Herbal / Drug Interactions

Gary W. Elmer, R.Ph., Ph.D.
Department of Medicinal Chemistry,
elmer@u.washington.edu
11/09/05

Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan 2, 2005
HerbalGram 2005;66:63

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

Red indicates risk for drug interactions
### Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005

**HerbalGram 2003;58:71**

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

Red indicates risk for drug interactions

Note: kava and pycnogenol fell off the top 20 list

Note: total herbal sales are estimated at $4.2 billion

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

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

- **Is the patient taking any herbal supplements?**

- **Does the herbal have efficacy for the intended use?**

- **Is the product reliable? (i.e., what are they REALLY taking?)**
Dietary Supplement Education Alliance Survey (Harris Interactive)
July 2001

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

Hypericin and Hyperforin in Eight Brands of St. John’s Wort

<table>
<thead>
<tr>
<th>– Product –</th>
<th>hypericin (%)</th>
<th>hyperforin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperifin</td>
<td>0.29</td>
<td>1.89</td>
</tr>
<tr>
<td>PNC</td>
<td>0.12</td>
<td>0.20</td>
</tr>
<tr>
<td>Brite-Life</td>
<td>0.22</td>
<td>1.16</td>
</tr>
<tr>
<td>ShopKo</td>
<td>0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>Shurfine</td>
<td>0.17</td>
<td>0.29</td>
</tr>
<tr>
<td>YourLife</td>
<td>0.28</td>
<td>0.19</td>
</tr>
<tr>
<td>Nature’s Balance</td>
<td>0.03</td>
<td>0.01</td>
</tr>
<tr>
<td>Natrol</td>
<td>0.25</td>
<td>0.48</td>
</tr>
</tbody>
</table>

* Usually want 0.3% hypericin and 1% hyperforin
Consumerlab.com

• Manufacturers whose products “pass” are listed on consumerlab’s website (www.consumerlab.com)

• A manufacturer whose product “passes” can (for a fee) include the consumerlab seal on their label

• Access is $24/yr and allows access to The Natural Products Encyclopedia, an excellent database on dietary supplements.

USP Dietary Supplement Verification Program

• Manufacturer must agree to meet standards set by USP and their monographs

• Must agree to inspections and random analyses of products

• USP analyzes the product and inspects the manufacturing facility

• Pharmavite is the first manufacturer to seek USP verification (Nature Made, Nature’s Resource) for their line of herbals and dietary supplements. The “USP” will appear on the labels.
Some “Name Brand” Botanicals

Warner Lambert
   Quanterra Mental® (ginkgo)
   Quanterra Prostate® (saw palmetto)
Whitehall-Robins Healthcare
   Centrum® botanicals line
Pharmaton (Boehringer Ingelheim)
   Ginsana ® (ginseng)
   Ginkoba ® (ginkgo)
   Venastat ® (horse chestnut)
   Movana ® (St. John’s wort)
SK-Beecham
   Alluna ® (valerian and hops)
Pharmavite
   Nature Made ®
   Nature’s Resource ®
Phyto-Phamica
   Nature’s Way

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

- 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>30%</td>
</tr>
<tr>
<td>CYP2C</td>
<td>28%</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>20%</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>13%</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>2%</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:

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; note: used garlic oil prep (500mg TID)

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

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

Questions remaining include

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

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

A= Cl caffeine (CYP 1A2)

B= Cl tolbutamide (CYP 2C9)


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

A= midazolam IV (CYP 3A4)

B= midazolam PO (CYP 3A4)
Echinacea

• Summary
  Efficacy: evidence for treatment not prevention
  Safety: good; rare allergy
  Drug interactions: Pharmacodynamic: don’t give to patients taking immunosuppressive drugs
  Pharmacokinetic: inhibits 1A2; may inhibit intestinal 3A4 but induce hepatic; clinical significance unclear
  Product selection: want standardized extract containing about 4% phenolics
  Dose: about 250mg QID for treatment

Questions remaining
Bleeds associated with ginkgo use

| Patientage | Ginkgo use | Othertherapy | Bleedref | 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.

---

Bleeds associated with ginkgo use

<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>

Non-linear Regression

Ki Values

---

2.

3.

4.

