Complementary and Alternative medicine

PHG 323

Drug Herb Interaction (Part 2)

Types of Drug-Herb Interactions

1. Decreased Bioavailability of Drug

- ↓ Absorption (fibers, mucilage herbs)
- ↑ Metabolism (by ↑ CYP 450 e.g. St John's Wort)
- ↑ Elimination (laxative or diuretic herbs)

2. Increased Bioavailability of Drug

- ↑ Absorption (Ginger, Black Pepper)
- ↓ Metabolsim (↓ CYP 450, eg. Grapefruit Juice)
- ↓ Elimination (Licorice- anti-diuretic)

3. Potentiation of Drug *via* Similar Activity

Example: diuretic drug (thiazides) and diuretic herb (green tea, crane berries, cactus)

4. Potentiation of drug *via* complementary activity

- ⬇ P-glycoprotein system (e.g. *Eleutherococcus senticoccus* with antibiotics*)*
- Fenugreek with insulin or oral hypoglycemic

5. Decreased effectiveness of drug *via* antagonistic activity

- CNS stimulant with CNS depressant.

6. Reduced side effects of drug

- Milk Thistle (*Silybum marianum:* hepatoprotective herb) and hepatotoxic drugs.

Simple Guidelines for Safe Use of Herbs

1. **When using a *herb or formula for the first time*, it is advised to take only 1/4 the recommended dosage to make sure the absence of adverse reaction, otherwise immediately stop using the herb. Slowly increase the dosage over 2 weeks to the recommended dose.**

2. **Always be strict to follow the *recommended use or dosage*. "If a little is good more must be better" does not apply here. Many herbs, particularly the stronger medicines used to treat chronic problems, are best used in small doses taken over an extended period of time.**

3. **There are *few herbs that are truly safe during pregnancy*. If a woman has a history of miscarriage or pregnancy problem consultation with competent physician is must before trying herbs.**

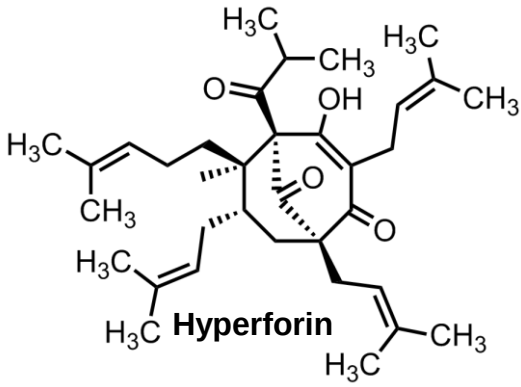
Simple Guidelines for Safe Use of Herbs

4. **Always *use common sense and careful judgment* when choosing appropriate remedies for you and be patient since the actions of many herbs are subtle and only appears when used over time.**

5. **If you are taking *prescription drugs*, interactions between some herbs and pharmaceuticals are possible. Discussing these possibilities with a clinical herbalist, knowledgeable pharmacist or physician is advised.**

St John's Wort (SJW)

- Over 66 million prescriptions were written in Germany for SJW (*Hypericum perforatum*) in 1994 for mild to moderate depression, compared to 30,000 for Prozac (antidepressant acting by selective serotonin reuptake inhibition).
- SJW alone has good safety profile, but with several drugs, it may cause pharmacokinetic and pharmacodynamic interactions.
- When SJW is combined with drugs that are substrates of CYP3A4, CYP2E1 and CYP2C19, and/or P-glycoprotein, lowering of plasma concentrations of a drug arise (pharmacokinetic interaction).
- Hyperforin in SJW is the supposed responsible ingredient for P-glycoprotein and CYP induction.



