Nutraceutical-Drug Interaction and CYP450 Pharmacology

Rodney McKeever, MD
UCLA K-30 Program
INTRODUCTION

- Plants used as medicines for thousands of yrs
- Used by all major cultures
  - Saw palmetto used in Egypt in the 15th century BC
  - Hippocrates used SJW for mood ailments in the 5th century BC
  - The Greek physician Galen (AD 129–200) devised the first pharmacopoeia describing the appearance, properties and use of many plants of his time
  - Herbal medicines flourished in Europe until the 17th century declined with the scientific revolution
  - European immigrants brought herbal traditions to America and acquired Native American influences
- After~1920, standardized synthetic pharmaceutical drugs replaced herbal therapies, felt to have larger pharmacological effects and more profitable
- Estimated more than 40% of Americans use alternative medical therapies, nutraceuticals (herbals/botanicals) account for a significant proportion
- >120 conventional drugs derived from plant sources
<table>
<thead>
<tr>
<th>Drug</th>
<th>Herb common name (Latin name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Belladona (Atropa belladonna)</td>
</tr>
<tr>
<td>Codeine</td>
<td>Poppy (Papaver somniferum)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Autumn crocus (Colchicum autumnale)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Foxglove (Digitalis purpurea)</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Ephedra (Ephedra sinica)</td>
</tr>
<tr>
<td>Reserpin</td>
<td>Rauwolfia (Rauwolfia serpentine)</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Willow bark (Salix purpurea)</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Jimson weed (Datura stramonium)</td>
</tr>
<tr>
<td>Taxol</td>
<td>Pacific yew (Taxus brevifolia)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Madagascar periwinkle (Catharanthus roseus)</td>
</tr>
</tbody>
</table>
Definitions/nomenclature

- Drugs are substances that alter the body's actions and natural chemical environment.
- A substance used in the diagnosis, treatment, or prevention of a disease or as a component of a medication.
Herbs are Drugs

- Though not classified so legally
- Have pharmacological potency and individualized pharmacokinetics
- Have a mixture of ingredients, some active, some “inactive” which yield effects
- Think about them as drugs and you will have less difficulty in counseling
Factors Affecting Bioavailability

- Physical properties of the drug (hydrophobicity, pKa, solubility)
- Formulation (excipients used, release methods)
- Relationship to food/meals
  - Interaction with foods – grapefruit juice (CYP3A4), acid/base
- Gastric emptying rate
- Circadian differences
- First-pass metabolism
- Gut (and brain) transporters (e.g. P-glycoprotein)
- Individual differences – Age, Gender, GI tract disease
### Table 1. Factors Influencing Drug Response

<table>
<thead>
<tr>
<th>Intrinsic</th>
<th>Physiologic</th>
<th>Extrinsic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>Absorption, distribution,</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Absorption, distribution,</td>
<td>metabolism, excretion</td>
<td>Climate</td>
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<tr>
<td>distribution, metabolism,</td>
<td>Age</td>
<td>Culture</td>
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<tr>
<td>excretion</td>
<td>Alcohol</td>
<td>Educational status</td>
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<tr>
<td>Body weight</td>
<td>Body weight</td>
<td>Language</td>
</tr>
<tr>
<td>Genetic conditions</td>
<td>Cardiovascular function</td>
<td>Socioeconomic factors</td>
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<tr>
<td>Genetic polymorphism of drug-</td>
<td>Diet</td>
<td>Definition/diagnostics</td>
</tr>
<tr>
<td>metabolizing enzymes</td>
<td>Diseases/conditions</td>
<td>Diet</td>
</tr>
<tr>
<td>Height</td>
<td>Height</td>
<td>Diseases/conditions</td>
</tr>
<tr>
<td>Race</td>
<td>Kidney function</td>
<td>Drug adherence</td>
</tr>
<tr>
<td>Receptor sensitivity</td>
<td>Liver function</td>
<td>Medical practices</td>
</tr>
<tr>
<td>Sex</td>
<td>Receptor sensitivity</td>
<td>Pollution</td>
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<tr>
<td></td>
<td>Smoking</td>
<td>Smoking</td>
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<tr>
<td></td>
<td>Stress</td>
<td>Stress</td>
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<tr>
<td></td>
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<td>Sunlight</td>
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<td></td>
<td></td>
<td>Therapeutic approach</td>
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</tbody>
</table>

Pharmacogenetics of drug metabolism

Drug metabolism is crucial in determining therapeutic and adverse effects

Genetic factors play an important role in individual differences of drug metabolism

- **Phase I**
  - Oxidation, reduction, hydroxylation, dealkylation, etc.
  - Aim: introduce a new functional group
  - Cytochrome P450 enzymes in hepatocytes attached to SER

- **Phase II**
  - Conjugation with glucuronic acid, glutathione, acetate, etc
  - Aim: to increase water solubility
  - Usually in the cytosol
Definition of a Nutraceutical: "Food, or parts of food, that provide medical or health benefits, including the prevention and treatment of disease." Dr Stephen DeFelice (Foundation for Innovation in Medicine)-coined the term "Nutraceutical" from "Nutrition" and "Pharmaceutical" in 1989. The term nutraceutical is commonly used in marketing but has no regulatory definition.

