

The *Natural* Way to the Slim & Sexy new you!

► *The use of daily herbal products for cosmetic gain*



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Learning Objectives

- Identify benefits and hazards of using herbals and natural supplements for weight loss, insomnia, and sexual dysfunction
- Differentiate between pharmacodynamic and pharmacokinetic properties of commonly used herbal and natural supplements for treating weight-loss, insomnia, and sexual dysfunction
- Identify potential drug-drug interactions with common herbals and natural supplements prescribed in the United States for weight loss, insomnia, and sexual dysfunction

Epidemiology

- Over 1500 herbal products available on the US market
- 4 out of 10 adults use complimentary alternative medicine (CAM)
 - 1 out of 9 children use CAMs
- Statistics correlate higher usage among patients unable to afford conventional therapies
- Prevalence of CAM use associated with gender, education level, smoking status, geographic location, cancer history, income status, and prior hospitalizations

Barnes PM and Bloom B. Complementary and Alternative Medicine Use among Adults and Children, United States, 2007. National Health Statistics Reports, 2008;12:1-24

What are we using and why?

Natural Product	Use among surveyed in 2007 (%)
Fish Oil/DHA/Omega 3 FA	37.4%
Glucosamine	19.9%
Echinacea	19.8%
Flaxseed oil	15.9%
Ginseng	14.1%
Ginkgo Biloba	11.3%
Coenzyme Q-10	8.7%
Green Tea Pills	6.3%
Cranberry	6.0%
Saw Palmetto	5.1%
Melatonin	4.6%

Barnes PM and Bloom B. Complementary and Alternative Medicine Use among Adults and Children, United States, 2007. National Health Statistics Reports, 2008;12:1-24

Risk vs. Benefit

Risks

- Largely unregulated
- Variability among quality of CAM products
- Difficulty to recognize active entity among several components
- Misconception that a natural product = safe
- No ADE and DDI evaluation requirements vs. prescriptions
- Lack of CAM knowledge taught in medical curriculum

Benefits

- Evidence-base medicine available for CAMs, with some (+) results
- Research with herbals can lead to development of more selective drugs
- (+) perception leading to compliance with medication
- Third-party evaluators available to aide with product variability

Pradhan R and Chatterjee MK. The CAM Education Program of The National Center on Complementary and Alternative Medicine. An Overview. Academic Medicine 2007;82(10):91-928

Insomnia's negative impact

- Commonly reported among adults
 - Up to 30% of patients report dysfunction
 - Severe insomnia ranges from 10%-15%
- Subjective effects on neurocognitive performance and appearance
- Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-30) evaluates patient's appearance due to insomnia
 - Cosmetic attribute of illness
 - No difference in perception among insomniacs and good sleepers



Egle et al. Insomnia, withdrawal, psychometric properties of the Pittsburgh Sleep and Anxiety, Sleep Scale and the Sleep Disturbance Questionnaire. Journal of Psychosomatic Research 2000;48(1):11-18
Image provided via Google Images

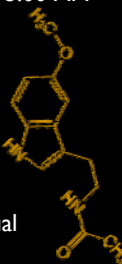
Melatonin

- Most popular CAM for sleep regulation and insomnia, however not an herbal
 - Natural physiological sleep regulating hormone
 - Very safe profile vs. other pharmacological treatments
- Physiology
 - Synthesized in pineal gland from 5-HT → Production and release regulated by suprachiasmatic nucleus (SCN) → Regulates sleep/wake cycle
- Pharmacology
 - Binds to MT₁ and MT₂ receptors primarily in the SCN

Pandey Prasad et al. Melatonin: Nature's most versatile biological signal. *EBM Journal* 2006;27(3):2613-2638.

Melatonin Pharmacokinetics

- Maximal concentrations between 2:00 & 3:00 AM
- Short t_{1/2} & Low bioavailability
 - Higher bioavailability in women
 - Lower circulating concentrations in elderly
 - High variation of bioavailability
- Metabolized through cytochrome P450 (CYP) pathways and conjugation
- Secretion occurs 2 hours prior to habitual bedtime



Pandey Prasad et al. Role of the Melatonin System in the Control of Sleep. *Thrombosis Prevention, CVD Drug* 2012;2(1):96-103. Image provided via Google Images.

