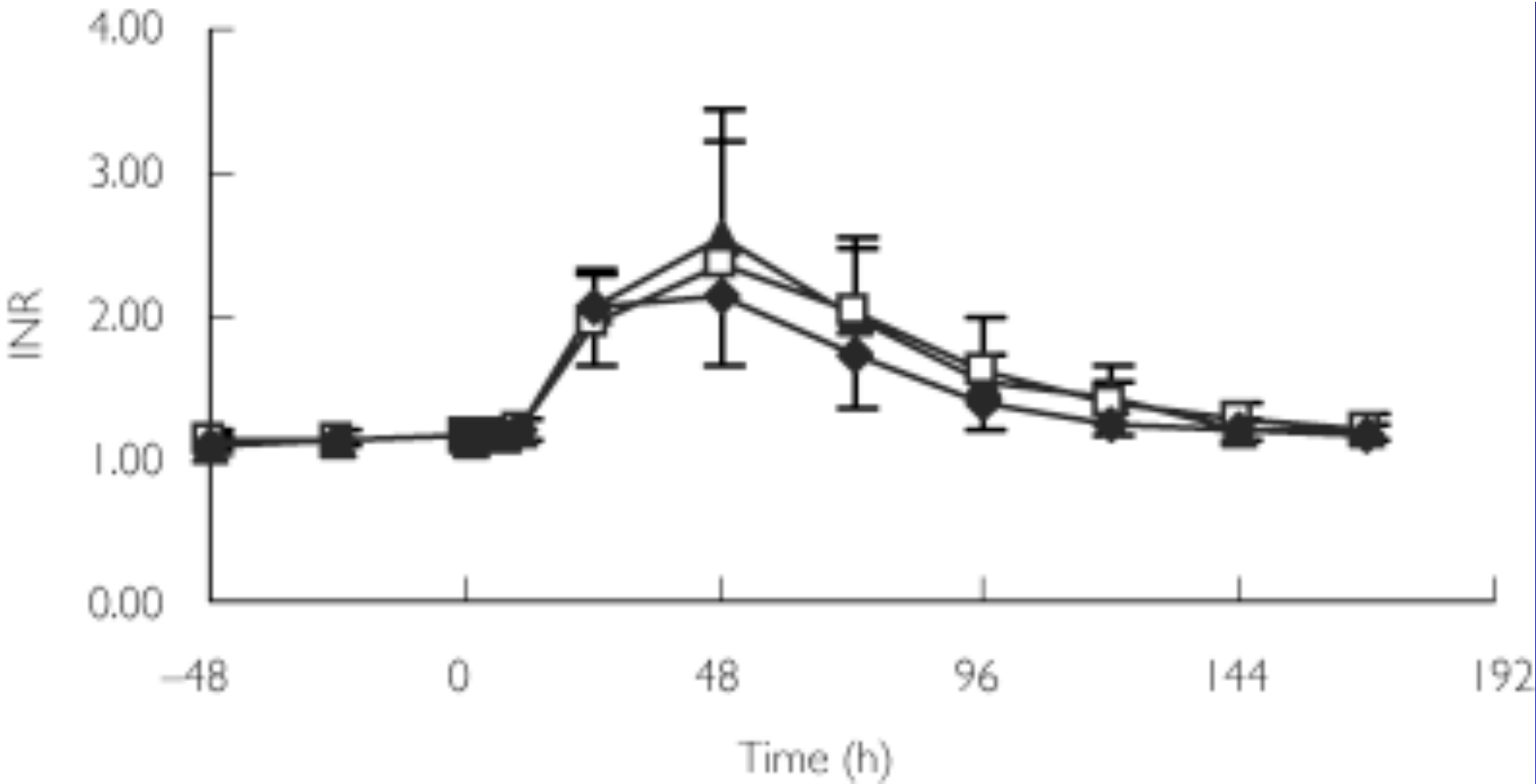
Mohutsky et al. Am J Ther 2006;13:24-31

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)

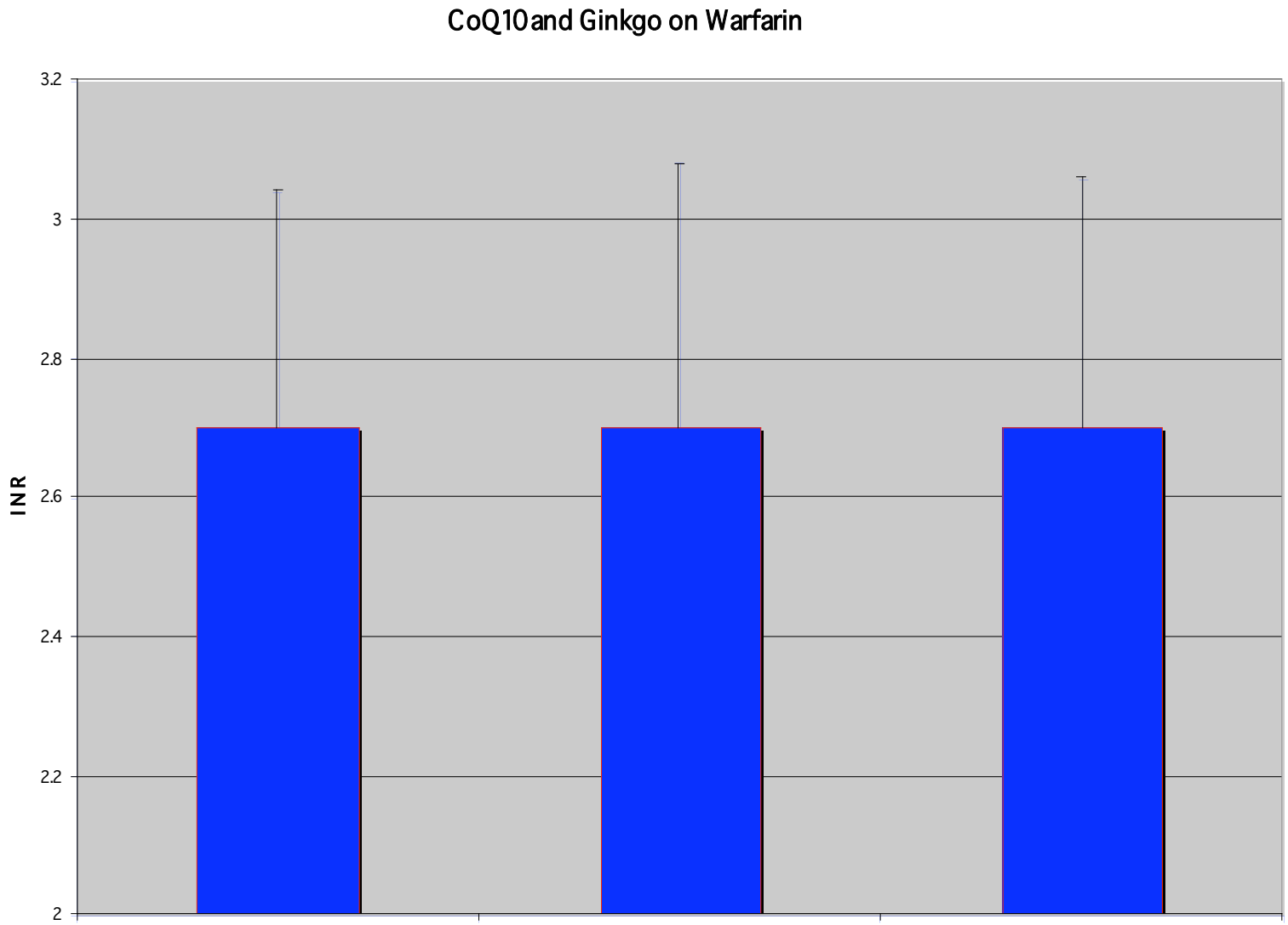
- No difference was seen between the clearances of the two arms of the study (diclofenac alone and diclofenac + Ginkgo)