“nutraceutical” is an umbrella term in the general vernacular to define herbs, supplements, vitamins or, at times, supplements that are actually illegally used FDA-approved drugs bought for specific uses and may cause severe drug interactions and/or death (e.g., dextromethorphan products).

Dietary supplements-can be “extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders.” These substances may be found in preparations such as fresh decoctions (chopped) or whole herbs (steeped as teas), tinctures (fresh or dried herbs preserved in alcohol), vinegar extracts, syrups, glycerites (in vegetable glycerin), miels (in honey), freeze-dried or powdered (which may come in bulk, tablet, troche, paste, capsule, or concentrate forms), suppositories, creams, gels liniments, oils, or compresses.

Functional foods are foods or food ingredients that may have health benefits in addition to providing traditional nutrients such as protein, carbohydrate, vitamins and minerals.
Dietary Supplements including botanicals:
- Vitamins, minerals, co-enzyme Q, carnitine, Ginseng, Gingko Biloba, Saint John's Wort, Saw Palmetto

Functional Foods:
- Oats, bran, psyllium and lignin's for heart disease and colon cancer
- Prebiotics - oligofructose for control of intestinal flora
- Omega-3 milk in prevention of heart disease
- Canola oil with lowered triglycerides for cholesterol reduction
- Stanols (Benecol) in reduction of cholesterol adsorption

Medicinal Foods:
- Health bars with added medications
Patients most likely to use Nutraceuticals

- Middle-aged women
- Patients with college education
- Patients with higher income
- Caucasians
- Patients diagnosed with cancer
- The elderly with chronic medical conditions
- Elderly Hispanic women
Reasons for herbal medicine use

- Constitutional
- Respiratory
- Arthritis
- Gut
- Hormonal
- Bladder
- No Reason

Ailments

% of Users
Disease/Condition for Which CAM Is Most Frequently Used*

*These figures exclude the use of megavitamin therapy and prayer.

Patterns of CAM usage

- It has been estimated that in the United States, 24% of the general population regularly take herbal products. Kauffman DW et al: Recent patterns of medication use in the ambulatory adult population of the United States. JAMA (2002) 287:337-344

- In 2006, it was found that 63% of US residents over 50 use CAM, and of these, 77% do NOT discuss it with their doctor! AARP (American Association of Retired Persons) and NCCAM. (National Center for Complementary and Alternative Medicine): What people 50 and older are using and discussing with their physicians. Washington DC: AARP 2007 via HerbalGram 75:p15

- Use is not limited to the lay public: according to one study in 2003, 84% of pharmacists have tried it (survey in Singapore, but international cohort tested) Khol HL, Teo HH, Ng HL. Pharmacists' patterns of use, knowledge, and attitudes toward complementary and alternative medicine. J. Altern. Comp. Med. (2003) 9(1):51-63

- Although many recommend CAM products, they admit that they consider their expertise in this area to be ‘inadequate’ Welna EM et al Pharmacists' personal use, professional practice behaviors, and perceptions regarding herbal and other natural products. J Am Pharm Assoc. (2003) 43(5):602-11
Case Report

62 y/o male h/o CLL presents with 3D h/o fatigue, SOB, fever and cough; Rx with chemotherapy for 3 mos PTA
Meds: valproic acid (1500mg q.d.) for post-traumatic sz disorder
Adm: orientedX4; hypoxic (PO2 56mmHg on 21%)
  Normocapnic (PCO2 37mmHg)
  CXR-B/L Pneumonia involving inferior lobes
Hospital course: bronchalveolar lavage with yeast no PCP (Pneumocystis carinii)
  →ATBx with Ceftriaxone, Clarithromycin and Voriconazole
  →Codeine 25mg T.I.D. given for cough
  →HD#4 ↓LOC with unresponsiveness; last dose of codeine 12h prior to ∆ in mental status
  →ABG PO2 56mmHg PCO2 80 mmHg on 50%
  →Rx with noninvasive ventilation (NIV) transferred to ICU
  →GCS 6 (E=1;V=1;M=4 withdraws to noxious stimuli) pupils pinpoint, no focal deficits noted
  →Repeat ABG post-NIV therapy→PO2 68mmHg/PCO2 56mmHg
  →↑BUN/Cr levels(45mg/dL/ 2.06mg/dL)
  →BUN/Cr normalized with hydration
  →valproic acid and ammonia levels WNL
  →IV naloxone (0.4mg) givenX 2doses resulted in dramatic ↑LOC
  →Placed on naloxone infusion resulting in normal LOC and resolution of respiratory failure
Disposition: 2D post acute event pt.had complete recovery
At the time of the pt’s coma:
• plasma morphine was 80 μg/L (normal 1-4 μg/L)
• morphine-3-glucuronide was 580 μg/L (normal 8-70 μg/L)
• morphine-6-glucuronide was 136 μg/L (normal 1-13 μg/L)
• CYP2D6 genotyping : ultra rapid metabolism

N Engl J Med 2004;351:2827-31
Codeine is a Substrate of CYP2D6

Consider the variation in codeine’s metabolism among PM, IM, EM, UM individuals

(methyl morphine)
Hepatic metabolism of Morphine

Morphine + UDP-glucuronide → Morphine-glucuronide + UDP → Urine, bile
Morphine Metabolism