Clinical Efficacy of Melatonin

- Multiple studies analyzing efficacy of melatonin
 - Majority of studies suggest mild improvement in sleep-onset latency, however there are mixed results
 - Dose and trial length vary
 - Leger et al. examined levels of 6-sulfatoxymelatonin and treatment response to melatonin in mixed population (n=396)
 - 30% of subjects (n=112) excreted low-levels of melatonin during the night w/insomniacs excreted lower levels overall vs. normal volunteers
 - Patients w/low excretion levels had significantly higher responses vs. the other treated group (58% vs. 47%, p<0.05)

Leger D, Lanson M, Zisapel N, Nocumand S. 6-sulfatoxymelatonin Excretion in Insomnia and its Relation to the Response to Melatonin Receptorantagonist Therapy. *Am J Med* 2008;118:91-95. Image provided via Google Images.

Valerian (*Valeriana officinalis*)

- Perennial plant native to North America
- Pharmacology
 - Flavonones derived from the plant contribute to pharmacological properties (flavonoid glycoside linarin, flavone 6-methylpigenin, & flavanone glycoside 2S(-) hesperidin)
 - ↑ GABA concentrations in the synaptic cleft
 - GABA reuptake inhibitor (?) or GABA enhancement (?)
- Commonly combined w/other CAMs



Breit S, Paulus A, Moore D, et al. Valerian for sleep: a systematic review and meta-analysis. *Am J Med* 2006;119(1):1005-1012. Image provided via DARECCT and Scamton. <http://www.bananafruit.com/valeriana>. An Evidence-Based Approach. St. Louis: Mosby Elsevier; 2010.

Valerian (*Valeriana officinalis*)

Clinical Efficacy

- Efficacy is variable among studies
 - Majority of studies have poor methodology, small number of participants, variant extracts used, and small duration
 - Most improvements seen were subjective
- Meta-analysis of valerian
 - (Sample of 29 trials included regarding efficacy and safety)
 - Majority saw significance in efficacy vs. placebo
 - Most rigorous studies showed ineffectiveness of valerian

Safety

- Minimal safety issues
 - Mild ADEs
 - Nausea/Diarrhea
 - CNS effects
 - Transient liver dysfunction
 - Avoid concurrent use with CNS depressants
 - May potentiate the effect of antiepileptic drugs
 - Mild-to-moderate CYP 3A4 inhibition
 - Theoretical interactions

Leah DM, Leland CA, Perry JL, and V. Valerian. A systematic review of valerian as an agent with sedative properties. *Phytotherapy Research* 2010; 11: 209-236. Image provided via Google Images.

Kava kava (*Piper Methysticum*)

- Popular herbal in the South Pacific
- Approx 15 active constituents known as kavapyrones contribute to pharmacological action
 - Difficulty with PK and PD properties, however individual constituents work synergistically together
- Pharmacology
 - Blockade of Na-gated channels, ↑ GABAergic transmission, & blockade of NE reuptake



Shin YH and Singh AN. Therapeutic Potential of Kava in the Treatment of Anxiety Disorders. *CNS Drug* 2002;16(1):71-74. Image provided via WebMD and Scamton. <http://www.bananafruit.com/valeriana>. An Evidence-Based Approach. St. Louis: Mosby Elsevier; 2010.

Kava kava (*Piper Methysticum*)

Clinical Efficacy

- CNS depressant qualities suggest efficacy with insomnia
- Wheatley D. *Tx. of stress-induced insomnia* (n=24)
 - ↓ in mean insomnia severity scores based on 300 point scale after 6 weeks of tx. (mean Δ of 30.9 points, $p < 0.05$)
- More plausible efficacy with anxiety
 - Anxiety effects correlated with buspirone (BuSpar®)

Safety

- Controversial drug
 - Banned in several countries
- Issues revolving around hepatotoxicity
 - FDA released consumer advisory on March 25, 2002 regarding potential risk
 - Probability estimated < 1 in 10 million daily doses
- Several kavapyrones are strong CYP inhibitors
- Product still readily available

Wheatley D. *Herb-Drug Interactions: A Handbook*. Boca Raton, FL: CRC Press; 2004:1201-1202.
Singh NN and Singh NN. Therapeutic Potential of Kava in the Treatment of Anxiety Disorders. *CNS Drugs* 2002; 16(11):731-743.
Warning on Kava and Liver in the Treatment of Insomnia. *Phytother Res* 2001; 15:248-251.

