CPFI 2019 Annual Conference

Herb-Drug Interactions: Pharmacokinetic Mechanisms and Implications for Patients

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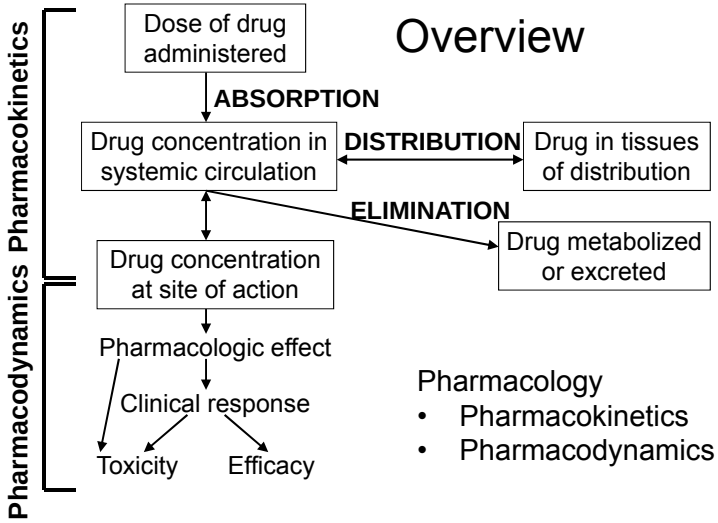
Objectives

- Describe mechanisms of inhibition and induction of drug clearance pathways (enzymes and transporters)
- Explain mechanisms of selected herb-drug interactions
- Apply these concepts to patient care

Overview



Pharmacology
- Pharmacokinetics
- Pharmacodynamics

Pharmacy Students and Dietary Supplements

- Axon et al, AJPE 2017: 81(5); article 92.
  - U.Arizona pharmacy students: twice as likely to have used DS (52% vs. 25% general pop.)
  - considered DS label info “unhelpful”
  - available research on DS “inadequate”
  - their education on DS “inadequate”
- DS sales in US 2017: ~$36,000,000,000

Absorption: First Pass Effect

- First-Pass Effect:
  - Drug orally administered
  - Solubility and permeability
  - Pass through enterocytes (transport and/or metabolism)
  - Liver may extract most, some, or little of the drug, before it gets to systemic circulation

$F_{oral} = F_a * F_g * F_h$

PK Implications of Hepatic First-Pass

- If first-pass is minimal, then...
- If first-pass is extensive, then...

First-Pass Effect: Resveratrol

- ~70% of oral dose gets "absorbed"
- Vast majority of this exists in the body as various metabolites
- <1% of oral dose gets into blood circulation as unchanged resveratrol
- So resveratrol absolute oral bioavailability is <1%!

Walle, Drug Metab Dispos 2004

Absorption of Herbals

- Druggability: in addition to receptor binding, a compound must have a favorable balance of solubility (to dissolve in GI fluids) and lipophilicity (to cross biological membranes)
- Many herbal components are hydrophilic and good bioavailability would not be expected
- However, data suggest that several gl**U**cosides have unexpectedly high oral bioavailability
  - May involve uptake via glucose transporters, such as SGLT (sodium-glucose transporters)

Bioavailability of Herbal Products

- Typically see two problems:

  1: compounds are too hydrophilic

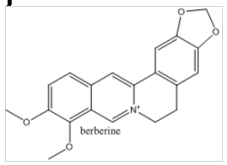
  2: compounds have functional groups susceptible to first-pass metabolism or gut degradation

Herbal Info Pitfalls: Bioavailability

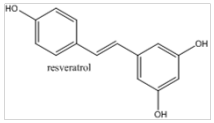
- Consider route of administration
- Consider interspecies differences
- Consider dose and formulation
- Consider what was actually measured

Herbal Transport

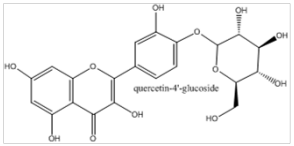
- Efflux transporters
  - P-glycoprotein:
    - berberine



