

Herbal Psychopharmacology

James W. Jefferson, MD

Clinical Professor of Psychiatry

University of Wisconsin Medical School

- 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

Objectives

- **Understand the ramifications of DSHEA**
- **Appreciate the current efficacy status of herbals for treating psychiatric disorders**
- **Be 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 safety
- **1962: Kefauver-Harris Amendment**
 - Proof of 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 and Kassirer, NEJM 9/17/98

“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 nineteen billion dollars on dietary supplements

Specter M. *The New Yorker*, Feb 2, 2004, pp 64-75

50 Ginseng Preparations

- Analyzed for ginsenosides
- Content varied from 1.9% to 9% (4.7 fold difference)
- 6 (12%) had none

Asian Patent Medicines from California Herbal Stores

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

Valerian
(Valeriana officinalis)

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?**

Valerian for Insomnia

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

Valerian-Drug Interactions

(14 days, healthy vol., n=12)

- No clinically significant effects on CYP2D6 (dextromethorphan) or 3A4 (alprazolam)
- Alprazolam C_{\max} \uparrow 20%
(AUC, $T_{1/2}$ unchanged)

Valerian and CYP450 Inhibition

(28 days, healthy subjects, n=12)

- No significant effect**

CYP1A2, 2D6, 2E1, 3A4

Valerian and CYP450 Inhibition

- **So far, so good**
- **Clinical studies-very limited data**
 - only in 24 healthy volunteers**

Ginkgo

(Ginkgo biloba)