Glucuronidation – renal elimination
Morphine-6-glucuronide (potent analgesic)
Morphine-3-glucuronide (excitatory side-effect)

↓

Demethylation
Normorphine (excitatory side effects)
CYP3A4 (grapefruit juice), CYP2C8 (quercetin)
Cytochrome P450 Enzymes

- Group of heme containing enzymes responsible for phase 1 oxidative metabolic reactions
- Family that detoxify compounds
- Absorbance of light at 450 nanometers (hence CYP450)
- On membranes of endoplasmic reticulum in liver, gut, brain, lung, kidney
CYP Nomenclature

- **Nomenclature of CYP genes:**
  - Arabic number for gene family
  - Capital letter for gene subfamily
  - Arabic number for individual gene

- CYP enzymes of different gene families have a 40% or more homology in their amino acid sequences, but enzymes within one subfamily may have different substrates, regulation, etc.

- Over 70% of total CYP content of the human liver is shared by seven subfamilies: CYP1A2, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E1, CYP3A

- **Extent of metabolism is determined by**
  - Affinity of substrate-enzyme complex
  - Relative abundance of a given CYP enzyme relative to the total CYP content
Cytochrome P450 Nomenclature, e.g. for CYP2D6

- CYP = cytochrome P450
- 2 = genetic family
- D = genetic sub-family
- 6 = specific gene

NOTE that this nomenclature is genetically based: it has NO functional implication
Cytochrome P450

Overview continued:

- At LEAST 50 (57) isoenzymes, grouped based on their a.a. sequences
- Example: CYP3A4: Cytochrome P450, family “3”, subfamily “A” and the 4th enzyme in the subfamily
- Most CYP-450 enzymes involved in drug metabolism belong to the three distinct families, CYP1, CYP2 and CYP3 (50% of all drugs)
  - Some drugs processed by several CYP450 isoenzymes
Relative Importance of P450s in Drug Metabolism:
- CYP3A
- CYP2E1
- CYP1A2
- CYP2C
- CYP2D6

Relative Quantities of P450s in Liver:
- CYP3A
- CYP2C
- CYP2E1
- CYP1A2
- CYP2D6

Cytochrome P450s (CYPs)

- Genetic variants are associated with altered drug levels, but not with disease

  - CYP2D6: 25% of drugs
  - CYP2C9: 5%
  - CYP2C19: 15%
  - CYP3A4: 50%
Drug Interactions (Liver)

- CYP Substrate
- CYP Inhibitor
- CYP Substrate
- CYP Inducer

↑ Substrate concentration → ↑ Toxicity
↓ Substrate concentration → ↓ Efficacy
Inducers and Inhibitors:

- An overwhelming subject → information overload!
- Primary method to eliminate drugs
- CYP mainly the liver; also GI epithelium and other tissues
- Pharmacogenetic factors → large number CYP isoenzymes
  - Most arise due to single nucleotide differences or polymorphisms (SNP) in genes encoding drug metabolism enzymes
  - May result in altered activity, altered stability of the enzyme, or introduction of a premature stop codon leading to a truncated protein
  - SNP errors can lead to mis-splicing of genes, complete gene deletion or gene amplification
  - Changes can lead to drug accumulation (toxicity), increased rates of drug elimination, and changes in activity / toxicity profiles due to altered formation of active metabolites
CYP2D6

- Metabolizes 25 – 30% of clinically “key” medications
  - Dextromethorphan
  - Beta-blockers
  - Antiarrythmics
  - Anti-depressants
  - Antipsychotics
  - Morphine derivatives – codeine, oxycodone, etc.
  - Others
- Most genetic variation (75 variants so far)
- Linked more commonly to slow/poor metabolizers
  - 1% - Asians
  - 2-5% - African Americans
  - 6-10% Caucasions

**Slower on average**
- Lower frequency of nonfunctional alleles
- Higher frequency of reduced activity alleles
CYP2D6

- Absent in 7% of Caucasians, 1–2% non-Caucasians
- Hyperactive in up to 30% of East Africans (Ethiopians)
- Catalyzes primary metabolism of:
  - Codeine
  - Many β-blockers
  - Many tricyclic antidepressants
- Inhibited by:
  - Fluoxetine
  - Haloperidol
  - Paroxetine
  - Quinidine
CYP2D6 is an Enzyme with Polymorphisms

- Approximately 80 nucleotide polymorphisms are known
- Four phenotype subpopulations of metabolizers:
  - Poor metabolizers (PM)
  - Intermediate metabolizers (IM)
  - Extensive metabolizers (EM)
  - Ultrarapid metabolizers (UM)
- Variations according to racial background
- More than 65 commonly used drugs are substrates
- Codeine is a well known substrate

* The Pharmacological Basis of Therapeutics
CYP2D6

Consequence of variants:
- PM: no active drug
- IM: less active drug - approximately 20% lower concentrations of morphine than in EM
- UM: more active drug - up to 800% higher concentrations of morphine than in EM

