Herbs and Women's Health

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Drugs from Herbs

- **Digitalis** (*D. lanata*)
- **Opiates** (*Papaver somniferum*)
- **Lidocaine** (*Erythroxylum coca*)
- **Warfarin** (*Melilotus officinalis*)
- **Oral contraceptives** (*Diascorea villosa*)
- **Cromolyn** (*Ammi visnaga*)

Commonly Used Herbs

- Black cohosh (*Cimicifuga racemosa*)
- Red clover (*Trifolium pratense*)
- Vitex (*V. agnus-castus*)
- St. John's wort (*Hypericum perforatum*)
- Ginkgo (*G. biloba*)

Black cohosh (*Cimicifuga racemosa)*

Contains triterpene glycosides, possibly formononetin

Black cohosh: Placebo-controlled

- 2 placebo-controlled trials
  - 85 women with breast cancer (20 mg b.i.d x 2 mos: no effect on hot flashes; only excessive sweating improved (Jacobsen 2001)
  - 80 women (black cohosh 4 mg b.i.d., CEE, placebo 4 mg bid x 3 mos.) HF improved in both groups, Kupperman, vaginal epithelium improved in black cohosh group (Stoll 1987)

Black cohosh: Treatment-controlled

- 2 treatment-controlled trials found black cohosh equivalent to estrogens in Kupperman index, other measures
  - 60 symptomatic women (80% menopausal) treated with BC 40 drops bid vs. CEE or diazepam x 3 mos (Warnecke 1985)
  - 60 symptomatic women (post hys, with ≥1 ovary) 4 mg bid x 6 mos, compared to estriol, E/P, or CEE (Lehmann-Willenbrock 1988)

Black cohosh: Other Studies

- 3 of 4 studies show no effect on LH
- Studies mixed on vaginal epithelium
- 2 studies (abstracts) found no effect on uterine endometrium at 98 days and 6 months (trials too short to see changes)
- Animal and *in vitro* estrogenicity studies are mixed

Black Cohosh and Breast Cancer

- 4 in vitro cell culture studies found no growth stimulation (3 found inhibition at some doses)
- Two recent studies found increased growth (Liu 2001, Löhning 2000 [abstract])
- Only in vivo study (ovx rats, DMBA) found that BC did not stimulate growth of tumors (Freudenstein 2000 [abstract])

Black cohosh: Counseling

- Some evidence of efficacy for menopausal symptoms
- Little effect in breast cancer treatment-induced menopausal symptoms
- Unclear whether or not it can cause endometrial or breast tissue stimulation
- Women taking BC long-term should be followed with vaginal ultrasound


Red Clover
(*Trifolium pratense*)

Red clover (*Trifolium pratense*) and hot flashes

- DBPC n=37 (40 mg or 160 mg Promensil™ qd x 12 weeks)
  - no difference in hot flash frequency among groups
  - no difference in scores, FSH, SHBG, vaginal epithelium (Baber RJ, Climacteric 1999;2:85)
- DBPC n=51 (40 mg qd x 7 months)
  - no difference in hot flash frequency between groups
  - no difference in Greene scores, SHBG, endometrial thickness, or vaginal epithelium (Knight DC, Climacteric 1999;2:79)

Red clover: Counseling

- No evidence of efficacy for menopausal symptoms
- Not the same as soybeans
- Possible concern about bleeding risk

Chaste tree
(*Vitex agnus-castus*)

•Contains viticin (an alkaloid) and flavonoids

• Inhibits prolactin activity *in vitro*

• May ↓ FSH and ↑LH

Vitex agnus-castus: Clinical trials

- 178 women with PMS 20 mg qd ZE 440 x 3 cycles): Symptom scores ↓ significantly more in treated group than placebo (Schellenberg 2001)
- RCT Agnolyt 3.5-4.2 mg vs B6 100 mg bid (last half of cycle x 3 cycles): Compared to baseline, symptom scores ↓ both groups) (Lauritzen 1997)
- DBPC trial of Vitex (20 mg qd x 3 months) in 52 women with luteal phase defect: Vitex ↓ prolactin, lengthened luteal phases (Milewicz 1993)

Vitex and ovarian hyperstimulation

- 32 yo infertile woman had developed single follicles with gonadotropin stimulation in 3 cycles
- After taking Vitex before and during early follicular phase of 4th cycle, ultrasound revealed three developing follicles on the right ovary and one on the left

(Cahill DJ Human Repro 1994;9:1469-70)

Negative Trials of Herbs for HF

- Evening primrose oil (2000 mg bid) n=56 RPCT x 6 months (Chenoy 1994)
- Ginseng (100 mg G115) n=384 RDBPCT x 16 weeks (Wiklund 1998)
- Dong quai (4.5 g/d) n=71 RDBPCT x 6 months (Hirata 1997)
- Chinese herb mixture n=78 RDBPCT x 3 months

Ginkgo (*G. biloba*)

- Contains ginkgolides (diterpene terpenoids), bilobalide, and flavonoids
- ↑ Blood flow to small vessels
- Scavenges free radicals
- May ↓ PAF

Ginkgo for dementia

- Meta-analysis identified >50 trials, included four with a total of 424 subjects
- Overall, significant effect translating to 3% difference in ADAS-Cog
- Concluded that 120-240 mg/day x 3-6 months benefited cognitive function

  (Oken BS, Arch Neuro1998;55:1409-15)

Ginkgo for dementia

- Systematic review of 9 randomized double-blind placebo-controlled trials concluded that ginkgo is more effective than placebo (Ernst 1999)

