Non-Prescription Products and Effects

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Disclosures: Kenneth Kellick, Pharm.D has nothing to disclose
Learning Objectives

• Upon the completion of this program the audience will:
  – List differences between herbal supplements and drugs
  – Describe ways by which the current regulation system for herbal supplements impacts the safety of these products
  – Name resources to determine scientifically accurate answers to patient inquiries regarding herbal supplements
  – Discuss the efficacy and safety of herbal supplements for a specific patient based on his current medications and health conditions
What is an Herbal Supplement?

• Herbs (botanicals) are plants or plant parts used for their scent, flavor, or therapeutic properties

• Herbal supplements are dietary supplement that contain herbs and are used for their health benefits

• Most herbal supplements are sold as capsules, tablets, extracts, or teas, and may contain a single herb or mixtures of multiple herbs
Dietary Supplement Regulation

- Dietary Supplement Health and Education Act (DSHEA) of 1994
  - Dietary supplements are regulated as foods
    - Includes vitamins, herbals, and medical foods
  - Manufacturers must ensure safety
    - No Food and Drug Administration (FDA) approval required before marketing
    - FDA can remove unsafe products from market
  - Comply with Current Good Manufacturing Practices (cGMPs)
    - Same GMPs as required for foods
Dietary Supplement Regulation

• Dietary Supplement Health and Education Act (DSHEA) of 1994
  – No false or misleading claims
  – No claims can be made about efficacy in treating/preventing specific conditions
    • e.g. “prevents heart attacks”
  – General health promotion claim is ok if followed by: “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease.”
    • e.g. “promotes heart health”
## Requirements for Drugs vs. Herbs

<table>
<thead>
<tr>
<th></th>
<th>Drugs</th>
<th>Herbs</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Proof of efficacy before marketing</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Proof of safety and tolerability in clinical trials</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Compliance with Good Manufacturing Practices</td>
<td>Yes (drug GMPs)</td>
<td>Yes (food GMPs)</td>
</tr>
<tr>
<td>Contents of product regulated by FDA</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Variability Between Products

• Study of active ingredient of commercial preparations of St. John’s Wort
  – 39 products tested (13 tablets, 26 capsules)
  – Actual active ingredient concentration:
    • Average 57.5% of label claim
    • Range 0.098% to 108.6%
    • 2 of 39 products were within 10% of stated potency
    • 6 of 39 products were within 20% of stated potency
Choosing a Product

• Efficacy/safety ratings
• Same brand as used in clinical study when possible
• USP verification - voluntary compliance with stricter manufacturing standards:
  • verifies ingredients are as stated on label
  • does not contain harmful ingredients
  • ingredients will release in the body
Information Resources

• *Natural Medicines Comprehensive Database
  – Subscription, professional level information
  – Free, consumer level information

• *Natural Standard
  – Subscription, professional level information

• Clinical Pharmacology
  – Subscription, professional level information (minimal herbal info)

• National Center for Complementary and Alternative Medicine (NCCAM)
  – Free, consumer level information

• Medline Plus: Herbal Medicine
  – Free, consumer level information
Search Results

Clinical Management Series:
Courses related to "ginkgo":
• Natural Medicines in the Clinical Management of Alzheimer's Disease

Natural Product Search:
Natural Product Names that BEGIN with "ginkgo":
• GINKGO
  • Full Monograph
  • Safety
  • Effectiveness
  • Adverse Reactions
  • Dosage/Administration
  • Mechanism of Action

Interactions with Drugs
Interactions with Herbs
Interactions with Food
Interactions with Lab Tests
Interactions with Diseases

Also Known As
People Use This For
Editor's Comments
References

Patient Education Handout: English | Spanish | French
Natural Medicines Database

- Information available:
  - Alternative names
  - Uses
  - Efficacy
  - Mechanism of action
  - Safety
  - Adverse reactions
  - Dosage/administration
  - Interactions
    - Herbs
    - Drugs
    - Foods
    - Lab tests
    - Diseases
Understanding the Ratings

• Natural Medicines Comprehensive Database
  – Effective
  – Likely Effective
  – Possibly Effective
  – Possibly Ineffective
  – Likely Ineffective
  – Ineffective

• Natural Standard:
  – A = Strong Positive Evidence
  – B = Positive Evidence
  – C = Unclear Evidence
  – D = Negative Evidence
  – E = Strong Negative Evidence
Top 10 Herbals by Sales