Dose Adjustment (change from standard dose):
- PM: Select a different drug
- IM: Modest decrease - 100%
- EM: 100%
- UM: Dramatic decrease in dose or a different
<table>
<thead>
<tr>
<th>Drug type</th>
<th>Metabolizer phenotype</th>
<th>Effect on drug metabolism</th>
<th>Potential consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug, needs metabolism to work (e.g., codeine metabolized to morphine)</td>
<td>Poor to intermediate</td>
<td>Slow</td>
<td>Poor drug efficacy, patient at risk of therapeutic failure</td>
</tr>
<tr>
<td></td>
<td>Ultradapid</td>
<td>Fast</td>
<td>Accumulation of prodrug, patient at increased risk of drug-induced side effects</td>
</tr>
<tr>
<td>Active drug metabolized to inactive drug (e.g., omeprazole [Prilosec] metabolized to 5-hydroxyomeprazole)</td>
<td>Poor to intermediate</td>
<td>Slow</td>
<td>Good drug efficacy</td>
</tr>
<tr>
<td></td>
<td>Ultradapid</td>
<td>Fast</td>
<td>Accumulation of active drug, patient at increased risk of drug-induced side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient requires lower dosage</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor drug efficacy, patient at risk of therapeutic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patient requires higher dosage</td>
</tr>
</tbody>
</table>

**NOTE:** Poor metabolizers have markedly reduced or absent enzyme activity; intermediate metabolizers have reduced enzyme activity; and ultrarapid metabolizers have high enzyme activity.
CYP2D6

- More than 50 alleles, encoding enzymes with inactive / decreased / increased / normal catalytic function, up to a 1000 fold variation in the population
- Poor metabolisers
  - are at risk of drug toxicity even at standard doses, resulting in poor compliance
  - may also present with treatment resistance to prodrugs that require activation (codeine)
- Ultrarapid metabolisers:
  - delayed therapeutic response or treatment resistance (29% of Ethiopians carry multiplicated functional CYP2D6 alleles)
- Also present in brain functionally associated with dopamine transporter, might have a role in dopaminergic transmission, there are differences in personality traits between PMs and EMs
### Distribution of CYP2D6 enzymes in different populations

<table>
<thead>
<tr>
<th>Variant alleles</th>
<th>Enzyme function</th>
<th>Allele frequency %</th>
<th>Caucasians</th>
<th>Asians</th>
<th>Black Africans</th>
<th>Ethiopians and Saudi Arabians</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*2xN</td>
<td>Increased</td>
<td></td>
<td>1-5</td>
<td>0-2</td>
<td>2</td>
<td>10-16</td>
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<tr>
<td>CYP2D6*4</td>
<td>Inactive</td>
<td></td>
<td>12-21</td>
<td>1</td>
<td>2</td>
<td>1-4</td>
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<tr>
<td>CYP2D6*5</td>
<td>No enzyme</td>
<td></td>
<td>2-7</td>
<td>6</td>
<td>4</td>
<td>1-3</td>
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<tr>
<td>CYP2D6*10</td>
<td>Unstable</td>
<td></td>
<td>1-2</td>
<td>51</td>
<td>6</td>
<td>3-9</td>
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<tr>
<td>CYP2D6*17</td>
<td>Reduced affinity</td>
<td></td>
<td>0</td>
<td>ND</td>
<td>34</td>
<td>3-9</td>
</tr>
</tbody>
</table>

Ingelman-Sundberg et al., 1999
CYP2D6 PMs and other narcotics

- Hydrocodone, Oxycodone, Dihydrocodeine, Tramadol
  - potentially decreased analgesia due to less conversion to active metabolites

- Morphine, Oxymorphone, Hydromorphone (8-10X potency of morphine with shorter duration)
  - Buprenorphine, Fentanyl
    - not metabolized by CYP2D6 – UGTs and/or CYP3A4 may be important

- Methadone
  - potential toxic due to less metabolic inactivation

- Armstrong SC and Cozza KL, Psychosomatics 2003; 44:167-71
Consequences of variant CYPs

- Inappropriate drug and metabolite concentrations
- Unanticipated metabolites
- Drug-drug interactions
- Non-compliance
- No or limited response
- ADRs

**DRUG** Metabolism $\rightarrow$ Reduced clearance $\rightarrow$ Alternate pathways $\rightarrow$ faulty conversion of pro-drug to active phase
CYP3A4 And P-Glycoprotein

- P-Glycoprotein and CYP3A4 control oral bioavailability of many drugs.
- P-Glycoprotein and CYP3A4 share many substrates and inhibitors.
Fig. 7. Diagrametic representation of P-glycoprotein-mediated drug efflux.
Foods That Affect Cytochrome P450

- Broccoli
- Cabbage
- Other Cruciferous Vegetables
- Spinach
- Leeks
- Onion
- Garlic
- Parsley
- **Grapefruit**
- Fried and charcoal broiled foods
- Smoked fish or meat
- Ham
- Sausage
Gene-environment interactions: variability

**Diet:** may alter hepatic cytochrome P450 activity

- **Smoked foods** (polycyclic aromatic hydrocarbons) increase CYP1A activity (Kall & Clausen 1995)
- **Cruciferous vegetables** (brussels sprouts, cabbage, broccoli): alter activity of selected CYP isoenzymes
  - Indole-containing vegetables (cabbage, cauliflower) upregulate CYP1A (Pantuck et al., 1989)
  - Isothyocyanate-containing vegetables (watercress) inhibit CYP2E1 (Kim & Wilkinson 1996)
- **Organosulfur compounds** (garlic) inhibit CYP2E1 and induce CYP1A, CYP3A and phase II enzymes
- **Grapefruit juice phytochemicals** influence CYP3A activity
- **Vitamins, spices**
Fruit Juices and CYP450
Grapefruit Juice: What’s the Story

Grapefruit juice intensifies some drugs

Q. Patients have come into my office waving your column about the dangers of grapefruit and drugs like Procardia and Flomax. Where does this come from? I can’t find this research anywhere. Is this interaction clinically important?

