What's Up With All These Supplements?

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Objectives

- Review AACE guidelines on supplement use
- List popular dietary supplements (weight loss, other)
- Discuss problems with supplements such as side effects, interactions, and complications
- Review data for and against disease management with supplements

AACE Guidelines on Supplement Use[1]

Define dietary supplements[2] :

- Product taken by mouth that contains a dietary ingredient intended to supplement the diet
- Vitamins, minerals, herbs/botanicals, amino acids, other (hormones, etc.)

List examples of products used for different endocrine disease scenarios (e.g., diabetes, obesity, thyroid disorders)

Discuss strategies for patient communication

Provide useful resources

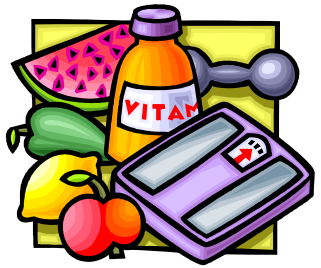
Discuss evidence

Discuss potential adverse effects and interactions (drug, disease, other products)

1. Endocrine Practice 2003; 9:417-470; 2. https://www.fda.gov/downloads/Food/DietarySupplements/UCM240978.pdf

Epidemiology of Use

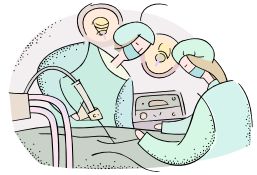
- 15% of Americans[1]
  - Females: 20.6%
  - Males: 9.7%
- 34% of those who had made serious weight loss attempt[2]
- One of top 20 reasons supplement use: weight loss[3]
- Costs[4]
  - 2016: $2.1 billion



1 J Am Diet Assoc 2007;107:441-447. 2 Obesity 2008;16:790-796. 3 JAMA Intern Med 2013:173:355-361.
4 Nutrition Business Journal 2016;21:3-7.

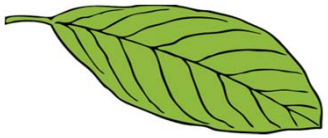
Concerns for Use

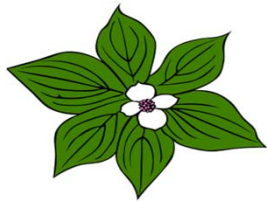
- Beliefs: supplements are natural/thus safe
  - "If available for sale, must be safe"
- Substitute for healthy diet, exercise
- Added ingredients[1]
  - Laxatives, diuretics, prescription wt loss meds, thyroid hormones, drugs to mask side effects (beta blockers)
- 23,000 ER visits/year due to ADRs from supplements[2]
  - Wt loss, Energy products: 72% of ADRs
    - Cardiovascular effects
- Product variability
  - Plant sources
  - e.g., Aristolochia substitution
- Adverse Effects[3,4]
- Drug interactions[5,6]
- Surgery precautions[7]



- JAMA:
  - FDA-recalled supplements containing banned substances (sibutramine, steroids, sildenafil, fluoxetine) back on shelf 6 months later[8]

1. Drug Saf 2009;32:453-456 2. N Engl J Med 2015;373:1531-40 3. Drug Safety 1997;17:342-56 4. N Engl J Med 2000;342:1686-92 5. JAMA 1998;280:1569-75
6. Lancet 2000;355:134-38 7. AORN J 1999;69:173-5,177-8,180-3 8. http://time.com/3554782/dietary-supplement-safety/





Common Examples

- Alpha Lipoic Acid
- Bitter Orange
- Caffeine
- Calcium
- Capsaicin
- Cha de Bugre
- Chitosan
- Chromium
- C-Linoleic Acid
- Dimethylamylamine
- Flaxseed
- Garcinia cambogia
- Glucomannan
- Green Coffee Bean Extract
- Green Tea
- HCG
- Irvingia gabonensis
- 7-keto-DHEA
- Phaseolus vulgaris
- Probiotics
- Red Raspberry Ketones
- Yohimbe

Alpha Lipoic Acid (Thioctic Acid)

