Herbal / Drug Interactions

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11/03/06

Table 1. Enrollees in CHS Study

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

*a The number in parentheses is the percent of the enrolled

Elmer et al. unpublished
Table 1b. Black Enrollees\(^a\)

<table>
<thead>
<tr>
<th>Study period</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total users</td>
<td>718</td>
<td>693</td>
<td>665</td>
<td>571</td>
</tr>
<tr>
<td>Rx users</td>
<td>682 (95)</td>
<td>634 (92)</td>
<td>614 (92)</td>
<td>521 (91)</td>
</tr>
<tr>
<td>CAM users</td>
<td>47 (7)</td>
<td>42 (6)</td>
<td>93 (14)</td>
<td>75 (13)</td>
</tr>
<tr>
<td>Vitamin/mineral users</td>
<td>200 (28)</td>
<td>191 (28)</td>
<td>229 (34)</td>
<td>245 (43)</td>
</tr>
<tr>
<td>OTC users</td>
<td>393 (55)</td>
<td>375 (54)</td>
<td>393 (59)</td>
<td>305 (53)</td>
</tr>
<tr>
<td>Rx plus CAM</td>
<td>45 (6)</td>
<td>34 (5)</td>
<td>84 (13)</td>
<td>69 (12)</td>
</tr>
<tr>
<td>Rx, CAM, OTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The number in parentheses is the percent of the enrolled

Table 1c. White Enrollees\(^a\)

<table>
<thead>
<tr>
<th>Study period</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total users</td>
<td>3655</td>
<td>3658</td>
<td>3254</td>
<td>2990</td>
</tr>
<tr>
<td>Rx users</td>
<td>3312 (91)</td>
<td>3257 (89)</td>
<td>2919 (90)</td>
<td>2738 (92)</td>
</tr>
<tr>
<td>CAM users</td>
<td>231 (6)</td>
<td>253 (7)</td>
<td>411 (13)</td>
<td>458 (15)</td>
</tr>
<tr>
<td>Vitamin/mineral users</td>
<td>1513 (41)</td>
<td>1516 (41)</td>
<td>1449 (45)</td>
<td>1836 (61)</td>
</tr>
<tr>
<td>OTC users</td>
<td>2242 (61)</td>
<td>2345 (64)</td>
<td>1870 (58)</td>
<td>1914 (64)</td>
</tr>
<tr>
<td>Rx plus CAM</td>
<td>193 (5)</td>
<td>209 (6)</td>
<td>327 (10)</td>
<td>394 (13)</td>
</tr>
<tr>
<td>Rx, CAM, OTC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) The number in parentheses is the percent of the enrolled

Table 3 All users of the top 20 CAM products by race\(^a\)

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

\(^a\) 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

- 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

<table>
<thead>
<tr>
<th>P450 Isozyme</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4</td>
<td>28%</td>
</tr>
<tr>
<td>CYP2C</td>
<td>20%</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>13%</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>7%</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>2%</td>
</tr>
<tr>
<td>Other</td>
<td>30%</td>
</tr>
</tbody>
</table>
Spontaneous spinal hemoatoma associated with garlic


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:


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: Mild benefit for use in hyperlipidemia
- 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
800mg BID for 30d (Wild Oats Market)(analyzed)

