Wellness & Women’s Health

Focus on Antioxidants & Other Dietary Supplements

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Objectives

- Analyze clinical evidence regarding supplement regimens to prevent/treat health-related conditions in women
- Evaluate efficacy, dosages, adverse drug reactions, and potential drug/herb interactions related to these herbal products
- Monitor & manage supplements, referring patients to a reputable pharmacist for more information
Menopause

- Pre-menopause, ovaries produce estradiol
- Post-menopause, extraglandular and fat tissue produce estrone
- Sxs: vasomotor, breast and urogenital atrophy, osteoporosis
- HRT – breast and uterine cancer, ↑ risk of cardiovascular events
- What about phytoestrogens?
Phytoestrogens

- Phenolics
  - Flavonoids (catechin)
  - Isoflavonoids
    - Isoflavones
    - Coumestans
  - Genistein
  - Daidzein

- Coumestans
Phytoestrogens

- Non-steroidal plant compounds that bind to estrogen receptors with 1/1000 the affinity of estradiol
- Weakly estrogenic and anti-estrogenic depending on dose, amount of endogenous sex hormones, and the target organ involved
- Classes: isoflavones (main), lignans (non phenolic), coumestans, saponins (non phenolic)
- American Menopausal Society position statement
Flavonoids (subclass of polyphenols)

- ~5000
- Six major categories:
  1. Flavonols (catechin, epicatechin): chocolate, tea, red wine, beans, apricot, cherry, grape, peach, blackberry, apple
  2. Flavonones (hesperetin, naringenin, eriodictyol): citrus fruits and juices
  3. Flavones (apigenin, luteolin): parsley, celery
  4. Isoflavones (daidzein, genistein): soy
  5. More Flavonols (quercetin, kaempferol, myricetin): onions, kale, broccoli, tomato, blueberry, apples, tea, red wine
  6. Anthocyanidins (cyanidin, pelargonidin, peonidin, delphinidin, malvidin): blueberry, black grape, cherry, blackberry, black currant, rhubarb, strawberry, red wine, plum, red cabbage
Isoflavones

- Isoflavonoids, a class of compounds with a diverse range of activities structurally distinct from phytoestrogens (i.e., genestein, daidzein, biochanin A, formononectin, puerarin)
- As antioxidants, reduce ROS, reduce RNS, increase NO
- Some isoflavones resemble estrogenic and anti-estrogenic compounds like SERMS
- Genistein and daidzein are found in soybeans, red clover, kudzu root bound to glucose as the inactive glycosides
- Intestinal glucosidases hydrolyze the glycosides to active aglycone compounds
- Women metabolize isoflavones better than men
- Effects of isoflavones on breast cancer unclear, especially estrogen-receptor positive
- DI: May counteract tamoxifen in theory
Most active isoflavone in soy

Structurally similar to 17β-estradiol (1/100-1/1000)

Binds to ERβ receptor with greater affinity than ERα, but also anti-estrogenic depending on tissue types (rat)

Can alter expression of progesterone receptor, the androgen receptor, and the oxytocin receptor

Intracellularly, inhibits tyrosine kinases

Affects cell cycle by inhibiting DNA topoisomerases I and II (like VP-16)

Isoflavones may promote cancer cell growth at lower doses (Liu 2005 Cancer Research)
Lignans

- Non-phenolic plant compounds with very weak estrogenic and anti-estrogenic activity
- Enterolactone
- Found in fruits, vegetables, whole grains, flaxseed, soybean sprouts
Coumestans

- Plant compounds
- Compete with estradiol for estrogen-receptor binding sites, resulting in higher circulating estradiol concentrations
- Found in alfalfa sprouts and clover seeds
- Not well researched
Soy

- Soybeans > tofu > soy milk regarding isoflavone concentration
- Genistein and daidzein bind to both α- (expressed in breast and ovarian cancer cell lines) and β-estrogen receptors (expressed in normal breast, uterine, ovarian tissue)
- Epidemiology: lower prevalence of vasomotor symptoms in populations that eat isoflavone-rich diets
- Hot flash reduction not supported by clinical data; FDA approved for cholesterol lowering
- Dose: 20-60 grams/day soy protein providing 34-76 mg isoflavones (1/4 block tofu, ¼ cup soy flour)
- 50 grams soy = 50-150 mg isoflavones
- SE – GI related
Black Cohosh

- Standardized to 1 mg triterpene glycosides calculated as 27-deoxyacetin (Remifemin) dose as 40 mg bid
- Not studied beyond six months
- MOA unknown
- Variable effects on LH; no effect on FSH, LH, sex-hormone binding globulin, prolactin, or estradiol in post-menopausal women
- May have selectivity for estrogen receptors, binding in bone but not uterus
- Open label trials without placebo arms reporting positive effects on symptoms
- Two small trials compared it with HRT with mixed results
- May be carcinogenic in mice
- SE – nausea, dizziness, headache
What Is Oxidative Stress and What Role Do Antioxidants Play In It?