Background	Mechanism	Uses	Side Effects	Drug Interactions
Coenzyme in body; In vivo: ↑ ATP production	Antioxidant ↓ food intake; affects 5'-AMP activated protein kinase Mitochondrial Respiratory enzyme cofactor	Peripheral neuropathy; Insulin sensitivity Wt loss	GI, Urticaria, Interferes with Hypo or Hyper thyroidism	Thiamine deficiency: possible toxicity ↓ Chemo effects + SU: Hypoglycemia

Diabetes Technol Ther 2000;2:401-13 Diabetes Care 1996;19:257-67

Alpha-Lipoic Acid (Thioctic Acid)

RDBPCT in N=228 overweight/obese[1]

- PL, 1200, 1800 mg/day x 20 weeks
- ↓ calories by 600 kcal/day
- Primary endpoint: wt change

Results

- Wt ↓ 1800 mg/day: 1.83 kg (2.1% ↓); P<0.05 vs Pl
- Wt ↓ 1200 mg/day: 1.1 kg (1.2% ↓)
- Wt ↓ PL: 0.8 kg (0.9% ↓)
- BMI ↓ 1800 mg/day: 0.72 kg/m^2 (2.2%); P<0.05 vs Pl
- ≥ 5% Wt ↓ 1800 mg/day: 21.6%; P < 0.01 vs Pl
- ≥ 5% Wt ↓ 1200 mg/day and Pl: 10%

Meta Analysis[2]

- 10 RDBPCTs in N=534 (ALA), 413 (Pl)
- 300-1800 mg/day; 8-52 weeks
- Only 3 of 10 studies were designed as weight management interventions

Results

- Wt ↓: 1.27 kg (95% CI -2.29 to -0.25)
- BMI ↓: 0.43 kg/m^2 (95% CI -0.76 to -0.03)

1 Am J Med 2011;124:85.e1-85e.8

2 Obes Rev 2017;18:594-601

Alpha Lipoic Acid - Summary

Coenzyme serves as a cofactor in enzyme complexes involved in energy production

Used for decades in Germany for peripheral neuropathy (many RCTs)

May help ↓ oxidative stress

Side effects and drug interactions are benign, but monitor thyroid function

Doses lower for neuropathy (600 mg)

Higher for weight loss (1200-1800 mg)

May be of benefit in overweight/obese persons with DM

Impact on weight loss is emerging;

Further study warranted

https://naturalmedicines.therapeuticresearch.com/

Flaxseed (*Linum usitatissimum*)

Background
Whole flaxseed, flaxseed oil, lignans
1 tbsp flaxseed – 2.35 g of ALA;
1 tbsp flaxseed oil has 7.249 g of ALA
Raw product has cyanogenic glycosides

Uses
↓ Lipids, BP, BG, weight

Mechanism
Fiber allows satiety
Antioxidant effects

Side effects
GI

Drug interactions
- Binds certain drugs; affects absorption
- Additive BP, BG, lipid lowering effects with BP, DM, lipid meds
- Flaxseed oil (High doses) may ↑ risk of bleeding in pts on warfarin

J Cardiovasc Pharmacol Ther 2005;10:23-7

Flaxseed – Systematic Review/Meta Analysis

45 RPCTs in N=2561
- Whole flaxseed
- Flaxseed oil
- Lignans

Results
- 28 Weight Trials in N=1837
  - Wt ↓ Weighted Mean Difference (WMD): - 0.99 kg (95% CI -1.67 to -0.31; P = 0.004)
- 35 BMI Trials in N=2209
  - WMD: -0.30 kg/m² (95% CI -0.53 to -0.08; P=0.008)
- 14 Waist Circumference Trials in N=912)
  - WMD: -0.80 cm (95% CI -1.4 to -0.20); P=0.008)

Subgroup Analyses – Best Results
- Whole flaxseed
- Doses ≥ 30 g/day
- Duration ≥ 12 weeks
- Persons with BMI ≥ 27 kg/m²
- Benefit mostly seen in lower quality studies

1. Obes Rev 2017;18:1096-1107

Flaxseed - Summary

- Highly popular
- Plant Omega-3 fatty acid
- Different forms used – whole flax, flaxseed oil, lignans