CYP 3A4
N=12 crossover, before and after 400mg QID Echinacea purpurea root extract for 8d
A= Cl caffeine (CYP 1A2)
B= Cl tolbutamide (CYP 2C9)
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; clinical significance unclear
  Product selection: want standardized extract containing about 4% phenolics
  Dose: about 250mg QID for treatment
  Questions remaining
A new study in the Journal of the American Medical Association shows that Ginkgold helps with age-related mental function.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Reference</th>
<th>N</th>
<th>Mean (SD)</th>
<th>Standardized Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Standardized Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Ginkgold twice daily less than 200mg/day special extract</td>
<td>130</td>
<td>-2.53 (2.40)</td>
<td>67</td>
<td>-2.10 (2.00)</td>
<td>0.02 (95% CI: 0.01, 0.03)</td>
<td>15.6</td>
<td>0.02 (95% CI: 0.01, 0.03)</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Ginkgold twice daily greater than 200mg/day special extract</td>
<td>38</td>
<td>-1.00 (3.00)</td>
<td>44</td>
<td>-1.20 (3.00)</td>
<td>0.06 (95% CI: 0.05, 0.07)</td>
<td>0.4</td>
<td>0.06 (95% CI: 0.05, 0.07)</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Ginkgold twice daily any dose</td>
<td>130</td>
<td>-2.53 (2.40)</td>
<td>67</td>
<td>-2.10 (2.00)</td>
<td>0.02 (95% CI: 0.01, 0.03)</td>
<td>15.6</td>
<td>0.02 (95% CI: 0.01, 0.03)</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: chi-squared 0.73 (df 2), p = 0.08
Test for overall effect: I² = 0.00

Test for heterogeneity: chi-squared 1.01 (df 1), p = 0.25
Test for overall effect: I² = 0.00

Test for heterogeneity: chi-squared 0.48 (df 1), p = 0.49
Test for overall effect: I² = 0.00

For the benefit of this breakthrough study shown the results actually used and tested Ginkgold®. Other treatment plans to be performed at your local doctor. For Ginkgold extract please reference to the study. Ginkgold extract was shown to increase brain activity in all the areas of the brain. As for better mental health, choose the best Ginkgold extract from nature’s own.
### Bleeds associated with ginkgo use

<table>
<thead>
<tr>
<th>Patient age</th>
<th>Ginkgo use</th>
<th>Other therapy</th>
<th>Bleed</th>
<th>ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>1 week</td>
<td>Aspirin</td>
<td>Iris</td>
<td>1</td>
</tr>
<tr>
<td>78</td>
<td>2 mos</td>
<td>Warfarin</td>
<td>Intracerebral</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>2 years</td>
<td>None</td>
<td>Subdural</td>
<td>3</td>
</tr>
<tr>
<td>61</td>
<td>6 mos</td>
<td>None</td>
<td>Subarachnoid</td>
<td>4</td>
</tr>
</tbody>
</table>

1. NEJM 336:1108, 1997
### Non-linear Regression

#### Ki Values

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Type of Inhibition</th>
<th>Ki (µg/ml)</th>
<th>α</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Mixed</td>
<td>11.2</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Competitive</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>CYP2A6</td>
<td>Mixed</td>
<td>21.2</td>
<td>2.1</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Competitive</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Competitive</td>
<td>133.1</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Mixed</td>
<td>17.0</td>
<td>2.5</td>
</tr>
</tbody>
</table>

#### 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)
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

Day 7 blood draw

Day 14 Blood draw

Diclofenac 50 mg every 12 hours

Ginkgo biloba 120 mg every 12 hours

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.


N=12 ginkgo for 7d; warfarin alone or in combination with ginkgo or ginger.
Ginkgo/Drug Interactions
other studies

- 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 (shaded circle is ginkgo, open circle is baseline) 140mg BID x 12d
**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?

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**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 prostate cancer growth
- **Soy-Cardiovascular Benefits** Favorable effects on cholesterol balance; “heart healthy”
  - Isoflavones inhibit CYP3A4 in vitro
### 6β-hydroxycortisol/cortisol ratio (CYP 3A4)

<table>
<thead>
<tr>
<th>herbal</th>
<th>Baseline Week 1</th>
<th>Treatment Week 2</th>
<th>Treatment Week 3</th>
<th>Washout Week 4</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>4.4 ± 2.4</td>
<td>3.7 ± 2.2</td>
<td>3.6 ± 1.8</td>
<td>3.7 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>4.9 ± 2.5</td>
<td>5.0 ± 2.0</td>
<td>4.6 ± 2.2</td>
<td>------</td>
<td>NS</td>
</tr>
</tbody>
</table>


### 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 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”

• 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

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

<table>
<thead>
<tr>
<th>herbal</th>
<th>Baseline Week 1</th>
<th>Treatment Week 2</th>
<th>Treatment Week 3</th>
<th>Washout Week 4</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>4.4 ± 2.4</td>
<td>3.7 ± 2.2</td>
<td>3.6 ± 1.8</td>
<td>3.7 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Soy isoflavones</td>
<td>4.9 ± 2.5</td>
<td>5.0 ± 2.0</td>
<td>4.6 ± 2.2</td>
<td>------</td>
<td>NS</td>
</tr>
</tbody>
</table>


---

**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.


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 Korean (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!
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.

