

Herb-Drug Interactions

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Topics

- Herb-Drug Interaction
- Herbs with higher risk of adverse reactions
- Management techniques
- Current regulation

Herb-Drug Interactions

- Basic Concept and Understanding of Interaction
- Pharmacokinetic Interaction
- Pharmacodynamic Interaction
- Examples of Herb-Drug Interactions
- Examples of Herb-Herb Interactions

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

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Absorption

- Binding in the Gastrointestinal Tract
- Change in pH in the Stomach
- Change in Intestinal Motility

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Binding in the GI Tract

- Questran (cholestyramine)
- Colestid (colestipol)
- Xenical (orlistat)

- *Wu Bei Zi* (Galla Chinensis)
- *Chi Shi Zhi* (Halloysitum Rubrum)
- *Yu Yu Liang* (Limonitum)

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Binding in the GI Tract

- *Wu Bei Zi* (*Galla Chinensis*)
- *Chi Shi Zhi* (*Halloysitum Rubrum*)
- *Yu Yu Liang* (*Limonitum*)

- *Xiao Hui Xiang* (*Fructus Foeniculi*)
- *Di Yu* (*Radix Sanguisorbae*)

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pH in the stomach

- Antacid
 - Maalox
 - Mylanta
 - Tums

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pH in the stomach

- *Hai Piao Xiao* (*Endoconcha Sepiae*)

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Others...

pH in the stomach

- Histamine-2 Receptor Antagonist
 - Tagamet (cimetidine)
 - Pepcid (famotidine)
 - Axid (nizatidine)
 - Zantac (ranitidine)

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pH in the stomach

- *Huang Lian* (Rhizoma Coptidis)
- *Wu Zhu Yu* (Fructus Evodiae)

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Others...

pH in the stomach

- Proton Pump Inhibitor
 - Prilosec (omeprazole)
 - Nexium (esomeprazole)
 - Pravacid (lansoprazole)
 - Protonix (pantoprazole)

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Intestinal Motility

- Drugs that increase intestinal motility may decrease absorption
 - Reglan (metoclopramide)

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Intestinal Motility

- Drugs that decrease intestinal motility may increase absorption
 - Haldol (haloperidol)

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Intestinal Motility

- *Da Huang* (Radix et Rhizoma Rhei)
- *Mang Xiao* (Natrii Sulfas)

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Others...

Absorption

- Solution:

Take herbs and drugs separately by 3-4 hours

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Distribution

- Two factors that contribute to Distribution Interactions:

- Narrow range of safety index
- Highly protein bound

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Distribution

- Narrow range of safety index
- Highly protein bound
 - Coumadin (warfarin)
 - Dilantin (phenytoin)

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Others...

Distribution

- Dilemma:
 - Difficulty/Impossible to predict interactions
- Solution:
 - Initiate the herbs at a lower dose;
 - Gradually increase the dose of the herbs;
 - Monitor the patient closely

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Metabolism

- Liver Enzyme Inducer:
 - Increased metabolism of herbs/drugs
 - Decreased therapeutic effect
- Liver Enzyme Inhibitor:
 - Decreased metabolism of herbs/drugs
 - Increased therapeutic effect

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Metabolism

- Liver Enzyme Inducer:
 - Dilantin (phenytoin)
 - Tegretol (carbamazepine)
 - phenobarbitals
 - pentobarbital
 - secobarbital
 - rifampin

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Metabolism

- Liver Enzyme Inducer:
 - Increased metabolism of herbs/drugs
 - Decreased therapeutic effect
- Gradual onset of enzyme induction (takes about 1-2 month before effect is observed)

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Metabolism

- Liver Enzyme Inhibitor:
 - Tagamet (cimetidine)
 - E.E.S. (erythromycin)
 - Alcohol (ethanol)
 - Diflucan (fluconazole)
 - Sporonox (itraconazole)
 - Nizoral (ketoconazole)

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Metabolism

- Liver Enzyme Inhibitor:
 - decreased metabolism of herbs/drugs
 - increased therapeutic effect
- Rapid onset of enzyme inhibition (takes about 2 weeks before effect is observed)

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Metabolism

- Liver Enzyme Inducer:
 - increased metabolism
 - decreased effect
 - increase the dosage
- Liver Enzyme Inhibitor:
 - decreased metabolism
 - increase effect
 - decrease dosage

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Metabolism

- *Huang Yao Zi* (Herba Dioscoreae Bulbiferae)
- *Guan Ye Lian Qiao* (Herba Hypericum) [AKA: St. John's Wort]
- *Dang Gui* (Radix Angelicae Sinensis)
- *Niu Bang Gen* (Radix Arctii)

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Others...