  - Breast cancer resistance protein:
    - resveratrol



- Uptake transporters
  - Glucose transporters (SGLT1, GLUT2):
    - quercetin glucosides



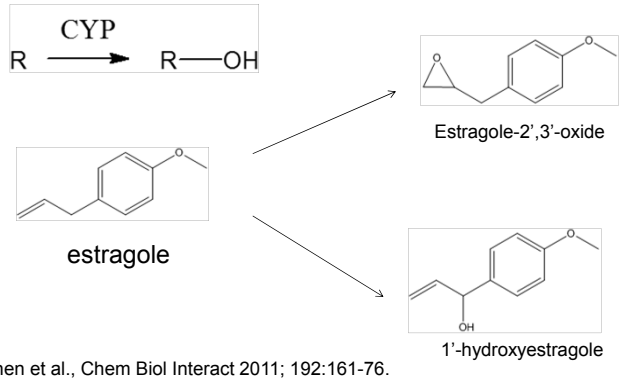
Herbal/Drug Metabolism

- Primarily in the gut wall and the liver
- Phase I reactions
  - Addition of small polar groups by oxidation, reduction, or hydrolysis
  - Convert lipid soluble drugs to inactive, more polar metabolites
- Phase II reactions
  - Formation of highly water soluble conjugates
  - Resulting compound is inactive and easily eliminated

Human Metabolic Enzymes

- PHASE I ENZYMES

  Cytochrome P450s (**CYP**)



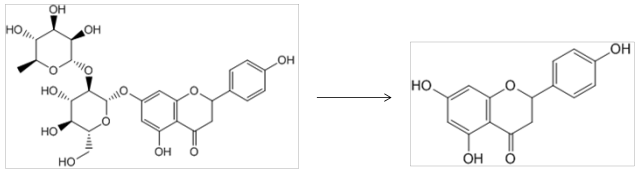
Chen et al., Chem Biol Interact 2011; 192:161-76.

Human Metabolic Enzymes

- PHASE I ENZYMES

  Saccharidases (various):

  ➢ Cleave glycones from glycosides to release aglycones



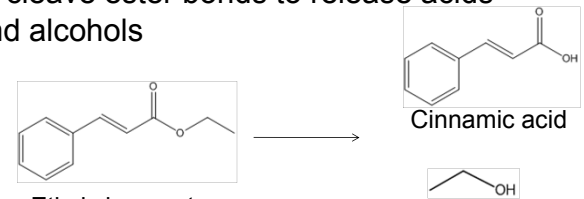
naringin — naringenin

Human Metabolic Enzymes

- PHASE I ENZYMES

  Esterases:

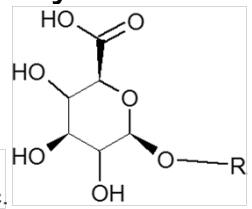
  ➢ cleave ester bonds to release acids and alcohols



Ethyl cinnamate — Cinnamic acid — ethanol

Human Metabolic Enzymes

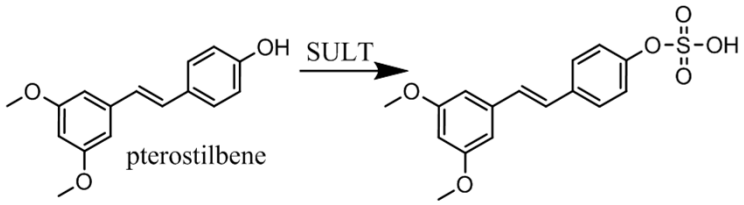
- PHASE II ENZYMES
  - Uridine diphosphate glucuronosyl-transferases (**UGT**)



  - Substrates:
    - Aromatic hydroxyls (phenols)
    - Aliphatic hydroxyls (alcohols)
    - Carboxyls (acids)
    - amines

