Herbal Psychopharmacology

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1. **Which of the following was responsible for herbal products "flooding" the U.S. market in recent years?**

   A. **Federal Food, Drug, and Cosmetic Act**

   B. **Kefauver-Harris Amendment**

   C. **Dietary Supplement Health and Education Act**

   D. **Nutrition Labeling and Education Act**

   E. **Food and Drug Modernization Act**

2. **Which of the following has been most closely associated with hepatotoxicity?**

   A. **Ginkgo**

   B. **Kava**

   C. **Saw palmetto**

   D. **St. John’s wort**

   E. **Valerian**

3. **Which of the following is the clinically most important effect of St. John's wort on the cytochrome P450 (CYP) system?**

   A. **1A2 inhibition**

   B. **2D6 inhibition**

   C. **2C9 induction**

   D. **2E1 induction**

   E. **3A4 induction**

4. St. John's wort has been most extensively studied for the treatment of which of the following disorders?

   A. Bipolar

   B. Posttraumatic stress

   C. Panic

   D. Major depressive

   E. Social anxiety

5. **A placebo-controlled, double-blind study found Ginkgo biloba to be ineffective for treating antidepressant-induced sexual dysfunction.**

   A. True

   B. False

Major Teaching Points

- Understanding the ramifications of DSHEA
- Appreciating the current efficacy status of herbals for treating psychiatric disorders
- Being aware of the potential effects of herbals on drug metabolism

Outline

I. Historical Overview – DSHEA and its Ramifications

II. Valerian

- A. Clinical Studies
- B. Drug Interactions

III. Ginkgo

- A. Clinical Studies
- B. Drug Interactions
- C. Bleeding

Outline (Cont'd.)

IV. Kava

- A. Clinical Studies
- B. Hepatotoxicity
- C. Drug Interactions

V. St. John's Wort

- A. Clinical Studies
- B. Mechanism of Action
- C. Side Effects
- D. Drug Interactions

Outline (Cont'd.)

VI. Other Herbals

- A. Uses
- B. Drug Interactions

VII. Juices

- A. Grapefruit
- B. Orange
- C. Pomegranate

VIII. Resources

- Historical overview
- DSHEA (1994)
- Clinical efficacy
- Drug interactions
- Words of warning

Herbs and plants are medical jewels
gracing the woods, fields and lanes
which few eyes see,
and few minds understand.
Through this want of observation and knowledge
the world suffers immense loss

Linnaeus 1707-1778

Progress?

- **1938: Food, Drug, and Cosmetic Act**
  - **Proof of drug safety**
- **1962: Kefauver-Harris Amendment**
  - **Proof of drug efficacy**
  - **Required reporting of adverse events**
- **1994: Dietary Supplement Health and Education Act (DSHEA)**
  (sponsored by Senator Orrin Hatch, signed by President Clinton)

Dietary Supplement Health and Education Act (1994)

- Removed supplements from food additive regulations
- Burden of proof on FDA
- No federal regs for purity, etc.
- No mandatory reporting of AEs

Since then, these products have flooded the market, subject only to the scruples of their manufacturers.

Angell M, Kassirer JP. N Engl Med 1998;339:839-841

- **“In the United States, the public spends almost $4 billion yearly on supplements, with little or no data on what they can expect.”** Lewis and Strom. Ann Int Med 136:617-618, 2002

- **In 2003, Americans spent $19 billion on dietary supplements** Specter M. The New Yorker, Feb 2, 2004, pp 64-75

- **In 2011, $$$$$$$$$$$$$$$$$$$$$$$$$$$$**

Because Claims of Preventing or Treating a Disease Are Not Allowed

- Shark cartilage - to maintain proper bone and joint function
- Saw palmetto - to promote prostate health
- Horse chestnut seed - to promote leg vein health

N Eng J Med 9/17/98

You May Get More or Less Than You Pay For

- 50 Ginseng preparations analyzed for ginsenosides
- Content varied from 1.9% to 9% (4.7 fold difference)
- 6 (12%) had <u>none</u>

Cui et al: Lancet 7/9/94

Asian Patent Medicines from California Herbal Stores

- **Undeclared pharmaceuticals -**
  ephedrine, chlorphenarimine, methyltestosterone, phenacetin
- **Heavy metal contamination -**
  lead, arsenic, mercury
- **32% of 260 medicines**

California Dept. of Health Services, NEJM 9/17/98

Tongkat Ali Power Plus: A Natural Remedy to Improve Sexual Health and Libido

- "Our products are natural herbal powder made in a more convenient-to-use form capsules"

BUT

- Analysis of 15 capsules found sildenafil, 59 mg/capsule. 10 of the 15 also contained tadalafil, 1.4 mg/capsule

Kenyon et al. J Clin Pharmacology 2006;46:1379-1381

American Roulette - Contaminated Dietary Supplements

- New England Journal editorial- October 15, 2009
- We still have a long way to go

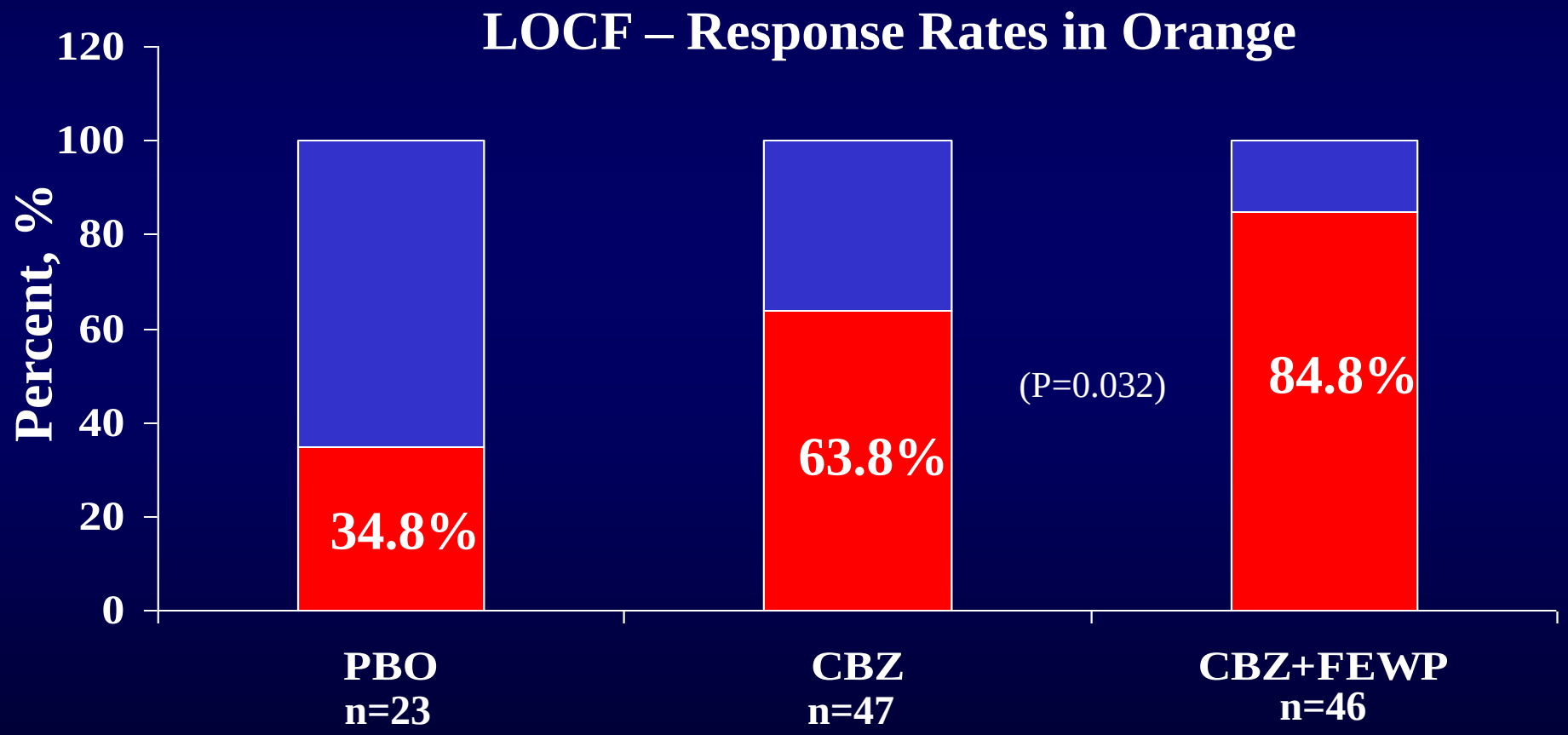
Cohen PA. N Engl J Med 2009;361:15231525

