

- My microphone and lecture capture software are behaving badly so I could not capture an audio narration of this presentation as I had hoped, so I have simply added some comments.
- We are moving on to the readily available stimulants – caffeine and nicotine, which work by completely different mechanisms than the “controlled stimulants”.

Stimulants Continued

Caffeine & It's Relatives

(the “Methylxanthines” or “Xanthines”)
 (“yellowish substances”)

Whereas cocaine only occurs naturally in the leaves of the coca shrub, caffeine & its relatives are found in dozens of plants from around the world.

Xanthines

- Found in about ~60 plant species, many of which contain a combination of xanthines
- Mild stimulants affecting body & brain
 - caffeine (strongest CNS action; most widespread use)
 - theophylline (strongest PNS action) (so theophylline used as asthma drug rather than caffeine)
 - theobromine ($\sim 1/10^{\text{th}}$ as potent as caffeine)

 - FYI - aminophylline, a theophylline derivative, is widely used medically

Ripening Coffee Beans



Coffea arabica

Picking Tea

- *Camellia sinensis*
- Leaves contain theophylline + caffeine as well as other nutritionally beneficial compounds:
 - Antioxidant polyphenols (anti-cancer & anti-cardiovascular problems)
 - Bone-beneficial fluoride & phytoestrogens



Cacao Tree & Cacao Beans from which we get cocoa

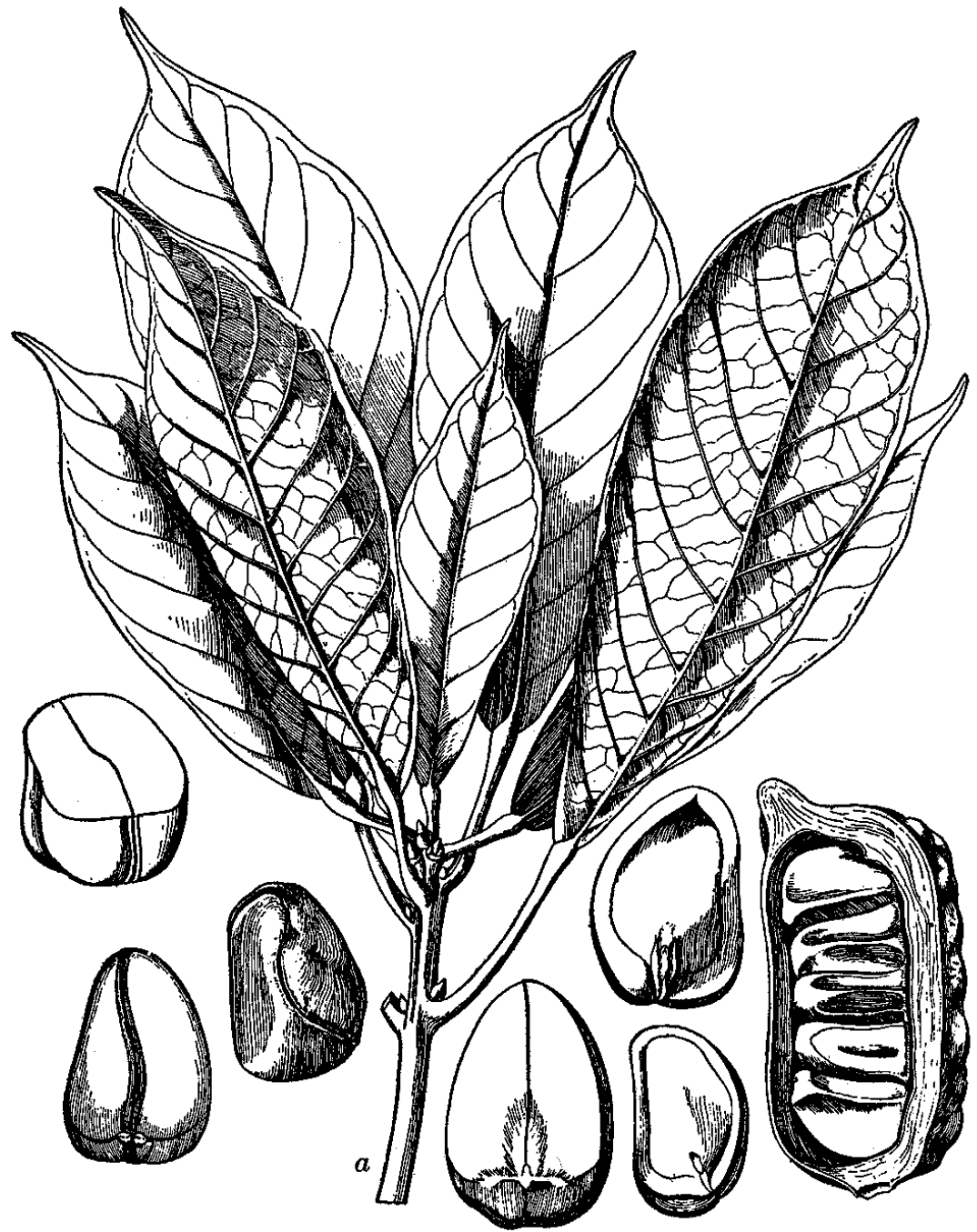


Theobroma cacao
(theobromine +caffeine)

Did you see the movie “Chocolat”?

Cola Nuts

- (which flavor all of our colas)



Cola nitida: a, leafy branch, $\frac{1}{4}$ nat. size; also longitudinal section of fruit, cross and natural longitudinal section of seed showing embryo enlarged.

Brazilian Guarana Berries



Used to produce many stimulant beverages and herbal stimulant products.



Yerba Mate' or Paraguayan Tea



- You can buy dried mate leaves @ health food stores.

Incredible Variety of Coffee/Caffeine Drinks



Also an incredible range of caffeine doses

Jolt Espresso 120 mg

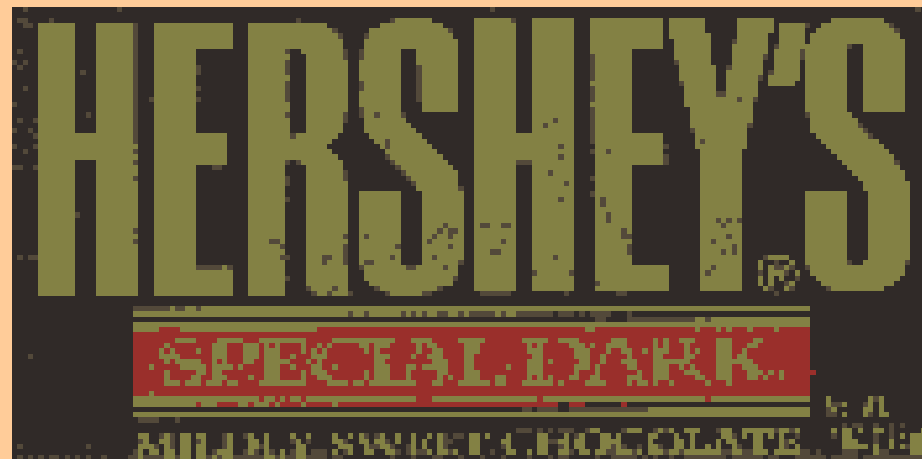
“Cocaine” energy drink – 280 mg caffeine

Some Starbucks large drinks: 400 – 500 mg



Chocolates

- 30 mg caffeine in this dark chocolate;
10 mg in 1 oz of most milk chocolates



Caffeine Containing Candy



- Generally
~15-45
mg per
piece



Caffeinated Gum

“A Kick in Every Stick!”



Claims that 1 Stick = 1 Cup of Coffee

OTC Medicines per tablet

Caffedrine 200 mg.

NoDoz 100 mg.

Vivarin 200 mg.

Anacin 64 mg.

Cope 32 mg.

Excedrin 65 mg.

Midol 32 mg.