- Ginkgo extract does not appear to interact with CYP2C9 substrates in humans



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

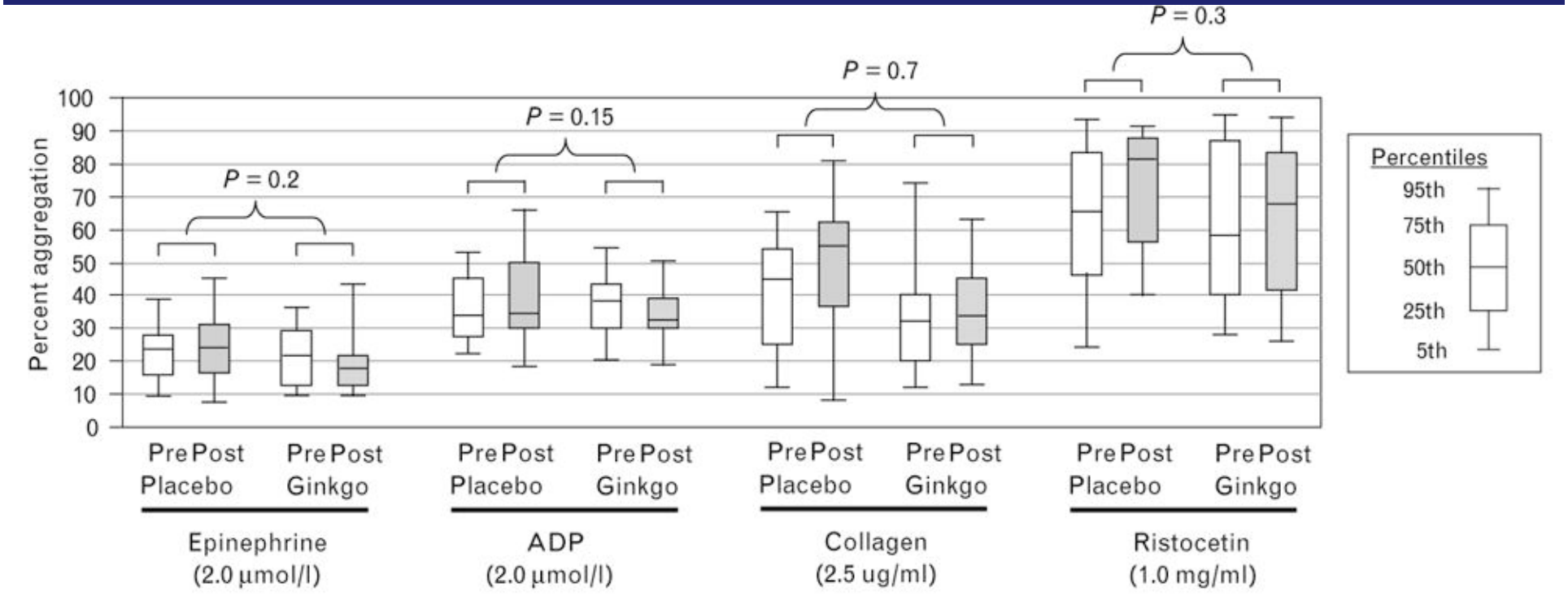


Engelsen et al, Thromb Haemost 2002;87:1075-6. N=21, double blind, crossover. Rx=1 month with 2 week washout. Dose of warfarin did not change.

Ginkgo and coagulation and pharmacodynamic interactions with antiplatelet adhesion inhibitors

Coagulation in healthy adults (in absence of other drugs)

Kohler et al. Blood Coagul Fibrinolysis. 2004;15:303-9. (company study). No effect on coagulation parameters in healthy adults after 7d of EGb761 120mg/d. n=50.



Platelet aggregation. Box-and-whiskers plots of percentage platelet aggregation for placebo ($n = 21$) and ginkgo ($n = 23$) groups for prestudy (white shading) and end-study (gray shading), using four agonists. Analysis of variance with two treatments and two time points. *P* values presented are for the treatment × time interaction. Statistical significance was not found with any of the four agonists.

Gardner et al. Blood Coagul Fibrinolysis 2007;18:287-293

Aspirin 325mg/d for two weeks prior to 4 weeks Ginkgold 300mg/d

Close this Window

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.*

Back to top

Bleed times; single dose n=80 cilostazol=Pletel clopidrogrel= Plavix

Ginkgo: Potential Interactions with other drugs (not involving blood coagulation)

- CYP3A4
  - 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
  - Study by Gurley and study by Ushida (see slides)
- Pgp (p-glycoprotein)
  - Mauro et al. Am J Ther 2003;10:247-251. No effect of multiple dosing of ginkgo on digoxin (Pgp) pharmacokinetics. N=8 crossover
- 2C19
  - Yin et al. Pharmacogenetics 2004;14:841-850. Small induction of 2C19 mediated hydroxylation of omeprazole. 140mg BID x 12d