Elimination

- Nephrotoxic drugs:
 - amphotericin B
 - methotrexate
 - tobramycin
 - gentimicin

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Elimination

- Nephrotoxic herbs:
 - *Guang Fang Ji* (Radix Aristolochiae Fangchi)
 - *Guan Mu Tong* (Caulis Aristolochiae Manshuriensis)
 - *Ma Dou Ling* (Fructus Aristolochiae)
 - *Qing Mu Xiang* (Radix Aristolochiae)
 - *Xi Xin* (Herba Asari)

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Aristolochic acid

- **Slimming regimen in Belgium**
- **5 drugs and 2 herbs**
 - fenfluramine,
 - diethylpropion,
 - cascara powder,
 - belladonna extract,
 - acetazolamide,
 - *Fen Fang Ji* (Radix Stephaniae Tetandrae)
 - *Hou Po* (Cortex Magnoliae Officinalis)

Aristolochic acid

- *Fang Ji*:
 - *Fen Fang Ji* (Radix Stephaniae Tetandrae)
 - *Guang Fang Ji* (Radix Aristolochiae Fangchi)
- *Mu Tong*:
 - *Chuan Mu Tong* (Caulis Clematidis Armandii)
 - *San Ye Mu Tong* (Caulis Trifoliata)
 - *Guan Mu Tong* (Caulis Aristolochiae Manshuriensis)
- *Ma Dou Ling* (Fructus Aristolochiae)
- *Qing Mu Xiang* (Radix Aristolochiae)
- *Xi Xin* (Herba Asari)

Others...

Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

Pharmacodynamic Interactions

- Synergistic Effect
 - $1+1=3$
- Antagonist Effect
 - $1+1=1$

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Drug-Drug Interactions

- Synergistic Effect with Drugs
 - Bactrim (sulfamethoxazole and trimethoprim)
 - Augmentin (amoxicillin & clavulanate p.)
 - Vicodin (hydrocodon & acetaminophen)
 - Tylenol #3 (codeine & acetaminophen)
 - cocktail approach to treating HIV & cancer.

Drug-Drug Interactions

- Antagonist effect with drugs
 - tetracycline with iron
 - activated charcoal with food

Herb-Herb Interactions

- Synergistic Effect with Herbs
 - *Shi Gao* (Gypsum Fibrosum) and *Zhi Mu* (Radix Anemarrhenae)
 - *Ru Xiang* (Gummi Olibanum) and *Mo Yao* (Myrrha)
 - *Tao Ren* (Semen Persicae) and *Hong Hua* (Flos Carthami)

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Herb-Herb Interactions

- Antagonist Effect with herbs
 - *Ren Shen* (Radix Ginseng) and *Wu Ling Zhi* (Excrementum Troglodyteri seu Pteromi)
 - *Ren Shen* (Radix Ginseng) and *Lai Fu Zi* (Semen Raphani)

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Herb-Drug Interactions

- Herbs with anticoagulant effects:
 - *Dan Shen* (Radix Salviae Miltiorrhizae)
 - *Dang Gui* (Radix Angelicae Sinensis)
 - *Chuan Xiong* (Rhizoma Ligustici Chuanxiong)
 - *Tao Ren* (Semen Persicae)
 - *Hong Hua* (Flos Carthami)
 - *Shui Zhi* (Hirudo)
 - *Yin Guo Ye* (Folium Ginkgo)
- Caution w/ anticoagulant or antiplatelet drugs

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Coumadin (warfarin)

- An anti-coagulant medication
- Blocks the re-cycling process of vitamin K
- Slow onset of action, long duration of action
- Lab monitor with INR (International Normalization Ratio)
- Symptom/Sign monitor with possible bleeding/bruises or clotting

Coumadin (warfarin)

- Over 1000 interactions documented
- Potential interaction with any other anti-coagulant or anti-platelet drugs
- Potential interaction with OTC drugs, dietary supplements, and food
- Potential adverse reaction with acupuncture
- Potential interactions with Chinese herbs

Herb-Drug Interactions

- *Salviae Miltiorrhizae (Dan Shen)* with Coumadin (warfarin)
 - Increase the absorption rate constant
 - Increase in AUC (area under the curve)
 - Increase in maximum concentration
 - Increase in elimination half-life
 - Decrease in clearance
 - Decrease in volume of distribution

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Others...