---

NEJM 336:1108, 1997

Neurology 50:1933-1934, 1998

Lancet 352:36-37, 1998

Neurology 46:1775-1776, 1996
Tolbutamide Human Study

- 6 Subjects (3 males, 3 females)
- Subjects ingested 500mg tolbutamide and collected 6-12 hour urine (Control phase)
- Followed by a 2 week wash-out period
- Subjects then ingested two 60mg *Ginkgo biloba* extract tablets 2 times a day for 3 days
- The morning of day 4 patients received a 500mg dose of tolbutamide along with the ginkgo and collected 6-12 hour total urine (Ginkgo phase)

Comparison of Tolbutamide Metabolic Ratios

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Ginkgo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic Ratio (4-methylhydroxytolbutamide + carboxytolbutamide / tolbutamide)</td>
<td>680 ± 323</td>
<td>610 ± 327</td>
</tr>
</tbody>
</table>
**Diclofenac Ginkgo biloba Interaction Study**

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

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

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

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

12 hour urine collected

**Comparison of Diclofenac Clearances from Plasma**

Control

Control 0.64 ± 0.36

Ginkgo

Ginkgo 0.61 ± 0.33
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
CoQ10 and Ginkgo on Warfarin


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

Ginkgo biloba summary

- Efficacy: good for dementia and poor peripheral circulatory problems
- Safety: good; rare bleeding episodes
- Drug interactions: no effect on 3A4,2C9 or 2D6 but may induce 2C19; inhibits platelet adhesion; possible pharmacodynamic interaction with “blood thinners” but not common
- Product selection: look for EGb761 extract
- Dose: 1-2 60mg tabs, BID
- Questions remaining include
  - Extent of memory improvement in younger patients?
  - Delay Alzheimer’s and dementia?
  - Help in other circulatory disorders?
  - Synergistic with other drugs and treatments?
Soy and Menopausal and Postmenopausal problems

• Hot flashes and other symptoms: soy flour as well as higher doses of soy isoflavones (100mg/d) will reduce

• Osteoposis- studies using high isoflavone soy indicate decreased loss of bone mass in postmenopausal women

Soy Effects on Cancers

• Long consumption of soy associated with lower rates of breast, endometrial and prostate cancers (Asian cultures)

• Soy and some soy isoflavones decrease prostate cancer and breast cancer growth in animal studies

• Genistein enhances effect of Adriamycin on breast cancer cells but blocks inhibitory effect of tamoxifen

• Soy-Cardiovascular Benefits

• Favorable effects on cholesterol balance; “heart healthy”

Other herbals used for menopausal symptoms

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

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

Flaxseed and Flaxseed oil – some evidence for benefit

Evening primrose oil- not consistent evidence for benefit

Chasteberry- helps in PMS but ? for menopause

Dong quai- no observed benefit in one good study

Yam- is a scam

Topical progesterone- works but risks same as HRT?
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
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; 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 quiniquifolius) 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!

St. John’s Wort

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

- Woelk et al. BMJ 321:536-539, 2000. SJW same as imipramine with fewer adverse effects in multicentered German study (n=324) in patients with mild to moderate depression


- Schrader et al. Int Clin Psychopharmacol 15:61-68,2000. SJW same as fluoxetine with fewer adverse effects in multicentered German study (n=240) in patients with mild to moderate depression
Interactions with St. John’s Wort -cyclosporin-

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

Markowitz et al. JAMA 290:1500,2003  n=12  14d of SJW
**Fig 3.** Comparison of intestinal P-glycoprotein/MDR1 and CYP3A4/villin expression ratios and erythromycin breath tests in humans. Eight healthy male volunteers were treated with St John’s wort extract for 14 days. Duodenal biopsy specimens (A, B) and 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 and 1% hyperforin
  – Dose: about 300mg TID for treatment
  – Questions remaining include
    • How best to use this herbal given that there are drug interaction problems
Kava (Kava Kava)

- Uses
  - mild tranquilizer

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

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

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

• Summary
  – Efficacy: long historical use; reasonable evidence for efficacy for mild to moderate anxiety.
  – Safety: hepatotoxicity, rash with long use,
  – Drug interactions: not with other anxiolytics or sedatives or liver toxic drugs (acetaminophen)
  – Advice: don’t take Kava!

– Questions remaining include
  • How effective is this for occasional use?
  • How prevalent is hepatotoxicity?
Potential Interactions of Goldenseal with CYP2D6 and CYP 3A4 substrates


Herbals affecting clotting

Andrographis panuca | Bogbean | Devil' claw | ginseng | Pau d’arco
---|---|---|---|---
angelica | Boldo | Dong quai | green tea | meadow sweet
anise | capscicum | Erigeron | hawthorn | prickly ash
arntica | 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

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

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

- Ginger
- Valerian
- Milk thistle
- Saw palmetto
- Kava
Herbals affecting drug management (i.e., herbal/drug interactions)

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

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

Reginster et al. Lancet 2001;357:251-256. N=212 all over 50 with osteoarthritis of the knee; 1500mg/d x 3 yr;
Glucosamine and type 2 diabetics

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

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

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

Red indicates risk for drug interactions
Top 20 Selling Herbals - Mass Market, 52 weeks ending Jan2,2005  
HerbalGram 2003;58:71

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

Red indicates risk for drug interactions

Note: kava and pycnogenol fell off the top 20 list

Note: total herbal sales are estimated at $4.2 billion

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

---

**References with Good Herbal/Drug Interactions Discussion**

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

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

- **The Natural Medicines Encyclopedia.**
  free with access subscription ($24/yr) to consumerlab.com www.consumerlab.com
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