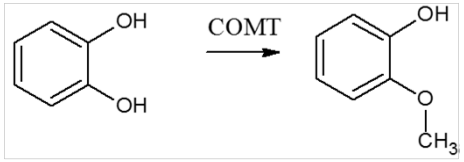
Human Metabolic Enzymes

- PHASE II ENZYMES
  - Sulfotransferases (**SULT**)
    - Substrates:
      - Aromatic hydroxyls (phenols)



Human Metabolic Enzymes

- PHASE II ENZYMES
  - Catechol-O-methyltransferases **(COMT)**
    - Substrates:
      - Catechols

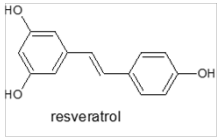


Enteric Metabolism

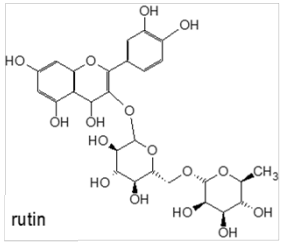
- Herbal constituents exposed to gut flora
- Gut flora metabolize compounds before reaching GI epithelium
- Some C=C double bonds reduced by bacteria
- Bacterial glycosidases and glucuronidases: cleave off sugars, release aglycones
- Aglycones may be less chemically stable in gut environment than the glycosides
- Aglycones may be more or less well absorbed than the glycosides

Enteric Metabolism

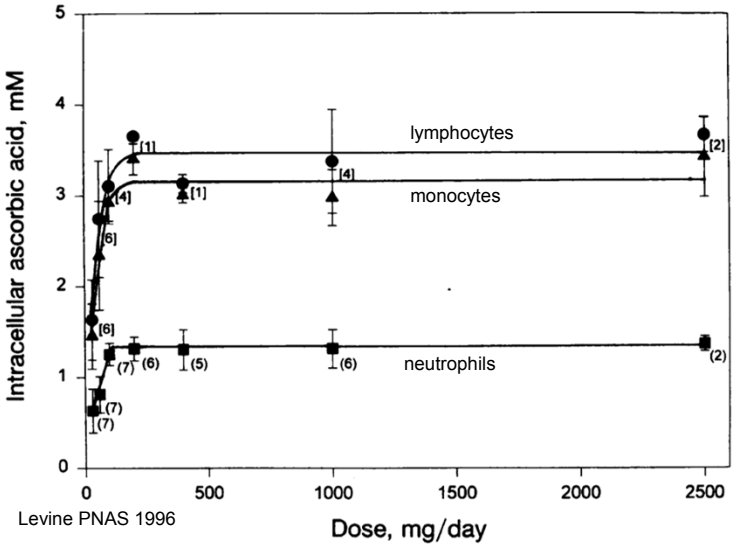
- Reduction of C=C bond:



- Cleavage of glycosides:



Consequences of Metabolism



Levine PNAS 1996

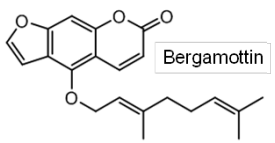
Quantitating an Herb-Drug Interaction

- Key PK Parameters:

Grapefruit Juice and Atorvastatin

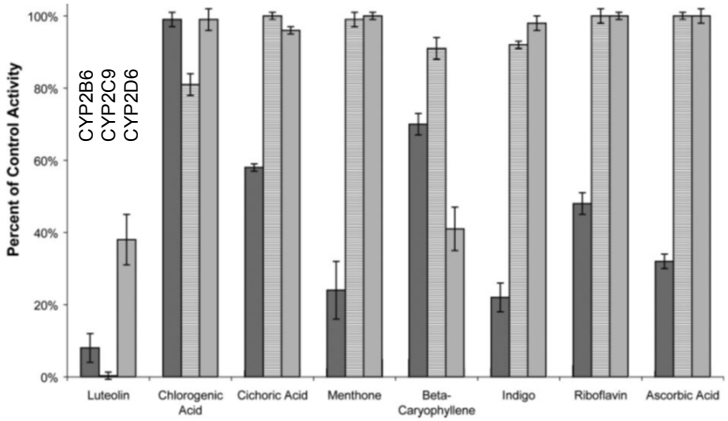
- GFJ increases atorvastatin (acid) AUC by 83%
- Mechanism? possibly CYP enzyme or ABC transporter inhibition
- Serious side effects (rhabdomyolysis) have been reported
- This interaction does not occur with pitivastatin