$4.1 billion total herbal supplement sales in 2010

2011 American Herbal Products Association Annual Report
<table>
<thead>
<tr>
<th>Herb</th>
<th>Latin name</th>
<th>US Dollar Sales</th>
<th>% Change 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cranberry</td>
<td><em>Vaccinium macrocarpon</em></td>
<td>$40,112,500</td>
<td>13.43</td>
</tr>
<tr>
<td>2. Soy</td>
<td><em>Glycine max</em></td>
<td>$18,611,700</td>
<td>10.21</td>
</tr>
<tr>
<td>3. Saw palmetto</td>
<td><em>Serenoa repens</em></td>
<td>$18,055,930</td>
<td>-3.97</td>
</tr>
<tr>
<td>4. Garlic</td>
<td><em>Allium sativum</em></td>
<td>$15,218,730</td>
<td>-9.21</td>
</tr>
<tr>
<td>5. Ginkgo</td>
<td><em>Ginkgo biloba</em></td>
<td>$14,628,650</td>
<td>1.88</td>
</tr>
<tr>
<td>6. Milk thistle</td>
<td><em>Silybum marianum</em></td>
<td>$12,834,460</td>
<td>14.01</td>
</tr>
<tr>
<td>7. Echinacea¹</td>
<td><em>Echinacea spp.</em></td>
<td>$10,914,500</td>
<td>-14.62</td>
</tr>
<tr>
<td>8. Black cohosh root</td>
<td><em>Actaea racemosa¹</em></td>
<td>$10,319,990</td>
<td>-0.53</td>
</tr>
<tr>
<td>9. St. John’s wort</td>
<td><em>Hypericum perforatum</em></td>
<td>$8,439,300</td>
<td>-4.38</td>
</tr>
<tr>
<td>10. Ginseng³</td>
<td><em>Panax ginseng</em></td>
<td>$6,596,372</td>
<td>-6.94</td>
</tr>
<tr>
<td>11. Valerian root</td>
<td><em>Valeriana officinalis</em></td>
<td>$5,455,633</td>
<td>23.02</td>
</tr>
<tr>
<td>12. Green tea</td>
<td><em>Camellia sinensis</em></td>
<td>$5,213,135</td>
<td>-8.85</td>
</tr>
<tr>
<td>14. Horny goat weed</td>
<td><em>Epimedium spp.</em></td>
<td>$3,059,464</td>
<td>7.05</td>
</tr>
<tr>
<td>15. Bilberry</td>
<td><em>Vaccinium myrtillus</em></td>
<td>$1,582,448</td>
<td>-11.24</td>
</tr>
<tr>
<td>16. Ginger</td>
<td><em>Zingiber officinale</em></td>
<td>$1,570,807</td>
<td>13.40</td>
</tr>
<tr>
<td>17. Grape seed</td>
<td><em>Vitis vinifera</em></td>
<td>$1,261,907</td>
<td>-10.96</td>
</tr>
<tr>
<td>18. Elderberry</td>
<td><em>Sambucus nigra</em></td>
<td>$797,915</td>
<td>-14.99</td>
</tr>
<tr>
<td>19. Aloe vera</td>
<td><em>Aloe vera</em></td>
<td>$747,787</td>
<td>17.31</td>
</tr>
<tr>
<td>20. Yohimbe</td>
<td><em>Paussinsyta jaehimbe</em></td>
<td>$446,382</td>
<td>-8.29</td>
</tr>
<tr>
<td>22. Kelp</td>
<td><em>Laminaria digitata</em></td>
<td>$333,512</td>
<td>41.42</td>
</tr>
<tr>
<td>23. Spirulina</td>
<td><em>Arthospira spp.</em></td>
<td>$299,648</td>
<td>26.49</td>
</tr>
<tr>
<td>24. Hawthorn</td>
<td><em>Crataegus spp.</em></td>
<td>$281,834</td>
<td>0.01</td>
</tr>
<tr>
<td>25. Cayenne</td>
<td><em>Capsicum annuum</em></td>
<td>$273,844</td>
<td>49.05</td>
</tr>
<tr>
<td>26. Red clover</td>
<td><em>Trifolium pratense</em></td>
<td>$258,558</td>
<td>-23.71</td>
</tr>
<tr>
<td>27. Olive leaf</td>
<td><em>Olea europaea</em></td>
<td>$230,452</td>
<td>-4.09</td>
</tr>
<tr>
<td>28. Horse chestnut seed</td>
<td><em>Aesculus hippocastanum</em></td>
<td>$216,235</td>
<td>-25.73</td>
</tr>
<tr>
<td>29. Dandelion</td>
<td><em>Taraxacum spp.</em></td>
<td>$212,674</td>
<td>3.76</td>
</tr>
<tr>
<td>30. Alfalfa</td>
<td><em>Medicago sativa</em></td>
<td>$150,615</td>
<td>45.99</td>
</tr>
<tr>
<td>31. Pycnogenol</td>
<td><em>Pinus pinaster</em></td>
<td>$139,619</td>
<td>-22.06</td>
</tr>
<tr>
<td>32. Dong Quai root</td>
<td><em>Angelica sinensis</em></td>
<td>$102,141</td>
<td>42.10</td>
</tr>
<tr>
<td>33. Feverfew leaf</td>
<td><em>Tanacetum parthenium</em></td>
<td>$102,071</td>
<td>6.38</td>
</tr>
<tr>
<td>34. Barley</td>
<td><em>Hordeum vulgare</em></td>
<td>$98,871</td>
<td>2.81</td>
</tr>
<tr>
<td>35. Cascara sagrada</td>
<td><em>Frangula purshiana</em></td>
<td>$90,111</td>
<td>-15.48</td>
</tr>
<tr>
<td>36. Eleuthero</td>
<td><em>Eleutherococcus senticosus</em></td>
<td>$77,507</td>
<td>14.62</td>
</tr>
<tr>
<td>37. Cat’s claw</td>
<td><em>Uncaria tomentosa</em></td>
<td>$69,809</td>
<td>-11.15</td>
</tr>
<tr>
<td>38. Eyebright herb</td>
<td><em>Euphrasia spp.</em></td>
<td>$61,281</td>
<td>-10.43</td>
</tr>
<tr>
<td>39. Maca</td>
<td><em>Lepidium meyenii</em></td>
<td>$57,560</td>
<td>-62.03</td>
</tr>
<tr>
<td>40. Licorice root</td>
<td><em>Glycyrrhiza spp.</em></td>
<td>$53,849</td>
<td>17.75</td>
</tr>
</tbody>
</table>

