Complementary and Alternative medicine

PHG 323

Drug Herb Interaction (Part 1)

Safety of herbal medicines

- Many people who use herbal preparations **believe that they are totally safe in all respects since they are natural**. In fact this is far from the truth and some herbal preparations can be potentially dangerous, even in therapeutic doses.
- The **concomitant phytotherapy** (herbal and herbal product medicines) **and pharmacotherapy is wide spread**.
- About 38 million adults in US (18.9% of the population) use herbs or other natural supplements, **but only one third tell their physician** about this use (Kennedy et al 2008).
- A recent survey (Bush et al, 2007) found that 15% of patients receiving conventional pharmacotherapy also take herbal products and, among these, potential **adverse herb-drug interactions were observed in 40% of patients**.

Bush TM ,et al. Alternat .Ther Health Med 2007; 13: 30-5.
Kennedy J, et al. Evid Based Complement Alternat Med 2008; 5: 451-6

Safety of herbal medicines

- **The interaction of herbs with drugs is a significant safety issue, especially for drugs with narrow therapeutic indices (e.g. warfarin and digoxin).**

Pharmacokinetics VS Pharmacodynamics HDI:

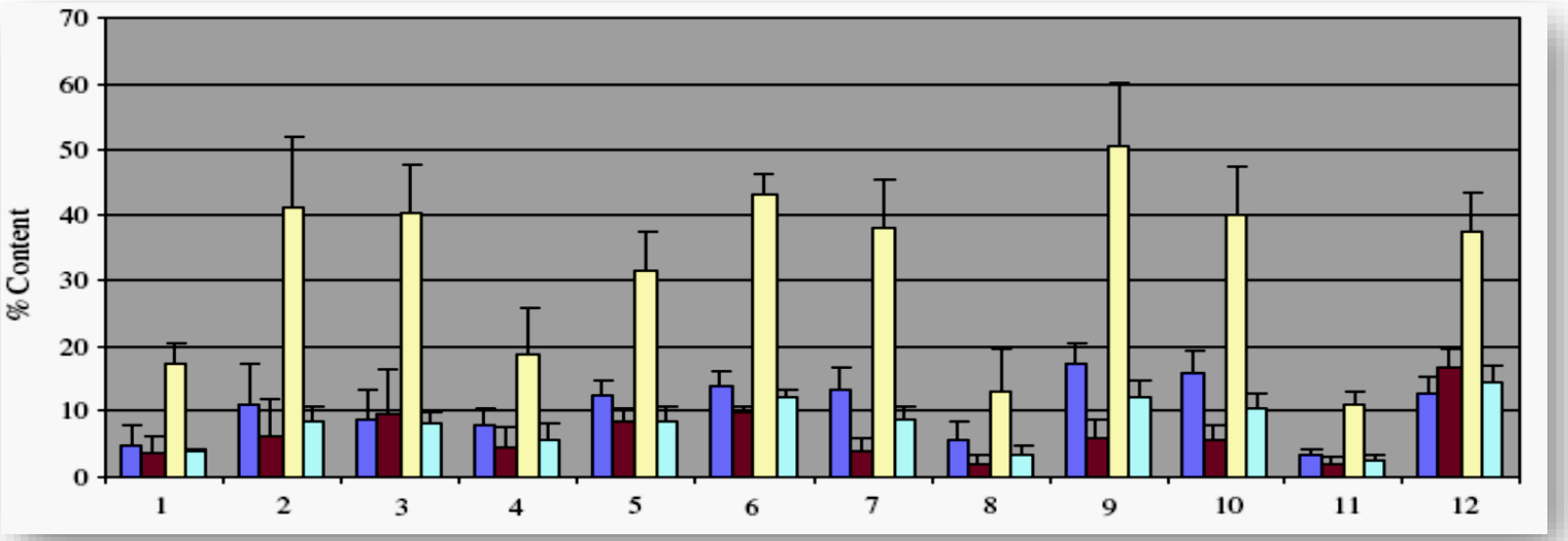
- **Most HDI studies so far have examined PK interactions and have been limited to very few conventional drugs and herbal drugs.**