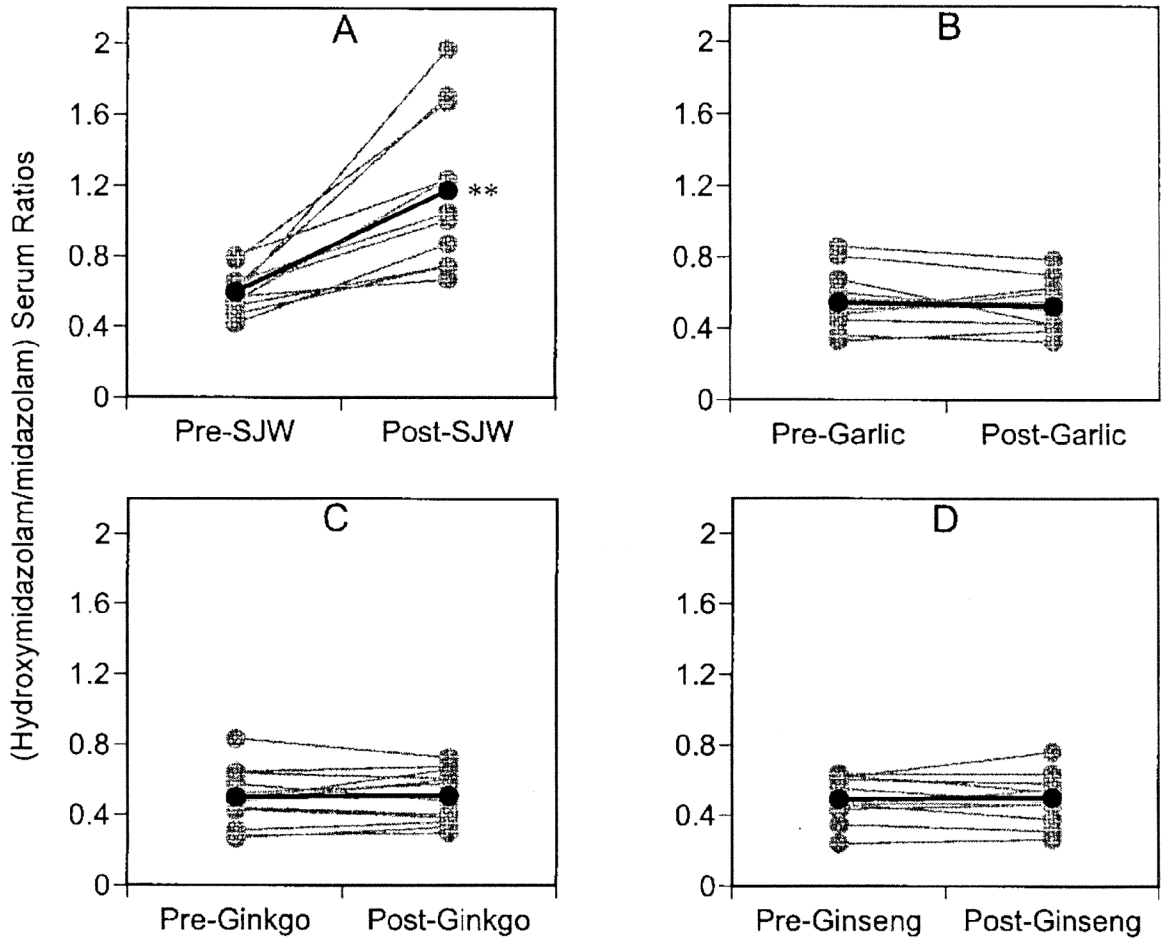
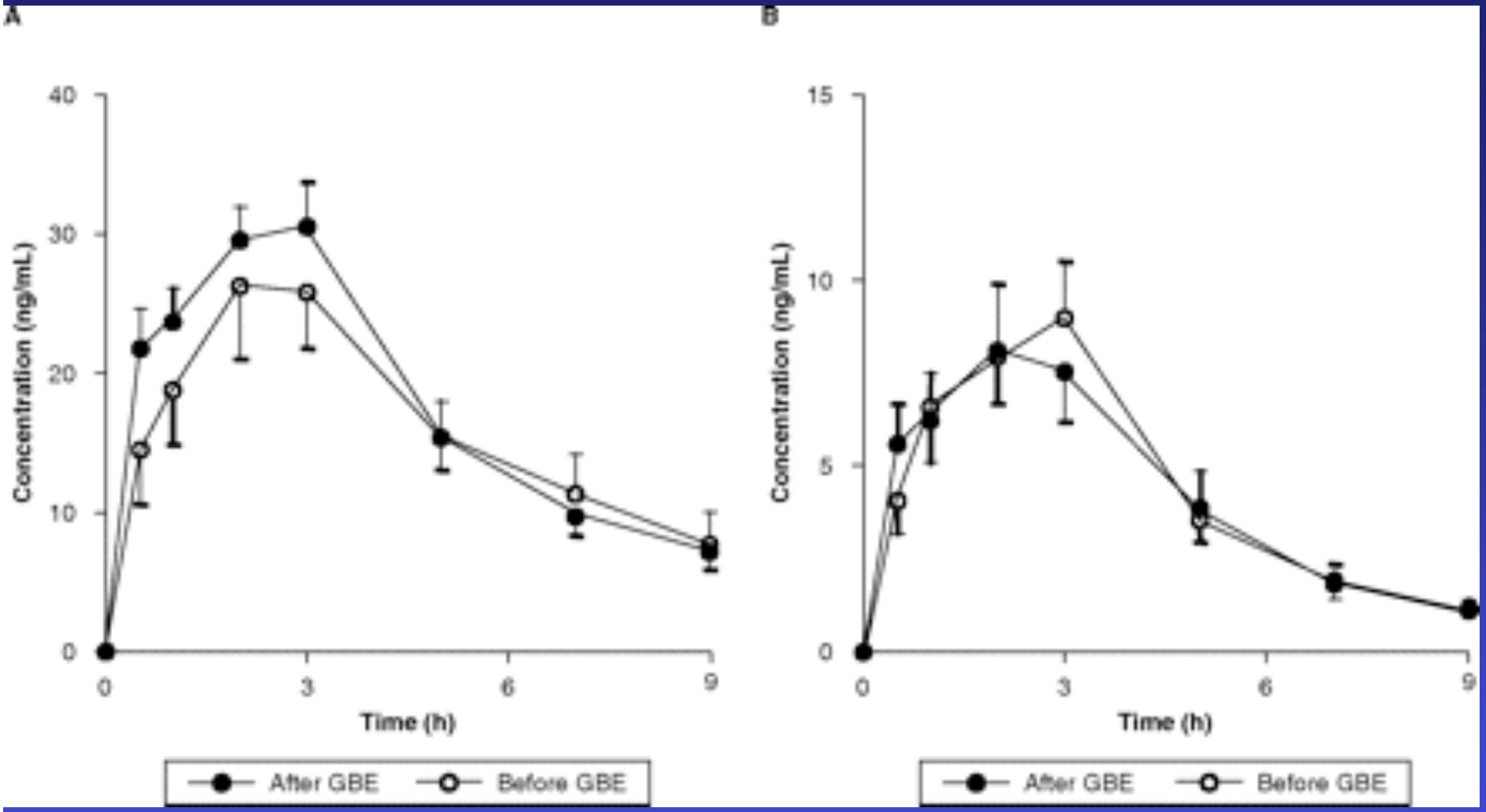


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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



Ushida et al. J Clin Pharmcol 2006;46:1290-8 n=12 CYP 3A4 probe is midazolam; note: use Ginkgold 120mg TID!

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 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; may inhibit platelet adhesion; *possible* (not necessarily probable!) interaction with "blood thinners" and warfarin 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
- **Osteoporosis-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 prostate 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 et al., Clin Pharm and Ther 2003;43:643-648

Soy

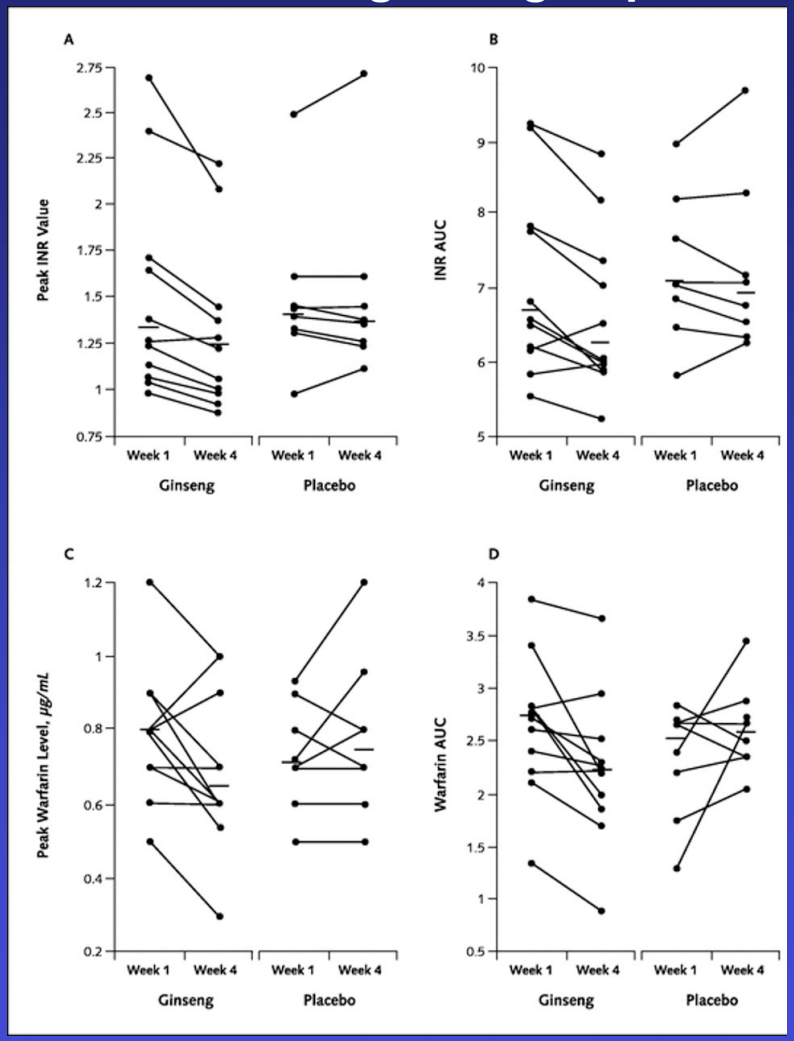
- **Efficacy**: increased soy ingestion **may** decrease hot flashes and other postmenopausal symptoms; cardiovascular benefits as well.
- **Safety**: good but use in breast cancer may be risky
- **Drug interactions**: **not with with tamoxifen but effect on CYP3A4 is unlikely**
- **Product selection**: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