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.**

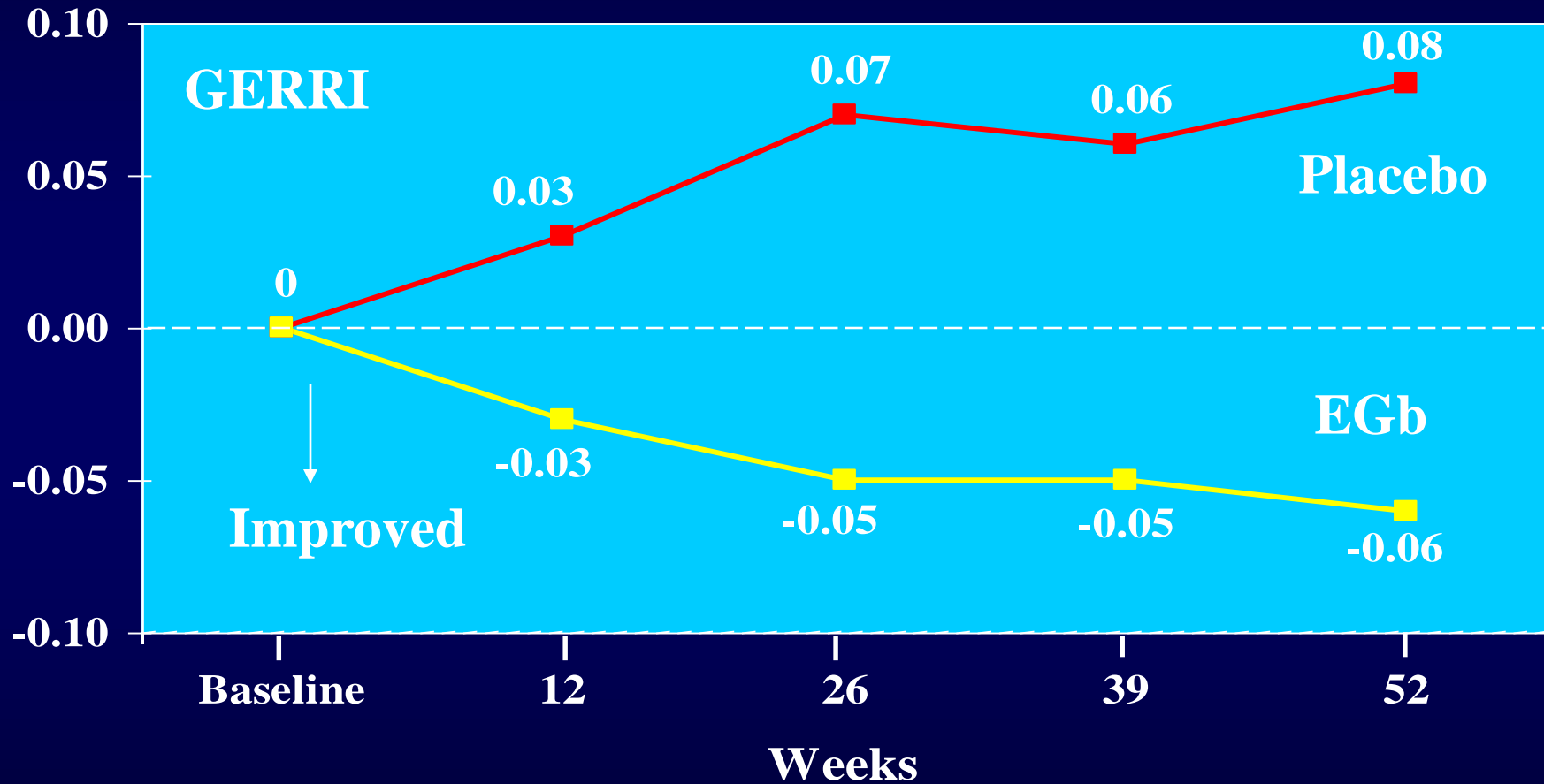
Ginkgo Biloba for Dementia

- **Inconsistent data**
- **Further research needed**
- **Cholinesterase inhibitors preferred**

Kurz and Van Baelen, Dement Geriatr Cogn Disord 2004;18:217-226

Diamond et al., Drugs Aging 2003;20:981-998

Extract of Ginkgo Biloba in Dementia



Ginkgo/Ginseng Combination and Cognitive Function

- **Healthy, middle aged volunteers
(n=256)**
- **14 week, double-blind, placebo**
- **Significant improvement on Index of
Memory Quality (7.5%)**

Ginkgo for Memory Enhancement

(6 week, double-blind, n = 230)

- Volunteers, over 60 years old**
- 40 mg t.id. versus placebo**
- No benefit, but well tolerated**

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

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

Ginkgo Biloba-Drug Interactions

- **Donepezil (2D6, 3A4 substrate)***
 - 30-days, 90 mg/day, n=14
 - no effect
- **Nifedipine (3A4 substrate)****
 - simultaneous, single dose, n=12
 - no effect overall
 - blood levels doubled in 2