Bush TM ,et al. Alternat .Ther Health Med 2007; 13: 30-5.
Kennedy J, et al. Evid Based Complement Alternat Med 2008; 5: 451-6

Reasons for increasing the likelihood of herb-drug interaction occurrence

- Most patients (70%) do not reveal their herbal use.
- There is no comprehensive inspection system for monitoring the adverse effects of herbs and herb-drug interactions in most countries. -→ Pharmacovigilance of natural health products.
- A single herb usually contains a number of bioactive components with varying degree of contribution to its pharmacological effects (network pharmacology) and hence drug interactions → difficulties in predicting the mechanisms of herb-drug interactions.
- Herbs have been used on a traditional basis, and rigorous preclinical and clinical assessments are not required by regulatory authorities.

- **Most clinical trials of herbs have limited value, because of poor design, small sample size and, above all, use of poorly defined products of uncertain composition and consistency because of the lack of good quality control.**



Silychristin, silydianin, silybin and isosilybin content varies from one Milk Thistle product to another

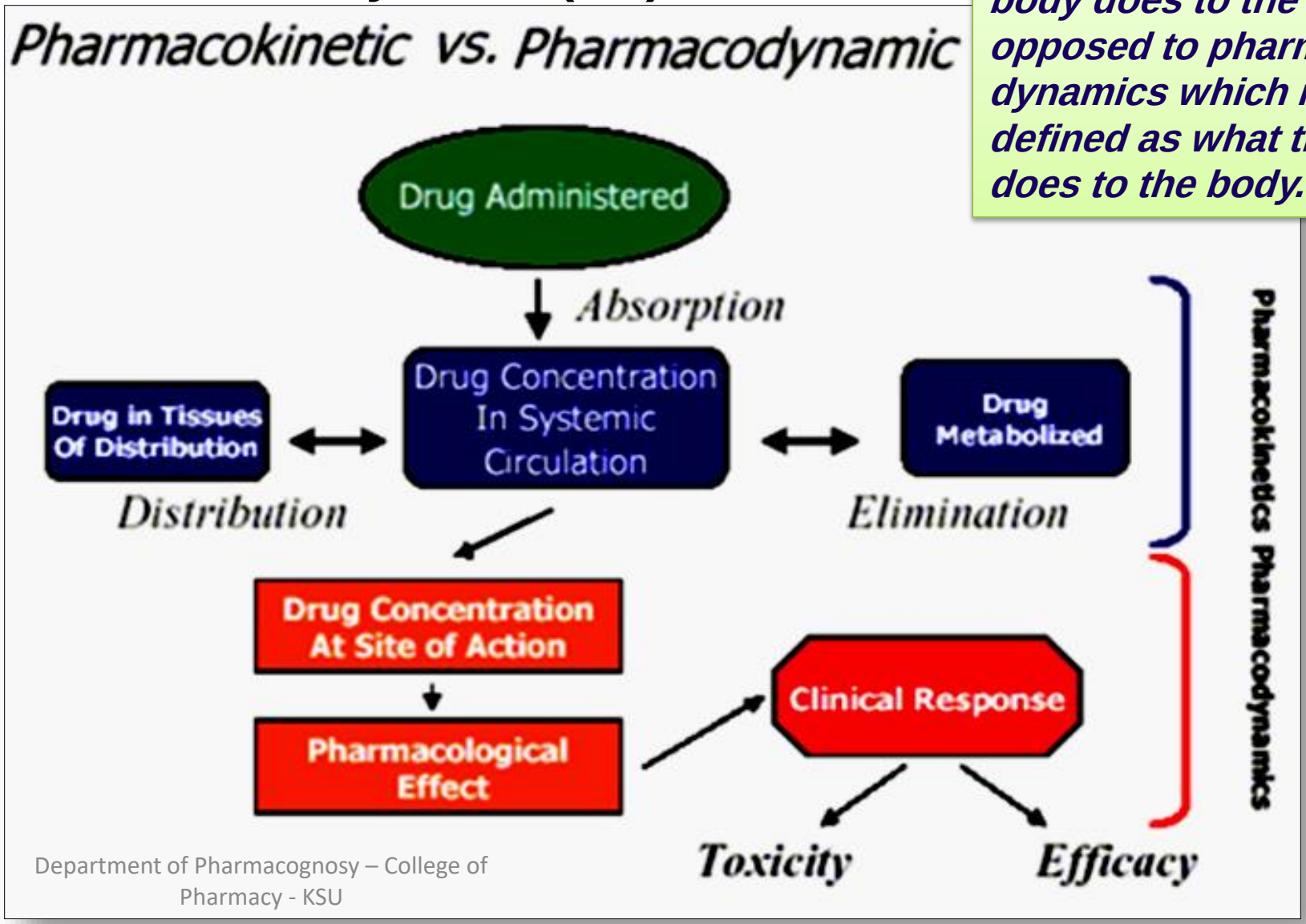
N.B.