http://cms.herbalgram.org/herbalgram/issue95/hg95-mktrpt.html
Top CV Herbs 2011

<table>
<thead>
<tr>
<th>Herb</th>
<th>2011 US DOLLARS</th>
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<tr>
<td>Garlic</td>
<td>$15,218,730</td>
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<td>Grape Seed</td>
<td>$1,261,907</td>
</tr>
<tr>
<td>Olive Leaf</td>
<td>$2,304,520</td>
</tr>
<tr>
<td>Pycogenol (pine bark)</td>
<td>$139,619</td>
</tr>
</tbody>
</table>
Hypertension Likely Effective

- Dash - Some clinical research shows that using the DASH diet significantly lowers systolic hypertension in patients with stage 1 isolated systolic hypertension after 8 weeks.
Hypertension—Possibly effective

- Alpha Linoleic Acid (ALA)
- Blonde Psyllium
- Calcium—Moderate or no effect
- Cocoa —Modest effect- is it the polyphenols?
- Cod Liver Oil—modest effect
- Coenzyme Q-10—systolic and diastolic HTN
- Fish oil—seems to help cyclosporine induced HTN. May help essential HTN
Interactions

• Coenzyme Q10-
  – concern that antioxidants such as coenzyme Q-10 might protect tumor cells from chemotherapeutic agents that work by inducing oxidative stress, such as the alkylating agents (e.g., cyclophosphamide, Cytoxan) and radiation therapy
  – Vitamin K analog- watch with warfarin
• Fish Oil
  – High doses of fish oils may have antiplatelet effects but unlikely as potent as ASA
  – Perhaps lower BP in addition to other antihypertensives (additive)
  – Oral contraceptives may blunt TG lowering of Fish Oil
  – Interaction with orlistat- decreased absorption due to binding of lipase in GI tract
HTN-Possibly Effective