- **Omeprazole (2C19, 3A4 substrate)*****
 - 12-day, 280 mg/day, n=18
 - CYP2C19 induction ~ 58% ↓AUC

*Yasui-Furukori et al., J Clin Pharmacol 2004;44:538-542

**Yoshioka et al., Biol Pharm Bull 2004;27:2006-2009

***Yin et al., Pharmacogenetics 2004;14:841-850

Ginkgo Biloba-Drug Interactions

(28-day, normal vol., n=12)

- **Dose: 60 mg qid**
- **No effect on phenotypic ratios:
CYP1A2, 2D6, 2E1, 3A4**

Gurley et al., Clin Pharmacol Ther 2002;72:276-287

Ginkgo Biloba-Drug Interactions

(14-day, normal vol., n=12)

- **Dose: 120mg bid (EGb 761)**
- **2D6 (dextromethorphan)**
 - no effect
- **3A4 (alprazolam)**
 - 17% ↓ AUC

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**
- **Rat data do not extrapolate well to humans**

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)

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

Kava

(Piper methysticum)

- **Properties**
 - **anxiolytic/sedative**
 - **muscle relaxant**
 - **analgesic**
 - **anticonvulsant**
- **Components (kavalactones)**
 - **methysticin**
 - **kavain**
 - **dihydrokavain**
 - **and others**