RCT of Kava kava & Valerian for treatment of Insomnia

- Jacobs et al.
- Randomized, 3-arm, placebo-controlled, double-blind clinical trial
 - A total of 391 participants were randomized to receive placebo (n=135), kava (n=121), or valerian (n=135)
 - All participants showed substantial improvements in Insomnia Severity Index (ISI) at 2 & 4 wks from baseline, with placebo showing the greatest reduction at 4 wks (-8.3 ± 6.8 for placebo vs. -8.1 ± 6.2 and -7.9 ± 6.1 for kava and valerian respectively)
- No statistical significance among treatment groups

Jacobs EA et al. An Internet-based Randomized, Placebo-controlled Trial of Kava and Valerian for Anxiety and Insomnia. *Phytother Res* 2002; 16:102-107.

Weight Loss & Sexual Dysfunction

- Major target among pharmaceutical companies and herbal manufacturers
 - Blockbuster industry
- Data suggests nearly 70 million Americans are trying to lose weight or prevent weight gain
 - Nearly 33% of Americans are currently overweight
- Prevalence of erectile dysfunction (ED) is up to 33% in men
 - Higher numbers among men w/comorbid disease states

Bacon CC, Millman BA, Kawachi I, et al. Sexual function in men older than 50 years of age: Results from the Health Professionals Follow-up Study. *Ann Intern Med* 2003; 139:161-168.
Chang CL, Chen YC, Tsai CJ, Chang HJ, Kuo MY. Weight loss and oxidative stress: An example of current trends. *Endocrine* 2006; 49:103-107.
Prevalence of overweight, obesity, and extreme obesity among adults—United States, 1996-98 through 2005-2006. http://www.cdc.gov/nchs/data/pressrel/obesity_adult_96-06.pdf.

Ephedra (*Ephedra sinica*)

- Ma haung
- Historically a popular OTC tx for weight loss
- Pharmacology
 - Plant leaves contain ephedrine and pseudoephedrine
 - ↑ NE & Epi → Direct stimulation of α & β receptors
- Strong evidence for efficacy, however safety remains the issue
 - Supplements banned by the FDA on April 12th, 2004
 - Combination with caffeine linked to ↑ cardiovascular events
- Still currently available online

Blumenthal M, Goldberg A, Cohen J. *Herbal Medicines: Comprehensive Clinical Pharmacology*. New York, NY: CRC Press; 2006.
Blumenthal M and Sorenson L. <http://www.naturaldatabase.com/Herbals/EphedraSinica.html>. © 2006, Mosby Elsevier, 2006.

Ginseng (*Panax ginseng*)

- One of the top ten herbals used in the United States by adults
- Utilized in multiple disease states
- Pharmacology
 - Classic aphrodisiac & stimulant
 - Properties derived from ginsenosides or steroidal saponins
 - Possible inhibition of pancreatic lipase(?) for weight loss
 - Enhancement of nitric-oxide (NO) release in corpus cavernosum
 - Relaxation of smooth muscles



Wheatley D and Bacon B. *Complementary and Alternative Medicine Use among Adults and Children*. 2006. 2007. National Health Statistics Reports. 2008; 13:1-7.
Wheatley D. *Herb-Drug Interactions: A Handbook*. Boca Raton, FL: CRC Press; 2004:1201-1202.
Kato N, Nakata S, and Kawanishi S. Weight Gain Reduction in Mice Fed Fat-rich Diets by Ginseng. *Phytother Res* 2005; 19:100-104.
Image provided via Blumenthal M and Sorenson L. <http://www.naturaldatabase.com/Herbals/PanaxGinseng.html>. © 2006, Mosby Elsevier, 2006.

Ginseng (*Panax ginseng*)

Clinical efficacy

- Lack of clinical evidence for use as weight loss supplement although there is widespread use
 - Primary studies conducted in animals
 - Weak recommendation
- Superior to placebo and trazodone for treatment of ED
- Systematic review shows positive effectiveness for improving symptoms of ED

Safety

- Low report of ADEs
 - Most common included:
 - Gastric upset
 - Headache
 - Constipation
 - Insomnia
- Drug interactions
 - Avoid use w/warfarin
 - ↓ INR
 - MAOIs
 - Increased risk of CNS effects
 - Alcohol

Wheatley D. *Herb-Drug Interactions: A Handbook*. Boca Raton, FL: CRC Press; 2004:1201-1202.
Jung H et al. Best efficacy for treating erectile dysfunction: a systematic review. *Int J Clin Pharmacol Ther* 2006; 34:44-50.
Blumenthal M and Sorenson L. <http://www.naturaldatabase.com/Herbals/PanaxGinseng.html>. © 2006, Mosby Elsevier, 2006.

