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Safety in Herb-Drug Combinations #3

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Safety in Herb-Drug Combinations #3

Review of Pharmacological Actions

Drug interactions are both pharmacodynamic and pharmacokinetic. Pharmacodynamics concern the actions of two or more drugs and pharmacokinetics concern the absorption, distribution, metabolism, and/or excretion of one or more drugs affecting another. Interactions can be additive, synergistic, and antagonistic. Additive interactions are those wherein the effects of two or more chemicals taken together is equal to the sum of taking them separately. Synergistic interactions occur when taking two or more substances together results in a stronger action than the sum of taking them separately. The substances increase each others' effects. Antagonistic interactions are when taking substances together weakens their overall effect.

Chinese Medicine (CM) uses differential diagnosis in determining the appropriate herbs. Herbal choices are based on the functions of the individual herbs and the overall function of a formula. When patients consume western medications with herbs, care must be taken not to alter the effects of the western medicine such that adverse reactions occur. This can happen when the herbal medicine is additive, synergistic, or antagonistic to the effects of the medication. If, however, the medication is of insufficient strength, herbal medicine can potentiate its effects for a better clinical outcome. Herbal medicines are commonly used to protect the patient from the side effects of western medications and to holistically balance the patient's constitution. In general, caution is needed more often in cases of excess rather than deficiency.

Herbal toxicity and herb-drug interactions have not surfaced as a major issue in the USA partially because the list of FDA allowable herbs is highly restricted such that most available herbs do not have harmful reactions with pharmaceuticals. The most common herb-drug interaction concern is that of warfarin (Coumadin). One concern is that herbal medicines may compete with warfarin for absorption. Commonly, the issue is to what extent and which herbs may decrease or increase the efficacy of warfarin. For example, herbs containing vitamin K may be antagonistic and blood invigorating herbs tend to be additive or synergistic.

Herb-drug interactions are not the only concern. There are food-drug interactions and food-herb interactions. Dietary irregularities often complicate treatment. In the case of a patient who consistently drinks excess amounts of coffee and refuses to curb this behavior, the properties of the coffee affect the usage of herbs- particularly those that raise the Qi, strengthen the Yang, warm the interior, or dry dampness.



1. Raise blood pressure & increase heart beat drugs

Medications may be used to intentionally raise blood pressure, heart beat rate, and strengthen contractility or these very same effects may be the adverse effects of medications and are undesirable consequences. Herbal medicine may serve to assist the functions of the medications in a synergistic or additive function or they may serve to quell the unwanted side effects of medications. Additionally, herbal medicine may have antagonistic effects thereby reducing the functional power of the medications.

Herbs that warm the interior and strengthen Kidney Yang and Qi must be used with caution when patients take drugs that raise the blood pressure or increase heart contractility (force of contraction). The herbs and the drugs have similar functions and therefore may have a synergistic or additive effect when combined. Care must be taken with the tonic herbs as not to induce tachycardia or excessively high blood pressure.

Alternately, herbs are helpful to assist the functions of the medications. If medications fail to bring blood pressure up to a normal range and are unable to strengthen the contractility of the heart, these herbs will help to restore balance, lift the blood pressure and strengthen contractility.

Herbs that anchor the Yang may lower blood pressure. When patients take medications that induce tachycardia and high blood pressure as adverse side effects, they are effective in helping to control these side effects.

Drug

A.

i.

Patients taking drugs that raise blood pressure and heart contractility should use caution if taking **alpha-agonists** such as **pseudoephedrine** (Sudafed). It is an agonist at alpha and beta adrenergic receptors which causes the release of endogenous norepinephrine (noradrenaline). It is known for causing vasoconstriction.

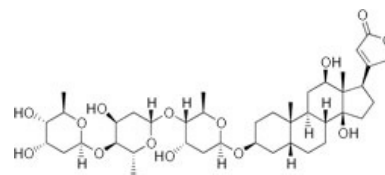
Pseudoephedrine also occurs in its natural form, ephedrine, in Ma Huang (ephedra). Caution is indicated when using Ma Huang with patients taking pseudoephedrine due to synergistic and additive effects.

ii.