Kava for Anxiety

- **Effective in 7 double-blind studies**
- **Meta-analysis of 3 studies**
 - **Kava > placebo by 10 points on HAM-A**

Pittler and Ernst. J Clin Psychopharmacol Feb 2000

Kava for GAD at Duke

(4 week, double-blind, n = 35)

- **Kava Pure (140 mg → 280 mg KI/day)**
- **Kava = Placebo on all measures**
- **High Anxiety: Placebo > Kava**
- **Low Anxiety: Kava > Placebo**

Kava for Anxiety

- **Internet-based, 4-week, double-blind, placebo-controlled**
- **100 mg total kavalactones tid**
- **Kava (n=121) = placebo (n=135)**

Kava Hepatotoxicity

- 78 cases associated with kava (causal ?)
- 11 liver transplants
- 4 deaths
- Jan 2003-banned in European Union, Canada;
FDA advisory in US
- Mechanism: drug interaction ?, ↓ glutathione ?,
extraction method?, idiosyncrasy ?????

Kava and CYP450 Inhibition

(28 days, healthy subjects, n=12)

- CYP2E1 – 40% inhibition**
- CYP1A2 – no effect**
- CYP2D6 – no effect**
- CYP3A4 – no effect**

Chronic Kava Drinkers Abstain for 30 days (n=6)

- **Caffeine metabolic ratio doubled**
- **Probes for 2C19, 2D6, 2E1, 3A4 not affected**
- **Kava drinking inhibits 1A2**

Kava-Drug Interactions

- **CYP450 potency similar to grapefruit juice? (3A4 inhibition in vitro, but not in vivo)**
- **Potentialiation of CNS-depressants (ALP/Kava coma)**
- **Antiplatelet activity**
- **MAO-B inhibition**
- **No clinical drug interaction studies thus far**

St. John's Wort
(Hypericum perforatum)

Bioactive Constituents of Saint John's Wort

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

St. John's Wort for Depression (meta-analysis of double-blind studies)

- **Versus placebo – 27 studies**
 MDD – minimal benefit
 Non-MDD – possible benefit
- **Versus standard antidepressant – 14 studies – similar efficacy**
- **“Current evidence...is inconsistent and confusing”**

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

- **Entry:** **HAM-D₁₇ ≥ 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

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**

St. John's Wort for Depression - 2005

- **Moderate Depressive Disorder (n=241)***
“Not inferior to sertraline”
- **Major Depression (n=251)****
“At least as effective as paroxetine”
- **Major Depression (n=163)*****
SJW = fluoxetine = placebo
- **Mild-Mod MDD (n=135)******
SJW > fluoxetine; SJW trend > PBO

*Gastpar et al., Pharmacopsychiatry 2005;38:78-86

**Szegedi et al., Br Med J 2005;330:503-506

***Bjerkenstedt et al., Eur Arch Psychiatry Clin Neurosci 2005;225:40-47

****Fava et al., J Clin Psychopharmacol 2005;25:441-447 (Oct)

St. John's Wort

Mechanisms of Action ?

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

Hyperforin in Rat Locus Coeruleus Increases Extracellular

- **Serotonin**
- **Norepinephrine**
- **Dopamine**
- **Glutamate**

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?**

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 and BC Pills

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

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)

P-Glycoprotein

- **A transmembrane efflux pump**
- **Located in intestine, liver, kidney, brain**
- **Decreases drug absorption, increases drug secretion**
- **Chemotherapy resistant cancer cells**

Pregnane X Receptor (PXR)

- **Nuclear receptor**
- **Activated by diverse xenobiotics**
- **Stimulates transcription of CYP3A and P-glycoprotein genes**
- **Activated by hyperforin, but not by hypericin**