- Aqua Ban 100 mg.
- Permathene 100 mg.
- Coryban-D 30 mg.
- Vanquish 33 mg.
- Dristan 30 mg.
- Triaminicin 30 mg.

- In many prescription meds too

Soft Drinks

- Mr. Pibb, Diet 57 mg./ 12 oz.
- Mountain Dew 54 mg./ 12 oz.
- Coca Cola, Diet Coke 46 mg./ 12 oz.
- Mr. Pibb 41 mg./ 12 oz.
- Dr. Pepper, Sunkist Orange 41 mg./ 12 oz.
- Pepsi Cola 38 mg./ 12 oz.
- Pepsi Light, Diet 36 mg./ 12 oz.
- Surge 51 mg./12 oz.
- Jolt 72 mg./12 oz.

- Of course size matters – “Big Gulp” = 190 mg.

“Energy” Drinks



- Bawls – guarana bev. 80 mg caffeine
- XTC Tea – unknown dose guarana, kola nut, caffeine, tea, kava kava, mate & ma huang



More Energy Drinks



PHOTO: COBEVNET.COM

320 mg caff in
24 oz can

Unknown dose caffeine+ guarana

- Often billed as the drinks of gamers, geeks, & clubbers



80 mg in this can; 116
mg in 12 oz. + taurine
and glucuronolactone

Caffeinated Water

Per 16.9 oz bottle
Water Joe 60-70mg
Aqua Java 50-60 mg
Aqua Blast 90 mg
Krank 20 100mg
Java Water 125mg





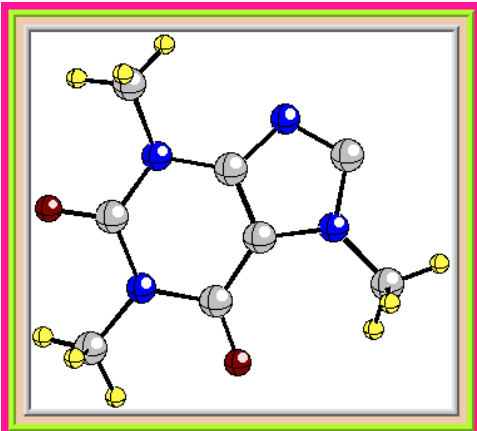
Others



“3.5 cups worth”

- Ben & Jerry’s Coffee Frozen Yogurt 85/cup
- Starbucks Coffee Ice Cream 40-60/cup
- Dannon Coffee Yogurt 45/cup
- Chips, seeds & cereal!
- Caffeinated chewing tobacco
- Caffeinated soap!!!
- Caffeinated pantyhose!!





Caffeine's Action

- Absorption takes 30-60 min.; CNS effects peak at **2 hrs.**
ED50 for mild arousal = 100-125 mg. in non-tolerant
- Half-life is ~3-7 hours in most adults, but significant genetic variability in metabolism (up to 12 hrs) (40-230 in newborns!)
- Longer half-life in infants, elderly & pregnant & those on birth control pills or SSRIs, especially Luvox, fluoxetine
- Half-life shorter (~1.5-3.5 hrs) in smokers and then rebounds to longer half life and increased sensitivity when quitting smoking, so that caffeine aggravates nicotine withdrawal

How Xanthines Work

- **Block receptors** for a natural calming/sleep-promoting neurotransmitter **adenosine**.
- Normally adenosine helps dilate cerebral blood vessels, slows heart, makes us sleepy, decreases body temp, constrict bronchioles
- By blocking adenosine caffeine causes the opposite effects: constricts cerebral blood vessels, increases HR, wakes us up, increases body temp, dilates bronchioles

Note: caffeine DILATES coronary arteries so does not decrease blood flow to heart the way cocaine does.