- Garlic- use powder (good for tick bites too)
- Green coffee (Starbucks Fans)-chlorogenic acids
- Olive –Extra Virgin (or olive leaf)
- Potassium-Supplement or foods high in K
- Pycogenol (extract of French Pine bark)  
  – -SBP only
Interactions

• Garlic
  – Increase INR with warfarin
  – May decrease effectiveness of some oral contraceptives
  – May decrease effectiveness of cyclosporine
  – Possible induction of CYP 3A4?
  – May decrease effectiveness of some NNRTIs and PIs

• Green Coffee
  – Alendronate - Separate coffee ingestion, including green coffee and alendronate administration by two hours. Coffee reduces alendronate bioavailability by 60%
  – Anticoagulants - may increase bleeding risk
  – Antidiabetic drugs - may impair glucose control
  – Beta- adrenergic drugs - possibly increased HR and inotropic effect
  – Schizophrenic (atypical antipsychotics) - may blunt effect
HTN- Possibly effective

- QI Gong – poor studies
- Sweet Orange- Is it the juice, Vit-C or the K+
- Vitamin C-Ascorbic Acid- Modest decrease in SBP
- Wheat Bran– Modest decrease in SBP/DBP
HTN Possibly ineffective

- EPA (Eicosopentanoic Acid)
- Gamma Linoleic Acid
- Oats
- Vitamin D
- Vitamin E
HTN-Insufficient Evidence

• Biofeedback
• Black seed
• Black tea
• Casein peptides
• Cocoa—particularly dark chocolate
• Coconut water
• DMSO (Dimethylsulfoxide)
• Flaxseed Oil
• Grape and grape seed-polyphenols
• Green Tea – Chinese data
HTN Insufficient evidence

- Hibiscus
- Hydroxymethylbutyrate (HMB)
- L-Arginine
- L-Citrulline
- Magnesium
- Meditation
- Oolong Tea – Chinese data
- Pomegranate – SBP Maybe
- Quercetin
- Soy
- Stevia
- Tomato Extract
- Yucca
HTN- Possibly ineffective

- EPA
- Gamma Linoleic Acid
- OATS
- Vitamin D
- Vitamin E
Cholesterol Likely Effective

• Barley
• Beta Glucans
• Beta-Sitosterol
• Blond Psyllium
• Niacin
• Oats
Sitostanols
Benecol Buttery Spread
Benecol Smart Chews
Benecol Soft Cheese Spread
Benecol Softgels
Benecol Olive Spread
Benecol Light Spread
Benecol Regular Spread
Benecol Yogurt Drinks
Benecol Dairy Free Drinks
CholestSure
Cholesterol – Possibly Effective

- Artichoke
- Avocado
- Black Psyllium
- Calcium
- Dash Diet
- English Walnut
- Flaxseed
- Grape Seed
- Green Tea
Drug Interactions

- Green Tea (chlorogenic acid)
  - Adenosine stress test – stop 24 hours before test
  - Amphetamines- contraindicated
  - Beta-Adrenergics- caution
  - Atypicals Antipsychotics- Caution
  - Cocaine-contraindicated
Cholesterol- Possibly Effective

• Guar Gum
• Jiaguloan (the immortality herb)
• Macadamia Nut
• Magnesium
• Olive Oil
• Pectin
• Red Rice Yeast
• Rice Bran
Red Rice Yeast Story

• Monacolin- K similar to Lovastatin (Aspergillus terrus)
• Other monacolins (J,L,X dihydromonacolin L, monacolin M and dihydromevinolin)
• Varying concentrations of citrin (mycotoxin)

• Varying concentrations of monacolins per capsule (0.31-11.5mg)

• One study of cholestin 2.4G/d, xuezhikang 1.2Gm/d and Zhibituo3 .15 Gm/D corresponds to 5mg, 10mg and 9mg of lovastatin respectively.

• Lipid lowering compares to 10-20mg simvastatin, pravastatin 10mg/d, lovastatin 20mg /day, atorvasatin 10mg/d and fluvastatin 10mg/d (Chinese studies).