- **A "possible interaction" refers to the possibility that one substance (A) may alter the bioavailability, or the clinical efficacy of another substance (B), when two or more substances are given concurrently. The net result may be an increase or decrease in the effect of one or both substances.**

Mechanisms of Herb Drug Interactions

I. Pharmacokinetic (PK) mechanism
II. Pharmacodynamic (PD) mechanism

Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmaco-dynamics which may be defined as what the drug does to the body.



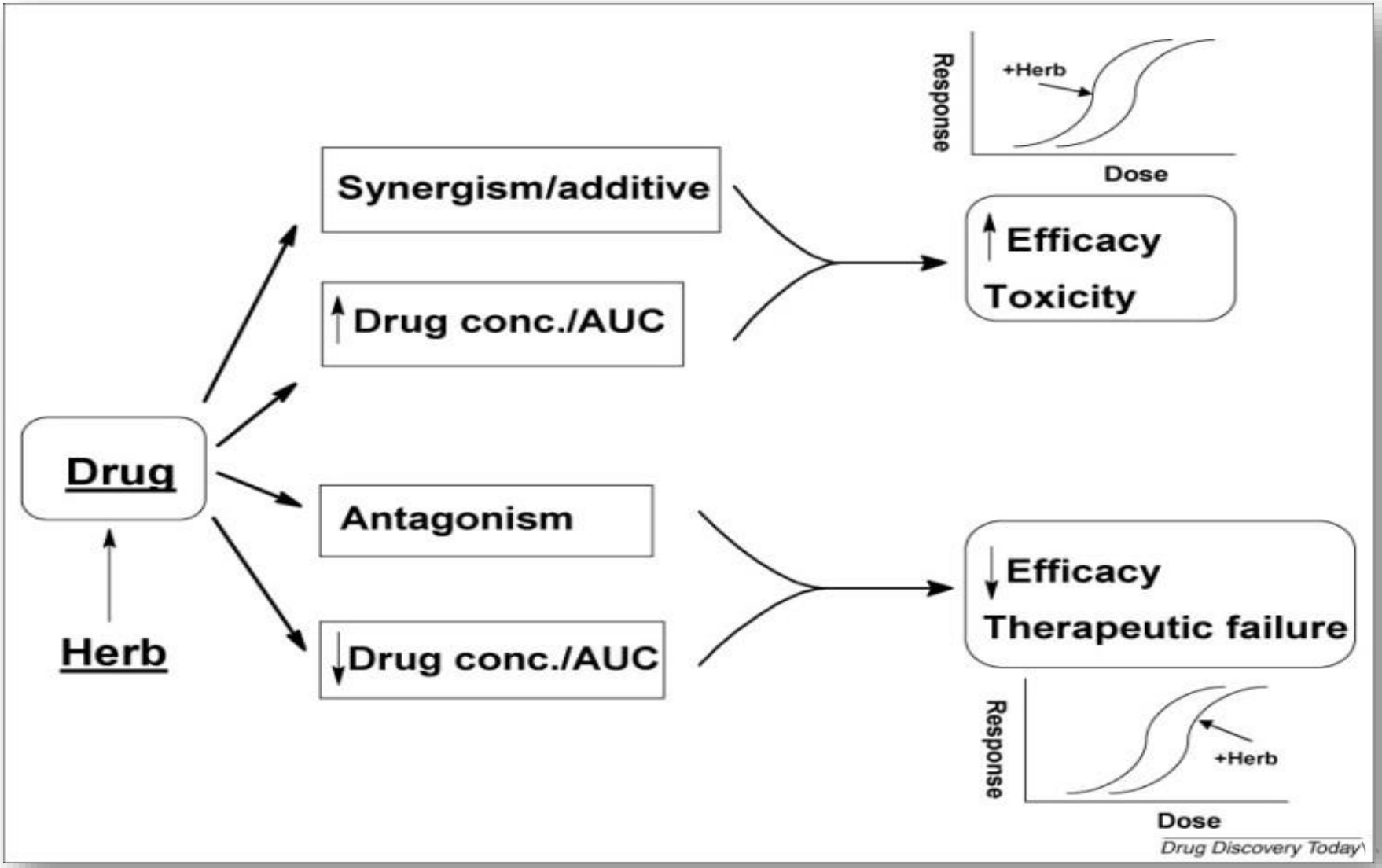
I. Pharmacokinetic (PK) Mechanisms of Interaction

