VITAMINS, SUPPLEMENTS AND HERBS – SEPARATING WHEAT FROM CHAFF

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UNC-Chapel Hill School of Medicine
Why are Supplements Important?

• CDC: 50% of Americans use supplements; majority of cancer patients use supplements during all phases of treatment

• Can augment / interfere with drug therapy

• AARP study: high level of supplement use age > 50, but 69% did not tell their doctors (gaps in communication can negatively affect outcomes and patient-provider relationship)

• What is “natural” is not synonymous with what is safe
Use of Vitamins, Supplements and Herbs Among Veterans

Significant number of primary care patients in VA system use vitamins and supplements.

Prevalence of medication substitution is high, strongly associated with prescription rationing due to cost.

Med Care 2014;52: S65–S69
Beliefs - Why People Use Supplements

• Maintain health, support self-healing mechanisms
• Relieve symptoms, shorten duration of self-limited disease
• Boost short-term immunity
• Used for chronic conditions not easily treated
• Alternative to prescription drugs
• Reduce side effects with prescription drugs
• May not have access to conventional health care
Product Quality

ConsumerLab - good source of credible supplement information, product quality testing results (www.consumerlab.com)

USP – indicator of higher quality; absence does not imply poor quality (relatively small # of companies participating)

NSF International

GMPs (as of 2010)
Herbal Preparations

Infusion – tea (pour near-boiling water over herb, steep covered)
Decoction – tea prepared by placing herb in cold water, bringing water to boil, simmer covered (stronger than infusion)
Tincture – herbs placed in mixture of alcohol and water (menstruum), steeped for several weeks (maceration) or percolated through a funnel

   Long shelf life

   1:5 indicates 1 kg herb mixed with 5 liters of menstruum

Fluid extract – similar to tincture, but is by definition a 1:1 extract (1:1 fluid extract is 5 times stronger than 1:5 tincture)
Glycerites – tinctures where solvent is mixture of glycerin and water
Standardized extract – allows for more accurate dosing

Adapted from work of T. Low Dog, MD
“Know 10 Well”
Calcium
Coenzyme Q10
Fish Oils
Magnesium
Multivitamins
Probiotics
Red Yeast Rice
SAMe
Turmeric
Vitamin D

“Know a Little”
Black Cohosh
Butterbur
Echinacea
Ginger
Ginseng
Glucosamine
Glutamine
Melatonin
Medicinal Mushrooms
Peppermint
Calcium


Some trials suggest significant increased risk of heart attack and CV death in people taking calcium supplements, even when paired with other anti-osteoporosis interventions


Positive correlation between serum calcium levels and vascular calcification

J Bone Miner Res 2010;25:2777-2785.

* Calcium supplements should only be recommended to patients who do not consume adequate calcium from dietary sources.
Calcium

Meta-analysis (59 trials)

Dietary calcium intake (n = 1,533)

Calcium supplementation (n = 12,257)

Conclusion: “Increasing calcium intake from dietary sources or by taking calcium supplements produces small non-progressive increases in BMD, which are unlikely to lead to a clinically significant reduction in risk of fracture.”

BMJ 2015;351:h4183
Calcium

- Food sources best (low-fat dairy, sardines, canned salmon with the bones, broccoli)

- Supplements: calcium citrate best with low stomach acid (elderly, patients taking antacids); calcium carbonate often better tasting but should be taken with food

- Men should not exceed 500mg of calcium in supplement form per day due to an association with increased risk of prostate cancer

Calcium

Institute of Medicine (IOM) and National Osteoporosis Foundation Recommend 1,200 mg calcium daily for women > 50

Average dietary intake in Western counties = 700-900 mg/day

Associated AEs include:

- Constipation
- Kidney stones
- CV events?
Coenzyme Q10

Fat-soluble, vitamin-like compound present in all cells (*ubiquinone*)
- converted to ubiquinol - may be more bioavailable