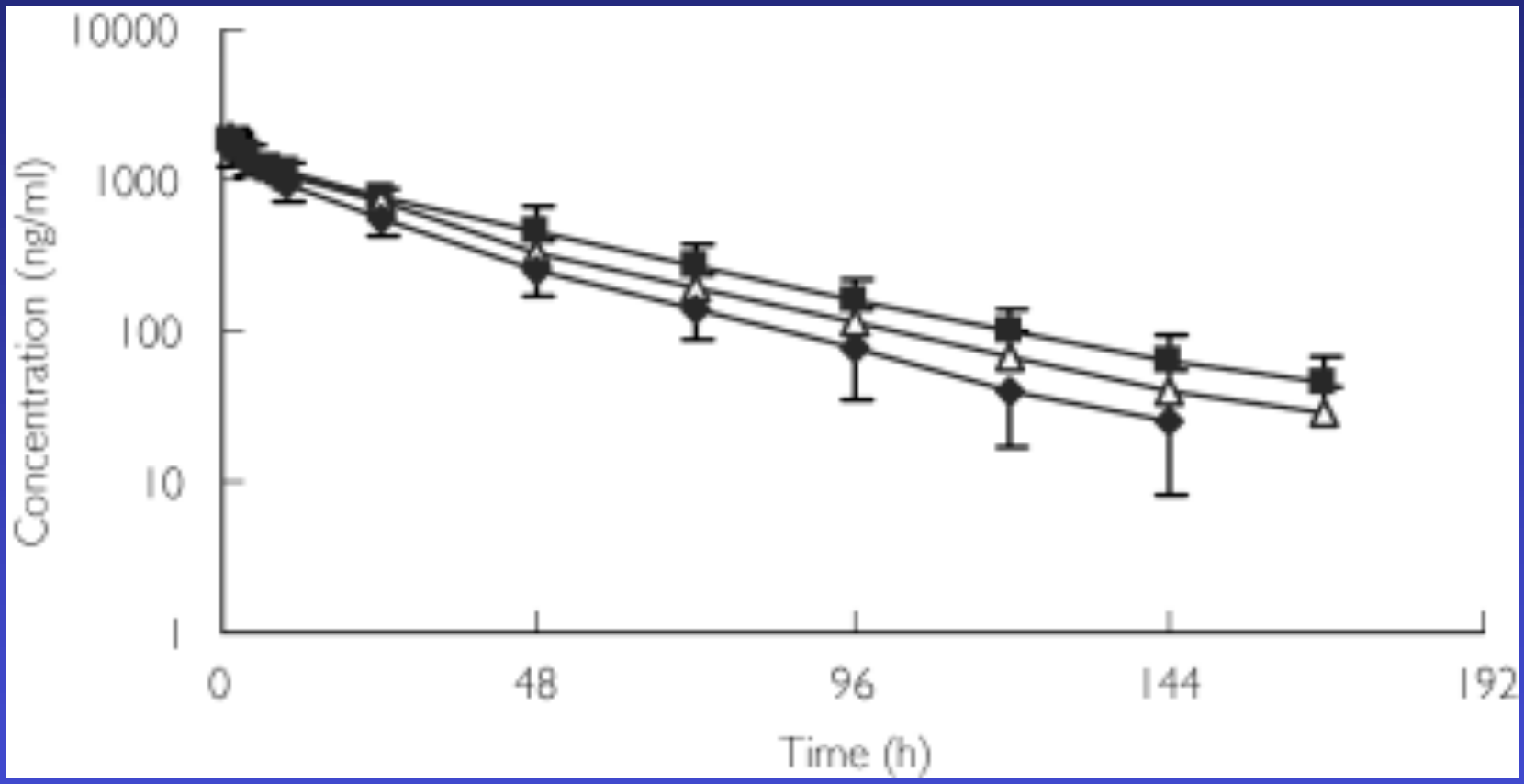
Changes in individual peak international normalized ratio (INR), INR area under the curve (AUC), peak plasma warfarin level, and warfarin AUC in weeks 1 and 4 in American ginseng or placebo groups



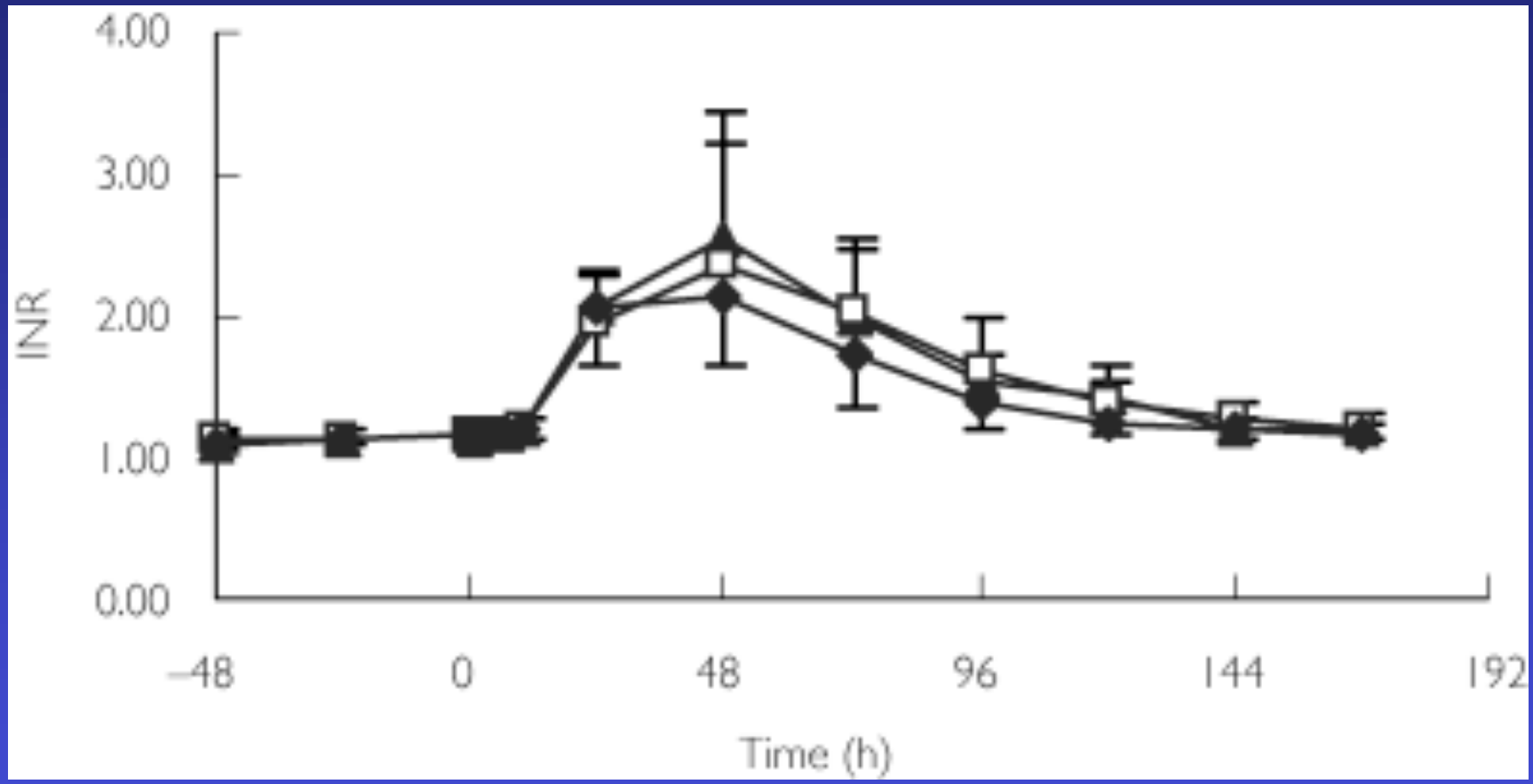
Yuan, C.-S. et. al. Ann Intern Med 2004;141:23-27

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)