A. One review for physicians was published in The Medical Letter (Aug 18, 1995). The interaction is very important although it is not mentioned in standard drug references. Certain drug levels can be increased up to 1,000 percent. We heard of a case in which a young man died from cardiac arrest after taking Seldane with grapefruit juice.

We are sending you our Guide to Grapefruit Interactions, which summarizes this research and lists other drugs that may be dangerous with grapefruit. Anyone who would like a copy plus our Guide to Drug and Food Interactions, please send $2 with a long (No. 10) stamped, self-addressed envelope to Graedon’s People’s Pharmacy.

Grapefruit juice affects medicines

Periodically, I like to put together a potpourri of medical facts that, although unrelated, are of general interest. Here are a few such items.

Most people know that certain drugs — such as tranquilizers, anti-depressants and amphetamines — can affect a user's judgment and vision. However, patients should be aware that many other medications can also interfere with sight.

In particular, anti-histamines, estrogen patches and oral contraceptives are being increasingly blamed for "dry eye syndrome," especially in persons who wear contact lenses. Dry eye syndrome is marked by scratchy sensations in the eyes, blurred vision, excess watering, and an tingation. He prescribed Fosamax.

This medication is so new, there's nothing in the PDR about it. What are the side effects? I'm concerned about the warning not to lie down for at least 30 minutes, as well as the instructions to take it at least an hour before eating breakfast. Will I be trading a good digestive system for strong bones? I play tennis and golf and am in good physical condition, foolish for me to take Fosamax.

What else can you tell me about interactions and absorption?
AN INGREDIENT IN GRAPEFRUIT JUICE INHIBITS CYP3A4

6',7', - Dihydroxybergamottin
Effects of grapefruit juice on felodipine pharmacokinetics and pharmacodynamics.
Pomegranate juice appears to cause interactions in a manner similar to grapefruit juice based on preliminary evidence. But there is conflicting reports on its interactions. Until more is known, err on the side of caution. Advise patients not to drink pomegranate juice if they are taking drugs metabolized by CYP3A4.
The nutraceutical industry in the US is about $86 billion. This figure is slightly higher in Europe and, in Japan, represents approximately a quarter of their $6 billion total annual food sales - 47% of the Japanese population consume nutraceuticals.
According to market reports the top 10 best selling herbs in 2007 were, in rank order:

- Garlic
- Echinacea
- Saw palmetto
- Ginkgo
- Cranberry
- Soy isoflavones
- Ginseng
- Black cohosh
- St. John's wort
- Milk thistle

http://takingcharge.csh.umn.edu

Dennis McKenna, PhD
Admit it... you've been secretly taking herbal remedies again!

John Byrne
Drug-Herb Interactions

- Types of Drug Interactions
  - Decreased bioavailability of drug
    - \( \downarrow \) Absorption (fibers, mucilage herbs, \( \uparrow \) p-glycoprotein)
    - \( \uparrow \) Metabolism (\( \uparrow \) CYP 450)
    - \( \uparrow \) Elimination (laxative or diuretic herbs)
  - Increased bioavailability of drug
    - \( \uparrow \) Absorption (Ginger, Cayenne, Black Pepper)
    - \( \downarrow \) Metabolism (\( \downarrow \) CYP 450, eg. Grapefruit Juice)
    - \( \downarrow \) Elimination (Licorice- anti-diuretic)
St. John’s Wort

- Suggested mechanism of antidepressant effect: inhibit reuptake of serotonin, dopamine, and norepinephrine, inhibition of monoamine oxidase, etc
- Has CNS effects on serotonin, NE, DA, COMT
- Possible serotonin syndrome with SSRI’s
- No in vivo MAOI effects
- Main concern is drug-herb interactions. Affects cytochrome P450 isoforms increasing metabolic activity
St. John’s Wort