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

St. John's Wort Increases Warfarin Clearance

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

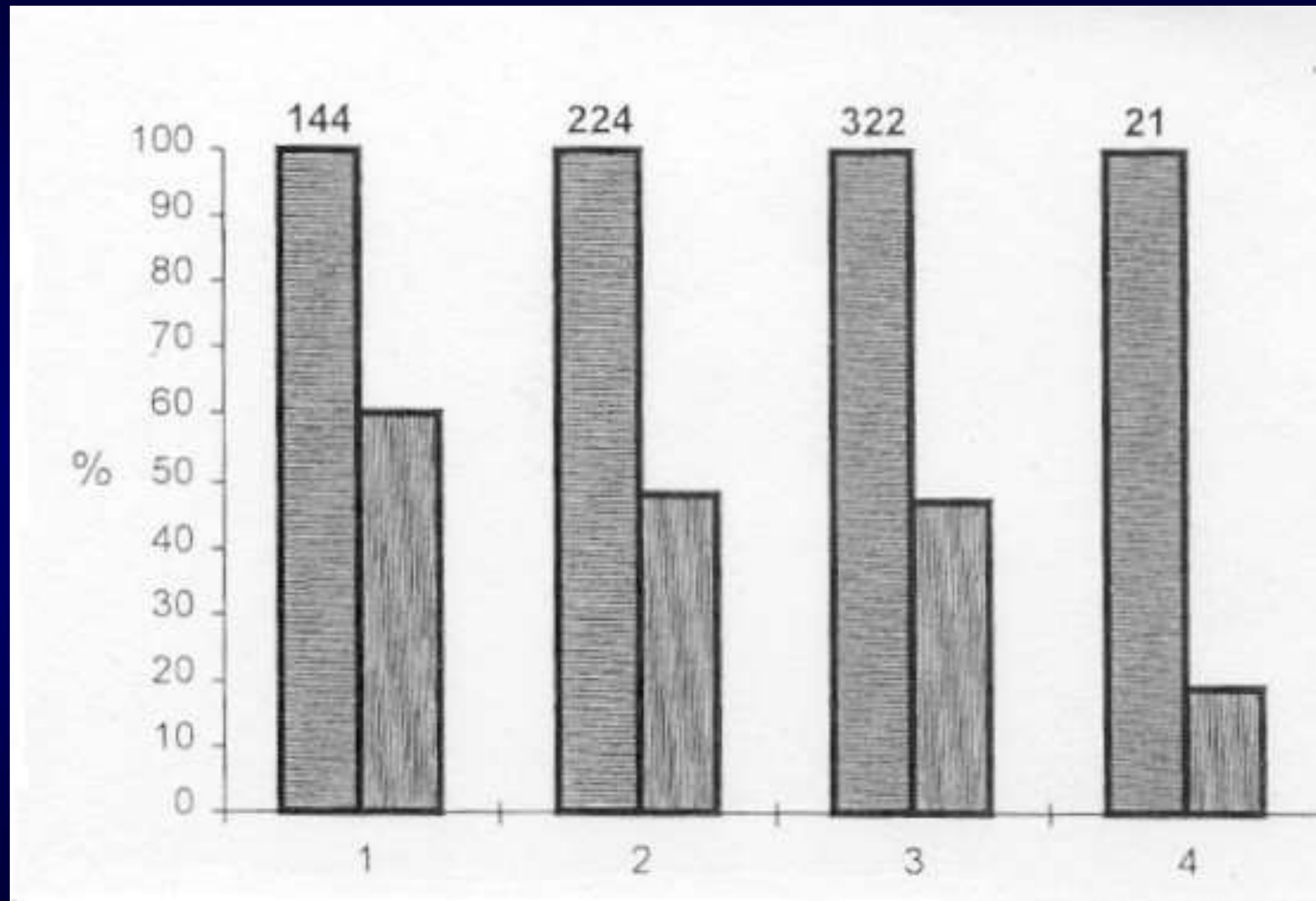
St. John's Wort and Alprazolam

- SJW - 300 mg tid for 14 days
- Alprazolam - 2 mg single dose
- Alprazolam (CYP3A4 substrate)
 - AUC ↓ x 2
 - Clearance ↑ x 2
 - $T_{1/2}$ 12.4 → 6.0 hours