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

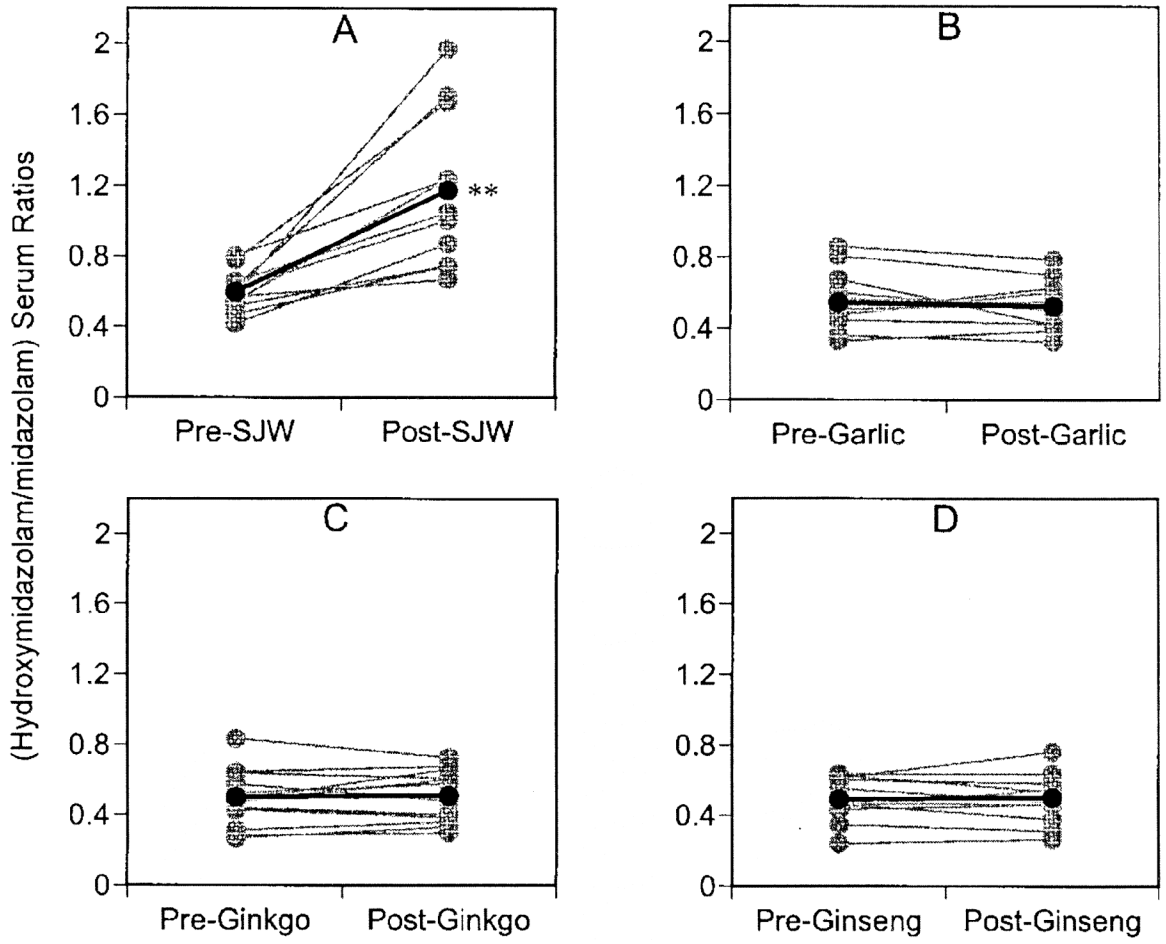


Fig 2. Comparison of presupplementation and postsupplementation phenotypic ratios (1-hydroxymidazolam/midazolam) for CYP3A4. **A,** St John's wort (SJW); **B,** garlic oil; **C,** *G biloba*; **D,** *P ginseng*. *Gray circles,* Individual values; *black circles,* group means. *Asterisks,* Statistically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

Gurley et al. Clin 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

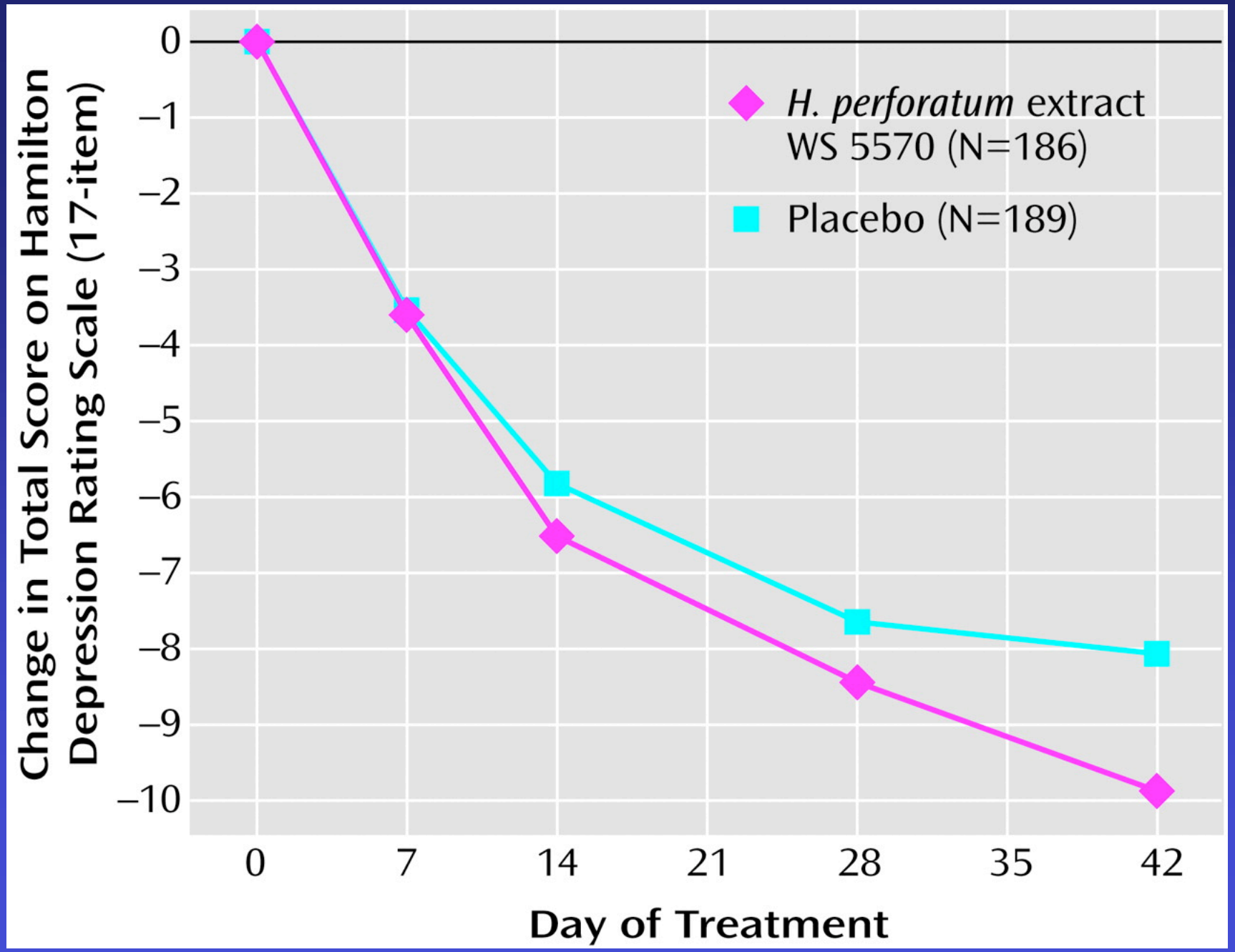
Safety: good;