FDA Issues Dietary Supplements Final Rule June 22, 2007

- To require good manufacturing practices (GMPs) for supplements
- To ensure quality production, accurate labeling, no contaminants,
- Effective August 24, 2007, but with 3-year phase-in for small companies
- Does not address efficacy and safety issues

http://www.fda.gov

Bipolar Depression: Free and Easy Wanderer Plus (double-blind adjunctive to carbamazepine)



Zhang et al. J Psychiatric Res, Epub 2005; J Psychiatric Res 2007;41:360-369

Free and Easy Wanderer Plus: Contents

• Bupleurum chinense	Dry root
• Scutellaria baicalensis	Dry root
• Zingiber officinale	Fresh root
• Angelica senensis	Dry root
• Gardinia jasminoides	Dry ripe fruit
• Paeonia suffruticosa	Dry root bark
• Paeonia lactiflora	Peeled, dry root
• Atractylodes macrocephala	Dry root, stem
• Poriae cocos	Dry sclerotium
• Mentha haplocalyx	Dry stem, leaf
• Glycyrrhiza uralensis	Dry root

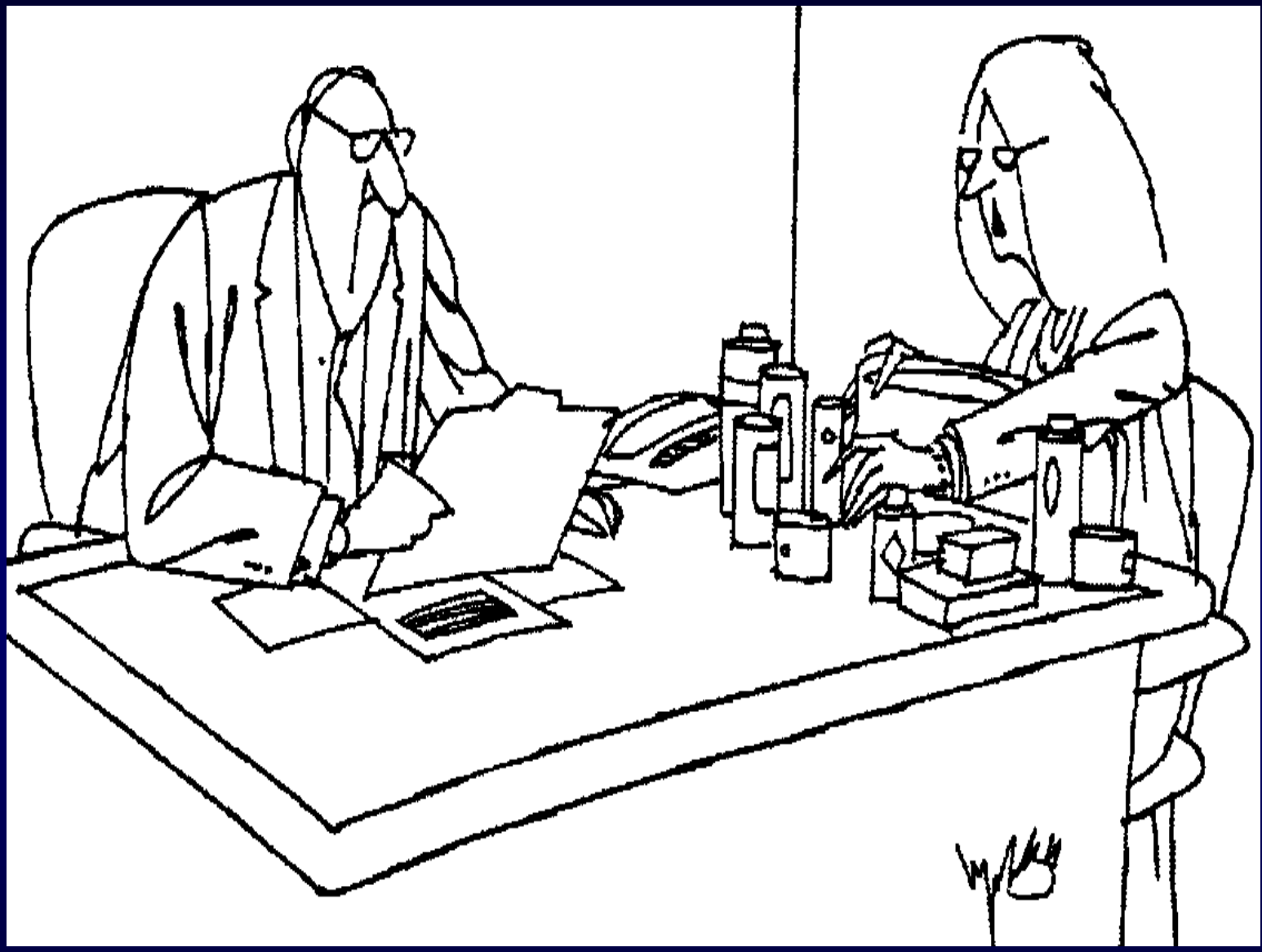
Zhang et al. J Psychiatric Res, Epub 2005; J Psychiatric Res 2007;41:360-369

“According to the FDA, there are more than 29,000 different dietary supplements available to consumers today.”

Gibson JE, Taylor DA, JPET 2005;314:939-944

“Since October 1994, when DSHEA became law, industry statements about life in a free society and the rights of consumers have frequently overridden practical arguments about the safety and efficacy of dietary supplements, resulting in a conversation that has privileged demagoguery over informed debate.”

- **Denham BE. JAMA 2011;306:428-429, July 27**



“Never mind the diagnosis. I just want your opinion of my herbal supplements.”

Valerian (Valeriana officinalis)

- Galen - the Phu plant
  (dried roots stink)
- U.S. Pharmacopoeia 1820-1942
  (the 19th century Valium)
- WWII - for shell shock
- Rat-catchers bait
- Cats-ecstasy

Valerian in Psychiatry

- **Insomnia**
  - Better than placebo in 6/7 double-blind studies
  - Slow onset (2-3 weeks)
- **Anxiety**
  - Only open-label reports
- Well tolerated (mild hangover?)
- Does odor defeat the blind?