Dose Dependent Body Effects

- Increased HR & BP; release of adrenaline
- Increased salivation & GI secretions (so may give you acid indigestion)
- Bronchodilation & increased respiration
- Increased metabolism & increases temp. (so may make you feel warm even if you are not drinking a hot beverage)
- Increased urination (diuretic effect)
- Constricts brain blood vessels – this helps relieve normal and migraine headaches
- Dilates other vessels including coronary arteries

CNS Effects

(similar to but milder than amphetamine effects)

- Increased wakefulness, decreased fatigue
- Increased attention, decreased boredom
- Mild mood elevation
- Increased motor activity
- Increased response to sensory stimuli
- Shortens reaction time

Caffeinism (too high a dose for you)

- restless, anxious, irritable, agitated, panic attack in some
- insomnia
- muscle tension & tremors
- rapid, sometimes irregular HR
- flushed, hot and sweaty
- nausea; increased urination
- sensory disturbances (visual, tinnitus, increased awareness of body sensations) (these can increase risk of panic attacks)
- Usually occurs at dose > 600 mg but depends on individual's sensitivity & tolerance

Withdrawal

- Regular use does produce moderate tolerance and dependence
- If you are dependent you will begin to experience withdrawal symptoms about 12-18 hrs after your last dose:
 - throbbing headache, worsens with exercise
 - fatigue, no energy, yawning
 - difficulty concentrating, slowed performance
 - glum, irritable, mild depression
 - If you sleep in on the weekend & wake up with a headache even though you didn't party the night before, consider if you might be in caffeine withdrawal
 - For a regular user withdrawal symptoms may last a week

Health Benefits

- Headache relief for normal and migraine headaches
- Moderate use – mild mood elevator & stimulant
- Used therapeutically in a variety of ways (cardiac stimulant, respiratory stimulant, anti-asthma, additive in some sedating daytime medications)
- May reduce risk of kidney stones, gallstones
- May help protect against Parkinson's disease and cognitive decline in aging
- Anti-oxidant actions may be beneficial
- Topically - prevention of skin cancer????

Health Risks?

- Primary risks to those with pre-existing conditions, e.g.:
 - may increase BP in those prone to hypertension
 - may aggravate ulcers or heartburn due to gastric reflux
 - may trigger or increase panic attacks in some, worsen generalized anxiety disorder bodily symptoms
- Caffeinism can be mistaken for anxiety disorders
- **High** doses may increase risk of miscarriage, stillbirth or decrease growth of fetus (6-10 cups/day or the equivalent). Also present in breast milk.
- May increase calcium loss if consumed without dairy & increase risk of osteoporosis
- May cause sleep problems
- Caffeine withdrawal is the cause of some headaches
- But all in all - low toxicity drug – LD50 ~ 5-10 g (50-100 Nodose tablets).

Motown on Campus Thurs!

Four Tops @ GBPAC

- http://www.dailymotion.com/video/x2uel6_the-four-tops-reach-out-ill-be-ther_music
- <http://www.youtube.com/watch?v=1y30rw3A7OU>
- <http://www.youtube.com/watch?v=5pVM00eooHl&feature=related>

Motown on Campus Thurs

The Temptations @ GBPAC

- <http://www.youtube.com/watch?v=ltRwmgYEUr8&feature=related>
- <http://www.youtube.com/watch?v=RfyFI-4ZsaE&feature=related>
- <http://www.youtube.com/watch?v=cDakhsaPTE0&feature=related>

Nicotine

A potent (average cig. contains .5-2 mg, only partially absorbed) and toxic (LD₅₀ = ~60 mg.) drug, with an even worse route of administration (smoking causes 1 out of 5 deaths in US each year (~440,000 per year))

Nicotine Basics

- Non-tolerant user experiences symptoms of mild nicotine poisoning:
 - Pale, sweaty
 - Dizzy, weak in the knees
 - Nausea, intestinal cramps
 - Sympathetic & CNS arousal
- Sufficient nicotine could kill you (seizures, respiratory paralysis) (kids, pets and farmers most at risk)