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!***

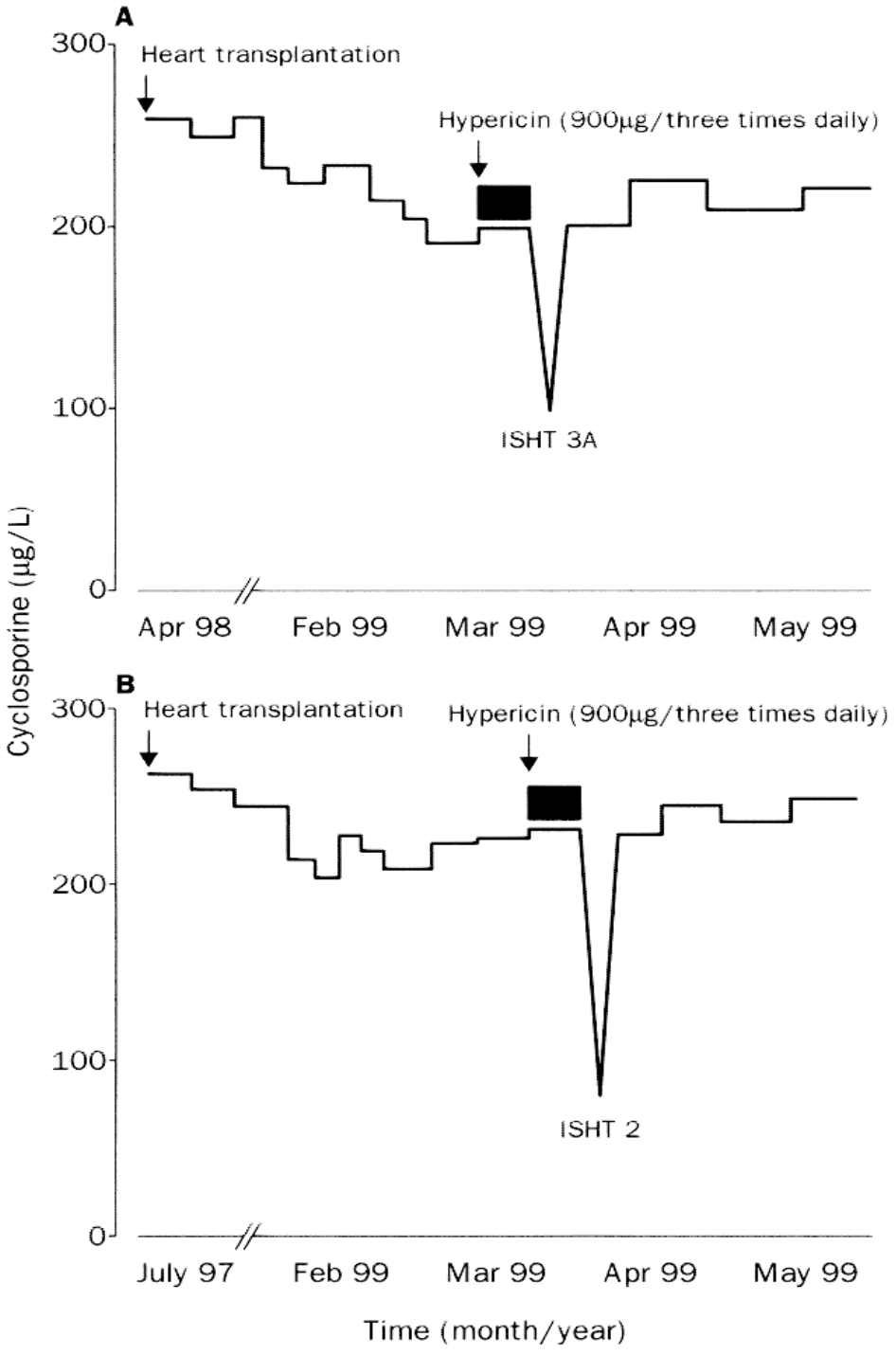


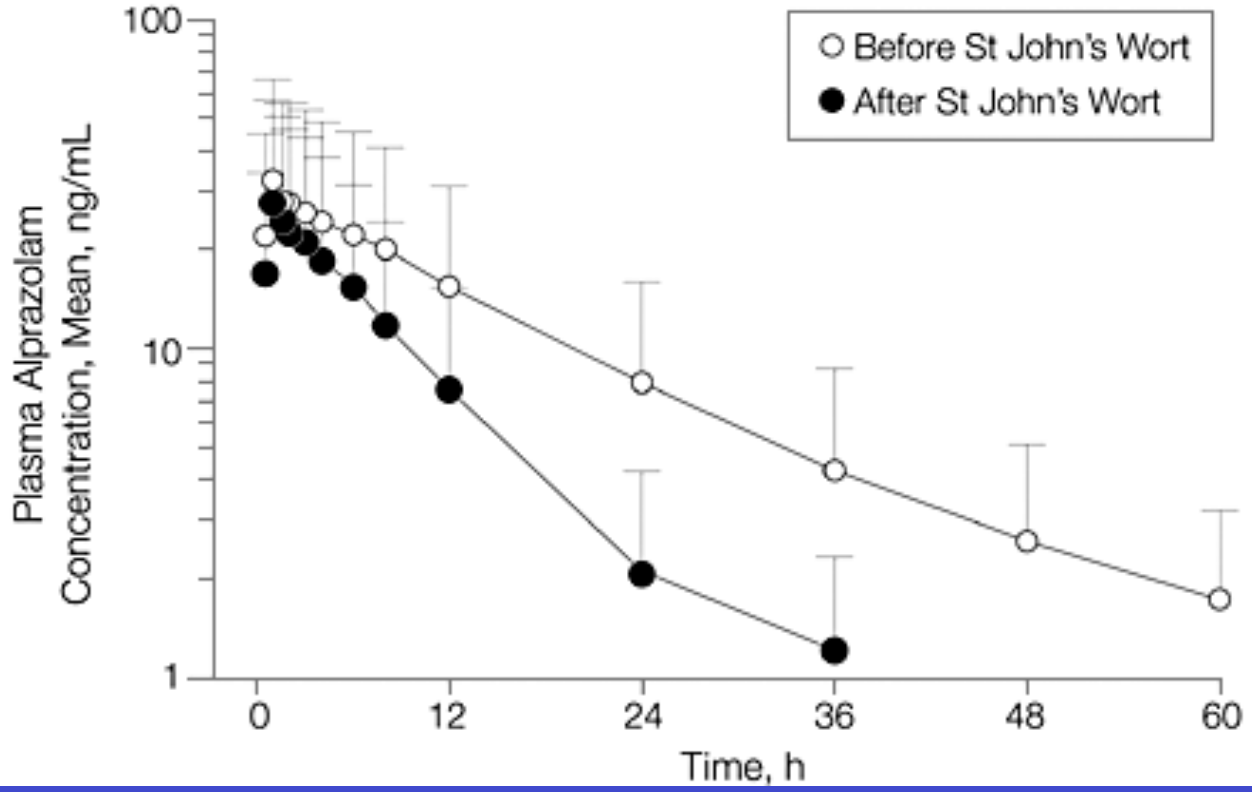
Lecrubier et al. Am J Psychiatry 2002;159:1361 n=375

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


A
300
200
100
0
Heart transplantation
Hypericin (900µg/three times daily)
ISHT 3A
Apr 98
Feb 99
Mar 99
Apr 99
May 99
B
300
200
100
0
Heart transplantation
Hypericin (900µg/three times daily)
ISHT 2
July 97
Feb 99
Mar 99
Apr 99
May 99
Cyclosporine (µg/L)
Time (month/year)