St. John's Wort and Carbamazepine (Healthy volunteers, n=8)

- **CBZ x 14 days, CBZ + SJW (300 mg tid) x 14 days**
- **No change in CBZ clearance**
- **Why?? (CBZ induces SJW?)**

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



HMG-CoA Reductase Inhibitors (Statins)

3A4

Atorvastatin*
(Cervistatin*)

Lovastatin

Simvastatin

2C19

Fluvastatin

2C9

Rosuvastatin

non-P450

Pravastatin

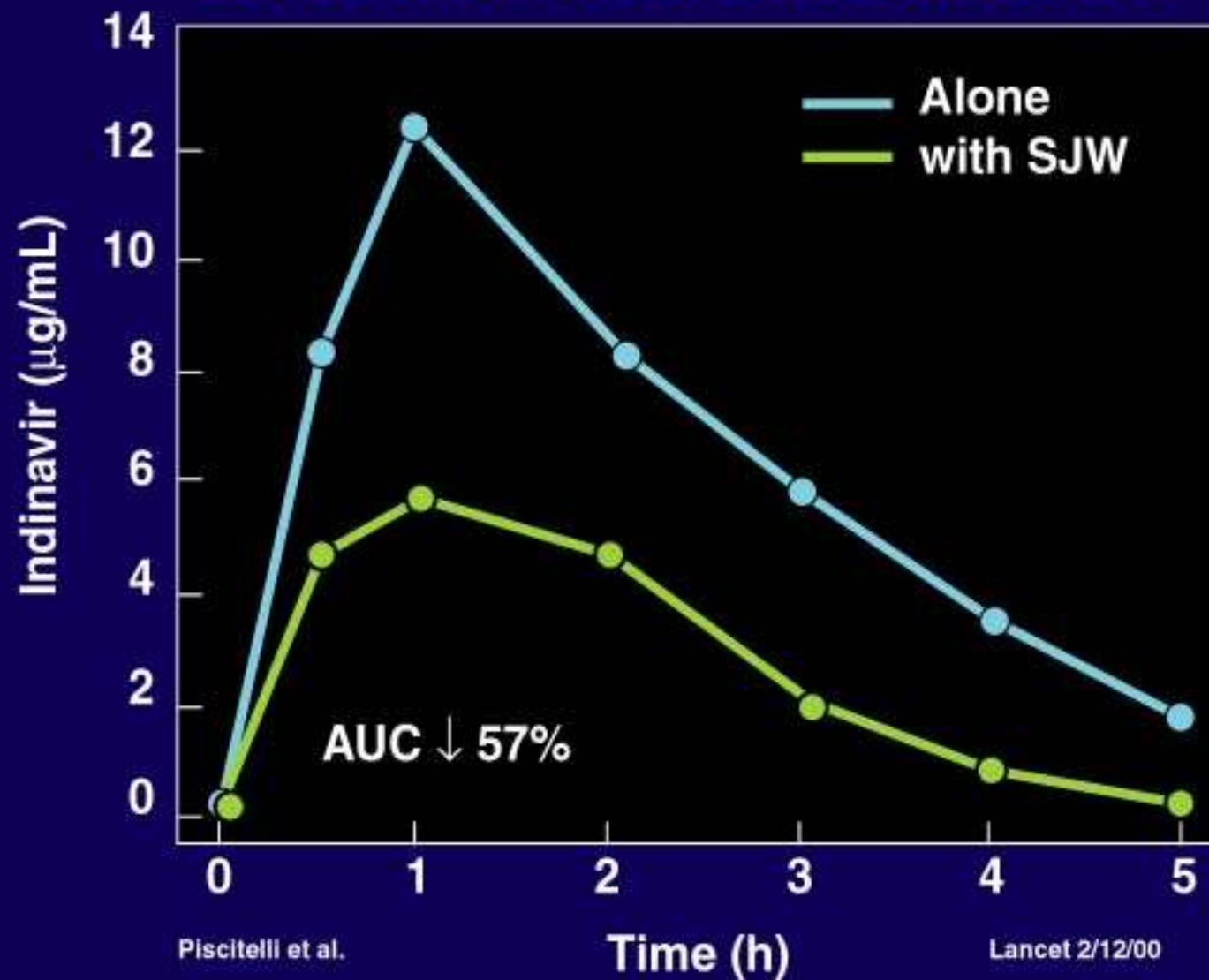
*Active metabolites

St. John's Wort and Statins

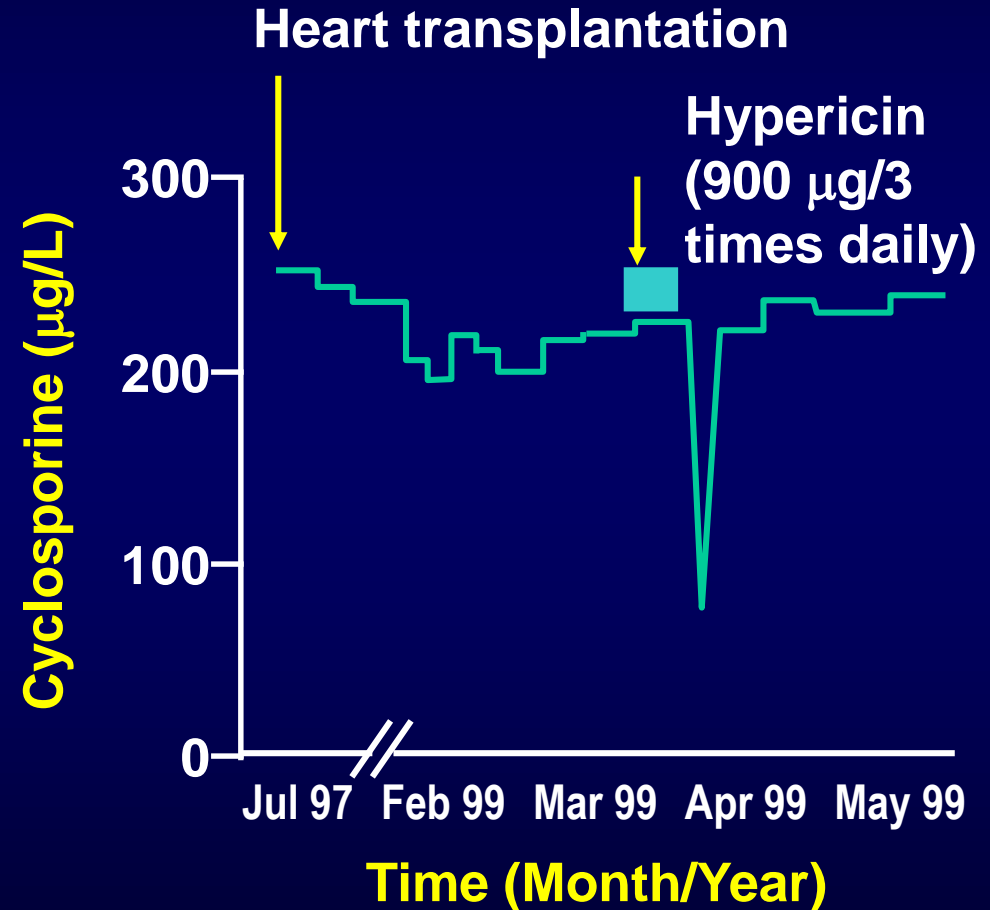
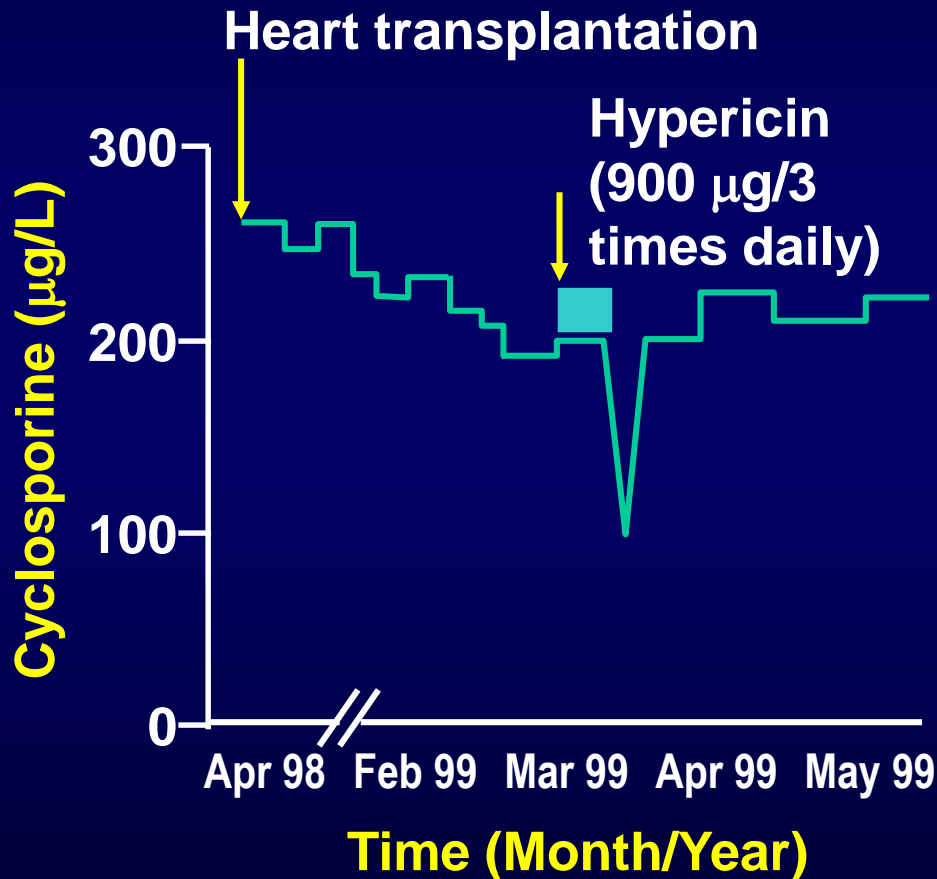
(n=16 healthy males, double-blind, placebo-controlled)