Krystal and Ressler. CNS Spectrums 10/01

Valerian for Insomnia

- Internet-based, 4-week, double-blind, placebo-controlled
- 6.4 mg valerenic acids hs (odor masked)
- Valerian (n=135) = placebo (n=135)

Jacobs et al., Medicine 2005;84:197-207

Valerian for Insomnia: Systematic Review and Meta-Analysis

- 16 randomized, placebo-controlled trials, N=1093
- Methodologic problems in most, and preparations, doses, durations varied considerably
- "The available evidence suggests that valerian might improve sleep quality"
- Better studies are needed

Bent et al. Am J Medicine 2006;119:1005-1012

Valerian-Hops Combo, Diphenhydramine (50 mg) and Placebo for Mild Insomnia

- 2-week, double-blind, placebo-controlled, n=184
- Sleep diaries, polysomnography (n=75), clinical ratings
- “A modest hypnotic effect” for both vs. placebo

Morin et al. Sleep 2005;28:1465-1471

Valerian Extract vs Valerian/Hops Extract for Non-Organic Insomnia

- 4-week, double-blind, placebo-controlled, n=30
- Objective home recorder system*
- ↓ Sleep latency:
  Valerian/hops > valerian = placebo

*A 1-channel, self-applicable, ambulatory EEG recording device

Koetter et al, Phytotherapy Res 2007;21:847-851

Valerian and CYP450 Inhibition

- So far, so good
- Clinical studies-very limited data
  (only in 24 healthy volunteers)
- Don’t forget pharmacodynamic interactions with other sedative drugs

Ginkgo Biloba Tree (Maidenhair Tree)

- Oldest living tree species (200 million years)
- Lives up to 1000 years
- Grows up to 122 feet
- Durable
  - only tree to survive Hiroshima
  - popular in NYC

Ginkgo Biloba Components

- **Flavonal glycosides**
  - Kaempferol
  - Quercetin
  - Isorhamnetin
  - Myricetin
- **Terpene lactones**
  - Ginkgolides
  - Bilobalide
- **Etc.**

Ginkgo Biloba for Cognitive Impairment and Dementia

- Cochrane Collaboration review through Oct 2006
  35 studies, meta-analysis of 29
- Evidence of benefit: "inconsistent and unconvincing"
- Side effects: "placebo-like"

Birks J, Grimley Evans J. Cochrane Database of Systematic Reviews 2007, Issue 2.Art No.: CD003120. Published in The Cochrane Library 2008, issue 4

Ginkgo Biloba is Not a Smart Drug in Healthy People: A Systematic Review

- Review of 15 randomized trials:
  7 single-dose, 8 longer-term
- Age 60 or less
- "No convincing evidence … for a robust positive effect."

Canter and Ernst, Hum Psychopharmacol Clin Exp 2007;22:265-278

Ginkgo for Prevention of Cognitive Decline (42-month, placebo-controlled, n=122 cognitively intact subjects ages ≥ 85)

- Overall: no protection against dementia or memory decline
- Good adherence group: + protective effect
- More strokes and TIAs in ginkgo group (7 vs 0, p=0.01)

Dodge et al. Neurology 2008;70:1809-1817

Ginkgo Evaluation of Memory (GEM)

- Federally funded, placebo-controlled
- Volunteers ages ≥ 75 years
  - Normal cognition, n=2587
  - Mild cognitive impairment, n=482
- Ginkgo biloba extract (EGb 761, 120 mg bid)
- Median follow-up 6.1 years

DeKosky et al. JAMA 2008;300:2253-2262 (Nov 19)

Ginkgo Evaluation of Memory (GEM)

- Ginko biloba NOT effective in ↓ overall dementia rate or Alzheimer disease incidence
- Ginko biloba also NOT effective in ↓ the rate of cognitive change over time
- Side effects or serious AEs: no significant difference, but hemorrhagic stroke: n=16 vs. 8

DeKosky et al. JAMA 2008;300:2253-2262 (Nov 19) ; Snitz et al. JAMA 2009;302:2663-2670, Dec 23/30)

But
Wait!

Ginkgo for Dementia with Neuropsychiatric Features

- 24-week, db, pbo-controlled, once daily 240mg Egb 761, n=404
- Statistically and clinically significant improvement in cognition and neuropsychiatric symptoms.
- Similar to changes with cholinesterase inhibitors

Ihl et al., Int J Geriatr Psychiatry, 2010, ePub

Ginkgo Biloba Extract for GAD (n=82) and Adjustment Disorder with Anxious Mood (n=25)

4-week, double-blind, placebo-controlled

- **Dose:** Egb 761- 240 mg or 480 mg/day
- **Results (HAM-A ↓): EGb 761 > placebo (both doses)**
- **Response:** 480 mg- **44%**
  240 mg- **37%**
  placebo- **22%**

Woelk et al. J Psychiatric Research 2007;41:472-480

Ginkgo Biloba vs. Methylphenidate for ADHD in Children and Adolescents

- 6-week, double-blind, n=50
- Dose: Ginkgo T.D. 80-120 mg/day; methylphenidate 20-30 mg/day
- Results: Ginkgo less effective, but fewer side effects

Salehi et al. Prog Neuro-Psychopharmacol & Biological Psychiatry 2010;34:76-80

Adjunctive Ginkgo Biloba in Chronic Schizophrenia

- 6 study meta-analysis (ginkgo n=466, PBO n=3620)
- Sample: 90% Chinese, 10% Turkish
- Ginkgo "produced statistically significant moderate improvement in total and negative symptoms"

Singh et al. Int J Neuropsychopharmacology 2010;13:257-271

Ginkgo Biloba for Antidepressant–Induced Sexual Dysfunction (n=37)

- 240 mg/day EGb761 vs. placebo
- 8 week, double-blind
- Ineffective!

Kang et al. Human Psychopharmacol 2002;17:279-284

Ginkgo Biloba and CYP450

- Small in vivo studies in humans—induction of 2C19, little or no effect on 1A2, 2D6, 2E1, 3A4 (small sample sizes)
- In vitro inhibition of 1A2, 2C9, 3A4 but only by certain constituents
- Generally mixed and inconsistent results

Ginkgo Biloba and Bleeding

- Subdural hematoma (2 cases)
- Subarachnoid hemorrhage (1 case)
- Intracerebral bleed (1 case)
- Vitreous hemorrhage (1 case)
- Spontaneous hyphema (1 case)
- Avoid with aspirin, NSAIDS, valproate, warfarin, etc.

Kava (Piper methysticum)

- Intoxicating pepper
- South Pacific ceremonial and social drink
- A stress and anxiety reducing herbal superstar?

Kava Drinking

"It gives a pleasant, warm and cheerful, but lazy feeling, sociable, though not hilarious or loquacious; the reason is not obscured."

Hocart, 1929

Hillary Clinton in a Kava Ceremony-1992

Kava (Piper methysticum)

- **Properties**
  - **anxiolytic/sedative**
  - **muscle relaxant**
  - **analgesic**
  - **anticonvulsant**

Components (kavalactones)

- **methysticin**
- **dihydromethysticin**
- **kavain**
- **dihydrokavain**
- **and others**

Kava Extract vs. Placebo for Anxiety

- 12 double-blind RCTs met inclusion criteria
- Meta-analysis of 7 using HAM-A scores
- Effective vs. PBO, but effect size small and "effect lacks robustness"
- Rigorous, large trials needed

Pittler and Ernst. Cochrane Database of Systematic Reviews, 2003

Kava for Anxiety

- **Internet-based, 4-week, double-blind, placebo-controlled**
- **100 mg total kavalactones tid**

Jacobs et al., Medicine 2005;84:197-207

Kava for Anxiety

- **Internet-based, 4-week, double-blind, placebo-controlled**
- **100 mg total kavalactones tid**
- **Kava (n=121) no more effective than placebo (n=135)**

Jacobs et al., Medicine 2005;84:197-207

Kava for Generalized Anxiety Disorder (pooled analysis of 3 small, double-blind, placebo-controlled studies)

- **Sample:** kava (n=28), placebo (n=30), venlafaxine XR (n=6)
- **Dose:** 14 mg → 280 mg kavalactones/day
- **Results:** Kava **not** effective (significant effects favored placebo)

Connor et al Int Clin Psychopharmacol 2006;21:249-253

Kava for Anxiety

- **The evidence base supporting kava as an anxiolytyic is rather sparse**
- **On the other hand, who can argue with hundreds of years of history?**

Jefferson JW. Psychopharm Review 2009;44:25-32

Kava Anxiety Depression Spectrum Study

- 3-week, db, PBO, cross-over, n=60
- ≥ 1-month of “elevated generalized anxiety”
- Aqueous extract of kava (250 mg kavalactones)
- Significant reduction in anxiety (HAM-A) and depression (MADRS)
- No hepatotoxicity

Sarris et al. Psychopharmacology 2009;205:399-407

Take good care of your liver

Kava Hepatotoxicity

- As of October 2005: 110 cases worldwide (causal ?)
- 11 liver transplants, 9 deaths
- Jan 2003-banned in European Union, Canada;
  FDA advisory in US
- Mechanism obscure: drug interaction,
  ↓glutathione, extraction method,
  toxic metabolite, idiosyncrasy, ????