- *San Qi (Radix Notoginseng)*
- *Da Ji (Herba seu Radix Cirsii Japonici)*
- *Xian He Cao (Herba Agrimoniae)*

Herb-Drug Interactions

- Diuretic Herbs: ⁽¹⁾
 - *Fu Ling (Poria)*
 - *Zhu Ling (Polyporus)*
 - *Che Qian Zi (Semen Plantaginis)*
 - *Ze Xie (Rhizoma Alismatis)*
- Caution with diuretic drugs ⁽²⁾

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Herb-Drug Interactions

- Antidiabetic herbs
 - *Zhi Mu* (Radix Anemarrhenae) and *Shi Gao* (Gypsum Fibrosum)
 - *Xuan Shen* (Radix Scrophulariae) and *Cang Zhu* (Rhizoma Atractylodis)
 - *Huang Qi* (Radix Astragali) and *Shan Yao* (Rhizoma Dioscoreae)
- Use with caution with antidiabetic drugs

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Shen (Spiriti) Calming Herbs

- Sedatives: Herbs that calm *shen* (spirit) often potentiates the sedative effect of sedative / hypnotic drugs.
- [Note: Many categories of drugs induce sedation, such as antihistamines, narcotic analgesics, barbiturates, benzodiazepines and others.]

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Herb-Drug Interactions

- General Interactions
 - Anticoagulants / Antiplatelets
 - Diuretics
 - Antidiabetics
 - Sedatives / Hypnotics
- Specific Interactions

Ma Huang (Herba Ephedrae)

- **General effect:** *Ma Huang* contains ephedrine alkaloids that stimulate the central nervous system and the cardiovascular system. Combining *Ma Huang* with cardiac glycosides may lead to cardiac arrhythmia.

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Ma Huang (Herba Ephedrae)

- **Stimulant effect:**
- *Ma Huang* should not be combined with other sympathomimetic drugs, such as ephedrine, pseudoephedrine, theophylline, caffeine, monoamine oxidase inhibitors (MAOI), or substances with similar properties.

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Ma Huang (Herba Ephedrae)

- **Beta blockers:** The effect of beta blockers may be reduced when combined with *Ma Huang* because of increased levels of norepinephrine caused by the herb.²⁰
- [Note: Examples of beta blockers include atenolol (Tenormin), metoprolol (Lopressor/Toprol), sotalol (Betapace), propranolol (Inderal), and labetalol (Normodyne/Trandate).]

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Chai Hu (Radix Bupleuri)

- **Tolbutamide:** It was demonstrated in one study that the formula *Xiao Chai Hu Tang* (Minor Bupleurum Decoction) reduced the bioavailability of tolbutamide after oral administration.
- *Xiao Chai Hu Tang* was found to accelerate the initial absorption rate, reduce the area under the plasma concentration-time curve, and decrease the overall bioavailability of tolbutamide.¹⁸

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Chai Hu (Radix Bupleuri)

- **Interferon:** It has been reported that increased risk of acute pneumonitis may be associated with use of interferon, *Xiao Chai Hu Tang*, or both in combination.
- Among patients with chronic hepatitis or liver cirrhosis, the frequency of drug-induced pneumonitis was:
 - 0.5% in those given only interferon-alpha
 - 0.7% in those given only *Xiao Chai Hu Tang*
 - 4.0% in those given both

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Huang Qin (Radix Scutellariae)

- **Antibiotics:** Concurrent use of baicalin, a flavone isolated from *Huang Qin*, was found to have synergistic antibiotic effect with beta-lactam antibiotics, such as ampicillin, amoxicillin, methicillin and cefotaxime.
- The addition of baicalin restored the effectiveness of these drugs against beta-lactam-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA).¹⁵

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Guan Ye Lian Qiao (Herba Hypericum)

■ **SSRI's:** Since St. John's Wort and SSRI both inhibit the reuptake of serotonin, concurrent use of both the herb and the drug may lead to "serotonin syndrome" with symptoms such as sweating, tremor, flushing, confusion and agitation.⁸

■ [Note: Examples of SSRI's include fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and fluvoxamine (Luvox).]