- Many popular uses - ↓ lipids, BG, BP,
- Women's health

- Studies emerging on use for obesity
- Studies have sub-optimal design with few numbers of subjects

- Mostly GI side effects;
- Do not use raw flaxseed
- Caution with bleeding if on anticoagulants

- Dose: Soluble fiber taken 2 hours before a meal (10-30 g)
- Some extracts also used

Garcinia cambogia

Background
Hydroxycitric acid

Uses
Culinary, purgative, antiparasitic, Wt loss

Mechanism
- ↓ fatty acid synthesis by inhibiting ATP citrate lyase (this may ↓ food intake)
- ↓ glycolysis, leading to ↑ glucagon production (↑ satiety)
- ↑ serotonin availability/release (well-being)

Side effects
HA, GI, hepatotoxic
Cough

Drug interactions
DM meds, statins?
Serotonergics, hepatotoxic agents

Garcinia cambogia Studies

Meta analysis of 12 RCTs with N=706 for 2-12 weeks:[1]

- Wt ↓ = 0.88 kg vs PL (p=0.05)

RDBPCT in N=86 persons in Korea (BMI 23-29)[2] (Maintained diet)

- GC 2 g/day or Glycine max 2 g/day or PL x 10 wks
- Results for weight
  - GC ↑ 0.65 kg; G max ↓ 0.18 kg; PL ↑ 0.68 kg (NS)
- Results for body fat
  - GC ↑ 0.67%; G max ↓ 0.16%; PL ↑ 1.39% (P <0.05 for each vs PL)
- Results for BMI
  - No difference between groups (+0.24 in each)

RDBPCT in N=43 persons (BMI ≥ 25) x 60 days[3] (500 kcal/day ↓

- GC 800 mg tid or PL
- Results for BMI
  - GC ↑ 0.17 kg/m^2; PL ↓ 0.24 kg/m^2 (NS)
- Results for body fat mass
  - GC ↓ 0.12%; PL ↑ 0.21% (NS)
- Results for TGs (mg/dL)
  - GC ↓ 22.9 (P=0.0002); PL ↑ 4.53 (P=0.04 for GC vs PL)

1. J Obes 2011;2011:509036. 2. Nutr J 2011;10:94. 3. Phytother Res 2014;28:887-91

Garcinia cambogia - Summary

- Weight loss is slight - meta analysis ~ 1% ↓ body wt[1]
  - Some studies have shown slight wt gain
- Lipid parameters may benefit (TGs)
- Long-term use studies not available thus long-term benefits are unknown[2]
- Often combined with other ingredients
- Consider possibility of serotonin syndrome and hepatotoxicity[3]

1. J Obes 2011;2011:509036. 2. Evid Based Complement Alterna Med 2013;2013:751658. 3. Ann Hepatol 2016;15:123-126

Green Tea *(Camellia sinensis)*

Background
- **Catechins (Epigallocatechin gallate [EGCG]); caffeine**
- **1 cup brewed tea: 240-320 mg catechins, 45 mg caffeine**

Highly consumed

Mechanism
- ↑ calorie/fat metabolism
- ↓ lipogenesis/fat absorption
- May ↓ CHO absorption/digestion
- Inhibits COMT(catalyzes NE breakdown, thus green tea ↑NE)
- Appetite suppression

Side effects
- GI discomfort, HA, dizziness
- Hepatotoxic? (ethanolic extracts; empty stomach)
- Cardiac (>300 mg/day); ↑ BP

Drug interactions?
- **Warfarin: Vit K content in GT**
- **Enhances caffeine, activating meds (ephedra, amphetamines, ß$_2$ agonists)**
- **Potentiates some BP meds (verapamil); ↓ effect of other BP meds (nadolol)**

Am J Clin Nutr 2010;91:73-81

Green Tea Studies

12 wk DBRPCT of N=128 with high waist circumference (34.25 in females; 35.4 in males)[1]

Green tea with 625 mg catechins+39 mg caffeine vs control (CL; 39 mg caffeine only)