Role in electron transport chain (ATP production), potent antioxidant, possible membrane stabilizer

Potential Indications:
Heart Failure  Hypertension  Migraine prophylaxis
Statin-induced myopathy  Parkinson’s disease  Mitochondrial dz

Dose: 100-300 mg daily; Parkinson’s – 1,200-2,400 mg daily

Precautions: may interfere with coumadin Rx; $$
Coenzyme Q10

“.. compared with placebo, coenzyme Q10 does not result in clinically significant reductions in systolic or diastolic 24-h ambulatory BP or heart rate in patients with the metabolic syndrome and inadequately treated hypertension, although there was a significant reduction in daytime diastolic BP loads.”

Figure 2 | Changes in daytime diastolic blood pressure loads from baseline following 12 weeks of treatment with coenzyme Q10 or placebo. *P < 0.05 for comparison of between-group changes.

Percentage of patients who required levodopa by the time until the investigator considered that the subject needed treatment with levodopa.

**Figure Legend:**

- **Treatment Groups**
  - **Placebo**
  - **Coenzyme Q₁₀, 300 mg/d**
  - **Coenzyme Q₁₀, 600 mg/d**
  - **Coenzyme Q₁₀, 1200 mg/d**

**Graph:**

- Y-axis: % of patients who required levodopa.
- X-axis: Time to requirement of levodopa, mo.

Fish Oils (Omega-3 Fatty Acids)

EPA + DHA (the essential fats within fish oils)
- eat fish or supplement?

Potential Indications Include:
  Hypertriglyceridemia
  Established cardiovascular disease (protection against SCD)
  Ocular / prenatal health
  Enhanced cognition?

Dosage: based on EPA + DHA content (generally EPA > DHA)
  General – 1,000-2,000 mg total EPA + DHA combined
  High triglycerides – 4,000 mg total EPA + DHA combined

Precautions: bleeding; seafood allergy; mercury
GISSI Study (11,324 pts)

Fish or Fish Oil Intake and Relative Risk of CHD Death in Prospective Cohort Studies and RCTs

Total of 16 prospective cohort studies (n = 326,572) and 4 RCTs (n = 35,115) from U.S., Europe, and Asia

Total risk reduction = 36%

Mozaffarian and Rimm. JAMA 2006;296:1885-1899
Fish Oils - Controversy

Meta-analysis: omega-3s do not provide protection against major CV events, but do reduce overall CV mortality and sudden cardiac death


Other studies: essentially no CV benefit whatsoever

**Fish Oils - Labels**

**Supplement Facts**

<table>
<thead>
<tr>
<th>Serving Size: 2 Softgels</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Servings Per Container: 30</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Amount Per Serving</th>
<th>%DV</th>
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</thead>
<tbody>
<tr>
<td>Calories</td>
<td>18</td>
</tr>
<tr>
<td>Calories from Fat</td>
<td>18</td>
</tr>
<tr>
<td>Fat</td>
<td>2 g</td>
</tr>
<tr>
<td>Total Omega-3 Fatty Acids</td>
<td>1,490 mg</td>
</tr>
<tr>
<td>EPA (Eicosapentaenoic Acid)</td>
<td>894 mg</td>
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<tr>
<td>DHA (Docosahexaeonic Acid)</td>
<td>446 mg</td>
</tr>
</tbody>
</table>

* Daily Value not established.