- **PK interactions result from alteration of absorption, distribution, metabolism, or elimination of the drug by herbal products or other dietary supplements.**
  - **Absorption: Drugs that affect GI motility (e.g lax.), pH modifiers.**
  - **Distribution: Highly protein-bound drugs.**
  - **Metabolism: Inducers (phenytoin, phenobarbitals) – Inhibitors (erythromycin, ethanol, ketoconazole,..etc).**
  - **Elimination: Slow rate of elimination → accumulation of herbs and drugs (drugs to worry about include methotrexate and gentamycin).**
- **Induction or inhibition of drug-metabolizing enzymes (e.g. cytochrome P450 3A4) and drug transporters (e.g. permeability glycoprotein: P-gp = multidrug resistance protein 1: MDR1) are the major mechanisms related to many pharmacokinetic drug–herb interactions.**

II. Pharmacodynamic (PD) Mechanisms

- **PD interactions may occur when the herbal constituents have either synergistic or antagonistic activity on a conventional drug → alteration of concentration-dependent activity of a therapeutic molecule at the site of action.**
- **A herb may potentially mimic, increase, or reduce the effects of co-administered drugs through simultaneous effects on the same drug targets (e.g. enzymes or receptors).**
- **Pharmacodynamic interactions are generally more difficult to predict and prevent than pharmacokinetic interactions.**
- **Preventing pharmacodynamic interactions is best achieved by supervising the patient closely and monitoring all clinical responses (signs, symptoms, and any abnormal reactions).**

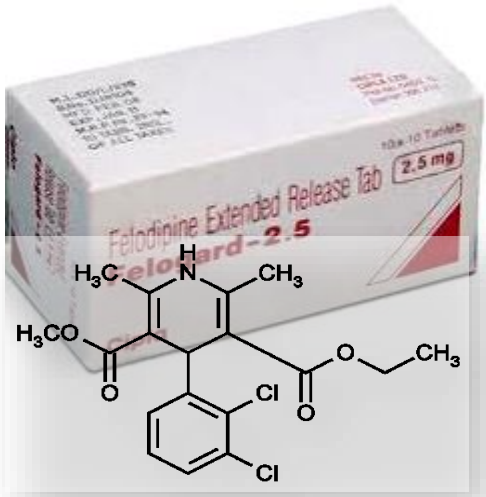
Possible clinical outcomes when a drug interacts with combined herbal medicines



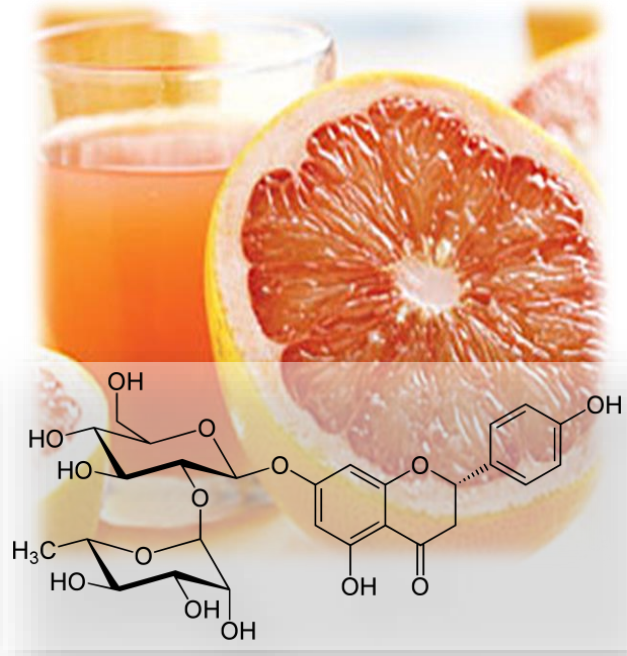
1st Reported major herb-drug interactions