Results:

- GT: 2.2 kg wt ↓ vs CL: 1 kg ↓(p=0.079) (BL wt 95.1 kg; BMI 32.2)
- Total abdominal fat area: GT: 7.7% ↓ vs CL: 0.3 % ↓ (p=0.013)

Minnesota GT Trial Sub-Analysis: 12-mo RDBPCT of N=237 overweight /obese women on decaffeinated GT or PL[2] (MGTT: designed to evaluate GT effect on breast CA risk factors)

Results:

- GT Wt ↓: 0.28 kg; PL Wt ↓: 0.14 kg (P=0.13)
- GT BMI ↓: 0.10 kg/m²; PL BMI ↓: 0.05 kg/m² (P=0.14)

1. J Nutr 2009;139:264-70. 2. J Nutr 2016;146:38-45.

Green Tea (*Camellia Sinensis*) - Summary

Cochrane review of RCTs lasting 12-13 weeks[1] evaluated 14 RCTs of N=1562 overweight/obese

Overall: Wt ↓ 0.95 kg more than PL

Analyzed 6 studies outside of Japan: Wt ↓: -0.04 kg (P=0.88)

Japan studies: Wt ↓ range: -0.2 kg to -3.5 kg (not similar enough to pool results)

Systematic Review: Meta Analysis of 15 RCTs of N=1243 (12 wk duration) of caffeine +/- GT[2]

Results: Caffeine + GT: ↓ wt 1.38 kg (-1.7,-1.1) vs Caffeine only

Some trials show benefit; others do not

Often used in combination products (banaba, caffeine, *Garcinia cambogia*)

Hot tea (not iced) may be preferred form[3]

Has 240-300 mg catechins and 45 mg caffeine

Acts synergistically with caffeine

Monitor LFTs, BP, effects of other drugs

Hepatic damage?[4,5]

More closely correlated with: consuming GT on empty stomach, and in combination products

1. Cochrane Database Syst Review; 2012;12:CD008650. 2. Am J Clin Nutr 2010;91:73-81.
3. Eur J Nutr 2013;52:1039-1048. 4. Drug Saf 2008;31:469-484. 5. Arch Toxicol 2015;89:1175-91

HCG

Background[1]
- **Proposed mechanism relates to caloric utilization for fetal support**
- **Simeons method popular in 1950s (Injections + 500 cal/day)**

Uses
- **Weight loss**
- **Maintains late follicular phase as gonadotropin releasing hormone antagonist**

Mechanism
- May ↑ metabolic consumption thus decreasing and eliminating abnormal fat stores
- Claim: redistributes fat from hips, thighs, stomach without hunger or irritability

Side effects[2]
- **↑ possibility of DVTs, PE**
- **Anxiety, TSH abnormalities,**
- **Ovarian hyperstimulation, testicular tumors**

Drug interactions
? May offset effects of anticoagulants

1 Ann Pharmacother 2013;47:e23 2 Int J Obesity 2012;36:385-386

HCG Studies

6-wk DBPCT in 40 females ≥ 18 years (mean age 37-38 years old)[1]

- HCG, Pl, BL weight: 78 kg vs 75 kg
- 125 IU IM 6 days/week PLUS 500 calorie/day diet started on day 4 vs PL injection + diet only group
- Results: HCG Gp Wt ↓ 9.05 kg; Diet Gp Wt ↓ 5.01 kg ($P < 0.001$)
- HCT Wt: ↓ 11.5%; Diet Gp: Wt ↓ 6.8% ($P < 0.001$)
- No changes in SBP or DBP

1. Am J Clin Nutr 1973;26:211-218.

HCG - Summary

Popular in the 50s (Simeon method - 500 calorie/day diet)

Available as injections, drops, lozenges, pellets

Years ago FTC ordered weight loss clinics to discontinue claim that HCG programs are safe and effective per FDA

Facilitates stromal cell decidualization (leiomyoma, endometriosis exacerbation?)

Prostatic hyperplasia, testicular tumors (male breast tumors?)