Richardson & Henderson, Br J Clin Pharmacol 2007;64:418-420

Kava Hepatotoxicity: 2010

- **"There is now sound evidence that liver injury was caused by both the traditional water-based kava extracts of the South Pacific and the medicinal solvent-based kava extracts of Western countries…"**
- **"…the kava product should be a water-based extract derived from peeled rhizomes and roots of a noble cultivar…of at least 5 years of age, …with a daily dose not exceeding 250 mg of kavalactones."**

Teschke R, Schulze J. JAMA 2010;304,2174-2175

Kava Dermopathy (Kani)

There is no admiration for the body and face of an awa drinker whose eyes are sticky and whose skin cracks like the bark of the kukui trees…

(from Titcomb, 1948)

Kava-Drug Interactions

- CYP450-small studies, conflicting data
- P-glycoprotein- no effect
- Potentiation of CNS-depressants (ALP/Kava coma)
- Antiplatelet activity
- No clinical drug interaction studies as of March 2011

Anke and Ramzan, J Ethnopharmacol 2004;93:153-168
Gurley et al., Drug Metabolism and Disposition 2007;35:240-245

St. John's Wort (Hypericum perforatum)

Bioactive Constituents of Saint John's Wort

- Phenylpropanes
- Flavonol glycosides
- Bioflavones
- Proanthocyanidins
- Xanthones
- Phloroglucinols (hyperforins)
- Naphthodianthrones (hypericins)

Nahrstedt and Butterweck: Pharmacopsychiat 30:129-134, 1997

St. John's Wort
Potential Mechanisms of Action

- 5-HT, NE, DA uptake inhibition (equipotent)
- GABA receptor binding
- MAO inhibition - very weak
- Protein kinase C inhibition
- Interleukin-6 suppression
- NMDA-receptor antagonism

Butterweck V. CNS Drugs 2003;17:539-562

Hyperforin in Rat Locus Coeruleus Increases Extracellular

- Serotonin
- Norepinephrine
- Dopamine
- Glutamate

Kaehler et al: Neuroscience Letters 20:199-202, 1999

Hypericum Extract STW3-VI vs Citalopram and Placebo in MDD (6-week, double-blind, n=388)

- **Entry:** HAM-D_{17} 20-24
- **Dose:** Extract 900 mg/day, Citalopram 20 mg/day
- **Efficacy (HAM-D ↓):**
  Extract = Citalopram > placebo*

Response:

Extract 52%, citalopram 56%, placebo 39%

*p<0.0001

Gastpar et al. Pharmacopsychiatry 2006;39:66-75

World Federation of Societies of Biological Psychiatry Guidelines for Treating Major Depressive Disorder in Primary Care

- "There is evidence from a substantial number of controlled trials that suggests" St. John's wort is "more effective than placebo for short-term treatment of mild to moderate depressive disorders." [Level A]
- Level A: Good research evidence to support the recommendation (yet most recent reference was Linde et al 2005)

Bauer et al., World J Biol Psychiatry 2007;8:67-104

St. John's Wort for Major Depression: Cochrane Database Review, Oct 8, 2008

- 29 randomized, double-blind trials:
  18 vs placebo, 17 vs standard antidepressants
- SJW extracts: superior to placebo; as effective as standard antidepressants, and better tolerated
- Results more favorable in German speaking countries

Linde et al. Cochrane Database of Systematic Reviews,
published online October 8, 2008

SJW vs Sertraline and Placebo in MDD (8 week, double-blind, n=340)*

- **Entry:** $HAM\text{-}D_{17} \geq 20$
- **Dose:** SJW 900-1500 mg (mean max 1299 mg)
  Sertraline 50-100 mg (mean max 75 mg)
- **Response:** SJW=sertraline=placebo on both primary outcome measures

Davidson et al. JAMA 2002;287:1807-1814

*NCCAM and NIMH funded

St. John's Wort vs. Sertraline and Placebo in MDD (A Research Surprise)

- Detectable plasma hyperforin
  - SJW group: negative in 17%
  - Placebo group: positive in 17%
- Did not influence overall outcome

Vitiello et al., J Clin Psychopharmacol 2005;25:243-249

Side Effects and Drug Interactions

St. John's Wort, Antidepressant Drugs and the Elderly

- 5 patients (ages 64 to 84)
  sertraline (4), nefazodone (1)
- 2-4 days on SJW
  nausea (5), vomiting (3), anxiety (3), restlessness (2), epigastric pain (1), confusion (1)
- Serotonin syndrome?

Lantz et al. J Geriatr Psychiatry Neurol 12:7-10, 1999

Hypericin in HIV-Infected Adults
(i.v. or p.o., n=30)

- No antiviral activity
- Severe phototoxicity 48%

Gulick et al: Ann Int Med 130:510-514, 1999

“I now have several anecdotal reports of (St. John’s wort) causing breakthrough bleeding in women on (oral contraceptives)”

C. Cracchiolo: Currents Affect Illness 17:11, 1998

St. John's Wort/Drug Interactions

- **CYP 1A2 – Induced (?)**
- **CYP 2B6 – Induced**
- **CYP 2C9, 2C19--Induced**
- **CYP 2E1 – Induced**
- **CYP 3A4 – Induced (esp. intestinal)**
- **P-Glycoprotein – Induced (Initial Inhibition)**

St. John's Wort and BC Pills

- Induces ethinyl estradiol and norethindrone metabolism
- ↑ breakthrough bleeding
- Reports of unplanned pregnancy

Hall et al., Clin Pharmacol Ther 2003;74:525-535

St. John's Wort and Digoxin

- Induction of P-glycoprotein
- Digoxin C_{max} ↓ 37%, AUC ↓ 25%
  (Hyperforin-rich preparation)
- Marked variability with dose and formulation

