

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)

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pH in the stomach

- Antacid
 - Maalox
 - Mylanta
 - Tums

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pH in the stomach

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

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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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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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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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Elimination

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

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Elimination

- Prevent ototoxicity and nephrotoxicity due to aminoglycosides
- Compound injection with *Huang Qi* (Radix Astragali) and *Lu Han Cao* (Herba Pyrolae)
- May prevent ototoxicity and nephrotoxicity due to aminoglycosides in guinea pigs

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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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Pharmacokinetic Interactions

- Absorption
- Distribution
- Metabolism
- Elimination

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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Eighteen Incompatibles (*Shi Ba Fan*)

- Rx *Glycyrrhizae* (*Gan Cao*) is incompatible
 - Radix Euphorbiae Kansui (*Gan Su*),
 - Radix Euphorbiae seu Knoxiae (*Da Ji*)
 - Flos Genkwa (*Yuan Hua*)
 - Herba Sargassum (*Hai Zao*)
- Rz *Aconiti* (*Wu Tou*) is incompatible with
 - Bulbus Fritillariae Cirrhosae (*Chuan Bei Mu*)
 - Bulbus Fritillariae Thunbergii (*Zhe Bei Mu*)
 - Fructus Trichosanthis (*Gua Lou*)
 - Rhizoma Pinelliae (*Ban Xia*)
 - Radix Ampelopsis (*Bai Lian*)
 - Rhizoma Bleilliae (*Bai Ji*)
- Rhizoma et Radix Veratri (*Li Lu*) is incompatible with
 - Radix Ginseng (*Ren Shen*)
 - Radix Glehniae (*Bei Sha Shen*)
 - Radix Adenophorae (*Nan Sha Shen*)
 - Radix Sophorae Flavescens (*Ku Shen*)
 - Radix Salviae Miltiorrhizae (*Dan Shen*)
 - Radix Scrophulariae (*Xuan Shen*)
 - Radix Paeoniae Alba (*Bai Shao*)
 - Radix Paeoniae Rubra (*Chi Shao*)
 - Herba Asari (*Xi Xin*)

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Nineteen Counteractions (*Shi Jiu Wei*)

- Sulfur (*Liu Huang*) & Mirabilium (*Mang Xiao*)
- Mercury (*Shui Yin*) & Arsenolite (*Pi Shuang*)
- Rhizoma Euphorbiae E. (*Lang Du*) & Lithargyrum (*Mi Tuo Seng*)
- Semen Crotonis (*Ba Dou*) & Semen Pharbitidis (*Qian Niu Zi*)
- Flos Caryphylli (*Ding Xiang*) & Radix Curcumae (*Yu Jin*)
- Nitrum (*Ya Xiao*) & Rhizoma Sparganii (*Shan Ling*)
- Cornu Rhinoceri (*Xi Jiao*) & Rz. Aconiti Kusnezoffii (*Cao Wu*)
- Cornu Rhinoceri (*Xi Jiao*) & Rhizoma Aconiti (*Chuan Wu*)
- Radix Ginseng (*Ren Shen*) & Rhizoma Trogopterorum (*Wu Ling Zhi*)
- Cortex Cinnamomi (*Rou Gui*) & Hallositum Rubrum (*Chi Shi Zhi*)

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Herb-Drug Interactions

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

Herb-Drug Interactions

- Herbs with anticoagulant effects:
 - *Dan Shen* (Radix Salviae Miltiorrhizae)
 - *Dang Gui* (Radicis Angelicae Sinensis)
 - *Chuan Xiong* (Rhizoma Ligustici Chuanxiong)
 - *Tao Ren* (Semen Persicae)
 - *Hong Hua* (Flos Carthami)
 - *Shui Zhi* (Hirudo)
- 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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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 (Spirti) 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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Niu Bang Zi (Fructus Arctii)

- **Acetaminophen:** *Niu Bang Gen* (Radix Arctii) has marked hepatoprotective effects. *Niu Bang Gen* suppressed the elevated SGOT and SGPT levels induced by carbon tetrachloride or acetaminophen in a dose-dependent manner. It also alleviated the severity of liver damage based on histopathological observations.

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Niu Bang Zi (Fructus Arctii)

- **Acetaminophen:**
- The mechanism of this hepatoprotective action is based on the antioxidative effect of *Niu Bang Gen* on hepatocytes, hence eliminating the deleterious effects of toxic metabolites from carbon tetrachloride or acetaminophen.⁹

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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)
- Sulfonyleureas: tolbutamide (Orinase), glipizide (Glucotrol), and glyburide (DiaBeta/Micronase)
- Sulfonamides: sulfadiazine, sulfisoxazole, sulfamethoxazole, trimethoprim/sulfamethoxazole (Bactrim/Septra), 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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Herbs with Higher Risks

- Aconite
- Datura

Toxicology

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

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Other Issues

- Pregnancy
- Nursing
- Geriatrics
- Pediatrics

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

Conclusion

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

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