Grapefruit Juice and Drugs

- In 1996, it was found that **Felodipine** (nifedipine, a calcium antagonist) in patients who consumed grapefruit juice showed surprisingly **high bioavailability** (3 times more) in the blood relative to those who consumed it alone.
- The juice **inhibits** major metabolic enzyme cytochrome P450 (CYP3A4) of small intestine → **decreases** drug metabolism before entering the blood stream.
- This effect was later attributed to the presence of furanocoumarins (e.g. **bergamottin**).



- **Naringin** (the major bitter flavonoid glycoside of grape fruit) also:
  - (1) **Inhibits** the drug-metabolizing cytochrome P450 enzymes (CYP3A4 and CYP1A2).
  - (2) Ingestion of naringin and related flavonoids can also affect the intestinal absorption of certain drugs, leading to either an increase or decrease in circulating drug levels.



- ***To avoid interference with drug absorption and metabolism, the consumption of citrus (esp. grapefruit) with medications is contraindicated.***
- **The intentional combination of grapefruit juice and a lowered drug dose might yield a desired result** of proper plasma levels of the drug with lower amounts ingested (hence, less side effects and toxicity; and lower drug costs): this is now an area of active research

http://powernetdesign.com/grapefruit/

Welcome to th

File Edit View Favorites Tools Help

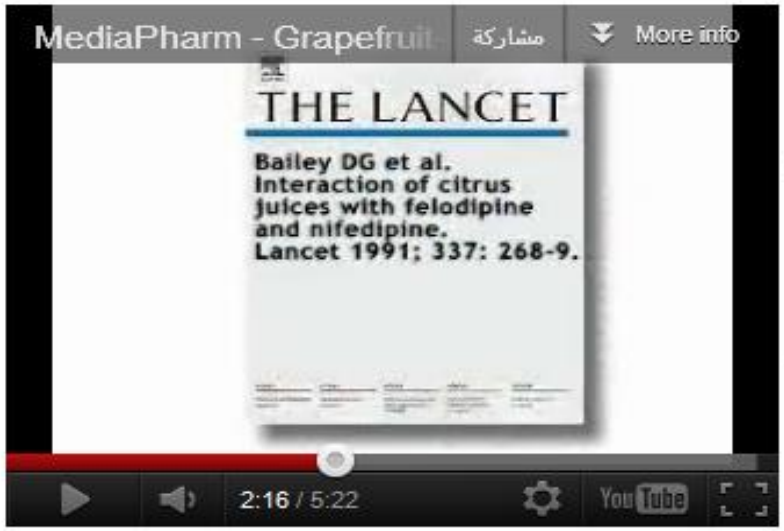
Google grape fruit drug interaction

Suggested Sites escop monographs - بحث ... Alternative Medicine Revi...

GRAPEFRUIT-DRUG INTERACTIONS WEBSITE

by myMediaPharm

- Interactions & Clinical Significance
- History of GJDIs
- Mechanism of Interaction
- Role of GJDIs in Therapeutics
- About the Author
- Frequently Asked Questions
- Summary of GJDIs (.pdf)
- Other Food Medication Interactions
- Email Dean Elbe, BSc (Pharm)
- GJDI References
- Home



myMediaPharm Video: The story of Grapefruit-Drug interactions discovery with Dean Elbe, PharmD, BCPP

This page is designed to bring you up-to-date information on the large body of research on grapefruit juice-drug interactions (GJDI's).

This page was created especially for pharmacists, but other health care professionals and members of the public may find the information contained herein useful as well.