- New FDA regulations for the dietary supplement industry aim to eradicate consumer concern and health risks associated with these products. Dietary supplement manufacturers and distributors are now required to follow Good Manufacturing Practices (GMPs) similar to those of the pharmaceutical industry. The FDA 21 Code of Federal Regulations (CFR) Part 111 was established to insure the identity, purity, quality, strength, and composition of dietary supplements and applies to those involved in the manufacture, packaging, labeling or holding of a dietary supplement, with the exception of retail establishments selling directly to consumers.
- The federal government is taking a tiered approach to enforcement: companies with more than 500 employees were required to become compliant by June 2008; companies with 21-499 employees must become compliant before June 2009; and companies with fewer than 20 employees will need to be compliant by 2010.
- To become compliant with the GMP guidelines, passed in 2007, dietary supplement companies need to perform analytical testing of their products. Analytical laboratory analysis falls under the category of “manufacture” as defined by FDA CFR. Therefore, if testing is not performed the dietary supplement company will be considered non-compliant regardless of the reason for not testing. Reasons for not testing range from it being cost prohibitive to it’s impossible as an option for raw materials, in-process or final products. Those non-compliant and unable to meet GMP guidelines will run the risk of not being able to sell their products due to regulatory agency action. This may result in some companies going out of business or, at the least, an increased need for analytical testing.

- http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2010/05/fda-posts-its-first-dietary-supplement-gmp-warning-letter
- <http://www.quicklabel.com/blog/2010/12/new-gmp-labeling-laws-for-dietary-supplements-in-the-usa/>
- <http://www.fda.gov/Food/DietarySupplements/GuidanceComplianceRegulatoryInformation/RegulationsLaws/ucm079496.htm#GMPS>

The Drug Discovery, Development and Approval Process

It takes 12-15 years on average for an experimental drug to travel from the lab to U.S. patients. Only five in 5,000 compounds that enter preclinical testing make it to human testing. One of these five tested in people is approved.

Discovery/ Preclinical Testing		Phase I	Phase II	Phase III	FDA	Phase IV
Years	6.5	1.5	2	3.5	1.5	15 Total
Test Population	Laboratory and animal studies	20 to 100 healthy volunteers	100 to 500 patient volunteers	1000 to 5000 patient volunteers	Review and approval process	Additional post marketing testing required by FDA
Purpose	Assess safety, biological activity and formulations	Determine safety and dosage	Evaluate effectiveness look for side effects	Confirm effectiveness, monitor adverse reactions from long-term use		
Success Rate	5,000 compounds evaluated	5 enter trials			1 approved	

Source: Pharmaceutical Research and Manufacturers of America, www.pfma.org

http://www.pacificbiolabs.com/drug_stages.asp#ind



Herbal or Natural Remedies or “Dietary Supplements”

Are “natural” remedies better?

Are “natural” remedies safe?

Are “natural” remedies worth the money?

Aren't “natural remedies” drugs???

- “Natural” plant products are not distinctly different from “drugs”. The majority of drugs are derived from or based on active ingredients found in plants.
- “Natural” does not mean “meant for the human body”. Nature is full of poisons!

Regulations Affecting Medications

- 1906 Pure Food & Drug Act (drug must be pure & accurately labeled)
- 1937 Federal Food, Drug & Cosmetic Act (drug must be demonstrated to be safe when used as directed)
- 1962 Kefauver-Harris Amendment (drug must be demonstrated to be effective before it can be marketed for that use)
- Evaluation of whether drugs meet these requirements continues today
- Except for Herbal/Natural Remedies!!