Possible thromboembolism: secondary to hormonal surge, vasoactive substance release, ↑ hypercoagulable state

Is weight loss actually due to hypocaloric diet?

Probiotics

Background

Trillions of gut microorganisms; obesity associated with "dysbiosis"

Obesity: suppressed Fiaf (fasting induced adipose factor [regulates fat storage]) results in ↑ LPL (↑ TGs in fat cells)

High fat diet: excess Gram-negative bacteria

Mechanism

Microbes allow calorie extraction from indigestible polysaccharides

↓ inflammation; strengthened intestinal epithelial barrier

Obesity: ↑ "bad" bacteria

Uses

Prebiotics: stimulate growth of beneficial bacteria

Probiotics: compete with pathogenic microbes for intestinal epithelial receptors

Side effects

↑ GI (gas, diarrhea, constipation)

Antibiotic resistance to pathogenic bacteria

Drug interactions?

Antibiotics, antifungals

Probiotics Studies

12-wk RDBPCT in 95 overweight Korean persons[1] (maintained usual diet/physical activity)

- Impact of *L curvatus* and *L plantarum*
- Body wt ↓ 0.65 kg vs 0.42 kg in PL (P=0.001)
- BMI ↓ 0.24 kg/m² vs 0.14 kg/m² in PL (P=0.001)
- Body fat percentage and body fat mass lower in Probiotic Gp

Meta analysis of 4 RPCTs for 3-8 wks in N=196 (wt) and N=154 (BMI)[2] (Low heterogeneity)

- Results: Mean diff in Body wt ↓ 1.77 kg vs PL (P=0.26)
- Results: Mean diff in BMI ↓ 0.77 kg vs PL (P=0.14)
- Used *Lactobacillus* species: *L salivarius*, *L plantarium*, probiotic yogurt (*L acidophilus*, *Bifidobacterium*) ± hypocaloric diet

1. J Funct Foods 2015;19:744-752. 2. Nutr Res 2015;35:566-575.

Probiotics Studies

Meta analysis of RCTs of a variety of different probiotics in lean, normal weight, obese adults/children[1]

- 14 RCTs in Adults: Wt Standardized Mean Difference (SMD): - 0.54 (-0.83 to -0.25)
- Adults' BMI: Absolute Mean Difference: - 0.43 (-0.54 to -0.33)
- Children: Wt slightly increased: SMD +0.20 (0.04 to 0.36)

Single RDBPCTs for 12 wks in N=66 (overweight) that took 2 grams bid of probiotic powder containing *Lactobacillus* species[2]

- Results: Body wt ↓ 0.6 kg for Probiotic Gp vs PL wt ↓ 0.46 kg (P=0.008)
- Results: BMI ↓ 0.23 kg/m^2 for Probiotic Gp vs PL BMI ↓ 0.15 kg/m^2 (P=0.008)
- Fat Mass also ↓ in Probiotic Gp

1. Microb Pathog 2017;106:146-161. 2. Food Funct 2017;8:250-261.

Probiotics - Summary

Animal studies: obese have ↑ Firmicutes, ↓ Bacteroidetes

↓ *Akkermansia muciniphila* in persons with ↑ body fat mass and glucose intolerance

↑ *A muciniphila*: Calorie restriction + fiber x 6 wks

(then 6-wks wt stabilization diet)[1]

Metformin also ↑ *A muciniphila*

Efficacy:

Which probiotics? Dose? Treatment duration?

Which form (fecal, synthetic transplants)?

What comprises a healthy microbiome?

Methodological issues with studies; conflicting results

Safety issues: Persons with Autoimmune diseases?