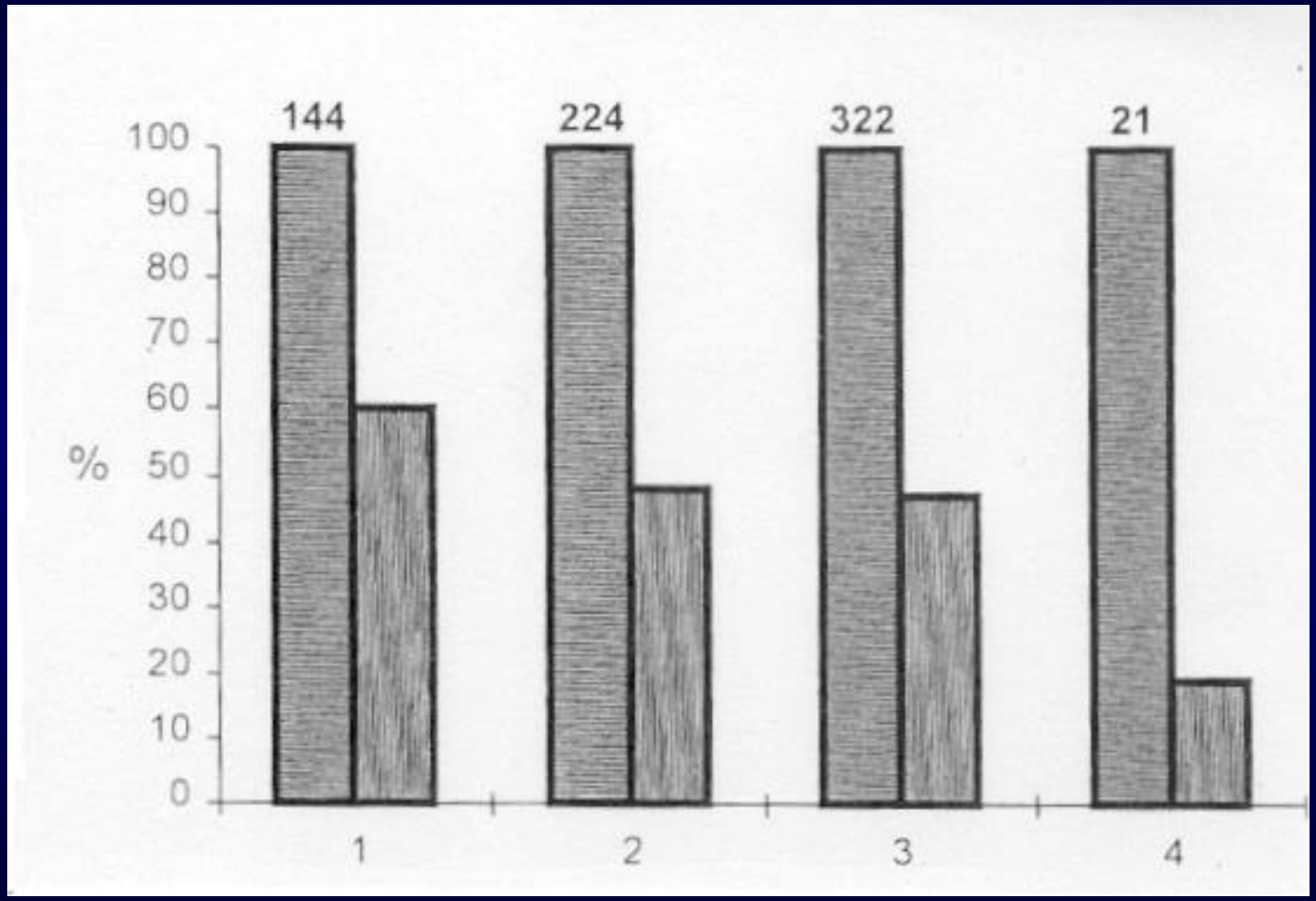
Mueller et al., Clin Pharmacol Ther 2004;75:546-557

St. John's Wort Increases Warfarin Clearance

- ↓ S-warfarin (2C9)
- ↓ R-warfarin (1A2, 3A4)
- ↓ INR (international normalized ratio)
- ↓ Anticoagulant effect

Jiang et al., Br J Clin Pharmacol 2004;57:592-599

St. John's Wort and Methadone (CYP3A4 substrate)



Eich-Höchi et al., Pharmacopsychiatry 2003;36:35-37

St. John's Wort and Statins
(n=16 healthy males, double-blind, placebo-controlled)

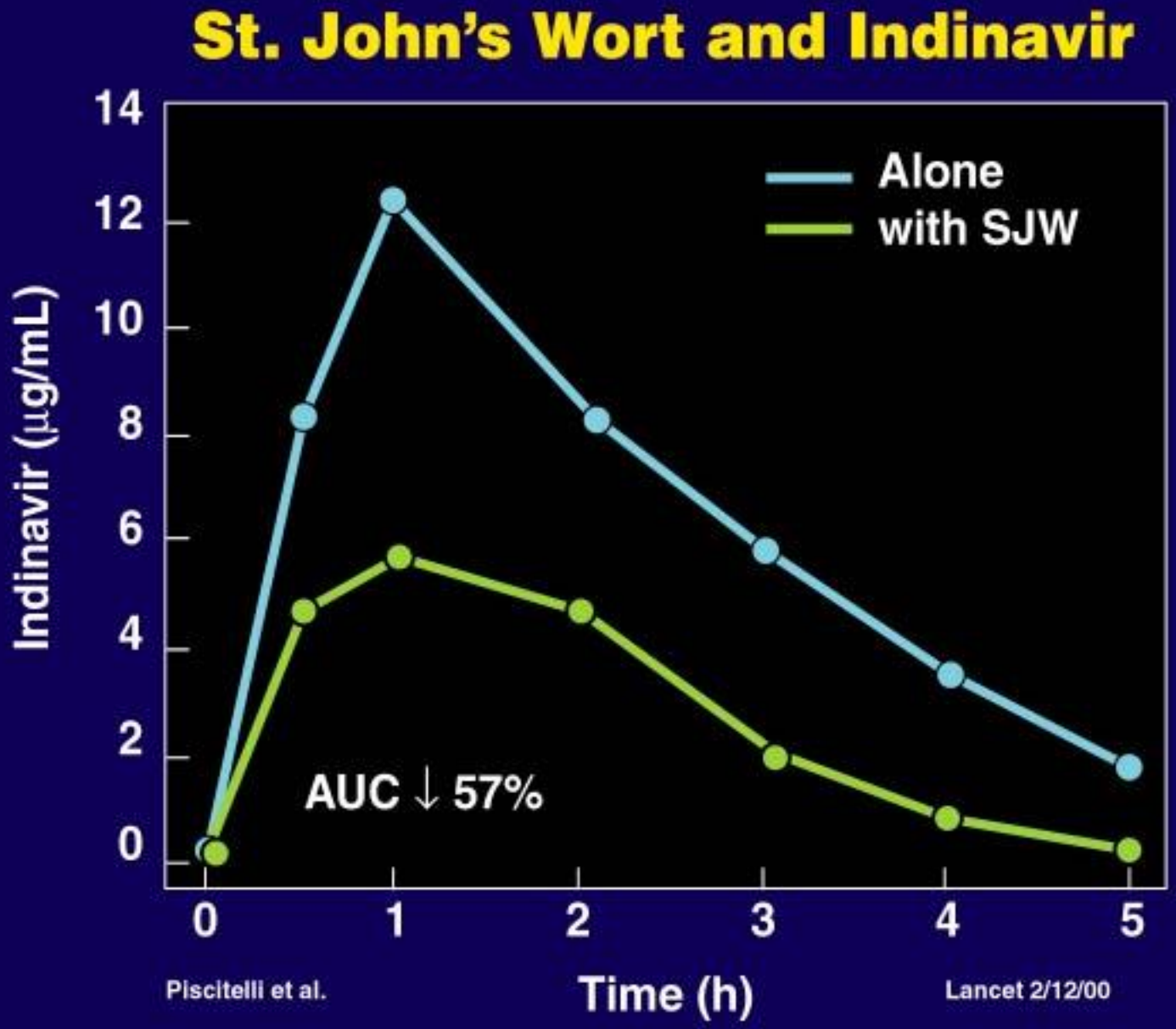
- **Simvastatin (3A4) - ↓ AUC about 50%**
- **Pravastatin (non-P450) – no change**

Sugimoto et al., Clin Pharmacol Ther 2001;70:518-524

HMG-CoA Reductase Inhibitors (Statins)