- Oxygen free radicals are molecules with an unpaired electron created during normal body metabolism.
- Free radicals promote good oxidation that produces energy and kills bacteria.
- In excess, oxygen free radicals get into cell membranes, can cause cell damage (oxidative stress), and over time may increase risk of cancer or cardiovascular disease.
- Antioxiants counteract free radicals in the cells to protect them.
- The body makes its own antioxidants including erythrocyte superoxide dismutase and other enzymes.
Figure 2. Possible inhibitory effects of cocoa flavonoids on oxidative stress and endothelial dysfunction.
Antioxidants in Dietary Supplements

- Vitamin A (carrots, spinach, sweet potato) **
- Beta Carotene (orange/yellow vegetables)**
- Vitamin E (eggs, almonds, walnuts, olive oil, asparagus, sweet potato) **
- Vitamin C (OJ, green pepper, raspberry, tomato)
- Selenium (tuna, turkey, oatmeal, rice, walnuts, brazil nuts)
- Lycopene (tomato) **
- Coenzyme Q10 (rice bran, soy, sesame seeds, sardines) **
- Soy Isoflavones (Genistein and Daidzein)
- Turmeric (Curcumin) (curry)
- N-Acetyl Cysteine – boosts glutathione
- Phytoestrogens (yams, soy)
- Green Tea Polyphenols (ECGC)

** = fat soluble

- Johns Hopkins under contract to AHRQ NIH funded
- 7 efficacy RCT’s, 5 efficacy & safety RCTs and 3 safety-related case reports
- Definition MVI & mineral supplements: ≥ 3 vitamins or minerals without herbs, hormones, or drugs
- Limitations: RCTs only for efficacy; findings may not apply to use of commercial MVI by general population
- Conclusions: “evidence is insufficient to prove the presence or absence of benefits from the use of MVI & mineral supplements to prevent cancer and chronic illness”
Hercberg. SU.VI.MAX Study. A randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. Arch Intern Med 2004

- N = 13017 patients not selected for risk factors
- Women (35 – 60 years), men (45 – 60 years)
- Vitamin C 120 mg, Vitamin E 30 mg, Beta-carotene 6 mg, Selenium 100 mcg, Zinc 20 mg vs placebo - prevention
- Endpoints: prevention of all-site cancers, ischemic heart disease, and all cause mortality
- Results: after 7.5 years, low dose antioxidant supplements lowered total cancer incidence and all cause mortality in men, not women based on relative risk when stratified by gender
- May be due to lower baseline antioxidant status in men than women
- Limitation: need biomarker research or biopsy tissue to establish that intervention agent reaches the target tissue in an appropriate concentration

- HDL-Atherosclerosis Treatment Study (HATS), NIH grant; RCT, 3 years
- N = 160, ≥ 3 stenoses of at least 30% of luminal diameter or one stenosis of at least 50%

- Grp 1: Zocor + niacin (max 4 grams daily)
- Grp 2: Antioxidant vitamins (800 IU vit E, 1000 mg vit C, 25 mg beta carotene, 100 mcg selenium)
- Grp 3: Zocor + niacin + antioxidant vitamins
- Grp 4: Placebo

- Endpoints: change in coronary stenosis and occurrence of death, MI, stroke, or revascularization

- Results: No change in cholesterol in Grps 2 + 4. Significant positive change in cholesterol in Grp 1. Stenosis progressed 4% in Grp 4 (p =0.16) and 1.8% in Grp 2 (p = 0.004). Stenosis regressed 0.4% in Grp 1 (p < 0.001). Frequency of clinical endpoints 24% in Grp 4, 3% in Grp 1, 21% in Grp 2, and 14% in Grp 3.
Osteoarthritis - Glucosamine Sulfate

- Not an herbal product
- Cellulose derivative
- n-acetyl-glucosamine (NAG) or HCL different chemical forms of glucosamine not as well absorbed as sulfate
- Use in Osteoarthritis-progressive degeneration of cartilage glycosaminoglycans (GAG)
- MOA theory-provide exogenous regeneration of cartilage for arthritis or prednisone-induced joint disease
- Study: 212 patients with knee osteoarthritis – 1500 mg glucosamine sulfate or placebo ever day x 3 years. In The Lancet January 27, 2001
- New 2005 NIH study with glucosamine HCL 500 mg tid – no improvement in knee pain except in small group who had moderate to severe pain
- Dose: 500 mg tid – 500 mg daily after 2-3 months, combined with fluids and exercise
- SE: increased blood sugar (what about type II diabetics), heartburn
- CI: allergic to shellfish chitin
Osteoarthritis - Chondroitin