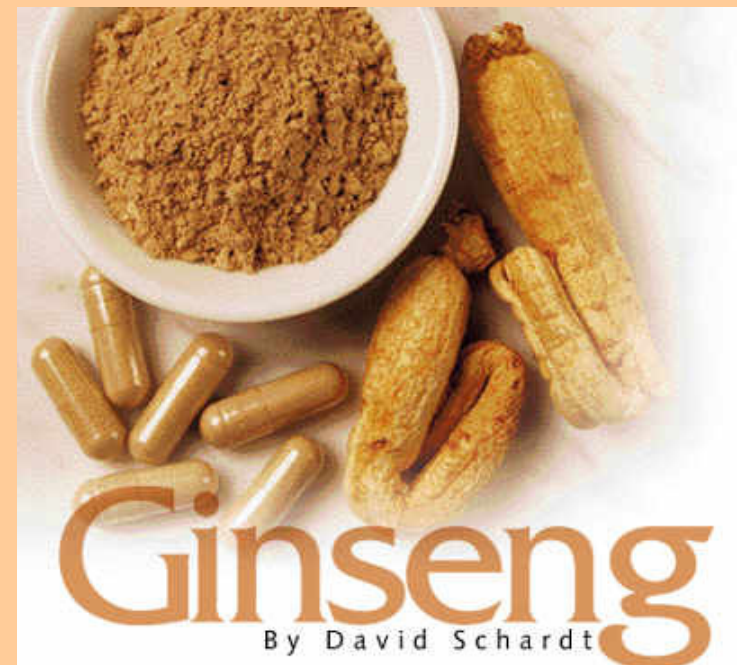
- Then came the 1994 Dietary Supplement Health Education Act allowing products labeled as such to be essentially free from FDA regulation

Herbal/Natural Remedies: Buyer Beware

- Purity, safety, dose, effectiveness or batch-to-batch quality control of herbals/supplements are **NOT** regulated by FDA (blame the lobbyists)
- No FDA regulation of claims made on packages except can't claim to treat a specific illness; no research required.
- Don't assume they are safe - read about them in reputable sources (Herbs of Choice, Honest Herbal). (RM333, Reference shelves)

Example: Ginseng (used to improve health and energy)

- Rite Aid Imperial ~.001% ginsenosides
- Naturally Korean ~.003%
- Solger Korean, Nature's Resource, KRG Korean Red ~.025%
- Ginsana ~.030%
- American Ginseng ~.050%
- Herbal Choice .065%
- Walgreen's Gin-Zing .076%



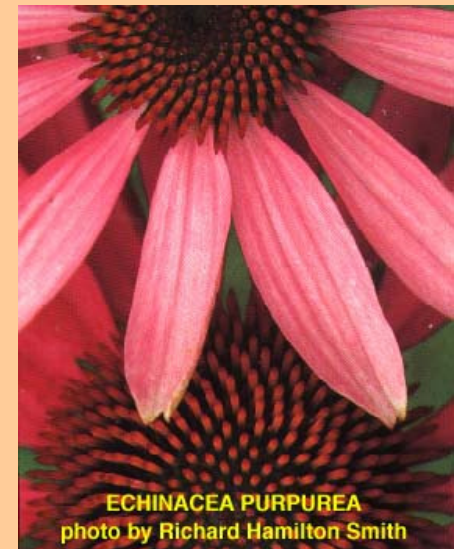
- Herbals/supplements have side-effects, adverse effects and drug-interactions, just like other drugs.



Even well-known herbs aren't safe for all

Chamomile –used as a digestive and anti-inflammatory, but may irritate those with ragweed/flower allergies

- Echinacea – may boost immunity but shouldn't be used in pregnancy or autoimmune disorders



Ephedra



Source of active ingredient in Herbal Ecstasy, Metabolife, and many other herbal stimulants, “energizers” or diet drugs, including Metabolife. It took a special action of the FDA to finally ban ephedra containing products in April, 2004.

Other Herbals of Interest

- Ginkgo- may improve blood flow to brain, sold for “mental sharpness” (but increases your tendency to bleed)



Kava

- South Pacific sedative/intoxicant
- antianxiety, sleep-promoting depressant-like action (interacts with other depressants)
- Can cause sedation, slurring, ocular & neck spasms, rash, Parkinson's Disease symptoms, possible liver damage



Valerian



- Also produces mild depressant action
- But can produce headache, paradoxical excitation, liver problems
- Kava and Valerian seem to act on GABA receptors like depressant drugs

- <http://www.youtube.com/watch?v=dK2hW6SyhDc>
- <http://www.youtube.com/watch?v=YKyM8Dz8mec&feature=related>