Yohimbine (*Pausinystalia yohimbe*)

- Derived from yohimbe bark extract
 - 10%-15% of represents active yohimbine hydrochloride
- The over-the-counter aphrodisiac
- Pharmacology
 - α_2 -adrenoceptor antagonist
 - Acts at presynaptic autoreceptors
 - ↑ sympathetic tone and outflow
 - ↓ peripheral adrenergic tone
 - Increases nerve transmission to genital tissue(?)



Copyright © 2007, Elsevier Inc. All rights reserved. In: Pharmacology and Therapeutics, 10th Edition, Elsevier, 2007, pp. 100-101.

Ullrich C and Sautter F. <http://www.ncbi.nlm.nih.gov/pubmed/12700000>. In: Ullrich C and Sautter F, eds. *Pharmacology and Therapeutics*. St. Louis: Mosby Elsevier, 2010. Image provided via Google Images.

Yohimbine (*Pausinystalia yohimbe*)

Clinical Efficacy

- Shows modest efficacy for improving ED
 - Mixed results
 - Trials do not use American Urological Association (AUA) standards
- Combination with L-arginine glutamate showed positive results
 - Statistically significant improvement with combination product compared to yohimbine monotherapy ($p=0.006$)

Safety

- Well tolerated therapy, however safety is a concern
 - Cardiovascular effects
 - ↑ Blood pressure
 - ↑ Heart rate
 - Psychogenic effects
 - ↑ insomnia
 - ↑ anxiety
 - ↑ tremor
 - Increased urinary frequency
- AUA panel does not recommend using yohimbine for ED

Walter L, Lewis M, George P, Wilson M, and Ismail H. Effect of yohimbine on all forms of erectile dysfunction and venous insufficiency. A New Oral Therapy for Erectile Dysfunction. *European Urology* 2002; 41: 605-611.

Montague et al. Chapter 1. The Management of Erectile Dysfunction. In: AUA website. <http://www.auanet.org>. Accessed 1/15/2010.

Tom SW, Wilson M, and Wilson M. Yohimbine: a clinical review. *Pharmacology & Therapeutics* 2001; 91:215-242.

Enzyte®

- The all natural-male enhancement
- Misconceptions...



Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving	% DV
Niacin ¹	30 mg	150%
Zinc (as zinc oxide)	30 mg	200%
Copper (as copper oxide)	4 mg	200%

Enzyte® Proprietary Blend: 541 mg
 Korean red ginseng root 10:1 extract, Ginseng biloba leaf standardized extract, pine bark saponin extract, Tribulus terrestris extract (45% saponins) (fruit and stem), L-arginine HCl, Ashwa sativa extract (aerial parts), horny goat weed standardized extract (Epimedium sagittatum) (whole plant), maca root, muira puama extract (aerial parts), octacosanol, saw palmetto berry, Swedish flower pollen extract

¹ Daily value (DV) not established
 Other ingredients: Dicalcium phosphate, microcrystalline cellulose, croscarmellose sodium, stearic acid, magnesium stearate, silica and film coat (hydroxypropyl cellulose, titanium dioxide, and FD&C blue #2 lake).

Image provided via Google Images.

Enzyte®

- No clinical studies performed to date with Enzyte® combination product for erectile dysfunction or other claimed "male-enhancing effects"
 - Use of ginseng as primary agent suggests efficacy in treating erectile dysfunction
 - Possible synergy with other combined agents
- Costs
 - 1 month supply of Enzyte® (\$39.99) vs. 1 month supply of Korean ginseng (\$13.49)

Pricing provided via <http://www.enzyte.com>

Summary

- CAMs, including herbal products, are a popular treatment choice among individual patients
- Use of CAMs for cosmetic reasons should not be recommended to patients, unless the treatment has proven efficacy and is appropriately tailored to the patient's needs
- Health care providers should become more aware of popular CAM products used for cosmetic purposes due to the high proportion of users among the general population

Questions

- 1.) A potential pharmacokinetic advantage of using melatonin for insomnia is its long half-life, which is useful for treating patients who have wake-after sleep onset insomnia.
- 2.) Yohimbine has similar pharmacological properties to clonidine, thus common adverse effects with use would be dry mouth, sedation, and hypotension.
- 3.) According to the U.S. Department of Health and Human Services, ginseng was one of the top ten natural products used among adults age 18 years and older in 2007.