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

St. John's Wort and Indinavir



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



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

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

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

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

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**

Odds and Ends

Saw Palmetto (*Serenoa repens*)

- **Prostate health**
- **Healthy subjects (14 days, n=12)**
 - CYP2D6 – no effect**
 - CYP3A4 – no effect**

Ginsengs

- **American (*Panax quinquefolius*)***
↓ Warfarin level and effect
- **Asian (*Panax ginseng*****
No effect – 1A2, 2D6, 2E1, 3A4
- **Siberian (*Eleutherococcus 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 hepatocyte 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**

Garlic (*Allium sativum* L.)

(14 healthy subjects, 14 days)

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

Garlic

(10 healthy subjects, 39 days)

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

Angelica dahurica

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

Goldenseal (*Hydrastis canadensis*)

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

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?

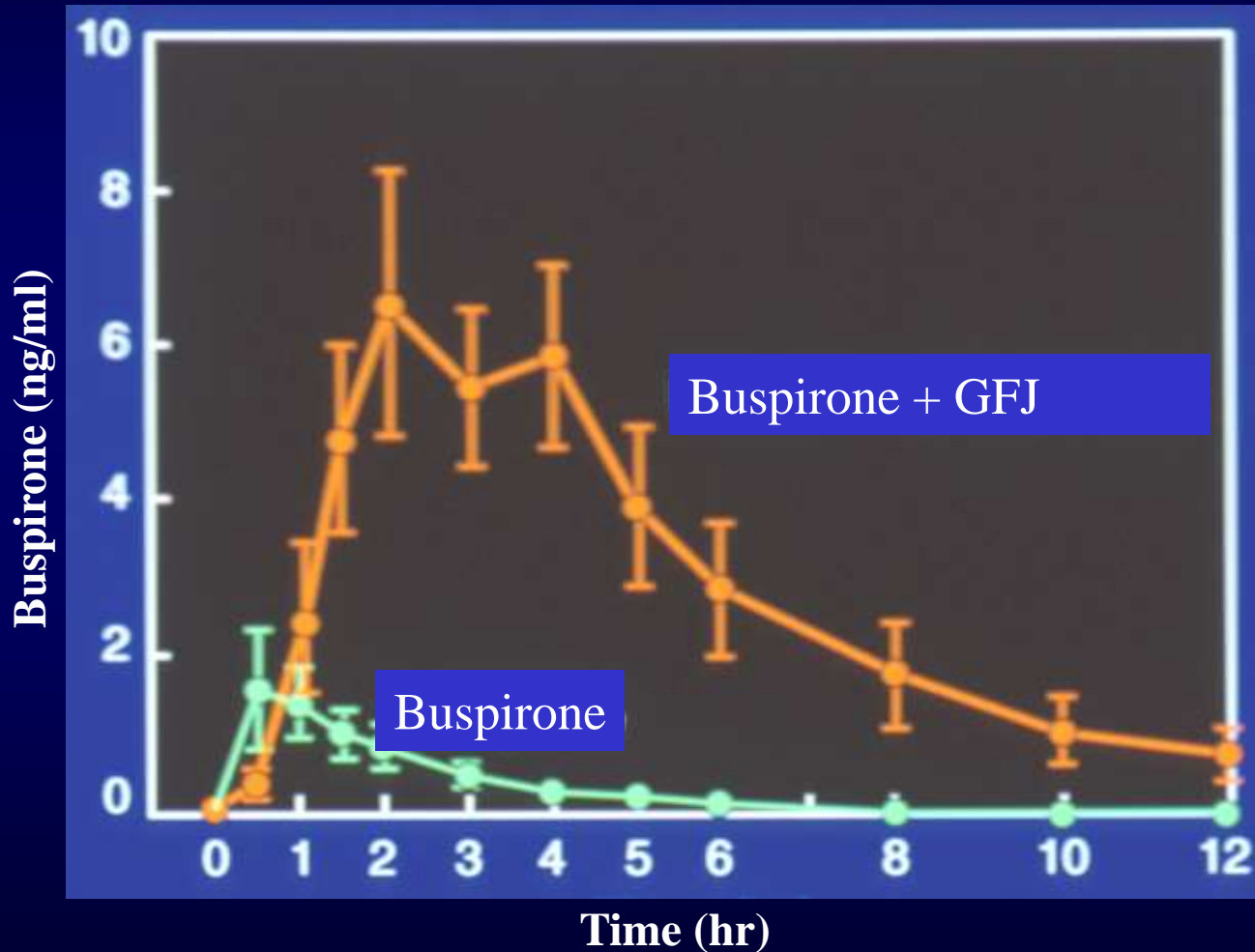
And Now the Juices

Grapefruit Juice

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

Buspirone and Grapefruit Juice

CYP3A4



Grapefruit Juice Also Inhibits

- **P-glycoprotein (P-gp)**
 - **Organic Anion-Transporting Polypeptide (OATP) -A and -B**
- (as does orange juice, but less potent)**

Orange Juice Decreases Atenolol Absorption (n=10 volunteers)

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

Pomegranate Juice (*Punica granatum*)

- Rats – intestinal 3A inhibition
Carbamazepine AUC ↑ x 1.5

PDR for Herbal Medicines
3rd edition, 2004

Medical Economics Company
Montvale, NJ

Alternative Medicine Foundation

www.amfoundation.org

- **Evidence based research resource for professionals**
- **Reliable consumer information**
- **HerbMed – interactive evidence-based herbal formulary**

QuackWatch

www.quackwatch.com

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