**Other Ingredients:** Ultra Refined Fish Oil Concentrate, Gelatin (softgel), Glycerin, Ammonium Hydroxide, Ethylcellulose, Coconut Oil, Stearic Acid, Sodium Algininate, Water, Mixed Tocopherols.
Magnesium
Magnesium

Possible Indications Include:
- Leg cramps
- Headaches (migraine)
- Tremor
- Fatigue
- Palpitations
- PPIs

Dosage: 300 – 600 mg daily (less diarrhea with chelate or glycinate)

Precautions: renal insufficiency
Magnesium

- USDA: only 32% of Americans meet Dietary Reference Intake (whole grains, nuts, leafy green vegetables)

- 40-80% of people with DM have low Mg stores – effects on blood pressure, lipids, and insulin resistance

- 10-20% of all hospitalized patients / 60-65% of ICU patients have low magnesium

- Regular alcohol use depletes magnesium

- Magnesium can alleviate constipation due to calcium supplementation
Magnesium:

600 mg / day

% Reduction in HA Frequency After 9-12 weeks

Cephalgia 1996;16:257-263.
Magnesium

Essential role in synthesis / metabolism of vitamin D

NHANES (2001-2006) and NHANES III data:

High intake of total / dietary / supplemental Mg independently associated with reduced risk of vitamin D deficiency / insufficiency

BMC Medicine 2013;11:187
Magnesium

After multivariable adjustment, the relative risk of SCD significantly lower in women in the highest quartile compared with the lowest quartile of dietary (RR = 0.63) and plasma (RR = 0.23) magnesium.

Linear inverse relationship with SCD strongest for plasma magnesium (P for trend = 0.003):

- Each 0.25-mg/dL (1 SD) increment in plasma magnesium associated with a 41% reduced risk of SCD.

Am J Clin Nutr 2011;93:253-260
In response to findings of 3 studies in same issue that found no benefits against CVD, cognitive decline or cancer incidence:

"The message is simple: Most supplements do not prevent chronic disease or death, their use is not justified, and they should be avoided."

The purpose of multivitamin use is not to prevent or cure chronic disease by themselves but to correct sub-optimal nutrient levels.
Choosing a Multivitamin

• No more than 5000 units pre-formed vitamin A (mixed carotenes generally better)
  - excess vitamin A associated with bone loss
  - smokers should not take beta carotene supplements
    potential increased cancer risk
• Vitamin E – mixed tocopherols and tocotrienols
• 100-200 mcg selenium, 15 mg of zinc, 0.5-2.0 mg copper and 400 mcg of folic acid
• Choose product without iron unless anemic
• Avoid product duplication (example – multivitamin plus B complex or specialty vitamin such as “blood sugar formula”, “eye formula”, etc.)
• No need for added herbs in multivitamin
Probiotics

Definitions:

Probiotics – microbes that when ingested improve host health beyond normal nutrition

Prebiotics – food for health-promoting organisms in the gut (oligosaccharides, polysaccharides)

Synbiotics – contain both pro- and prebiotics

Potential Indications Include:

Atopy  
C. difficile  
Colic  
IBS  
IBD  
Antibiotic-associated diarrhea (prophylaxis and treatment)  
Preventing URIs  
Obesity  
Mood disorders
Probiotic Therapy and Prevention of Hospital-Acquired Diarrheal Illness

FIGURE 2. Survival curve for “free of diarrhea” time. Kaplan-Meyer plot of percentages of children in the hospital that remained free of diarrhea related to the regimen (Lactobacillus GG vs. placebo).
Probiotics

** Effects are strain-dependent

Some of the better researched strains:

- Lactobacillus GG
- Lactobacills reuteri
- Bifidobacterium infantis
- VSL #3 (mix of 8 organisms)

Dosage: no agreed upon standard

- $1 \times 10^8 - 1 \times 10^9$ CFU (Colony Forming Units)

Precautions: immunocompromised; pancreatitis; severely ill
## Probiotics – Clinical Indications