Patients taking drugs that raise blood pressure and heart contractility should use caution if taking **phenylephrine**. Phenylephrine (Neo-Synephrine) is an alpha adrenergic receptor agonist that is used as a decongestant. It is also used to dilate the pupil and increase blood pressure. It is marketed as a substitute for pseudoephedrine (Sudafed). It may cause hypertension as a side effect and is contraindicated in patients with epilepsy or for those taking anticonvulsant medications. The drug interaction may cause seizures.

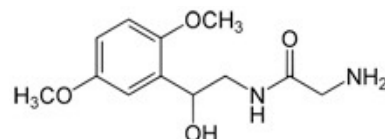
B.

Caution should be used if a patient is using digoxin to increase heart contractility. **Digoxin (Digitalis)** increases myocardial contractility, decreases heart rate, and increases blood pressure due to increased stroke volume. It is extracted from the digitalis lanata plant (Woolly Foxglove). Digitalis lanata is highly toxic and may be fatal if ingested, particularly for children. **Shu Di Huang** (Chinese Foxglove, Radix Rehmanniae Glutinosae Conquिताe) is not related to digitalis lanata and does not share its toxic properties.



C.

Midodrine (Amatine, ProAmatine, Gutron) is a vasopressor/antihypotensive agent. Approved in 1996 for the treatment of orthostatic hypotension, the FDA proposed withdrawing this approval in 2010 because the manufacturer did not complete the post-market required studies. Orthostatic hypotension is also known as a “head rush” or “dizzy spell” and is when a person’s blood pressure suddenly drops upon standing. Midodrine is metabolised into an active metabolite which is an alpha-receptor agonist and activates alpha-adrenergic receptors of both venous and arteriolar vasculature. This increases vascular tone and elevates blood pressure.



D.

Fludrocortisone (Florinef) is a synthetic corticosteroid which is used to replace aldosterone for patients with adrenal insufficiency as in the case of Addison’s disease. It is also used for orthostatic intolerance (OI). OI is a disorder of the autonomic nervous system which occurs

upon standing. Upon standing, the blood pressure drops suddenly, cerebral blood flow is inhibited and there may be loss of consciousness. It can also be relieved by sitting or reclining.

Fludrocortisone may cause water retention, sodium retention, high blood pressure, headaches, low blood potassium levels, increased risk of infection, impaired wound healing, thinning of skin, dyspepsia, peptic ulcer, depression, weight gain, menstrual cycle changes, partial vision loss due to cataracts, glaucoma, and increased intracranial pressure.

Herb

Fu Zi (RadLateralis Aconiti Carmichaeli) strengthens the devastated Yang and benefits the Qi and Yang. It is toxic and is contraindicated during pregnancy. Use extreme caution with patients who have a history of cardiovascular disorders or are taking antiarrhythmic drugs.

Overdose of Fu Zi may be treated with Rou Gui if taken within the first several hours. The Rou Gui tea induces vomiting within approximately 15 minutes and the toxin is expelled. Overdose symptoms include tremors, numbness of the lips, mouth, and tongue; irregularities of the heart rate and rhythm, excess salivation, nausea, dizziness, vomiting, diarrhea, difficulty breathing, and decreased blood pressure. Overdose may be fatal.

Ren Shen (Radix Ginseng) and **Dang Shen** (Radix Codonopsis Pilosulae) strengthen the Qi. Ren Shen is stronger and Dang Shen is milder and for chronic conditions.

Huang Qi (Radix Astragali Membranaceus) raises and strengthens the Qi up to surface and from interior to exterior.

Lu Rong (Cornu Cervi Parvum) strengthens, warms and raises the Qi and Yang and nourishes Kidney Jing.

Ge Jie (Gecko) warms and encourages the Kidney Yang.