- **Clinical studies proved that SJW has been shown interaction with a number of drugs as it decreases the plasma level of these drugs via induction of cytochrome P450 (CYP) and/or P-glycoprotein induction→ reduces drug plasma concentrations (and/or increases the clearance).**

- **Examples of these drugs are:**

1) **Immuno-suppressants e.g. cyclosporine**

- **Immunosuppressants medications used to prevent organ rejection in people who have received a liver, kidney or heart transplant.**

- **It works by slowing down the body's defense system (immune system) to prevent the body from rejecting a transplanted organ.**

➢ One study under the title:

Drug Interaction between St. John's Wort and Cyclosporine

❑ OBJECTIVE:

To report a probable drug interaction between the herbal dietary supplement St. John's wort and cyclosporine.

❑ CASE REPORT:

- **A 29-year-old white woman who received a cadaveric kidney and pancreas transplant, with stable organ function and stable cyclosporine concentrations began self-medicating with St. John's wort.**
- **After taking St. John's wort supplements for four to eight weeks, her cyclosporine concentrations became subtherapeutic; this was associated with organ rejection.**

Ann Pharmacother; 2000, 34 (9), 1013-1016

➢ One study under the title:

Drug Interaction between St. John's Wort and Cyclosporine

❑ CASE REPORT: (cont.)

- **Four weeks after stopping St. John's wort, her cyclosporine concentrations again became therapeutic.**
- **Subsequent to this rejection episode, she has developed chronic rejection and now has returned to dialysis.**

Ann Pharmacother; 2000, 34 (9), 1013-1016

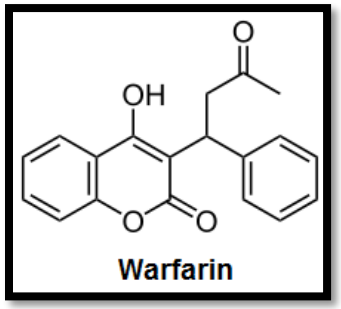
Clinical studies proved that SJW has been shown interaction with a number of drugs, including:

2) **Oral contraceptives**
3) **Cardiovascular drugs e.g. Digoxin and Verapamil**
4) **Anticancer drugs e.g. Irinotecan**
5) **CNS Drugs (as antidepressants and anxiolytics)**
6) **Hypoglycaemics e.g. Gliclazide**
7) **Anti-inflammatories e.g. Methadone (opioid type)**
8) **Antimicrobials e.g. Erythromycin.**
9) **GIT drugs e.g. Omeprazol**
10) **Anticoagulant e.g. Warfarin**
11) **Antiviral e.g Indinavir**

The over all effect of SJW is decreasing the plasma level of these drugs via induction of cytochrome P450 (CYP) and/or P-glycoprotein induction→ reduces drug plasma concentrations (and/or increases the clearance)

Herb-Warfarin Interactions

- The anticoagulant warfarin has numerous drug-drug interactions of variable quality of evidences.



PK

1. Its absorption may be **decreased** from GIT due to **mucilage** (in comfrey, psyllium) or **laxative** herbs (Senna, rhubarb etc)
2. Experimental data showed that CYP450 which affect the metabolism of the active S-enantiomer of warfarin may be **inhibited/induced** by Saw palmetto, Kava, Bromelain.

PD

1. Its action may be potentiated by herbs that **decrease platelet aggregation** (e.g. Salix).
2. Herbs with **coumarin** content (though coumarin is a relatively weak anticoagulant)

► Warfarin and herbs

- **American ginseng (Panax quinquefolius) – RCT (randomized controlled trial) in healthy volunteers indicated moderately reduced INR (international normalized ratio), warfarin levels. So, avoid with warfarin.**

- **Many Asian herbs has known platelet aggregation inhibition (Lab) but no clinical study.**

- **Garlic (*Allium sativum*) – Continuous ingestion of garlic or garlic oil can decrease platelet aggregation.**