<table>
<thead>
<tr>
<th>Clinical Condition</th>
<th>Effectiveness</th>
<th>Specific Strain of Organism and Strain References</th>
<th>Analysis References</th>
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<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
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<tr>
<td>Infectious childhood—treatment</td>
<td>A</td>
<td><em>Saccharomyces boulardii</em>,15 LGG,16 <em>Lactobacillus reuteri</em> SD211217</td>
<td>15-18</td>
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<tr>
<td>Prevention of infection</td>
<td>B</td>
<td><em>S. boulardii</em>,15 LGG16</td>
<td>15, 16, 18</td>
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<tr>
<td>Prevention of AAD</td>
<td>A</td>
<td><em>S. boulardii</em>,19 LGG,20 combination of <em>Lactobacillus casei</em> DN114 G01,</td>
<td>19-21</td>
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<tr>
<td></td>
<td></td>
<td><em>Lactobacillus bulgaricus</em>, sfn <em>Saccharomyces thermophilus</em></td>
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<tr>
<td>Prevention of recurrent CDAD</td>
<td>B/C</td>
<td><em>S. boulardii</em>,11 LGG,22 bacteriotherapy14</td>
<td>11, 12, 14, 22</td>
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<tr>
<td>Prevention of CDAD</td>
<td>B/C</td>
<td>LGG,11 <em>S. boulardii</em>22</td>
<td>11, 22</td>
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<tr>
<td><strong>IBD</strong></td>
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<tr>
<td>Pouchitis</td>
<td>A</td>
<td>VSL#323-25</td>
<td>23-25</td>
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<tr>
<td>Preventing and maintaining remission</td>
<td>C</td>
<td>VSL#326</td>
<td>26</td>
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<tr>
<td>Induce remission</td>
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<tr>
<td>Ulcerative colitis</td>
<td>B</td>
<td><em>Escherichia coli</em> Nissle27, VSL#328</td>
<td>27-29</td>
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<tr>
<td>Inducing remission</td>
<td>A</td>
<td><em>E. coli</em> Nissle,30 VSL#329</td>
<td>28-30</td>
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<tr>
<td>Maintenance</td>
<td>C</td>
<td><em>E. coli</em> Nissle,31 <em>S. boulardii</em>,32 LGG33</td>
<td>31-33</td>
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<tr>
<td>Crohn’s</td>
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<tr>
<td><strong>IBS</strong></td>
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<tr>
<td>Immune response</td>
<td>A</td>
<td>LGG, <em>Lactobacillus acidophilus</em> NCD01748,13 and <em>Bifidobacterium bifidum</em> NCD01453</td>
<td>13, 47</td>
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<tr>
<td><strong>Necrotizing Enterocolitis</strong></td>
<td>B</td>
<td><em>Lactobacillus acidophilus</em> NCD01748,13 and <em>Bifidobacterium bifidum</em> NCD01453</td>
<td>13, 47</td>
</tr>
<tr>
<td>C</td>
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<tr>
<td>*<em>Recommendations From 2008</em></td>
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<tr>
<td><strong>Allergy</strong></td>
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<tr>
<td>Atopic eczema associated with cow’s milk allergy</td>
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<tr>
<td>Treatment</td>
<td>A</td>
<td>LGG, <em>Lactobacillus acidophilus</em> LAFT1, <em>Lactobacillus plantarum</em>, <em>Bifidobacterium lactis</em>, <em>Lactobacillus johnsonii</em></td>
<td>40, 41</td>
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<tr>
<td>Prevention</td>
<td>A</td>
<td>LGG, <em>Bifidobacterium lactis</em>41</td>
<td>41</td>
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<tr>
<td><strong>Radiation enteritis</strong></td>
<td>A</td>
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<tr>
<td>VSL#3,42 <em>L. acidophilus</em>43</td>
<td>C</td>
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<tr>
<td><strong>Vaginosis and vaginitis</strong></td>
<td>C</td>
<td><em>L. acidophilus</em>,44 <em>Lactobacillus rhamnosus</em> GR-1,45 <em>L. reuteri</em> RC1446</td>
<td>44-46</td>
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*Check 2008 references for further elaboration on strains used and their availability.

*Reference48 was made available after the workshop meeting on April 8, 2011 but believed to be significant enough to qualify this probiotic to be in a B category.