Overall, no definitive evidence of Probiotic benefit[2]

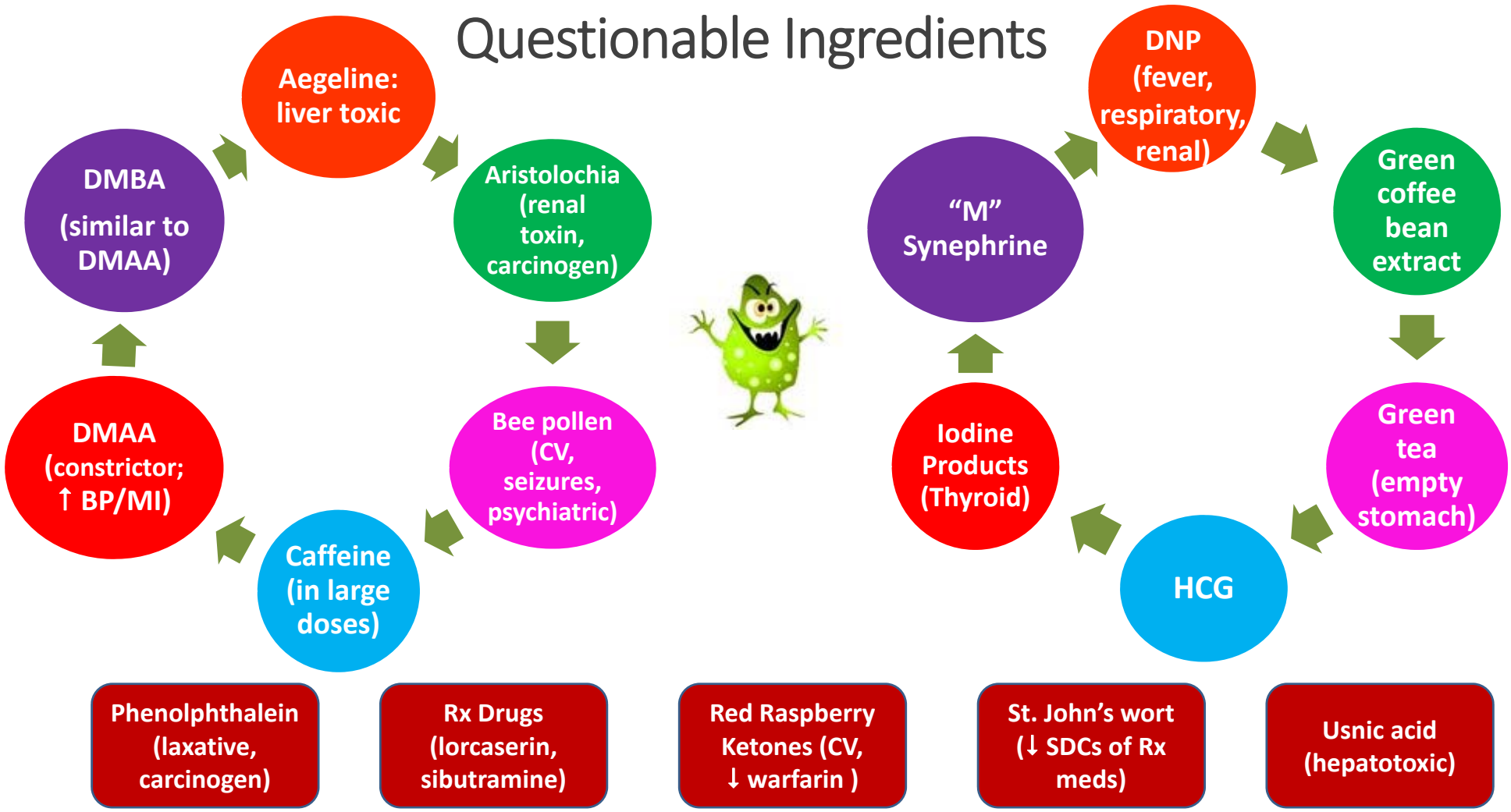
1. Gut 2015; doi:10.1136/gutjnl-2014-308778 2. Nutr Res 2015;35:566-575.