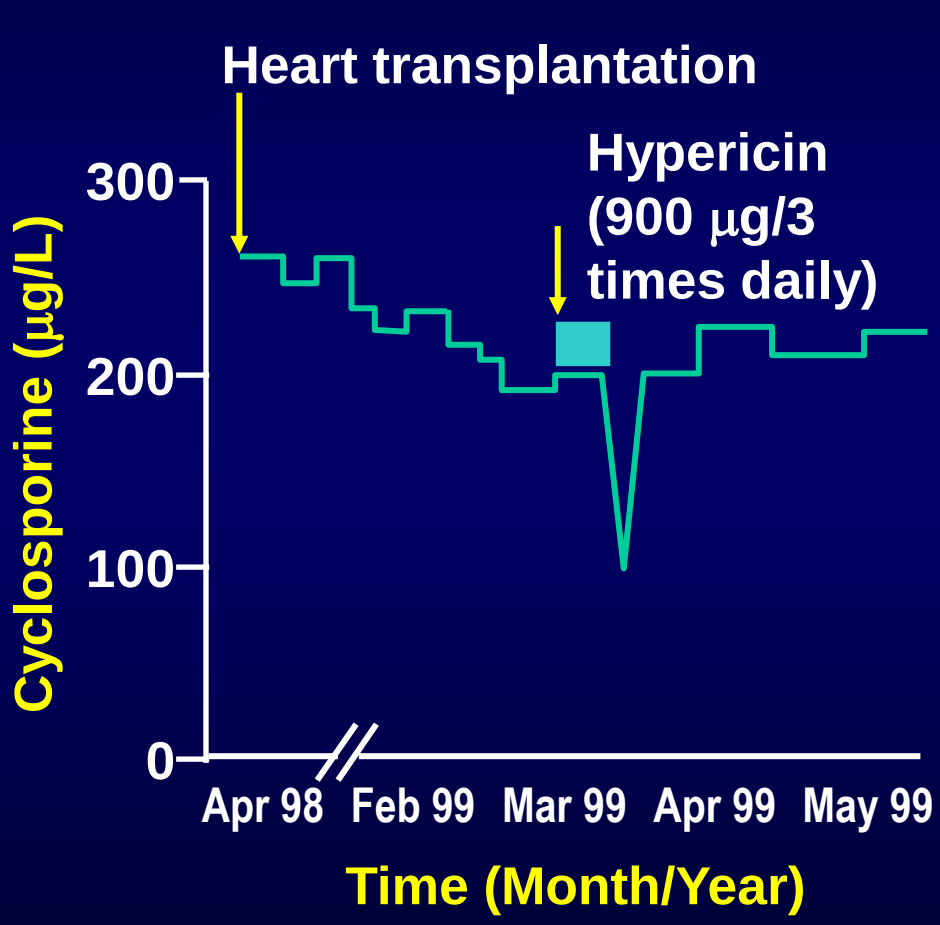
	CYP	P-gp
Atorvastatin (Lipitor)	3A4	yes
Fluvastatin (Lescol)	2C9 (75%)	no
Lovastatin (Mevacor)	3A4	yes
Pravastatin (Pravachol)	no	no
Rosuvastatin (Crestor)	no (2C9-10%)	no
Simvastatin (Zocor)	3A4	yes

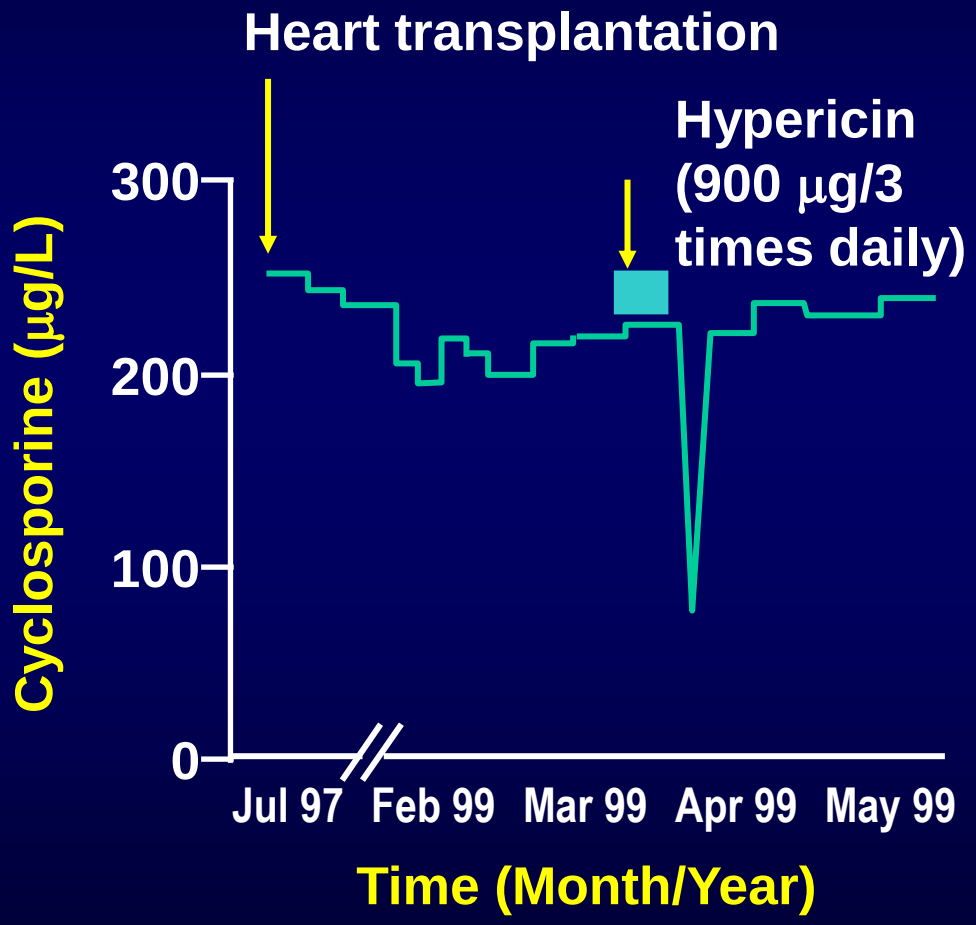
Neuvonen et al, Clin Pharmacol Ther 2006;80:565-581
Holtzman et al, Pharmacotherapy 2006;26:1601-1607



Piscitelli et al. Lancet 2000;355:547-548

Effect of St. John's Wort on Cyclosporine Blood Level





Ruschhitzka et al. Lancet. 2000;355:548-549

St. John's Wort Decreases Cyclosporine Blood Levels in Kidney Transplant Patients (n=30)

- Mean trough level ↓ 47%
- Range of decrease 33-62%

Breidenbach et al. Transplantation 2000;69:2229-2230

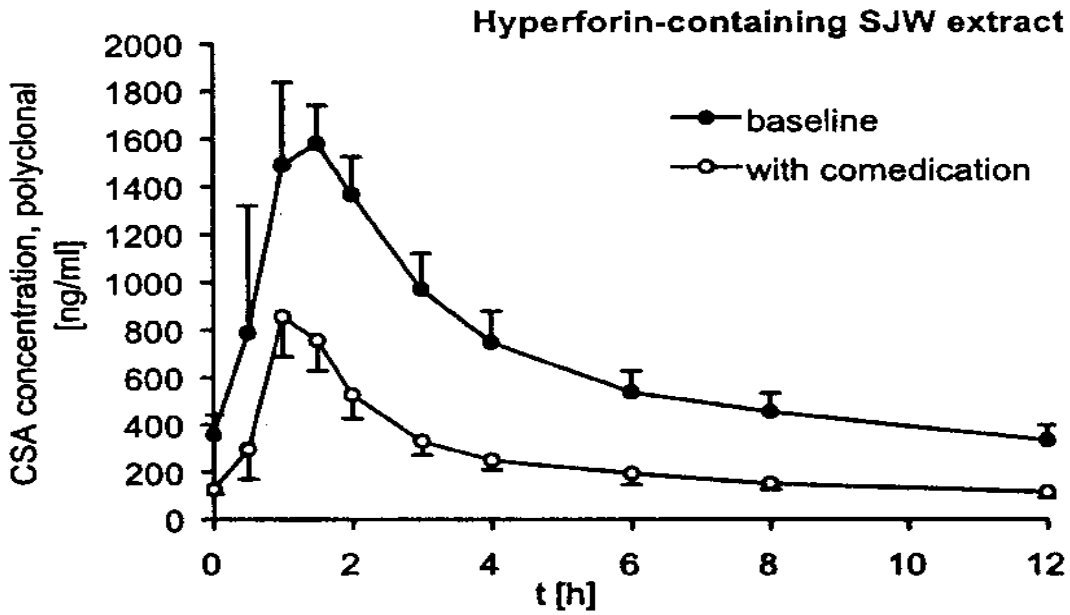
Hyperforin and Cyclosporine AUC
(renal transplant patients, n=10)