AAD indicates antibiotic-associated diarrhea; CDAD, *Clostridium difficile*-associated diarrhea; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; LGG, *Lactobacillus* GG.
Fig. 1. Various important actions of resveratrol that form the basis of its benefit in various diseases. Resveratrol activates SIRT1 and PGC-1α and improves the functioning of the mitochondria. Resveratrol binds to TyrRS to potentiate a signaling cascade drive...

Gustavo Tomas Diaz-Gerevini, Gaston Repossi, Alejandro Dain, María Cristina Tarres, Undurti Narasimha Das, Aldo Renato Eynard

**Beneficial action of resveratrol: How and why?**


http://dx.doi.org/10.1016/j.nut.2015.08.017
CONCLUSIONS: Four-week intake of an FMPP by healthy women affected activity of brain regions that control central processing of emotion and sensation.
Red Meat, Gut Bacteria, and CVD Risk

Figure 2. Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level.

Data are shown for 4007 participants in the clinical-outcomes study. The P value is for all comparisons.
Red Yeast Rice
Red Yeast Rice

Prepared from white rice fermented with yeast - a “natural” statin

Monacolin K → Lovastatin

Potential Indications Include:
- Dyslipidemia; statin intolerance; philosophically opposed to statins

Dosage: start with 600 mg BID; standard dose ends up being 1,200 mg BID

Precautions: similar to those with prescription statin therapy
Red Yeast Rice

- Cholesterol lowering
- Antidiabetic
- Anti-inflammatory
- Anticancer
- Hypotensive
- Osteogenic
- Cardioprotective

Red Yeast Rice

LDL-C reduced by 21%

“Red yeast rice and therapeutic lifestyle change decrease LDL cholesterol level without increasing CPK or pain levels and may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.”

Ann Intern Med 2009;150:830
Red Yeast Rice

Meta-analysis (13 RCTs with 804 subjects)

Significant lowering effects on:
- Total Cholesterol
- Triglycerides
- LDL-C

No significant effects on HDL-C

No serious side effects reported

“RYR is an effective and relatively safe approach for dyslipidemia...may be an alternative approach in patients with...statin-related adverse effects...could be used for the primary and secondary prevention of coronary heart disease.”

PLoS ONE 2014;9:e98611
SAMe

S-Adenosyl-L-Methionine - involved in methyl group transfers

Potential indications include:
  - Depression - low CSF levels associated with depression; PO / IV crosses blood brain barrier
  - Osteoarthritis
  - Cholestasis / hepatic disorders

Dosage: 400-1600 mg daily in divided doses (often 200 / 400 mg TID)

Precautions: insomnia; serotonin syndrome when combined with other antidepressants; may trigger manic episode in bipolar patients
SAMe
FIGURE 1. Change in HAM-D Scores During Treatment Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo. 

- Change in HAM-D Total Score
- Baseline, Week 1, Week 2, Week 3, Week 4, Week 5, Week 6, Endpoint (LOCF)
- SAMe
- Placebo

SAMe in Antidepressant Non-Responders

FIGURE 2. HAM-D Response and Remission Rates Among Antidepressant Nonresponders Randomly Assigned to S-Adenosyl Methionine (SAMe) or Placebo. a

- Placebo + Antidepressant (N=34)
- SAMe + Antidepressant (N=39)

Turmeric (Curcuma longa)
Turmeric (*Curcuma longa*)

Member of ginger family; major ingredient of curry and mustard

Potential Indications include:
- Osteoarthritis
- Rheumatoid arthritis
- Dyspepsia
- Anti-cancer

Dose: 200-400 mg TID curcumin or 4,000 mg / day turmeric

* piperine

Precautions: possible mild anticoagulant activity; may cause gallbladder contractions
Turmeric (Curcuma longa)
Turmeric (Curcuma longa)

Anti-oxidative and anti-inflammatory molecular targets of diabetes for curcumin

Curcumin

Molecules 2015;20:9183
The Path of Vitamin D

Sun Exposure

Vitamin D3 (Cholecalciferol)

Liver
(25-Hydroxyvitamin D)

Kidney
1,25 di-hydroxyvitamin D (Calcitriol = Active hormone)

Food

Main storage form of Vit D. Order this when checking levels.
Nl > 30 ng/ml

↑ Levels to compensate for ◀ stores can give false reassurance
Mortality from Ovarian Cancer
1970-1994

From National Cancer Institute. Cancer Mortality Maps & Graphs.14
Which Form of Vitamin D?