• Other miscellaneous compounds in RYR may provide additional lipid lowering independent of monocolin

Journal of Clinical Lipidology; 2013;7:117-122
## Summary of RYR products

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean + SD</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>RYR strength mg/dosing unit</td>
<td>534.6 + 239.3</td>
<td>600</td>
</tr>
<tr>
<td>Total recommended daily RYR dose, mg</td>
<td>1500.3 + 1194.7</td>
<td>1200</td>
</tr>
<tr>
<td>Recommended units/d</td>
<td>2.9 + 3</td>
<td>3</td>
</tr>
<tr>
<td>Estimated monacolin K mg/d</td>
<td>22.5 + 32.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Estimated citrinin mcg/day</td>
<td>189.9 + 274.6</td>
<td>85.6</td>
</tr>
</tbody>
</table>

From 12 commercially avail 600mg capsule products
(citrinin is mutagenic at concentrations of 0.2-1.7mcg/g and available in some food colorings)
Cholesterol Possibly Effective

- Safflower
- Sitostanol
- Soy
- Soybean Oil
- Sweet Orange
- Yogurt
Possibly Ineffective

- Acacia
- Amaranth
- Cod Liver Oil
- Coenzyme Q10
- Flaxseed oil
- Garlic
- Guggul
- Inulin
- Lecithin
- Red Clover
Insufficient Evidence

- Activated charcoal
- Alfalfa
- Aloe
- Apitherapy (royal jelly)
- Bean Pod
- Black Current
- Black Seed
- Chitosan
Cholesterol-Insufficient Evidence

- Cocoa
- Coconut oil
- DHA
- Fenugreek
- Glucomannan
- Grape Seed
- Hibiscus
- Hydroxymethyl butyrate (HMB)
- Hyperimmune egg powder
- Inositol Nicotinate
Cholesterol- Insufficient Evidence

- Irvingia Gabonesis (African Mango)
- Job’s Tears
- Krill Oil
- Larch Arabinogalactan
- Policosinol
- Pomegranate
- Pycogenol
- Quercetin
- Royal Jelly
Cholesterol- Insufficient Evidence

• Sunflower Oil
• Vitamin C
• Vitamin D
• Vitamin E
• Vitamin K
• White Mulberry
• Yucca
Diabetes-Possibly Effective

- Agaricus Mushroom
- Alpha Linoleic Acid
- Beer
- Blonde Psyllium
- Caffeine, Coffee
- Cinnamon
- Chromium
- Flaxseed
- Ginseng, American
- Glucomannan
Diabetes- Possibly Effective

- Guar Gum
- Magnesium
- Milk thistle
- Niacin
- Oats
- Prickly pear cactus
- Soy
- White Mulberry
- Wine
- Xanthan gum
Diabetes- Possibly Ineffective

- Beta Carotene
- Cranberry
- DHA/EPA
- Garlic
- Jambolan
- Lutein
- Lycopene
- Selenium
- Tomato
- Vitamin C
- Wheat Bran
Diabetes- Likely Ineffective

- Fish Oil
Diabetes- Insufficient Evidence

- Aloe
- Apple Cider Vinegar
- Artemisia Herba-Alba
- Banaba
- Biotin
- Bitter Melon
- Black Tea
- Branched Chain Amino Acids
- Buckwheat
Diabetes- Insufficient evidence

- Buckwheat
- Calcium
- Cassia Cinnamon
- Chia
- Cocoa
- Coenzyme Q
- Diacylglycerol
- Fenugreek
- Fig
Diabetes Insufficient Evidence

- Flaxseed Oil
- Genseng, Panax
- Green tea
- Gymema
- Holy Basil
- Ivy Gourd
- Manitate Mushroom
- Meditation
- Olive
Diabetes Insufficient Evidence

- Oolong Tea
- Ozone Therapy
- Pycogenol
- Qi Gong
- Salacia
- Stevia
- Vanadium
- Vitamin D
- Vitamin E
- Yoga
Summary

• Herbal supplements are regulated as dietary supplements, not drugs
  – Implications for safety and product consistency
• Resources available for unbiased information
  – Efficacy
  – Safety
  – Interactions
• Always do a complete prescription and non-prescription history
References

• Natural Medicines Comprehensive Database. [http://naturaldatabase.therapeuticresearch.com]
• Natural Standard. [http://www.naturalstandard.com]
• Clinical Pharmacology. [http://www.clinicalpharmacology.com/]
• National Center for Complementary and Alternative Medicine. [http://nccam.nih.gov/]
• Journal of Clinical Lipidology; **2013**;7:117-122