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Cross-allergy

■ *Da Qing Ye* (Folium Isatidis), *Ban Lan Gen* (Radix Isatidis) and *Qing Dai* (Indigo Naturalis)

■ Sulfonylureas: tolbutamide (Orinase), glipizide (Glucotrol), and glyburide (DiaBeta/Micronase)

■ Sulfonamides: sulfadiazine, sulfisoxazole, sulfamethoxazole, trimethoprim/sulfamethoxazole (Bactrim/Septa), and erythromycin/sulfisoxazole (Pediazole).]

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Fu Zi (Radix Aconiti Lateralis Praeparata)

■ **Antiarrhythmics:** Patients who have a past history of cardiovascular disorders or are taking antiarrhythmic medications should take *Fu Zi* with extreme caution.¹³

■ [Note: Examples of antiarrhythmics include quinidine, procainamide (Pronestyl), disopyramide (Norpace), flecainide (Tambocor), propafenone (Rythmol), and amiodarone (Cordarone).]

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Chuan Wu (Radix Aconiti Preparata)

- **Antiarrhythmics:** Patients who have a past history of cardiovascular disorders or are taking antiarrhythmic medications should take *Chuan Wu* with extreme caution.¹⁰
- [Note: Examples of antiarrhythmics include quinidine, procainamide (Pronestyl), disopyramide (Norpace), flecainide (Tambocor), propafenone (Rythmol), and amiodarone (Cordarone).]

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Cao Wu (Radix Aconiti Kusnezoffii)

- **Antiarrhythmics:** Patients who have a past history of cardiovascular disorders or are taking antiarrhythmic medications should take *Cao Wu* with extreme caution.⁵
- [Note: Examples of antiarrhythmics include quinidine, procainamide (Pronestyl), disopyramide (Norpace), flecainide (Tambocor), propafenone (Rythmol), and amiodarone (Cordarone).]

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Da Fu Pi (Pericarpium Arecae)

- **Antipsychotics:** It has been suggested that an exacerbation of extrapyramidal effects may occur with concurrent use of neuroleptic drugs and betel nuts. Two cases of severe extrapyramidal symptoms were reported, when patients with chronic schizophrenic disorders treated with depot neuroleptics also consumed a heavy dose of betel nuts for a long period of time.^{4,5}
- [Note: Examples of antipsychotics include chlorpromazine (Thorazine), fluphenazine (Prolixin), thioridazine (Mellaril), and haloperidol (Haldol).]

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Bing Lang (Semen Arecae)

- **Antipsychotics:** It has been suggested that an exacerbation of extrapyramidal effects may occur with concurrent use of neuroleptic drugs and betel nuts. Two cases of severe extrapyramidal symptoms were reported when patients with chronic schizophrenic disorders treated with depot neuroleptics also consumed a heavy dose of betel nuts for a long period of time.^{16,17}
- [Note: Examples of antipsychotics include chlorpromazine (Thorazine), fluphenazine (Prolixin), thioridazine (Mellaril), and haloperidol (Haldol).]

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Shan Zha (Fructus Crataegi)

- **Digoxin (Lanoxin):** Both *Shan Zha* and digoxin have marked cardiotoxic effects. Therefore, concurrent use of *Shan Zha* and digoxin (Lanoxin) should be monitored carefully to avoid possible side effects.¹⁷

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Ren Shen (Radix Ginseng)

- **Antidepressants:** It has been suggested, but not been documented, that induction of mania may occur in depressed patients who mix antidepressants and *Ren Shen*.
- In rare cases, the concurrent use of *Ren Shen* and phenelzine has led to manic-like symptoms.^{29,30}
- [Note: Examples of similar antidepressants are as follows: monoamine oxidase inhibitors (MAOI) such as phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan).]