Grapefruit Juice Effects :



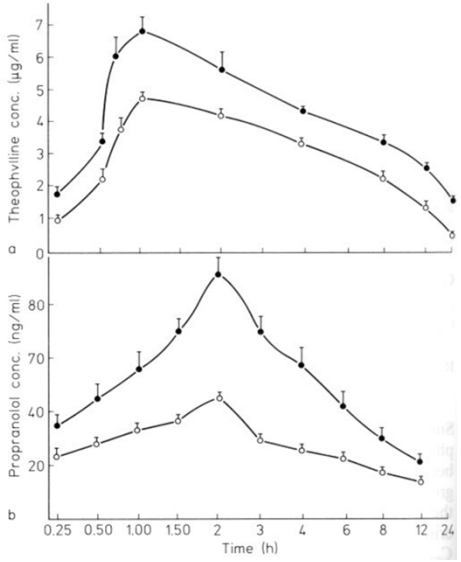
- <u>Inhibition of several CYP enzymes</u>
- nisoldipine: 500% (5-fold)
- cyclosporine: 300%
- terfenadine: 55% increase in fexofenadine AUC
- felodipine: 2-3 fold increase.
- HMG CoA reductase inhibitors (e.g. lovastatin,simvastatin, atorvastatin)

Interactions between Natural Products and CYP Enzymes



Foti DMD 2007

Black Pepper: Enzyme Inhibitor



Bano EJCP 1991

CYP Inhibition

Product	Component	Enzyme Isoform(s)
citrus fruit	bergamottin, tangeretin	CYP1A2, 3A4
milk thistle	silybin	CYP2E1, 3A4
soy	isoflavones (genistein, daidzein)	CYP1A1, 1A2, 1B1, 2E1
St. John's wort	hyperforin, quercetin	CYP3A4
various	flavonoids	CYP1A1, 1A2, 2B6, 2C9, 2D6

•Transporter inhibition also likely;
•not as well established in the literature

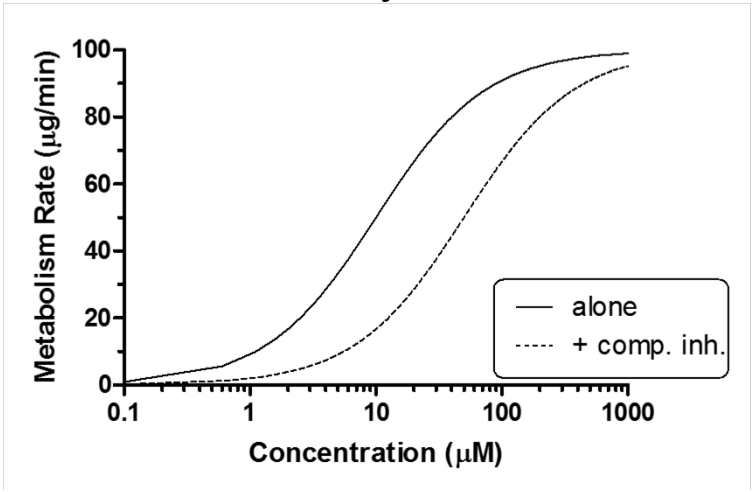
Cytochrome P450 (CYP) Inhibitor

- Compound that decreases CYP450 enzyme activity leading to decrease in metabolism rate of substrate
- Decreases clearance and increases concentrations (AUC) of substrate
- One compound can be both an inhibitor and substrate (erythromycin)