- St. John's Wort 900 mg/day
  - High HYF ↓52%
  - Low HYF No change

Mai et al., Clin Pharmacol Ther 2004;76:330-340

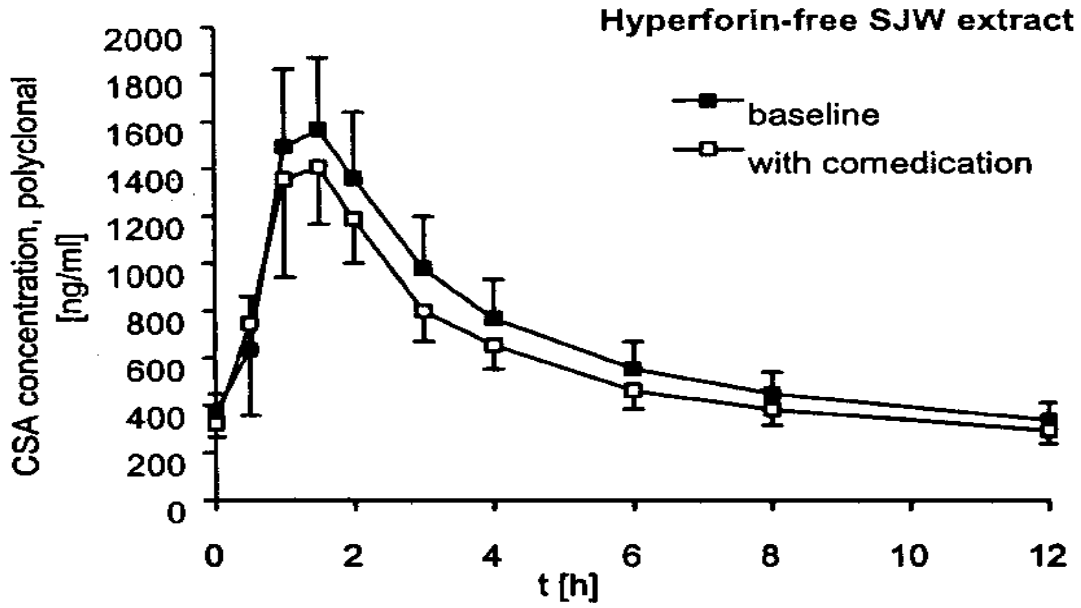
Hyperforin-containing

Hyperforin-free



St. John's Wort and Cyclosporine

Mai et al., Clin Pharmacol Ther 2004;76:330-340



Hyperforin Content in SJW
(8 Commercial Preparations)

- **Range: 0.01% to 1.89%***
- **A 189-fold difference!**

***It was 3.1% in the US sertraline/placebo study**

De Los Reyes and Koda. Am J Health-Syst Pharm 2002;59:545-547

Odds and Ends

Sympathyl for Mild to Moderate GAD

- 3-month, db, PBO, n=264
- Sympathyl: Two plant extracts (Cratagus oxacantha and Eschscholtzia californica) plus magnesium
- HAM-A response: Sympathyl 45%, PBO 32% (p=.017)

Hanus et al. Curr Med Res and Opinions 2004;20:63-71

Silexan for Subsyndromal GAD (NOS)

- 10-week, db, PBO, n=221
- Silexan: lavender oil from Lavandula angustifolia
- Response: Silexan 76.9%, PBO 49.1% (p<0.001)
- Remission: Silexan 60.6%, PBO 42.6% (p=0.009)

Response= ≥50%↓ HAM-A or PSQI (Pittsburgh Sleep Quality Index
Remission=HAM-A<10 or PSQI <6

Kasper et al. Int J Clin Psychopharmacology 2010;25:277-287

Euphytose vs Placebo for Adjustment Disorder with Anxious Mood

- **4-week, db, PBO, n=182**
- **Euphytose: Combination of extracts of *Crataegus, Ballota, Passiflower, Valeriana* (mild sedatives) and *Cola, Paullinia* (mild stimulants)**
- **HAM-A < 10 at day 28: Euphytose 42.9%**
  Placebo 25.3%
  (p=0.012)

As of May 2010, this was the only article found in a PubMed search of Euphytose

Bourin et al. Fundam Clin Pharmacol 1997;11:127-132

Matricaria recutita (Chamomile) Extract for Generalized Anxiety Disorder

- 8-week, db, PBO, n=57
- Dose: start 220 mg, max 880 mg
- HAM-A ↓: Chamomile > PBO over time (p=0.047)
- Only trends on secondary efficacy measures
- Future studies needed

Amsterdam et al. J Clin Psychopharmacol 2009;29:378-382

Ginsengs

- American (Panax quinquefolius)*
  ↓ Warfarin level and effect
- Asian (Panax ginseng)**
  No effect – 1A2, 2D6, 2E1, 3A4
- Siberian (Eleutheroccus senticosus)
  No effect – 2D6, 3A4***
  ↑ digoxin level (n=1)****

*Yuan et al., Ann Intern Med 2004;141:23-27
**Anderson et al., J Clin Pharmacol 2003;43:643-648
***Donovan et al., Drug Metab Dispos 2003;31-519-522
****McRae S., Can Med Assoc J 1996;155:293-295

Milk Thistle (Silybum marianum)

- GI, liver, gall bladder problems
- Human hepotocyte culture*
  - CYP3A4 – inhibition
  - UGT– inhibition
- Healthy subjects (n=10)**
  - Indinavir (3A4) – no effect

*Venkataramanan et al., Drug Metab Dispos 2000;28:1270-1273
**Piscitelli et al., Pharmacotherapy 2002;22:551-556

Echinacea purpurea
(coughs, colds, bronchitis, etc)
(12 healthy subjects)

- CYP1A2 – inhibition
- CYP2C9 – little effect
- CYP2D6 – no effect
- CYP3A
  - intestinal – inhibition
  - hepatic - induction

Orski et al., Clin Pharmacol Ther 2004;75:89-100

Garlic (Allium sativum L.)
(14 healthy subjects, 14 days)

- Antibacterial, antiparasitic, antilipidemic, antihypertensive, immunostimulant
- Dextromethorphan (CYP2D6)
  - No change
- Alprazolam (CYP3A4)
  - No change

Markowitz et al., Clin Pharmacol Ther 2003;74:170-177

Garlic
(10 healthy subjects, 39 days)

- **Saquinavir (CYP3A4)**
  AUC ↓ 51%
- **P-glycoprotein induction?**

Piscitelli et al., Clin Infect Dis 2002;34:234-238

Angelica dahurica

- Chinese herbal – allergy and cold
- Inhibits metabolism (rats)
  - tolbutamide (2C)
  - nifedipine (3A)
  - bufurol (2D1)
  - testosterone (2C11)

Ishihara et al., J Pharm Pharmacol 2000;52:1023-1029

Goldenseal (Hydrastis canadensis)

- "A cure-all type herb"
- 28 days, healthy subjects, n=12
  CYP2D6 – strong inhibition
  CYP3A4 – strong inhibition

Gurley et al., Clin Pharmacol Ther 2005;77:415-426

FastOne Dietary Supplement

- Kola nut, grape, green tea, ginkgo biloba
- CYP1A2 induced ~200% in 3 days in humans (n=4)
  - more potent than smoking
  - carcinogenic potential?