Ginkgo for dementia and AAMI

- RCT n=214 (210 completed) elderly with AD, VD, or AAMI treated with placebo or EGb761 (160 or 240 mg) x 12-24 weeks
- No effect on neuropsych testing, verbal learning, clinical assessment, self-reported health, memory, behavior (van Dongen 2000)

Ginkgo: possible mechanisms

- Antioxidant
- Inhibits platelet aggregation
- Ginkgolides and bilobalides increase tolerance to hypoxia
- Inhibits phospholipase A
- Stabilizes membranes
- Decreases capillary fragility
- Increases cerebral blood flow

Ginkgo: adverse effects

- German post-marketing survey of 10,815 patients found that 183 reported side effects
  - Nausea (37)
  - Headache (24)
  - Stomach problems (15)
  - Diarrhea (15)
  - Allergy (10)
  - Anxiety or restlessness (8)
  - Sleep disturbances (8)
  - Other (68)

Ginkgo biloba and bleeding

- Ginkgo alone
  - subarachnoid hemorrhage (Vale 1998)
  - subdural hematoma (Gilbert 1997)
- With other drugs
  - Aspirin – hyphema (Rosenblatt 1997)
  - Acetaminophen - bilateral subdural hematomas (Rowin 1996)
  - Warfarin - intracerebral hemorrhage (Matthews 1998)

Toxins in *Ginkgo biloba* seeds

- Ginkgolic acids may cause rash
  - German regulations require <5 ppm ginkgolic acids
- 4'methoxypyridoxine
  - Undercooked seeds
  - Gin-nan sitotoxism


St. John’s wort (*Hypericum perforatum*)

St. John's wort for depression

- Meta-analysis of 23 controlled trials
- St.Johnswort significantly better (OR 2.67, CI 1.8-4.0) than placebo in 15 trials with a total of 1008 patients
- St. Johnswort equivalent to TCAs in 8 trials with a total of 749 patients (OR 1.10, CI .93-1.31 for single preparations; OR 1.52, CI 1.52 for combination treatments)

(Linde K. BMJ 1996; 313: 253)

St. John's wort and fluoxetine

- RCT n=149 patients with mild-moderate depression compared 400 mg bid dry extract LoHyp 57 to fluoxetine(=5 mg) x 6 weeks
- Both treatments beneficial and equivalent (HAM-D)
- A/E x 17 in fluoxetine group (8 withdrew) and 12 in SJW group (Harrer G. Arzneim-Forsch 1999;49:289)

SJW and major depression: Shelton

- DBRCT n=200 tested SJW extract 900 mg x 8 wks
- No effect of treatment or time × treatment interaction
- Remission significantly higher in SJW group (14.3%) vs. placebo 4.9%
- A/E: Headache (41% vs 25%) (Shelton 2001)

Hypericum: Mechanism

- Hypericum ↓reuptake 5-HT, NA, DA (≈2 µg/ml); downregulates ß1 adrenoreceptors and upregulates 5-HT_2
- Hyperforin ↓ reuptake 5-HT, NA, DA (80-200 nmol/L)
- Hypericin has modest affinity for sigma receptors, moderate affinity for $GABA_A$, $GABA_B$, NMDA receptors
- Standardized extracts: 0.3% hypericin or 3% hyperforin

SJW adverse events: case reports

- Induction of mania/hypomania: 5 case reports (Moses 2000, Nierenberg 1999, Schneck 1998)
- Anxiety with autonomic arousal (Brown 2000)
- Subacute toxic neuropathy (pain and allodynia after sun exposure) in 35 y.o. woman (Bove 1998)
- Adynamic ileus in 67 y.o. diabetic female (Tran 1997)
- Hypotension under anesthesia (Irefin 2000)

SJW and Photosensitivity

- Case reports: Pruritic rash; subacute polyneuropathy; burning pain after phototherapy
- Single-dose (1800-3600 mg SE LI 160) and SS (1800 mg x 1 d, then 2700 mg x 7 d) caused no ↑erythema; single-dose↑UVB pigmentation
- Sensitivity to UVA ↑20% after 3600 mg single dose; ↑21% after 600 mg tid (11.3 mg hypericins)
  (Brockmoller 1997)
- Bullae reported after topical application
  (Lane-Brown 2000)

SJW and Cataracts

- Calf lenses incubated with hypericin caused photopolymerization of crystallins
  (Schey 2000)
- Clinical implications unclear

SJW and MAO inhibition

- *In vitro:* At high concentrations (50 mcg/mL), mixed results; some reports of weak MAO inhibition
- *In vivo:* no MAOI effects after administration 300 mg/kg hypericum to rats
- pK: plasma (steady state) 8.5 ng/mL (Cott 1997)
- Clinical reports: No reports of MAOI effects

SJW and Drug Interactions

- Lowers levels of indinavir, digoxin, tricyclic antidepressants, anticoagulants, cyclosporine
- May increase serotonergic effects of SSRIs
- May increase breakthrough bleeding with OC; no pregnancies reported

"You don't often see a real silk lining, these days . . ."

ADRs and DDIs

- In hospitalized patients in 1994
  - Incidence of serious ADRs 6.7%
  - Incidence of fatal ADRs 0.32%

    (Lazarou 1998;JAMA 270:1200-05)
- Of 1000 patients admitted to a geriatric unit
  - 538 exposed to 1087 potential DDIs
  - 30 experienced adverse effects attributable to DDIs (Doucet 1996;JAGS 44:944-48)

Herb-Drug Interactions: Counseling

- Medications requiring monitoring should be checked after initiation or discontinuation of St. John's wort
- Patients on warfarin should have an INR 7-14 days after starting any herb
- Consider bleeding time in anticoagulated patients on regular ginkgo or garlic
- Discontinue herbs 14 days before surgery

"Ulrich, that's bad science and you know it!"