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

CYP 3A4

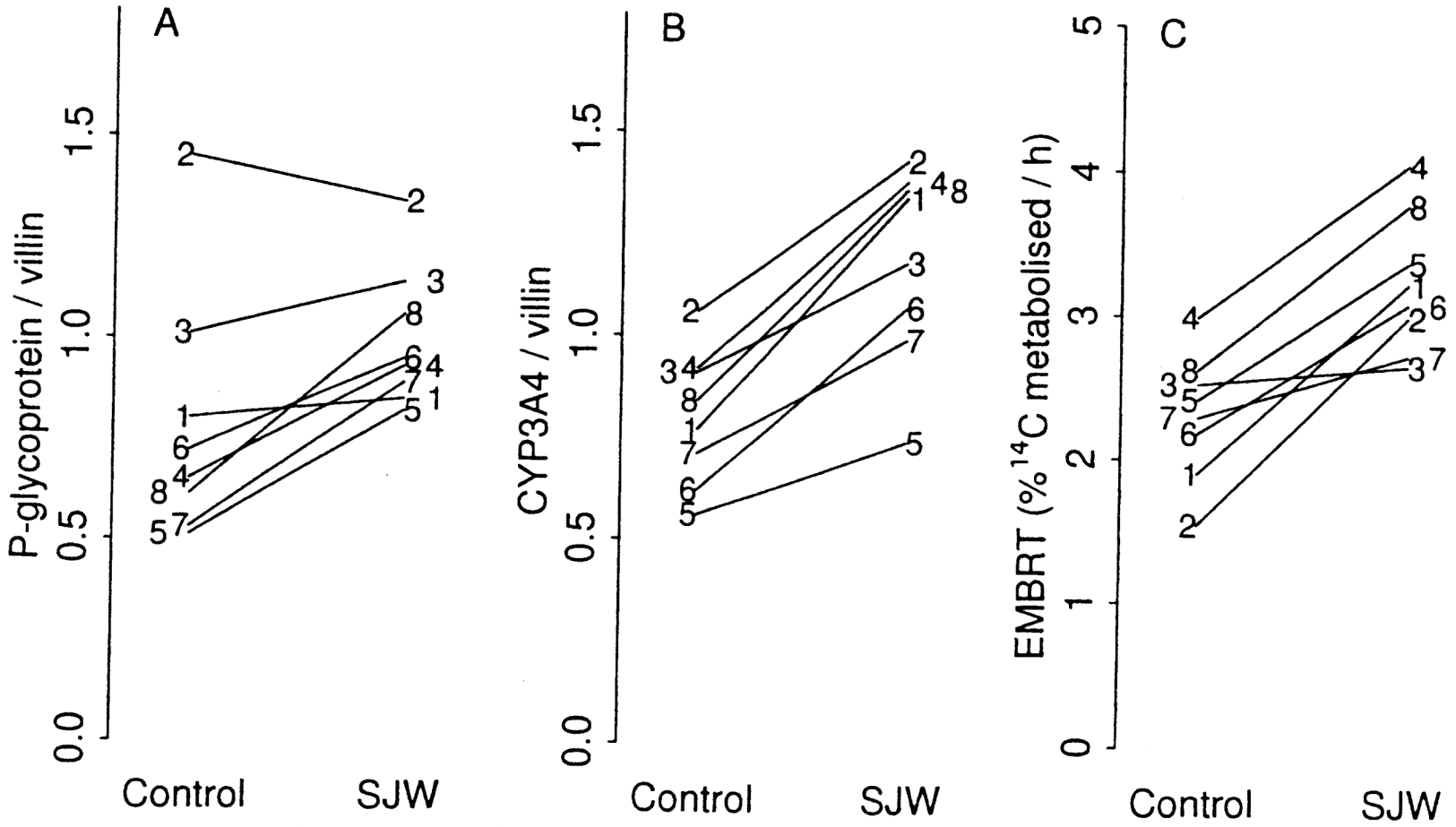


Fig 3. Comparison of intestinal P-glycoprotein/MDR1 and CYP3A4/villin expression ratios and erythromycin breath tests in humans. Eight healthy male volunteers were treated with St John's wort extract for 14 days. Duodenal biopsy specimens (**A, B**) and ^{14}C-erythromycin breath tests (EMBRT; **C**)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

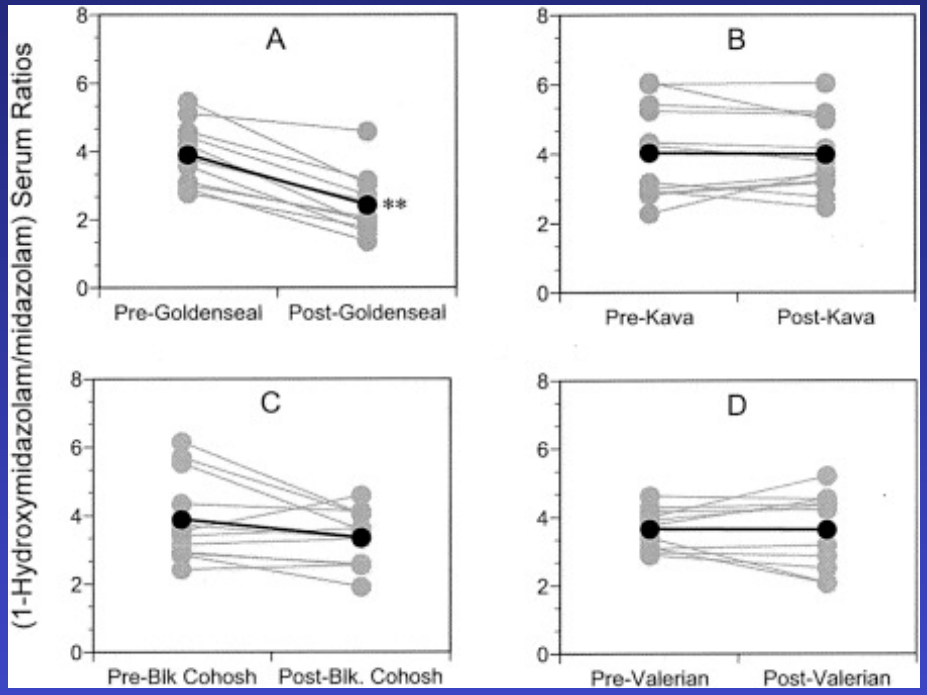
Drug	CYP	Effect	Management
HIV protease inhibitors (nelfinavir,ritonavor,saquinavir)	Induce 3A4	↓	Stop and measure viral load
HIV non-nucleoside RTI (efavirenz,nevirapine)	Induce 3A4	↓	Stop and measure viral load
warfarin	Induce 2C9	↓	Stop and adjust warfarin dose
cyclosporin	Induce P-glycoprotein	↓	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

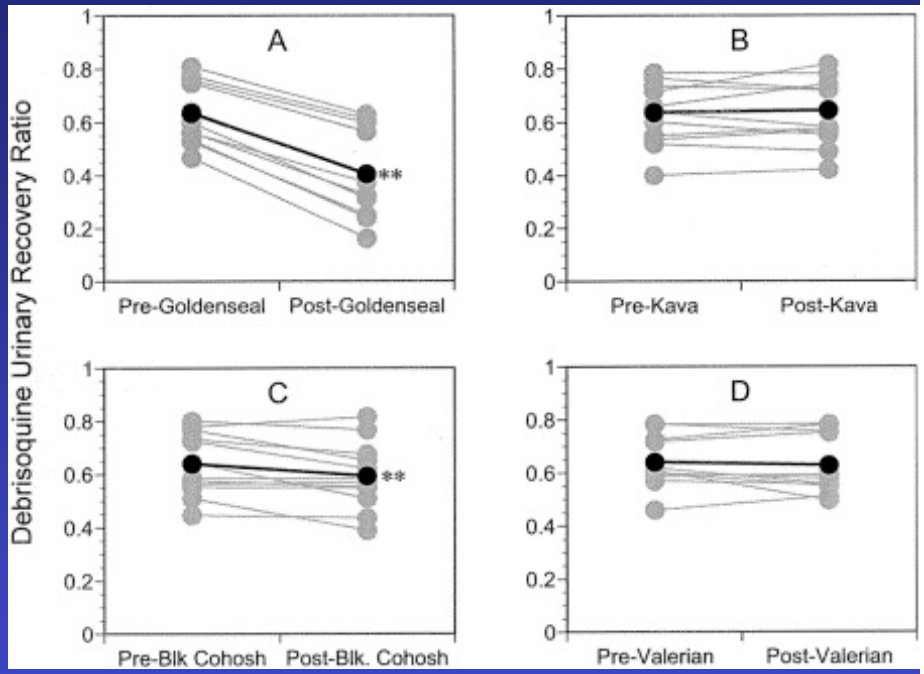
St. John's Wort

- **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 broad spectrum 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***


Nature Made
HERBS
Echinacea-
Goldenseal
60

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.