- Can reduce levels of cyclosporine (transplant rejection), indinavir (HIV inhibitor), OCP’s, digoxin (P-glycoprotein transporter), many others.
- Can also affect coagulation factors
- Half-life 43.1 hrs (hypericin) and 9 hrs (hyperforin)
- Possible prolongation of anesthesia
- Stop at least 5 days before surgery
### Summary of SJW Interactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP</th>
<th>Effect</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV protease inhibitors</strong></td>
<td>Induce 3A4</td>
<td>↓</td>
<td>Stop and measure viral load</td>
</tr>
<tr>
<td>(nelfinavir, ritonavir, saquinavir)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV non-nucleoside RTI</strong></td>
<td>Induce 3A4</td>
<td>↓</td>
<td>Stop and measure viral load</td>
</tr>
<tr>
<td>(efavirenz, nevirapine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>warfarin</td>
<td>Induce 2C9</td>
<td>↓</td>
<td>Stop and adjust warfarin dose</td>
</tr>
<tr>
<td>cyclosporin</td>
<td>Induce P-glycoprotein</td>
<td>↓</td>
<td>Stop and adjust cyclosporine dose</td>
</tr>
<tr>
<td>oral contraceptives</td>
<td>Induce 3A4</td>
<td>↓</td>
<td>Stop and use alternate birth control</td>
</tr>
<tr>
<td>anticonvulsants</td>
<td>Induce 3A4</td>
<td>↓</td>
<td>Stop and adjust anticonvulsant dose</td>
</tr>
<tr>
<td>digoxin</td>
<td>Induce P-glycoprotein</td>
<td>↓</td>
<td>Stop and adjust digoxin dose</td>
</tr>
<tr>
<td>theophylline</td>
<td>Induce 1A2</td>
<td>↓</td>
<td>Stop and adjust theophylline dose</td>
</tr>
<tr>
<td><strong>Triptans</strong> (sumatriptan)</td>
<td>Increase serotonin</td>
<td>↑</td>
<td>Stop</td>
</tr>
<tr>
<td>SSRI (fluoxetine, sertraline, etc)</td>
<td>Increase serotonin</td>
<td>↑</td>
<td>Stop</td>
</tr>
</tbody>
</table>
Echinacea

- Caution: in pts with asthma, atopy, allergic rhinitis, esp ragweed allergy
- Caution: in pts w liver dysfx (↑hepatic microsomal enzymes) or transplants/immuno-supression
- D/C prior to surgery (↑levels of sedation when taken with midazolam)
- Acts on CYP3A?
Garlic

- Allicin main ingredient
- Platelet aggregation inhibition
- Also has anti-hypertensive, anti-neoplastic, antilipemic, antibiotic effects
- Like St. John's wort, SOME garlic preparations also induce CYP3A4. Many of the same interactions caused by St. John's wort can also be caused by garlic. But not all garlic preparations seem to cause these interactions - depend on allicin content.
- D/C ~7 days before surgery
<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>3</th>
<th>6</th>
<th>17</th>
<th>Other Changes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>−OH</td>
<td>−OH</td>
<td>−CH₃</td>
<td>−</td>
</tr>
<tr>
<td>Heroin</td>
<td>−OCOCH₃</td>
<td>−OCOCH₃</td>
<td>−CH₃</td>
<td>−</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>−OH</td>
<td>=O</td>
<td>−CH₃</td>
<td>(1)</td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>−OH</td>
<td>=O</td>
<td>−CH₃</td>
<td>(1), (2)</td>
</tr>
<tr>
<td>Levoorphanol</td>
<td>−OH</td>
<td>=H</td>
<td>−CH₃</td>
<td>(1), (3)</td>
</tr>
<tr>
<td>Levallophan</td>
<td>−OH</td>
<td>=H</td>
<td>−CH₂CH=CH₂</td>
<td>(1), (3)</td>
</tr>
<tr>
<td>Codeine</td>
<td>−OCH₃</td>
<td>−OH</td>
<td>−CH₃</td>
<td>−</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>−OCH₃</td>
<td>=O</td>
<td>−CH₃</td>
<td>(1)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>−OCH₃</td>
<td>=O</td>
<td>−CH₃</td>
<td>(1), (2)</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>−OH</td>
<td>=CH₂</td>
<td>−CH₂</td>
<td>(1), (2)</td>
</tr>
<tr>
<td>Nalorphine</td>
<td>−OH</td>
<td>−OH</td>
<td>−CH₂CH=CH₂</td>
<td>−</td>
</tr>
<tr>
<td>Naloxone</td>
<td>−OH</td>
<td>=O</td>
<td>−CH₂CH=CH₂</td>
<td>(1), (2)</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>−OH</td>
<td>=O</td>
<td>−CH₂</td>
<td>(1), (2)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>−OH</td>
<td>−OCOCH₃</td>
<td>−CH₂</td>
<td>(1), (4)</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>−OH</td>
<td>=H</td>
<td>−CH₂</td>
<td>(1), (2), (3)</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>−OH</td>
<td>−OH</td>
<td>−CH₂</td>
<td>(1), (2)</td>
</tr>
</tbody>
</table>
CYP3A Inhibition/Induction: Nutraceutical implications

• Several studies suggest that GFJ affects intestinal but not hepatic CYP3A4; but repeated dosing (three times a day) of large amounts (200-240ml, double strength) over several days can inhibit hepatic CYP3A4 as well (JJ Lija et al, Eur J Pharmacol 2000; 56:411; ML Veronese et al, J Clin Pharmacol 2003; 43:831)

• Morphine is metabolized by the gut wall in addition to the liver, therefore its actions possibly may be enhanced by the inhibitory effects of grapefruit juice on the CYP3A metabolism.

• Morphine has a relatively high hepatic extraction ratio and therefore its activity should not be affected by enzyme induction however there have been reports concerning possible interactions...