Answer – vitamin D3

- Cholecalciferol (D3) – derived from sheep’s wool

- Ergocalciferol (D2) – derived from plant and fungal sources

- Vitamin D2 far less potent, shorter duration of action; dosing is NOT equivalent (50,000 units D2 is not equal to effects expected from 50,000 units of D3)
Vitamin D and Multiple Sclerosis

“Among patients with MS treated with interferon beta-1b, higher 25(OH)D levels were associated with lower rates of MS activity on MRI.”

JAMA Neurol 2015;72:1458-1465

“... some clinical findings already strongly suggest that vitamin D status influences the relapse rate and radiological lesions in patients with MS...”

Ther Adv Neurol Disord 2013;6:81-116
Vitamin D and Bone Health

Widespread use of vitamin D for osteoporosis prevention in community-dwelling adults without specific risk factors for vitamin D deficiency may be inappropriate.

Vitamin D not a compound mainly responsible for maintenance of bone calcium content - rather for maintenance of circulating calcium concentrations (crucial for cardiac and neuronal function).

“Bone is merely a reservoir that can be drawn on for this purpose.”

Vitamin D

• Best free source is sunlight — 15-20 minutes of unprotected exposure several times a week
  - confounding factors (geography, season, sunscreen)

• Consider celiac disease if supplementing and levels still low

• Caution with sarcoidosis, lymphoma, TB (can lead to increased production of 1,25 vitamin D, hypercalcemia)

• Know your vitamin D level?

• 1000 IU/d = ↑ level by 8-10 ng/ml
Distributions of serum 25 OH vitamin D in 128 statin-treated patients with myalgia at study entry and in 493 statin-treated asymptomatic patients.

Know A Little Something About...

Black Cohosh
Butterbur
Echinacea
Ginger
Ginseng
Glucosamine
Glutamine
Melatonin
Medicinal Mushrooms
Peppermint
Black cohosh (*Cimicifuga racemosa*)

Potential Indications Include: menopausal hot flashes

Dose: 20-40 mg BID (Remifemin is best studied product)

Precautions: safety data only out to 6 months of use; autoimmune hepatitis; unlikely to possess estrogen-like activity but concerns persist
Black Cohosh (*Actea racemosa*)

Black cohosh does not appear to have estrogenic activity (*in vitro*, animal and human studies)

Effect on vasomotor symptoms likely due to actions on hypothalamic serotonergic neurons, and not estrogen-like activity


Also does not appear to increase breast density

*Int J Oncol* 2003;23(5):1407–12
*Support Care Cancer* 2007;15(8):913–21
*Menopause* 2006;13(4):678–91
Butterbur (*Petasites hybridus*):

Reduced headache frequency by 48% vs. placebo

Seasonal AR – effect comparable to cetirizine (Zyrtec)


*BMJ 2002;324:144-146.*

75 mg BID x 4 months
Echinacea

Genus contains 9 species; *E. purpurea*, *E. angustofolia*, *E. pallida*

Consensus that echinacea extracts display immunologic activity (macrophage activation, cytokine expression)

Potential Indications Include: treatment (not prevention) of uncomplicated viral URI

Dose: wide variety of doses recommended

Precautions: allergy to daisies; autoimmune disease; HIV
Ginger (Zingiber officinale)

Potential Indications Include:
- Morning sickness
- N/V with chemotherapy
- Osteoarthritis
- Motion sickness
- Gastroparesis
- Dysmenorrhea