All information presented on this website is intended for educational purposes only. Although based on the same information your doctor or pharmacist rely on, it is not intended to be complete or exhaustive or in any respect a substitute for proper medical care and consultation with your personal physician or pharmacist. Thank you.

Last update: December 06, 2011

Website Design by myMediaPharm

248076

Search
Entire Site
Search
Search the GDI website

myMediaPharm.com
Health information with a personal touch

- When drug clearance is significantly altered (PK) or when the target of a drug is identical (PD) as that of herbal component, a significant drug interaction with herbs may occur. Therefore, combined use of herbal medicines with drugs may alter drug efficacy leading to over- or under-treatment.

- Drug–herb interaction may cause adverse reactions that may be minor, moderate, life threatening or lethal.

- Herbal medicines that are able to modulate intestinal and hepatic CYPs and P-gp will alter the bioavailability and clearance of co-administered drugs.

- Example: long-term treatment of St. John's wort (SJW) reduces plasma levels of co-administered cyclosporine, digoxin, indinavir, nevirapine, oral contraceptives, warfarin.

- **The decreased blood concentrations of cyclosporine and tacrolimus (immunosuppressant drugs) observed in patients also taking SJW was associated with transplant graft rejection observed in all of these cases.**

- **Cases have been reported where the combined use of SJW and selective serotonin-reuptake inhibitors (e.g. sertraline and nefazodone: antidepressants) caused symptoms characteristic of central life threatening serotonergic syndrome in the elderly. This is mainly caused by an inhibitory effect of SWJ on serotonin transporters in the central nervous system (increasing serotonin level in the brain).**

- **St. John's wort is has the most studied herb-drug interactions and has the most evidences for significant interactions with medications.**

- **Ginseng induced mania when used concomitantly with phenelzine (antidepressant and anxiolytic).**
- **Garlic may enhance the effect of hypoglycaemic drugs.**

Who is at risk of herb-drug interaction?

- **People with Cardiac or CVD disease**
  - Take drugs with narrow therapeutics indices
  - Anticoagulants, cardiac glycosides
- **People with liver or renal diseases**
  - Metabolism and elimination
- **Elderly People**
  - Chronic drugs
- **Diabetics**
  - Effects on glucose control
- **Depression**
  - May be using St. John's Wort
- **HIV patients**
  - Medicines susceptible to interactions

Predicting / Preventing Interactions - A Few Simple Rules

1. **Follow Traditional Knowledge to predict and prevent possible synergies or antagonisms with prescription drugs:**

   - **Mucilagenous herbs e.g. Psyllium (a bulk forming laxative) may reduce absorption and thus effectiveness of some medications e.g. Carbamazepine (anticonvulsant) and Digoxin**

Predicting / Preventing Interactions - A Few Simple Rules

1. Follow Traditional Knowledge to predict and prevent possible synergies or antagonisms with prescription drugs:

- **Hawthorn (*Crataegus* sp., used to treat heart disease) may potentiate the action of Digoxin and Beta-blockers.**

- **Vitamin K-containing herbs such as green tea should not be consumed in large amounts if taking blood thinners (Dicoumarol).**

2. **Use formulas thus lower dosages of herbs with potential problems.**

- **In traditional HM, herbs are usually used in formulas, thus reducing the amount of any one herb ingested.**

3. **Take herbs & drugs separately (by 2-3 hours).**

4. **When adding herbs to already established drug regimens, start at low dose and gradually increase the dose. Then, monitor patients carefully.**

5. **Avoid starting or stopping medications and herbs suddenly.**

6. **Avoid red flags: e.g. Warfarin - as it interacts with over 200 foods, drugs, etc.**

7. **Studies indicate SJW has the ability to stimulate Phase I liver detoxification (cyclic P-450 activity-CYP3A4, CYP2D6 and CYP2E1) and P-Glycoprotein activity in the gut.**