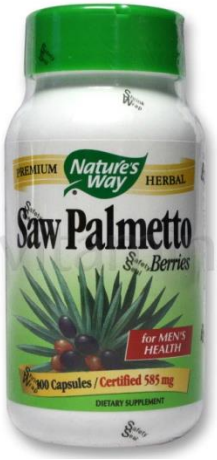
- **Ginkgo (Ginkgo biloba) – Ginkgolide B decreases platelet activating factor (PAF), extract inhibits thromboxane in diabetics (Lab). Case report suggests interaction.**

- **Green tea (*Camellia sinensis*) – Case reports showed decreased INR in patient drinking 1 gal/day (3.78 L) green tea – vitamin K effect.**

► Warfarin and lipid-based agents

- **Omega-3 fatty acids (in fish oil, algal formulas) – a case report of increased INR in a stabilized warfarin patient.**

- **Saw palmetto – lipid extract. Case report of intraoperative hemorrhage (without warfarin) and increased INR in 2 warfarin patients.**



Herbals That May Interact with Anticoagulant Therapy

Salicylate-Containing Herbals	Coumarin-Containing Herbals	Herbals with Antiplatelet or Antithrombotic Activity	Vitamin K–Containing Herbals
Meadowsweet	Angelica	Angelica	Alfalfa
Red clover	Asafoetida	Arnica	Parsley
Willow bark	Celery	Asafoetida	Cornsilk
	Fenugreek	Black tea	Watercress
	German chamomile	Boldo	
		Borage	
		Bromelain	
		Buchu	
		Capsicum	
		Clove	
		Fenugreek	
		Feverfew	
		Flaxseed	
		Asian ginseng	

Garlic-Drug interactions

- **The well-known adverse interaction between garlic and warfarin is presumably due to the antiplatelet effects of garlic.**
- **Garlic extract is potentially interacting with chlorpropamide (associated with a risk of hypoglycemia)**
- **Garlic and antiviral acting by protease Inhibition e.g. Saquinavir should be avoided (garlic has a role in induction of drug-metabolizing enzymes (CYP2C9 and CYP3A4) decreasing the plasma level of the antiviral i.e. increased clearance of Saquinavir).**

Herbs-Digoxin interactions

- Avoid internal consumption of *Aloe vera* (having strong purgative effect) → ⬇ serum potassium (K^+) levels and increase toxicity of digoxin.
- Avoid use with the herb Licorice as its diuretic effect can result in low (K^+) levels and increase toxicity of digoxin.
- Avoid HAWTHORN BERRY, which can potentiate digoxin action, since it acts synergistically.
- Avoid herbs with digoxin-like substances, e.g. *Eleuthrococcus senticosus* (Siberian ginseng) as it increases digoxin levels or interferes with digoxin assay.
- Avoid use with Quinine (Quinine is found in tonic water), which may increase digoxin levels
- Avoid taking Psyllium fibers, which decreases digoxin absorption, within two hours of taking medication.

Gingko-Drug interactions

Ginkgo (*Ginkgo biloba*)

Drug	Mechanism of Gingko	Outcomes
Aspirin	Antiplatelet activity	↑ bleeding risk
Ibuprofen	Antiplatelet activity	↑ bleeding risk
Haloperidol (antipsychotic)	Scavenge free radicals produced by hyperdopa-minergic activity	↓ drug toxicity
Omeprazole	Induction of CYP2C19 enzymes	↓ drug effect
Trazodone (antidepressant)	GABA-ergic activity	↑ drug effect
Valproic acid (anticonvulsant)	Contaminants of leaf/seed that may contain neurotoxins	↑ drug toxicity

Checking for herb-drug interactions

- Natural Standard (www.naturalstandard.com). Subscription service.
  - Partial database at MedlinePlus.gov
- Natural Medicines Comprehensive Database (www.naturaldatabase.com). Subscription service.
- Lexi-Interact. Subscription service (www.lexi-comp.com)
- MicroMedex – Altmedex. Subscription service (www.micromedex.com)
- Some misleading information but generally err on the side of pointing out interactions for which there is little to no evidence base.