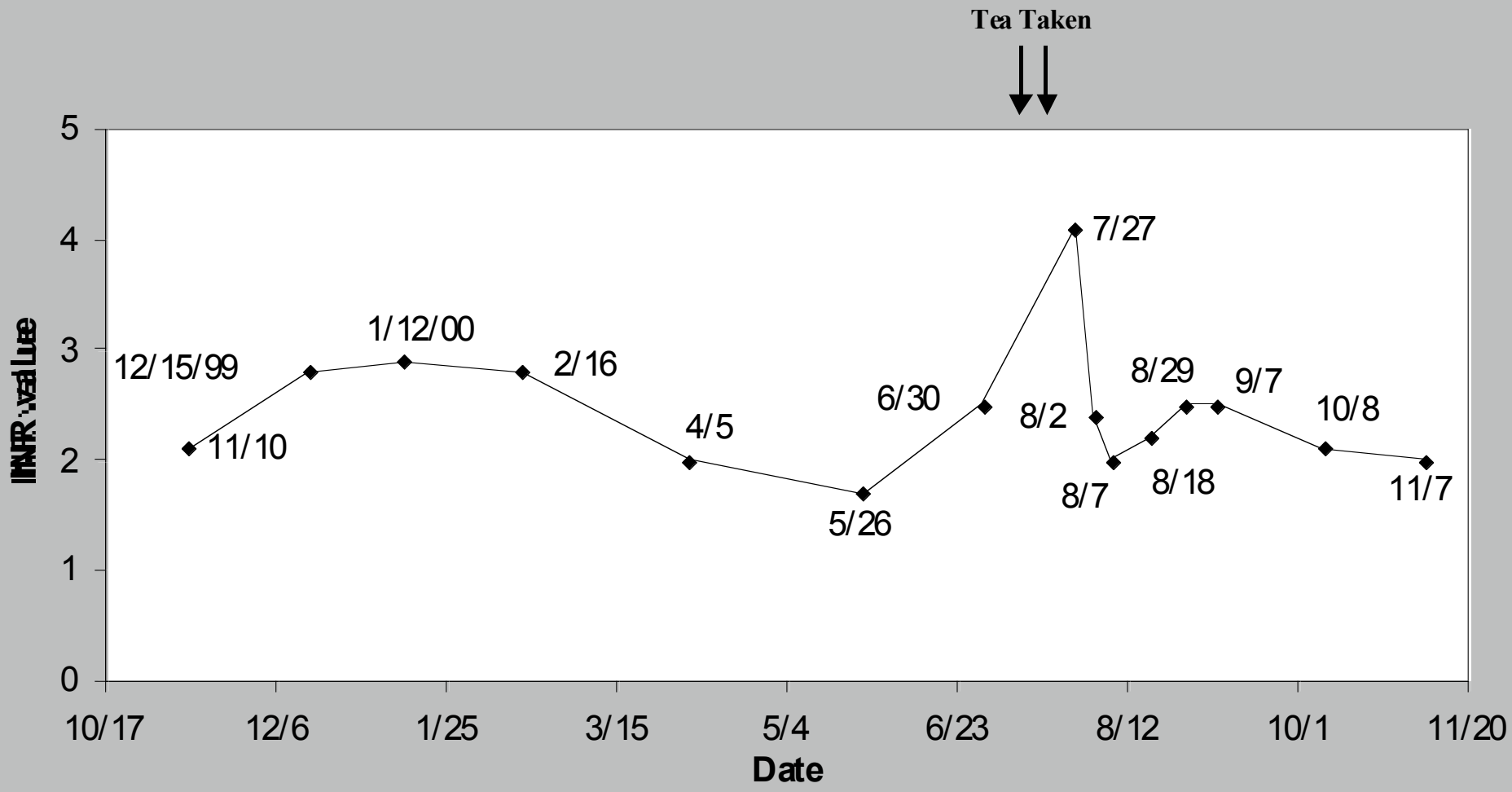
Andrographis panucula	Bogbean	Devil' claw	ginseng	Pau d'arco
angelica	Boldo	Dong quai	green tea	meadow sweet
anise	capsicum	Erigeron	hawthorn	prickly ash
arnica	celery	Evening primrose oil	horse chestnut bark	passionflower
Asafoeta	chamomile	feverfew	Huang qi	popular
Baikal skullcap	clove oil	fish oil	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	turmeric	vitamin E	wintergreen oil
wild carrot	wild lettuce	willow	wood ear mushroom	woodruff

Herbs with clotting problems reported in humans

Ginkgo and garlic and St. John's wort- see earlier notes

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
Lycium barbarum	case report of increased INR
Danshen -	case reports of increased INR with warfarin
Dong quai -	case reports of increased INR with warfarin
American Ginseng -	decreased INR with warfarin (Panax quinquifolius)
Green tea -	case report of decreased INR with warfarin but huge amount
CoQ10 -	case reports of decreased INR with warfarin but human study showed no effect on INR
Glucosamine-	increased INR cases with warfarin
Chondroitin-	increased INR cases with warfarin

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

Table 4a Significant Risk of CAM-drug Adverse Interaction n=5052 (16,173 interviews)

Potential Event	Mechanism[a]	Number[b]	Occurrences[c]
Risk of bleeds			
Aspirin		no. patients	all occurrences
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

Elmer et al. Ann Pharmacother 2007;41:1617-1624

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%)

Elmer et al. Ann Pharmacother 2007;41:1617-1624

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

- 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

Knudsen J, Sokol GH. Potential glucosamine-warfarin interaction resulting in increased international normalized ratio: Case report and review of the literature and MedWatch database. Pharmacotherapy 2008;28:540-8.

several cases plus 20 reports from FDA MedWatch database. Increased INR on warfarin plus glucosamine or glucosamine/chondroitin

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**


Full Throttle
Energy Drink
Full Throttle
Energy Drink
KMX
Energy Drink
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Take action.
Test the limits.
Push them!
Lightly
Carbonated
Drink Chilled
KMXUSA.COM
KMX
Energy Drink
Made with Choline, Ginseng,
Guarana and Yerba Maté
Contains B-Vitamins
Von Dutch
1.99


Freshëns
Smoöthie
COMPANY
NEW!
Quality Blended
Boosters With Natural Ingredients
Try a Freshëns Smoöthie Fortified
with MET-Rx Boosters
Multi-Vitamin BOOSTER
with 100% DV of Vitamin A, C, D and B Vitamins
NEW!
500 mg of Vitamin C!
Immune BOOSTER
with Vitamin C, Vitamin E and Zinc
Fat Burner (METABOLISM BOOSTER)
with Tyrosine, Taurine, L-Carnitine and Caffeine
Ephedra Free!
NEW! Buttercream Flavor!
Protein BOOSTER
with Exclusive Metamyosyn® Protein
Memory BOOSTER
with Choline and B Vitamins
Improved!
New Formula!
Energy BOOSTER
with Taurine, Vitamin C, Niacin, Vitamin B-12 and Caffeine

Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	Possible interaction
1. soy	may block action of tamoxifen
2. cranberry	
3. garlic	product dependent Inhibition of 3A4; enhance warfarin effect
4. ginkgo	may increase bleed risk; may induce 2C19
5. saw palmetto	
6. echinacea	may inhibit CYP 1A2
7. black cohosh	weak 2D6 induction action (?)
8. milk thistle	
9. ginseng	Panax quiquifolius may induce 2C9
10. St. John's wort	definitive interactions; induce 3A4, other CYP and Pgp
11. Green tea	
12. Evening primrose oil	may enhance warfarin effect
13. valerian	
14. Horny goat weed	enhance warfarin effect and increase BP

Red indicates risk for drug interactions

Top 20 Selling Herbals for 2007- Mass Market
HerbalGram 2008;78:61-62

Product	**possible interaction**
15. bilberry	
16. grape seed	
17. Yohimbe	affect BP medications
18. red clover	
19. Horse chestnut seed	
20. ginger	

Red indicates potential risk for drug interactions

Note: total herbal sales are estimated at $4.7 billion

The above figures include only sales from food stores, drug stores, and mass market retailers but with Wal-Mart figures not included. It does not include warehouse buying clubs (Costco), 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)(11/13/08)

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. Risk may be over stated based on recent evidence.
5. Ginkgo may induce CYP2C19 so may lower 2C19 substrates
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 2008

- **Natural Medicines Comprehensive Database.**
  Online version updated "daily". UW Healthlinks http://www.naturaldatabase.com/; $92

Recent Reviews

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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**