• It has been reported that morphine induced respiratory depression and the potentiation of analgesia occurs by enhancement of CYP3A4 inhibition by cimetidine. (Lam AM, Clement JL Canadian Anaesthetists Society Journal 1984; 31:36-43.; Bluhm R, et al Life Sciences 1982; 31:1229-32)

• GFJ and others (i.e., goldenseal) are known also to inhibit the activity of the CYP3A4 isoenzyme and can potentiate the effects of drugs that are metabolized by this mechanism. (Bailey DG, et al. Br J Clin Pharmacol. 1998; 46:101-110; Gurley BJ et al, Clin. Pharmacol. Ther. 83, 61-69. 2008)

• Rifampin-inducer of CYP3A4 decreases both morphine levels and its analgesic effect (Fromm et al, Pain 1997)
Drug-Herb Interactions (HDI)

- Marked lack of clinical data
- HDI Difficult to predict
  - Cannot assume no interaction
  - Cannot simply ignore patient use
  - Cannot blindly recommend against general use
  - Cannot ignore potential benefits
HDI: Evidence Based Approach

- quality and quantity of herb varies between manufacturers
  - Variability seen between batches produced by the same company.
- contaminated and/or adulteration
  - estimated 25% of Asian patent medicines contain evidence of heavy metals
    - 7% contain undeclared prescription medicines
      - benzodiazepines, NSAIDs, steroids.

- Reputable standardized product used and carefully described?
- Product used analyzed for marker compounds?
- Same batch used throughout study?
- Doses appropriate?
- Steady state study to discern CYP induction?
- Is observation consistent with known mechanisms of action?
- Is observation consistent with literature observations?
- Crossover, randomized, placebo controlled human volunteer study with appropriate n?
JCAHO Mandate

- The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued requirements regarding medication listed in hospital medical record (2005 National Patient Safety Goals FAQs).
- Requires that herbs/supplements/nutraceuticals-includes "alternative and complementary interventions" that may be used individually, in combinations of alternative or complementary interventions, or in combination with medications." be documented in the medical record.
Base on your genetic profile you should take Drug A instead of Drug B
## SORT: Key Recommendations for Practice

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype testing may predict persons who are poor metabolizers or are nonresponsive to drugs metabolized by CYP450 enzymes.</td>
<td>C</td>
<td>1, 2, 6</td>
<td>Large, prospective trials needed to demonstrate that genotype testing improves outcomes and is cost-effective</td>
</tr>
<tr>
<td>Genetic variations in CYP450 metabolism should be considered when patients exhibit unusual sensitivity or resistance to drug effects at normal doses.</td>
<td>C</td>
<td>4, 35, 36</td>
<td>Studies demonstrate a link between adverse effects and variant CYP450 alleles</td>
</tr>
<tr>
<td>Patients should be monitored closely for the development of adverse drug effects or therapeutic failures when a potent CYP450 enzyme inhibitor or inducer is added to drugs metabolized by one or more CYP450 enzymes.</td>
<td>C</td>
<td>10, 11, 14, 18, 31, 32</td>
<td>Well-recognized cause of clinically significant drug interactions</td>
</tr>
<tr>
<td>Severe toxicity can result if CYP450 enzyme–inhibiting drugs are added to the following medications: atypical antipsychotics, benzodiazepines, cyclosporine (Sandimmune), statins, or warfarin (Coumadin).</td>
<td>C</td>
<td>10, 11, 19, 24, 30</td>
<td>Particularly true if substrate drug depends on only one CYP450 enzyme for metabolism</td>
</tr>
<tr>
<td>Because they are known to cause clinically significant CYP450 drug interactions, always use caution when adding the following substances to medications that patients are taking: amiodarone (Cordarone), antiepileptic drugs, antidepressants, antitubercular drugs, grapefruit juice, macrolide and ketolide antibiotics, nondihydropyline calcium channel blockers, or protease inhibitors.</td>
<td>C</td>
<td>10, 11, 14</td>
<td>Are either potent inhibitors or inducers of CYP450 enzymes</td>
</tr>
</tbody>
</table>

*CYP = cytochrome P.*

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 323 or [http://www.aafp.org/afpsort.xml](http://www.aafp.org/afpsort.xml).*
## SORT: KEY RECOMMENDATIONS FOR PRACTICE

<table>
<thead>
<tr>
<th>Clinical recommendation</th>
<th>Evidence rating</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physicians should consider the potential for genetic factors (intrinsic and extrinsic) to influence drug response.</td>
<td>C</td>
<td>2</td>
</tr>
<tr>
<td>When a clear genotype-response relationship has been identified and commercial testing is available, pharmacogenetic testing is preferable to the use of ethnic or race categories to individualize therapy.</td>
<td>C</td>
<td>10-12, 54, 55</td>
</tr>
</tbody>
</table>

*A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see [http://www.aafp.org/afpsort.xml](http://www.aafp.org/afpsort.xml).*
AmpliChip CYP450 Test

- Developed in 2003 by Roche Pharm.
- DNA microarray can detect 29 polymorphisms of CYP2D6 and 2 polymorphisms of CYP2C19
- Approx. $500
- Roughly 100,000 deaths in the US alone
- 25 million people affected
Is CYP genotyping cost-effective?