Enzyme Inhibition: Clinical Implications

- What clinical implications might you expect from an herb-drug interaction resulting in enzyme (or transporter) inhibition?
  - drug toxicity
  - increased side effects ("off-target")
  - need to reduce dose
  - decreased patient adherence to med regimen
  - increased health care utilization

Metabolic Enzyme Inhibition



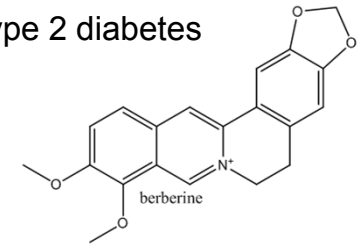
Enzyme Kinetics

Other HDI's

- Black Cohosh
  - inhibits CYP2D6
  - with atorvastatin: hepatotoxicity
- Goldenseal
  - inhibitor of CYP3A4 & CYP2D6
- Sesamin (from sesame/oil)
  - suicide inhibitor of CYP2C9

Berberine HDI

- Berberine: used for type 2 diabetes

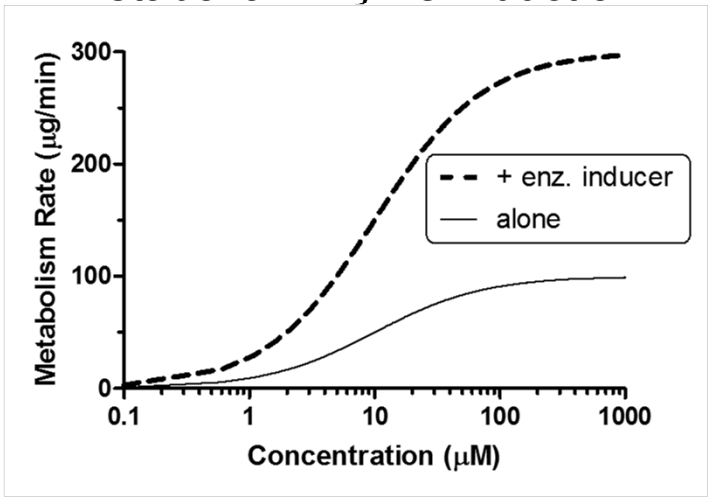


- inhibits multiple drug clearance mechanisms:
  - metabolism by CYP3A
  - efflux transport by P-glycoprotein (P-gp)
  - renal clearance by organic cation transporters (OCT's)

CYP Inducer

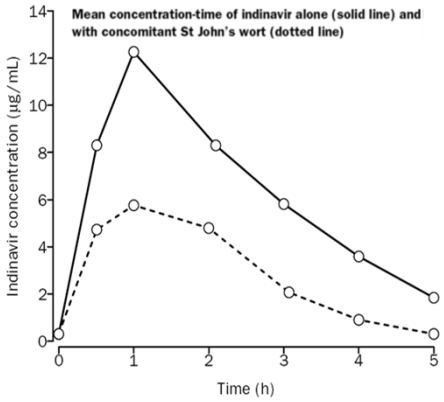
- Compound that increases CYP enzyme activity leading to increase in metabolism of substrate
- Inducers can affect multiple CYP enzymes (carbamazepine, rifampin)
- Can be an inducer of one enzyme and inhibitor of another (omeprazole)
- Typically increases the level of enzyme production
- Takes time (3-14 days)