Sample Drug Interactions

- Ginkgo or Ginseng and blood thinners
- St. John's Wort & antidepressants
- Ephedra & caffeine, decongestants, stimulants
- Kava & sedatives, alcohol, sleeping aids, antipsychotics

St. Johns-Wort (*Hypericum perforatum*)

- ~300 mg of .3% extract is effective in treating mild-moderate depression (not serious cases)
- takes 2-4 weeks for hypericin to work (like drugs)
- Blocks reuptake of 5HT, NE and DA
- side effects: restlessness, stomach upset, dry mouth, dizziness (like drugs)
- don't use WITH other antidepressants; don't use in pregnancy, affects CYP enzymes



Steroids

- A family of hormones produced by the gonads and adrenal glands, or the drugs which act like these hormones

Main Groups of Natural Steroids

- Those primarily produced by gonads
 - Androgenic (masculinizing) steroids (like testosterone)
 - Estrogen & Progesterone (feminizing)
- Those produced by the adrenal glands
 - Adrenocortical steroids (aka corticosteroids) like cortisol
 - Reduce inflammation; released when we are exposed to prolonged stress, to allow us to continue to respond
 - Drug substitutes: cortisone, hydrocortisone, prednisone

Ma Huang, Ephedra, and Ephedrine Containing Products

- Wide range of “herbals” and “supplements” and some OTCs contain these stimulants
- amphetamine-like effects on body, but not quite as psychoactive
- properly used (low doses, occasional) these have been safe and beneficial (e.g. Anti-asthma)
- higher doses or unknown doses much riskier, even in young people (causing stroke, heart attack)
FDA banned sale starting 4/4/04.



Betel Nuts & Leaves

- Chewed regularly by 200 million in Asia, India and Indonesia – addictive stimulant somewhat like nicotine

“Dietary Supplements” also has included hormone-like substances

- Androstenedione or “Andro” (one step away from testosterone) was freely available as a supplement until another special legislation by Congress (Anabolic Steroid Control Act of 2004) clarifying and extending the definition of anabolic steroids.



Melatonin

- Hormone which promotes sleepiness. May be useful to readjust sleep cycle when traveling, but also advertised falsely as an anti-aging remedy.

- So it is even more important to be a cautious informed consumer of natural/herbal remedies and supplements since regulatory agencies, in this case, cannot protect you.



250 mg. aspirin
250 mg. acetaminophen
65 mg. caffeine



250 aspirin
250 aceto.
65 caffeine

250 mg. aspirin
250 mg. acetaminophen
65 mg. caffeine



500 aceto.
65 caffeine



250 mg. aspirin
250 mg. acetaminophen
65 mg. caffeine

250 aspirin
250 aceto.
65 caffeine



Toxic Herbs Still Sold

- Chapparal & Comfrey – causes liver damage
- Ephedra (Ma huang) – hi BP and HR, increased risk of stroke, heart attack
- Lobelia – vomiting, seizures, coma
- Yohimbe – GI problems, psychosis, paralysis

Examples of herbal side effects

- Ginkgo – bleeding
- St. John's Wort – GI upset, fatigue, dizziness, confusion, dry mouth, allergic reactions; affects metabolism of other meds
- Ephedra – hi BP, arrhythmias, anxiety, insomnia, tremors, kidney stones
- Kava – sedation, slurring, ocular & neck spasms, rash, PD-like symptoms



Yaupon, Cassena - Ilex vomitoria

Aka Cassina or Yaupon- used by Native Americans to brew a caffeine containing beverage

Herbal/Natural Remedies: Buyer Beware

- Brands may vary 80 fold in concentration of active ingredient – some may be inactive!
- Select standardized brands with concentration and dose information. (Nature's Way, Quanterra, Lichtwer, Bayer)
- Tell your doctor what you are taking – **herbs can produce drug interactions and side effects;** avoid herb mixtures
- Even beneficial herbs, like beneficial drugs, may not be for every person.