Other Products

Product	Mechanism	Evidence
Citrus aurantium Bitter Orange	Synephrine ("p" vs "m") ↑ Energy expenditure/lipolysis; ↓ appetite	Controversial; replaced "ephedra" Cardiotoxicity; ↑ resting metabolic rate, energy expenditure; modest wt ↓
Irvingia gabonensis African Mango	↓ adipogenesis, leptin levels; binds to bile acids; stool excretion	GI, HA, insomnia; study design problems; modest wt ↓
Phaseolus vulgaris White Kidney Bean	Inhibits α-amylase, thus blocks CHO absorption; Appetite ↓	Used as food; GI, HA; modest wt/fat ↓ ; PPG ↓
Rubus idaeus Red Raspberry Ketones	May ↑ metabolism by increasing NE induced induced lipolysis and thermogenesis; ↑ adiponectin (Structure similar to synephrine, capsaicin)	Palpitations, stimulant effects; ↓ BG/INR; mismatch between amount ingested as a food (up to 3.8 mg/day) and amount as a supplement (100 to 1400 mg/day) Open-label trial in Japanese; studies mostly in combo products

https://ods.od.nih.gov/factsheets/WeightLoss-HealthProfessional/

Questionable Ingredients



https://naturalmedicines.therapeuticresearch.com/

Evaluating Internet Information

- How to evaluate information on the internet –

http://www.fda.gov/Food/DietarySupplements/UsingDietarySupplements/ucm110567.htm#tips

Ask these questions:

Who operates the website?

What is the purpose? (Educate, sell?)

Information source (Studies, testimonials)?

Information current? (Date posted)

How reliable is the internet?
Easy way to spread myths;
Beware of overly emphatic language (ALL CAPS)
or "This is not a hoax" or "Send this to everyone you know"

Appropriate Patient References - FDA

Tips for the Dietary Supplement User[1]

- Do I need to think about my diet?
- Should I check with my doctor?
- Are there interactions?
- What should I do if I am to have surgery?
- Who's responsible for safety?

Tips for Older Dietary Supplement Users[2]

- Are there risks because of my age?
- Should I stop my regular medicines?
- How will I be able to spot false claims?
- Should I check with my doctor?
- Should I take the products in to "checkups?"

1. https://www.fda.gov/Food/DietarySupplements/UsingDietarySupplements/ucm110567.htm 2. https://www.fda.gov/Food/DietarySupplements/UsingDietarySupplements/ucm110493.htm

Supplement Use: Specific Guide to Help Patients

- Ask patients about supplement use ("nonconfrontational" manner)
- Examine labels and look up unfamiliar substances
- Address concerns about risks
- Consider that supplements are not FDA approved
- State recommendations based on evidence ("science over anecdote")

Dietary Supplement Health & Education Act (DSHEA) Label Information: "…has not been evaluated by the FDA and it is not intended to diagnose, treat, cure, or prevent any disease."

Appropriate References

- Natural Medicines (https://naturalmedicines.therapeuticresearch.com/)
  - Product is result of merger between Natural Medicines Comprehensive Database and Natural Standard (Evaluates evidence, effectiveness, side effects, interactions, pregnancy issues)
- Dietary Supplements for Weight Loss. Fact Sheet for Health Professionals. NIH Office of Dietary Supplements website (https://ods.od.nih.gov/factsheets/WeightLoss-HealthProfessional/)
- The Cochrane Collaboration (http://www.cochrane.org)
  - Updated databases and systematic reviews of different treatments
  - Regularly updated evidence-based information

Appropriate References

- AACE Medical Guidelines for Use of Dietary Supplements and Nutraceuticals
  - Endocrine Practice 2003; 9:417-470

- Obesity Society Position Statement; emphasize need for long-term data showing benefits/safety
  - http://www.obesity.org/publications/position-and-policies/medicinal-or-curative
- Obesity Society Position Statement on HCG
  - http://www.obesity.org/publications/position-and-policies/hcg-ineffective
- FDA Medwatch

Conclusions

Myth: "products are 'natural' and don't have side effects"

Not a substitute for healthy nutrition, physical activity

- Variable forms (pills, beverages, extracts, bars)
- Variable doses, content of active ingredients, studies often don't report content
- Combination products

No standardized duration for studies

Studies don't report whether supplement content verified

- sometimes subjects are normal weight)
- No standardized outcomes (5%, 10% ↓ body weight)
- No long-term studies

Check reputable resources

Communication is key!

QUESTIONS?