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Ci Wu Jia (Rx et Caulis Acanthopanacis)

- **Digoxin:** An elevated serum digoxin level was documented in one patient taking both digoxin and *Ci Wu Jia*. When *Ci Wu Jia* was discontinued, the serum digoxin level returned to normal. When *Ci Wu Jia* was re-introduced, the serum digoxin level increased.
- The exact mechanism of this action is unclear. Proposed reasons included conversion of components in *Ci Wu Jia* to digoxin *in vivo*, interference with digoxin elimination, or false serum assay results.¹⁹

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Gan Cao (Radix Glycyrrhizae)

- **Corticosteroids:** It has been suggested that the use of *Gan Cao* may alter the therapeutic effects of systemic corticosteroids. Glycyrrhizin, one of the components of *Gan Cao*, is a strong inhibitor of 11 beta-hydroxysteroid dehydrogenase and may prolong the biological half-life of the systemic corticosteroids.³³
- [Note: Examples of corticosteroids include cortisone, prednisone (Orasone), dexamethasone (Decadron), hydrocortisone (Cortef), methylprednisolone (Medrol).]

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Gan Cao (Radix Glycyrrhizae)

- **Drug overdose:** *Gan Cao* speeds the metabolism of drugs such as chloral hydrate, urethane, cocaine, picrotoxin, caffeine, pilocarpine, nicotine, and barbiturates, and treats overdose of these agents.³⁵

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Ying Su Ke (Pericarpium Papaveris)

- **Depressant effect:** Phenothiazines, monoamine oxidase inhibitors, and tricyclic antidepressants may exaggerate and prolong the depressant effect of *Ying Su Ke*.

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Chinese Herbal Toxicology

- Serious poisonings due to Chinese herbal medicine...
 - 61% by aconite roots
 - 15% by herbs with anticholinergic properties (datura and areca)
 - 24% others..

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Toxicology... aconite roots

- Tetraplegia caused by...
 - *Chuan Wu* (Radix Aconiti Preparata)
 - *Cao Wu* (Radix Aconiti Kusnezoffii)

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Toxicology... aconite roots

- Cardiac arrest cause by...
 - Aconitine containing herbs
 - severe overdose
 - ventricular tachycardia, fibrillation, cardiac arrest, and death.

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General Antidotes

- *Rou Gui* (Cortex Cinnamomi), 3-5 grams in tea.
- Decoction of *Sheng Jiang* (Rhizoma Zingiberis Recens), *Gan Cao* (Radix Glycyrrhizae), *Gan Jiang* (Rhizoma Zingiberis), *Lu Dou* (Semen Phaseoli Radiati), *Hei Dou* (Semen Glycine Max), *Huang Lian* (Rhizoma Coptidis), *Ren Shen* (Radix Ginseng) and *Huang Qi* (Radix Astragali).

Specific Antidotes

- Irregular heartbeat: decoction of 20 grams of *Ku Shen Gen* (Radix Sophorae Flavescentis) and 10 grams of *Gan Cao* (Radix Glycyrrhizae).
- Coldness of the extremities, extremely weak pulse, and shortness of breath: decoction of *Ren Shen* (Radix Ginseng), *Gan Cao* (Radix Glycyrrhizae), and *Gan Jiang* (Rhizoma Zingiberis).

Toxicology... A/C herbs

- Herbs with anti-cholinergic properties
 - *Man Tuo Luo* (*Datura metel*, *D. innoxia*, *D. stramonium*, *D. tabula*, *D. fastusa*)
 - *Bing Lang* (*Semen Arecae*)
 - *Da Fu Pi* (*Pericarpium Arecae*)

Toxicology... A/C herbs

- Herbs with anti-cholinergic properties
 - *Man Tuo Luo* (*Datura metel*, *D. innoxia*, *D. stramonium*, *D. tabula*, *D. fastusa*)
 - *Bing Lang* (*Semen Arecae*)
 - *Da Fu Pi* (*Pericarpium Arecae*)