- MOA – increases water in joints by stimulating productive of hyaluronic acid by synovial cells
- From shark cartilage or bovine trachea
- Chondroitin sulfates are structurally related to LMW heparanoid, danaproid (Orgaran)
- Sulfates are large molecules, not well absorbed
- Takes 2-3 months to work
- AE’s – nausea, HA, anti-platelet
- DI – Coumadin, NSAIDs, Plavix, etc
- Found in combination with glucosamine sulfate and MSM
Osteoarthritis - Methyl Sulfonyl Methane (MSM)

- Sulfur donor, derived from DMSO
- Anti-inflammatory agent on muscle (by limiting release of inflammatory mediators) and analgesic on C nerve fibers; may also increase blood flow, reduce muscular spasm
- Not disease modifying; source of biological sulfur (component of proteins, connective tissues, hormones, enzymes)
- Long-term effects unknown
- Dose: 500 mg – 1,000 mg daily
- Side Effects: upset stomach
- Drug Interactions: other analgesics

3. Robb-Nicholson C. By the way, doctor. Is MSM as good as it sounds? Harv Womens Health Watch 2002; Aug;9:8
Osteoarthritis - Ginger


N = 247 knee patients
255 mg ginger extract, or placebo bid x 6 weeks
Results – reduced knee pain on standing (p = 0.048)
AE’s – mild GI effects


N = 75 Hip or knee patients
170 mg ginger extract, ibuprofen 400 mg, or placebo tid x 3 weeks each
Results – ibuprofen > ginger or placebo
No difference between ginger extract and placebo in a test for multiple comparisons
No serious adverse events; bruising/bleeding possible due to effects on platelets
Turmeric Root (Curcuma longa)

- Curcumin (curry) – volatile oil; Curcuminoid compounds include tumerone, atlantone, diaryl deptanoids, zingiberone
- Antioxidant properties noted in phenolic fraction (curcuminoids) isolated from a liquid extract of turmeric in vitro (Selvam 1995), and comparable with vitamin C
- Antioxidant in Alzheimer’s Disease to lower plaque load in transgenic mouse model
- American Institute for Cancer Research says curcumin prevents stomach, colon, oral, esophageal, breast cancers…more research needed regarding apoptosis
- Curcumin thought to be as effective anti-inflammatory as NSAIDs in treatment of osteoarthritis by stimulating corticosteroid release (Broadhurst 1997, Ammon 1993) or by inhibiting leukotrienes and prostaglandin synthesis; touted as COX-II inhibitor in vitro
- Dose: 300 mg tid, standardized to 95% curcuminoids per dose
- SE: GI ulcer
- DI: possible additive effects on platelets (NSAIDs, aspirin, Ticlid, Plavix)
"Conceptual Template"
(for organizing both diagnostic and therapeutic options)

Comprehensive, Collaborative, Personalized

"Stratified Stepped-care Model"

Biochemical
Structural (anatomic)
Movement (functional)
Environment
Mind-Body
Energy

CAM Biochemical
CAM Structural
Surgery
Less Aggressive
Less Costly
Less Risky
Less Passive
Less Aggressive
More Costly
More Risky
More Passive

Patients
Risk Stratified
Evidence
Ranked
## Complementary & Alternative

- Acupuncture
- Alexander Technique
- Aromatherapy
- Ayurvedic
- Biofeedback
- Chakra
- Color Therapy
- Craniosacral Therapy
- Guided Imagery
- Healing Touch
- Herbology
- Homeopathy
- Journaling
- Laughter Therapy
- Massage Therapy
- Meditation
- Music Therapy
- Naturopathy/Nutrition
- Pilates
- Reflexology
- Reiki
- Rolfing
- Shamanism
- Spiritual Retreats
- Tai Chi/Yoga
- Traditional Chinese Medicine (Qi)
- Water Therapy
What is the Practice of Holistic Pharmacy?

- Bridging with physician partners; focus on safety
- Building patient/pharmacist partnerships – empowerment & advocacy in healthcare system
- Motivational coaching (i.e., Rx/OTC, dietary supplements, lifestyle, emotional, social, spiritual)
- Referrals to other credible holistic practitioners
- Respect for diverse cultures & healthcare models
- [www.rxintegrativesolutions.com](http://www.rxintegrativesolutions.com)