Metabolic Enzyme Induction



Effect of St. John's Wort on Indinavir

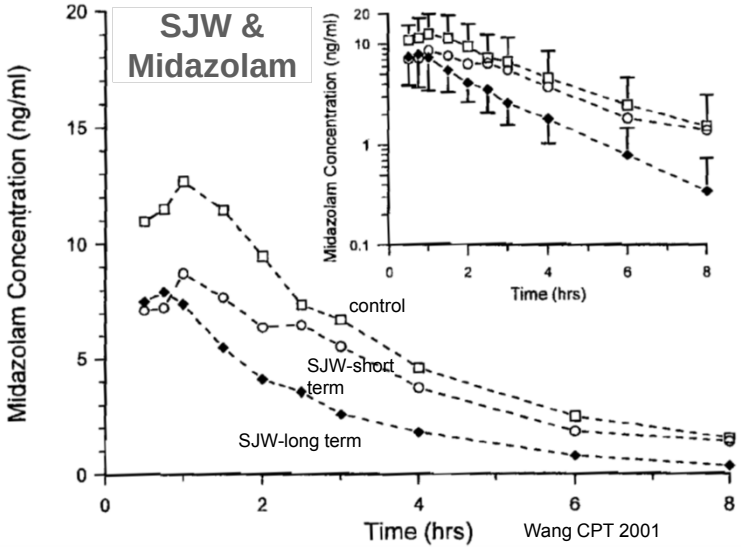
Piscatelli et al. Lancet 355:547, 2000



- Dosed with SJW 14 days
- Indinavir AUC: 57% decrease
- Indinavir trough conc: 81% decr.
- Induction of CYP3A4

Enzyme Induction: Clinical Implications

- What clinical implications might you expect from an herb-drug interaction resulting in enzyme (or transporter) induction?
  - loss of efficacy
  - decreased side effects
  - altered metabolite profile
    - decreased formation of active metabolite
    - increased formation of toxic metabolite
  - need to increase dose
    - toxicity when herb discontinued
  - decreased patient adherence to med regimen
  - increased health care utilization



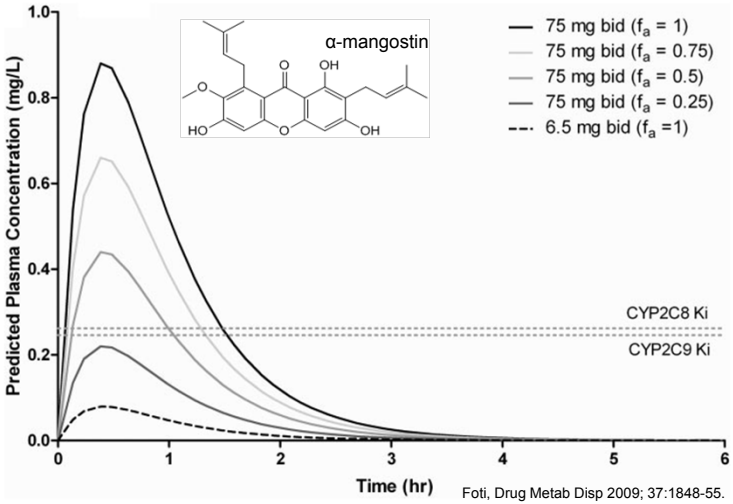
Patient Case

- A patient new to your pharmacy comes in with 2 new Rx's. You collect all the info, and find out the patient takes 3 oz. BID of Xango® juice. Does this pose any concern for herb-drug interactions?