Other Issues

- Pregnancy
- Nursing
- Geriatrics
- Pediatrics

Herbs & Pregnancy

- Prohibited herbs:
 - *Ba Dou* (Fructus Crotonis)
 - *Qian Niu Zi* (Semen Pharbitidis)
 - *Ban Mao* (Mylabris)
 - *Shang Lu* (Radix Phytolaccae)
 - *She Xiang* (Moschus)
 - *San Leng* (Rhizoma Sparganii)
 - *E Zhu* (Rhizoma Curcumae)
 - *Shui Zhi* (Hirudo)
 - *Meng Chong* (Tabanus)

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Herbs & Pregnancy

- Use with caution:
 - *Tao Ren* (Semen Persicae)
 - *Hong Hua* (Flos Carthami)
 - *Da Huang* (Radix et Rhizoma Rhei)
 - *Zhi Shi* (Fructus Aurantii Immaturus)
 - *Fu Zi* (Radix Aconiti Lateralis Praeparata)
 - *Gan Jiang* (Rhizoma Zingiberis)
 - *Rou Gui* (Cortex Cinnamomi)
- Others: Herbs that induce contraction of uterus

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Nursing

- Presence of herbs in the breast milk
- Lipophilic vs. hydrophilic substances

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Dosing

- Geriatric patients
- Pediatric patients
- Body weight

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Common Adverse Reactions

- Nausea and vomiting
- Constipation or diarrhea
- Headache
- Allergic reaction

Regulatory Issues

- Drug vs. Supplement vs. Food
- Aristolochic acid
- Pyrrolizidine alkaloids
- Ephedrine alkaloids
- Citrus herbs
- Manufacturing issues

Aristolochic acid

- Slimming regimen in Belgium
- 5 drugs and 2 herbs
 - fenfluramine,
 - diethylpropion,
 - cascara powder,
 - belladonna extract,
 - acetazolamide,
 - *Fen Fang Ji* (Radix Stephaniae Tetandrae)
 - *Hou Po* (Cortex Magnoliae Officinalis)

Aristolochic acid

- *Fang Ji*:
 - *Fen Fang Ji* (Radix Stephaniae Tetandrae)
 - *Guang Fang Ji* (Radix Aristolochiae Fangchi)
- *Mu Tong*:
 - *Chuan Mu Tong* (Caulis Clematidis Armandii)
 - *San Ye Mu Tong* (Caulis Trifoliata)
 - *Guan Mu Tong* (Caulis Aristolochiae Manshuriensis)
- *Ma Dou Ling* (Fructus Aristolochiae)
- *Qing Mu Xiang* (Radix Aristolochiae)
- *Xi Xin* (Herba Asari)

Pyrolizidine alkaloids

- Comfrey
- *Kuan Dong Hua*
(Flos Farfarae)

Ephedrine Alkaloids

- *Ma Huang*
(Herba Ephedrae)
- *Ban Xia*
(Rhizoma Pinelliae)

“Citrus Herbs”

- *Zhi Shi* (Fructus Immaturus Citri Aurantii)
- *Zhi Ke* (Fructus Citri Aurantii)
- *Chen Pi* (Pericarpium Citri Reticulatae)
- *Qing Pi* (Pericarpium Citri Reticulatae Viride)
- Chemical Composition: synephrine; N-methyltyramine; hesperidin; neohesperidin; nobiletin; desmethyl nobiletin; quinoline; narcotine; noradrenaline; quinoline; tryptamine; tyramine; n-methyltyramine; naringin; rhoifolin; tengeretin; and lonicerin.

Modern Pharmacology of Chinese Herbs, 1997, 636

Others...

Manufacturing Issues

- Heavy metals
- Drugs
- Undeclared ingredients

Manufacturing Issues

- Food GMP: USA

- Pharmaceutical GMP: Taiwan, Japan, Europe, etc.

Quality Control Measures

- Good Manufacturing Practice (GMP)
 - Heavy metal
 - Harmful bacteria
 - Total bacterial count
 - Drugs
 - Purity of herbs
 - Identity of herbs
- Request for certificate of analysis

TLC (Thin Layer Chromatography)

HPLC (High Performance Liquid Chromatography)

COA - Certificate of Analysis

Conclusion

- Educate and general public on the effect of herbal medicine
- Increase education and training among practitioners
- Regulation of herbs as "traditional medicine"