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 14C-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.


### Summary of SJW Interactions

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

- 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

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**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


Herbals affecting clotting

<table>
<thead>
<tr>
<th>Andrographis panulca</th>
<th>Bogbean</th>
<th>Devil’ claw</th>
<th>ginseng</th>
<th>Pau d’arco</th>
</tr>
</thead>
<tbody>
<tr>
<td>angelica</td>
<td>Boldo</td>
<td>Dong quai</td>
<td>green tea</td>
<td>meadow sweet</td>
</tr>
<tr>
<td>anise</td>
<td>capsicum</td>
<td>Erigeron</td>
<td>hawthorn</td>
<td>prickly ash</td>
</tr>
<tr>
<td>arnica</td>
<td>celery</td>
<td>Evening primrose oil</td>
<td>horse chestnut bark</td>
<td>passionflower</td>
</tr>
<tr>
<td>Asafoeta</td>
<td>chamomile</td>
<td>feverfew</td>
<td>Huang qi</td>
<td>popular</td>
</tr>
<tr>
<td>Baikal skullcap</td>
<td>clove oil</td>
<td>fish oil</td>
<td>horseradish</td>
<td>quassia</td>
</tr>
<tr>
<td>Bilberry</td>
<td>coleus root</td>
<td>fenugreek</td>
<td>kava</td>
<td>red clover</td>
</tr>
<tr>
<td>Black current seed</td>
<td>danshen</td>
<td>garlic</td>
<td>licorice</td>
<td>reishi mushroom</td>
</tr>
<tr>
<td>Bladderwrack</td>
<td>dandelion root</td>
<td>ginger</td>
<td>onion</td>
<td>Sha shen</td>
</tr>
<tr>
<td>Bomelain</td>
<td>Danshen</td>
<td>ginkgo</td>
<td>papain</td>
<td>Shinpi bark</td>
</tr>
<tr>
<td>Sweet birch oil</td>
<td>Tonka bean</td>
<td>tumeric</td>
<td>vitamin E</td>
<td>wintergreen oil</td>
</tr>
<tr>
<td>wild carrot</td>
<td>wild lettuce</td>
<td>willow</td>
<td>wood ear mushroom</td>
<td>woodruff</td>
</tr>
</tbody>
</table>
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 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 quinquefolius)
Green tea - case report of decreased INR with warfarin but huge amount

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Table 4a  Significant Risk of CAM-drug Adverse Interaction

<table>
<thead>
<tr>
<th>Potential Event</th>
<th>Mechanisma</th>
<th>Numberb</th>
<th>Occurrencesc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of bleeds</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic3,25-27</td>
<td>PD</td>
<td>147</td>
<td>214</td>
</tr>
<tr>
<td>Ginkgo24,28</td>
<td>PD</td>
<td>102</td>
<td>127</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic25-27</td>
<td>PD</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Ginkgo29</td>
<td>PD</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Ginseng32,33</td>
<td>PKd</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garlic23,25-27</td>
<td>PD</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Ginkgo24,30,31,54</td>
<td>PD</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginkgo24,30,31</td>
<td>PD</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>281 (5.6%)</td>
<td>380</td>
</tr>
</tbody>
</table>
Seem to have low pharmacokinetic drug interaction potential based on recent studies

- Ginger
- Valerian
- Milk thistle
- Saw palmetto
- 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)

- 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

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 quinquefolius 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
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


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