Dosage: fresh ginger root (made into tea, candied, as seasoning) OR 250 mg capsules TID-QID standardized to 4% volatile oils or 5% 6-gingerol/6-shogaol

Precautions: high intakes may increase bleeding risk
Panax ginseng

Also called Asian ginseng; adaptogen – helps normalize physiology, improves resistance to stress, increases stamina

Potential Indications Include:
- Recovery from significant illness
- Type 2 diabetes
- COPD
- Immune support
- Lack of energy
- Bronchitis

Dose: typical is 100-200 mg daily

Precautions: reports of prolonged use (> 3 months) being associated with vaginal bleeding, mastalgia; may interfere with coumadin Rx; may potentiate effects of hypoglycemic agents; insomnia
Glucosamine

Protein involved in production and support of joint cartilage, synovial fluid, and connective tissue

Forms: hydrochloride, sulfate; often paired with chondroitin

Potential Indication: osteoarthritis

Dose: 500 mg TID

Precautions: shellfish allergy; occasional GI upset; may interfere with coumadin Rx

*note – concerns about increasing BS in those with DM disproved
Glucosamine - Osteoarthritis

Patented crystalline glucosamine sulfate (pCGS) formulation at dose of 1500 mg once daily superior to other GS and glucosamine hydrochloride formulation and dosage regimens:

- may delay joint structural changes
- long-term reduction in need for additional pain analgesia and NSAIDs
- >50% reduction in costs associated with medications, healthcare consultations and examinations over 12 months
- reduction in need for TJR for at least 5 years following treatment cessation

Semin Arthr Rheum 2015 – accepted manuscript
Glutamine

Non-randomized, controlled trial, n=45 receiving high-dose paclitaxel and either usual care (n=12) or glutamine (n = 33) 10 g TID x 4 days

Glutamine: significant decrease in severity of sensory neuropathy (P<.05), better motor function (P=.04), less gait disturbance (P=.016)

Second non-randomized, controlled trial (n=46) receiving high-dose paclitaxel – glutamine group (n=17) had significantly less weakness (P=.02), better vibratory sensation (P=.04), less toe numbness (P=.004) after 32 days

Clin Oncol (R Coll Radiol) 2005;17(4):271–6
Glutamine

N=86 metastatic colon cancer patients - oxaliplatin / 5-FU

N=44 given glutamine 15 g BID for first 7 days of chemotherapy

Reduced incidence of moderate grade neuropathy after 2 (17 vs 39%), 4 (5 vs 18%), and 6 cycles (12 vs 32%)
Less interference with activities of daily living (17 vs 41%) and less reduction in chemotherapy (7 vs 27%)

No difference in response to chemotherapy or survival

Oncologist 2007;12(3):312–9
Glutamine

The most abundant free amino acid in humans

Tumors and tumor cell lines rapidly consume the amino acid glutamine and use it to supply metabolic pathways that support cell growth and proliferation.

The pineal gland begins producing melatonin in the evening. Melatonin levels peak in the middle of the night. Melatonin levels decline to low daytime amounts.
Melatonin - Cancer

Endogenous hormone synthesized in and secreted by pineal gland

- stimulates apoptosis
- reduces tumor growth factors
- decreases endothelial growth factor
- possesses anti-inflammatory activity

Support Care Cancer 2002;10;110-6
Melatonin

Oncostatic, cytotoxic and antiproliferative actions, as well as antioxidant effects

Several studies suggest supplementation may improve survival of chemotherapy-treated patients with some solid tumors

Melatonin

Randomized clinical trial of cisplatin + etoposide + melatonin in 100 people with metastatic non–small-cell lung cancer

- improved tumor response rates

Same group of investigators observed similar results in study of 250 patients with various metastatic solid tumors receiving several different chemotherapy regimens