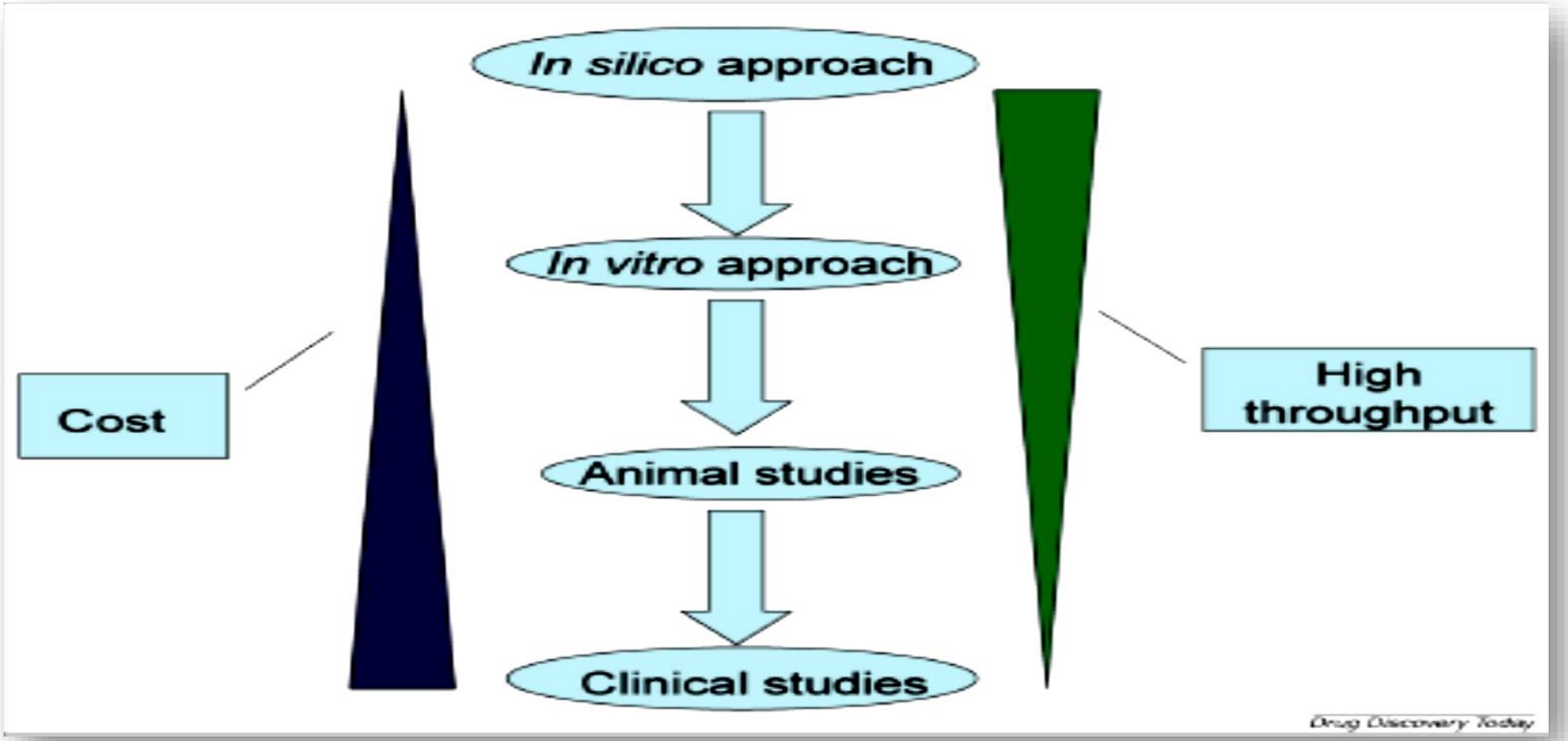
Medications known to be metabolized via these pathways may have reduced blood levels if taken with SJW. Therefore avoid using SJW with protease inhibitors, Cyclosporin, Irinotecan, Digoxin and Warfarin.

How to identify drugs that may interact with herbal medicine?

- ***In vitro*** **models (experiments done outside of living organisms)**
- ***In vivo*** **systems (experiments done in living organisms).**
- ***In silico*** **methods (performed on computer or *via* simulation).**

Each of these models has advantages and limitations, and a combination of these methods will provide the most accurate information on how herbal medicines affect CYPs and P-gp for example.

Various approaches to identify drugs that may interact with herbal medicines



- The hierarchy shows the increased cost but decreased ability of conducting high throughput studies from in silico to human studies.