Ryn and Chung, Food and Chemical Toxicol 2003;41:861-866

Woohwangcheongsimwon Suspension: Potent 2B6 Inhibition

- Traditional Chinese and Korean Rx for hypertension, arteriosclerosis, coma, stroke
- Contains 29 herbs
- Potential interaction with 2B6 substrates

Kim H et al. Drug Metab Dispos 2008;36:1010-1015

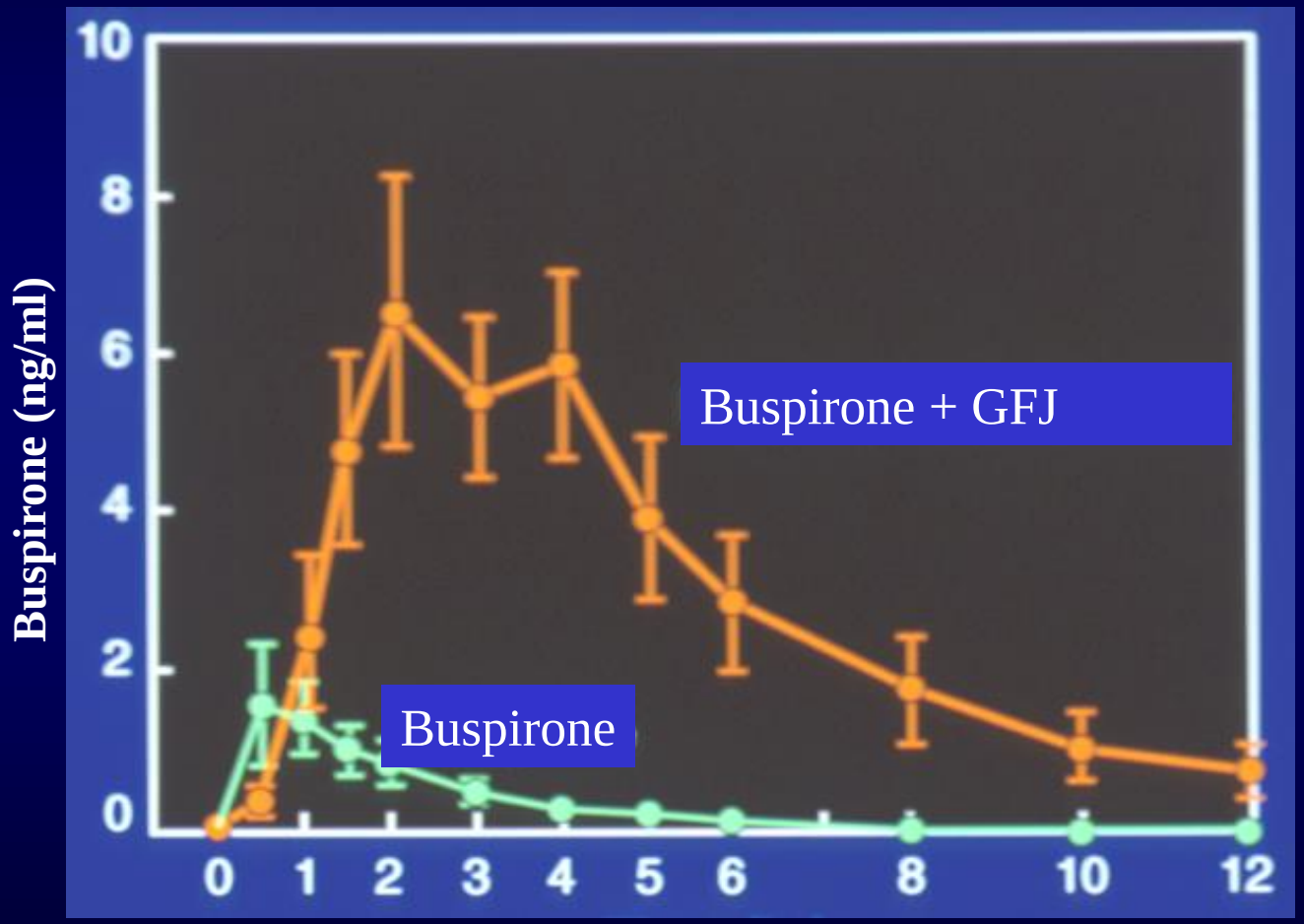
And Now the Juices

Grapefruit Juice

- **Inhibits CYP3A4 (gut wall), 1A2, 2A6, 2B6**
- **Cyclosporine levels ↑ 300%**
- **Lovastatin peak conc. ↑ 12-fold**
- **Felodpine peak conc. ↑ 500%**
  (bp and rate effects double)
- **Saquinavir AUC ↑ 220%**

Buspirone and Grapefruit Juice

CYP3A4 inhibition



Lilja et al. Clin Pharmacol Ther 1998;64:477-483

Grapefruit Juice Also Inhibits

- P-glycoprotein (P-gp)
- Organic Anion-Transporting Polypeptide (OATP) -A and -B

(as does orange juice, but less potent)

Satoh et al., Drug Metab Dispos 2005;33:518-523,2005

Seville (Sour) Orange Juice

- **It does inhibit CYP3A4, but apparently not P-glycoprotein**

Penzak et al. J Clin Pharmacology 2001:41:1059-1063

Orange Juice Decreases Atenolol Absorption (n=10 volunteers)

- 200 ml tid – juice or water
- C_{max} ↓ 49%, AUC ↓ 40%
- Inhibition of OATP?

Lilja et al., Eur J clin Pharmacol 2005;61:337-340

Pomegranate Juice (Punica granatum)

- **Rats: intestinal 3A inhibition**
  Carbamazepine AUC ↑ x 1.5
- **Human liver microsomes: CPY2C9 inhibition**
- **Human volunteers: No effect on CYP3A activity (midazolam clearance)**

Hidaka et al., Drug Metab Disp 2005;33:644-648
Nagata et al. Dug Metab Distribution 2007;35:302-305
Farkas et al. J Clin Pharmacology 2007;47:286-294

Resources

- **PDR for Herbal Medicines, 4th edition 2007**
- **National Center for Complementary and Alternative Medicine (Part of NIH)** http://nccam.nih.gov
- **Alternative Medicine Foundation** www.amfoundation.org
- **QuackWatch** www.quackwatch.com

National Center for Complementary and Alternative Medicine (Part of NIH)

- Explore CAM in the context of rigorous science
- Train CAM researchers
- Disseminate authorative information
- Support integration of proven CAM therapies
- http://nccam.nih.gov

Alternative Medicine Foundation
www.amfoundation.org

- **Evidence based research resource for professionals**
- **Reliable consumer information**
- **HerbMeD: interactive evidence-based herbal formulary**

1. **Which of the following was responsible for herbal products "flooding" the U.S. market in recent years?**

   A. **Federal Food, Drug, and Cosmetic Act**

   B. **Kefauver-Harris Amendment**

   C. **Dietary Supplement Health and Education Act**

   D. **Nutrition Labeling and Education Act**

   E. **Food and Drug Modernization Act**

2. **Which of the following has been most closely associated with hepatotoxicity?**

   A. **Ginkgo**

   B. **Kava**

   C. **Saw palmetto**

   D. **St. John’s wort**

   E. **Valerian**

3. **Which of the following is the clinically most important effect of St. John's wort on the cytochrome P450 (CYP) system?**

   A. **1A2 inhibition**

   B. **2D6 inhibition**

   C. **2C9 induction**

   D. **2E1 induction**

   E. **3A4 induction**

4. St. John's wort has been most extensively studied for the treatment of which of the following disorders?

   A. Bipolar

   B. Posttraumatic stress

   C. Panic

   D. Major depressive

   E. Social anxiety

5. **A placebo-controlled, double-blind study found Ginkgo biloba to be ineffective for treating antidepressant-induced sexual dysfunction.**

   A. True

   B. False

Conclusions

- **Limited, often conflicting, clinical data (best with St. John's wort)**
- **Marked variability in active ingredients**
- **Often undeclared ingredients**
- **More regulation necessary**
- **More research necessary**

Answers to Pre & Post Lecture Exams

1. C
2. B
3. E
4. D
5. A