J Pineal Res 2003;35:12-15
Eur J Cancer 1999;35:1688-1692
# Melatonin

<table>
<thead>
<tr>
<th>Wang et al. [116]</th>
<th>Cancer Chemother Pharmacol 2012 (review)</th>
<th>761 pts</th>
<th>Solid tumor cancers</th>
<th>20 mg/die</th>
<th>Melatonin as an adjuvant therapy for cancer led to substantial improvements in tumor remission, 1-year survival, and alleviation of radiochemotherapy-related side effects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills et al. [92]</td>
<td>J Pineal Res 2005 (review)</td>
<td>643 pts (between 1992 and 2003)</td>
<td>Solid tumor cancers</td>
<td>Not specified</td>
<td>Melatonin reduced the risk of death at 1 year (relative risk: 0.66, 95% confidence interval: 0.59–0.73, 12 = 0%, heterogeneity ( P \leq 0.56 )). Effects were consistent across melatonin dose, and type of cancer.</td>
</tr>
<tr>
<td>Cerea G et al. [124]</td>
<td>Anticancer Res 2003</td>
<td>30 pts (15 + 15)</td>
<td>Metastatic colorectal cancer</td>
<td>20 mg/die</td>
<td>This preliminary study shows that the efficacy of weekly low-dose CPT-11 in pretreated metastatic colorectal cancer patients may be enhanced by a concomitant daily administration of the pineal hormone MLT.</td>
</tr>
<tr>
<td>Lissoni P et al. [128]</td>
<td>Eur Urol 1997</td>
<td>14 pts</td>
<td>Metastatic prostate cancer</td>
<td>20 mg/die</td>
<td>A decrease in PSA serum levels greater than 50% was obtained in 8/14 (57%) patients, a survival longer than 1 year was achieved in 9/14 (64%) patients. The concomitant administration of the pineal hormone MLT may overcome clinical resistance to LHRH analogs and improve clinical conditions in metastatic prostatic cancer patients.</td>
</tr>
</tbody>
</table>

Medicinal Mushrooms

Ganoderma lucidum (Reishi/Ling Chi)
photo by Tom Volk
Medicinal Mushrooms

Extracts tested in a variety of cancers have shown potential health benefits:

- improved immune parameters (solid tumors) – beta-1,3-D-glucans
- increased disease-free survival
- possibility of enhanced tumor response
- improved QOL

Data strongest for proprietary Coriolus extract PSK (3 g per day)

Promising data associated with other extracts, including Maitake (Grifola frondosa), Reishi (Ganoderma lucidum), and Shiitake (Lentinus edodes)
Medicinal Mushrooms

Polysaccharide extract (PSK) of medicinal mushroom *Trametes versicolor* / *Coriolus versicolor* (Turkey Tail)

Randomized trial n=207 stage 2+3 colorectal cancer patients who had received conventional treatment

5 years’ follow-up: treated group had greater percentage of 5-year disease-free survival and decreased relative risk of regional metastases

Br J Cancer 2004;90(5):1003–10
Medicinal Mushrooms

Meta-analysis of three trials (10 articles)
N=1,094 subjects with colorectal cancer

PSK use associated with significant improvement in overall survival (RR = 0.71) and disease-free survival (RR = 0.72)

Another meta-analysis of 8 randomized, controlled trials, N=8,009 gastric cancer patients
- increased survival (HR = 0.88)

Peppermint (*Mentha piperita*)

Menthol: primary component of essential oil, responsible for spasmolytic effects (reduces smooth muscle contractions through calcium channel blocking effect)

Potential Indication: irritable bowel syndrome (IBS)

Dosage: enteric-coated capsules per label directions

Precautions: may worsen GERD (reduces lower esophageal sphincter pressure); dermatitis (applied topically); avoid application near nares of infants (bronchospasm, apnea); bile duct obstruction
Peppermint (Mentha piperita)

“Peppermint oil is a safe and effective short-term treatment for IBS.”

J Clin Gastroenterol 2014;48:505-512
Chinese Medicinal Herbs
Be well