- Genotype-based dose selection reduces costs by reducing costs associated with ADRs
  - Clin Chem 2004 50(9):1623-33
  - Thromb Haemost. 2004 Sep;92(3):590-7
- Identify individuals at high-risk for ADRs; give less expensive drugs to low-risk individuals
Recommendations before having anesthesia:

- **STOP** taking the herbal product at least two weeks prior to the scheduled procedure or surgery to prevent side effects.
- Inform the surgeon and anesthesia provider that pt. is taking an herbal product. Elicit as much information about the herbal products they are taking (dose, frequency, etc.).
- When asked about medication history, include all herbal products, over-the-counter drugs, dietary supplements, minerals, and teas.
- If uncertain of the contents of an herbal product, have the pt. bring the product and the container it comes in to the preoperative anesthesia interview.
- Make sure that someone close to the patient is aware their taking an herbal product. (In the event of an emergency, this person can share this information with healthcare providers).
- Emphasize that herbal products need to be treated as medicine. Even if the product is natural, it still may be harmful when combined with anesthetics.
<table>
<thead>
<tr>
<th>Source</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concise Guide to Drug Interaction Principles for Medical Practice: Cytochrome P450s, UGTs, P-glycoproteins(^{14})</td>
<td>Comprehensive guide to drug interactions with useful charts and representative cases</td>
</tr>
<tr>
<td>Indiana University School of Medicine drug interaction table (<a href="http://medicine.iupui.edu/flockhart/table.htm)%5C(%5E%7B16%7D%5C">http://medicine.iupui.edu/flockhart/table.htm)\(^{16}\</a>)</td>
<td>Continually updated table of important substrates, inhibitors, and inducers with direct links from each drug name to a PubMed list of citations</td>
</tr>
<tr>
<td>Drugs section in the Lexi-Complete PDA software package from Lexi-Comp</td>
<td>This PDA software includes a section on cytochrome P450 enzyme activity for each drug narrative</td>
</tr>
</tbody>
</table>

\(UGT = \text{uridine diphosphate-glucuronosyltransferase; } PDA = \text{personal digital assistant.}\)

Information from reference 14 and 16.
### Databases URL Cost/year

<table>
<thead>
<tr>
<th>Database</th>
<th>URL</th>
<th>Cost/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Medicines Comprehensive Database</td>
<td><a href="http://www.naturaldatabase.com">www.naturaldatabase.com</a></td>
<td>$92</td>
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<tr>
<td>Natural Standard</td>
<td><a href="http://www.naturalstandard.com">www.naturalstandard.com</a></td>
<td>$99</td>
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<tr>
<td>Herbmed</td>
<td><a href="http://www.herbmed.org">http://www.herbmed.org</a></td>
<td>Free</td>
</tr>
<tr>
<td>MD Anderson Complementary/Integrative Medicine</td>
<td><a href="http://www.mdanderson.org/departments/CIMER">www.mdanderson.org/departments/CIMER</a></td>
<td>Free</td>
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<tr>
<td>Memorial Sloan-Kettering</td>
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<td>Free</td>
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<tr>
<td>Cancer Center Integrative Medicine</td>
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<td>Free</td>
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<tr>
<td>Service Herb and Botanical Information</td>
<td><a href="http://www.mskcc.org/mskcc/html/11570.cfm">www.mskcc.org/mskcc/html/11570.cfm</a></td>
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<tr>
<td>MayoClinic.com</td>
<td><a href="http://www.mayoclinic.com">www.mayoclinic.com</a></td>
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<tr>
<td>General Information</td>
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<td>NIH</td>
<td><a href="http://www.healthfinder.gov/">www.healthfinder.gov/</a></td>
<td>Free</td>
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<tr>
<td>National Center for CAM (NCCAM)</td>
<td><a href="http://nccam.nih.gov">http://nccam.nih.gov</a></td>
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<td>NCI</td>
<td><a href="http://www.cancer.gov/cancerinfo">www.cancer.gov/cancerinfo</a></td>
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<td>ACS</td>
<td><a href="http://www.cancer.org">www.cancer.org</a></td>
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<td>Quackwatch</td>
<td><a href="http://www.quackwatch.org">www.quackwatch.org</a></td>
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<tr>
<td>Herb Quality Information</td>
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<tr>
<td>ConsumerLab.com</td>
<td><a href="http://www.consumerlab.com">www.consumerlab.com</a></td>
<td>$24</td>
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<tr>
<td>Consumer Reports</td>
<td><a href="http://www.consumerreports.org">www.consumerreports.org</a></td>
<td>$24</td>
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<tr>
<td>United States Pharmacopeia</td>
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<td>Internet Information Quality</td>
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<td>AMA</td>
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<td>Health on the Net Foundation</td>
<td><a href="http://www.hon.ch">www.hon.ch</a></td>
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<td>Regulatory Information</td>
<td><a href="http://www.cfsan.fda.gov/~dms/supplmnt.html">www.cfsan.fda.gov/~dms/supplmnt.html</a></td>
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</tbody>
</table>
Summary

- Known or potential herb-CYP interactions exist, and further studies on their clinical and toxicological roles are warranted. Given that increasing numbers of people are exposed to a number of herbal preparations that contain many constituents with potential of CYP modulation, high-throughput screening assays should be developed to explore herb-CYP interactions.

- Clinical implication of such drug herbal interactions depends on a variety of factors such as dose, timing of herbal intake, dosing regimen, route of drug administration and therapeutic range.

- Drug–herbal interactions in human are likely to be highly variable because of inter-individual differences in food habits, age, health status, genetic make up and metabolizing capacity, but the impact may be significant.

- There are a huge number of other drug-metabolizing enzymes, which may be of importance for individual drugs and chemicals and which are not covered by current screening systems.
References
(partial list)

Comments/Questions?