Xango® Juice

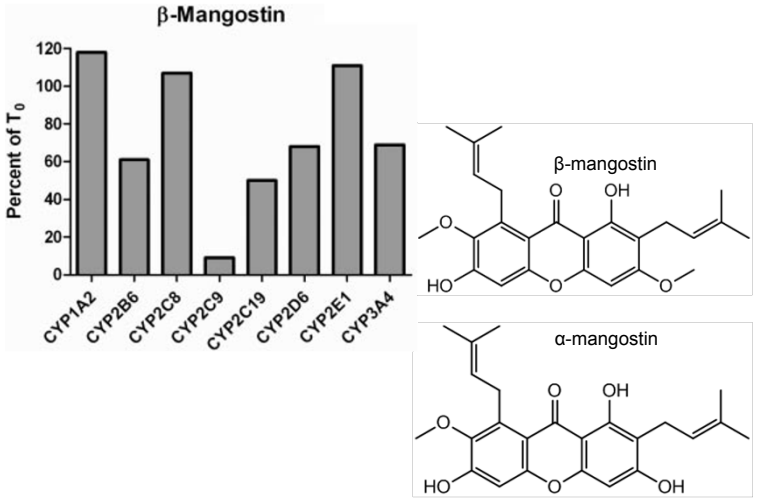
- Mix of mangosteen and other juices
- High concentration of xanthones
- "...stacks of supporting research..." (www.xango.com)
- "...insufficient evidence at this time to support the use of mangosteen..." (*Nutrients* **2013**, *5*(8), 3163-3183; doi:10.3390/nu5083163)
- Website video (2012):
  - "people wonder…" (about interactions with drugs)
  - "Xango is a *natural* food, used by millions"
  - "…not regulated by the FDA…"
  - "Xango is for everyone."

Predicted Herb-Drug Interaction



Foti, Drug Metab Disp 2009; 37:1848-55.

Predicted Herb-Drug Interaction

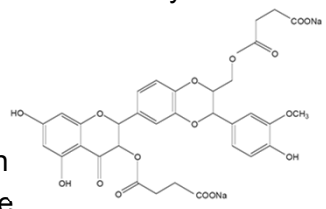


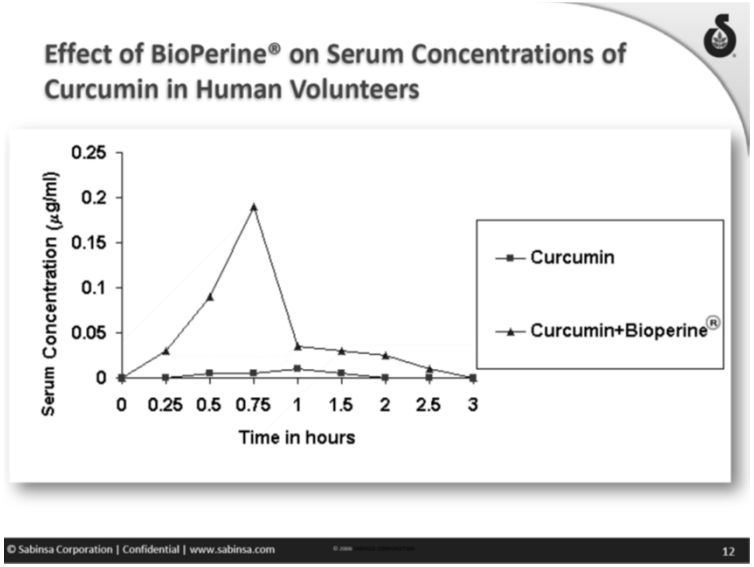
Positive Herb-Drug Interactions

- Silymarin or ellagic acid: may protect against hepatotoxicity of acetaminophen (Girish Fund.Clin.Pharmacol. 2008; 22:623-32)
- Grapefruit juice: lower drug doses to save $?
  - Issues:

Natural Products Interactions

- Amatoxins: mushroom poisons
  - polypeptides, accumulate in liver & kidney
  - diarrhea, liver failure, death
- Silibinin:
  - from milk thistle extract
  - antidote for amatoxin poison
  - inh. hepatic amatoxin uptake
  - stim. hepatic protein synth.
  - product: “Legalon SIL” in clinical trials





Pharmacist’s Role in Rational Phytotherapy

- Obtain herbal meds usage history
- Counsel patients regarding the differences between FDA-regulated medications and herbal therapies
- **Screen patient’s med profile for drug-herb interactions**
- Provide safety and efficacy information on use of herbal products

Pharmacist’s Role in Rational Phytotherapy (cont’d)

- Evaluate literature, interpret clinical (and pre-clinical) data
- Report observed HDI to FDA
- Publish case reports
- Design appropriate clinical studies