Suo Yang (Herba Cynomorii Songarici) and **Yin Yang Huo** (Herba Epimedii) warms the Kidney Yang and moistens the intestines. Suo Yang is stronger to warm the Yang and benefits Kidney Jing to treat impotence, amenorrhea, and infertility. Suo Yang also benefits Liver Yin. Yin Yang Huo is stronger to benefit the flow of Yang and increases libido.

Bai Ji Tian (Rhizoma Bletillae Striatae) warms the Kidney Yang and expels wind damp Bi pain.

Bu Gu Zhi (Fructus Psoraleae Corylifoliae) warms the Kidney and Spleen Yang and stops early morning diarrhea.

Xian Mao (Rhizoma Curculiginis Orchiodis) strongly warms the Kidney Yang and powerfully treats impotence, incontinence, infertility, and spermatorrhea. It is toxic and may cause palpitations and numbness and swelling of the tongue. Long term use is discouraged due to its toxicity.

Gou Ji (Rhizoma Cibotii Barometz) warms the Kidney and Heart Yang and expels wind damp cold Bi pain.

Xu Duan (radix Dipsaci Asperi) warms the Kidney Yang and promotes blood circulation.

Gu Sui Bu (Rhizoma Drynariae) warms the Kidney yang and heals bone fractures. Gu Sui Bu treats tinnitus and numbness caused by streptomycin.

Long Gu (Os Draconis) stabilizes and astringes Heart and Kidney Yang.

Mu Li (Concha Ostreae) and **Shi Jue Ming** (Concha Haliotidis) stabilizes Liver Yang. Mu Li dissolves nodules. Shi Jue Ming brightens the eyes.

Zhen Zhu Mu (Concha Margaritiferæ) stabilizes the Liver Yang and benefits the eyes.

Case I

An 83 year old female is taking **midodrine** to raise her blood pressure due to her heart condition. Recently she had a car accident with the neck, shoulder and lower back adversely affected. Her tongue is dark red with purple dots on the side. Pulse is small and rapid.

Diagnosis:
Heart and Kidney Qi and Yin deficiency
Qi and blood stagnation

She was prescribed **Gou Ji** (Rhizoma Cibotii Barometz) and **Xu Duan** (Radix Dipsaci Asperi) for her injury but complains that her heart beat is faster with palpitations. After lowering the dosage of **Gou Ji** (Rhizoma Cibotii Barometz) and **Xu Duan** (Radix Dipsaci Asperi), there were no further reports of side effects and the patient's condition significantly improved.

Case II

A 76 year old female is taking **fludrocortisone** to raise her blood pressure due to congenital low blood pressure. Even with the medicine, her blood pressure is remains very low. Her tongue is teeth marked and the pulse is weak and deep.

Diagnosis:
Spleen and Kidney Qi and Yang deficiency.

She took **Huang Qi** (Radix Astragali Membranaceus) and **Xu Duan** (radix Dipsaci Asperi) which raised her blood pressure to the normal range. She is now feeling strong and energized. **Huang Qi** (Radix Astragali Membranaceus) and **Xu Duan** (Radix Dipsaci Asperi) strengthen Qi and Yang and also promote blood circulation.



Dang Shen

2. Lower blood pressure drugs - Antihypertensives

Use caution with raising the Qi and Yang herbs when patients are taking medications to control high blood pressure. There are potential synergistic and additive pharmacodynamic interactions.

Drug

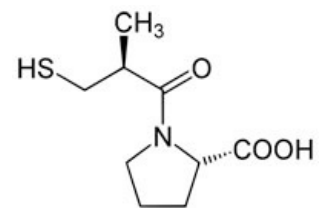
There are many classes of antihypertensives including:

A.

ACE inhibitors (angiotensin converting enzyme inhibitors), these are the "prils": ramipril, enalapril, lisinopril.

Angiotensin converting enzyme (ACE) raises blood pressure by constricting blood vessels and ACE inhibitor drugs prevent constriction by ACE and therefore lower blood pressure. ACE inhibitors are primarily used for hypertension and congestive heart failure. Historically, the discovery of an orally inactive peptide from snake venom led to the development of the first ACE inhibitor, Captopril.

Side effects of ACE inhibitors include hypotension, headache, fatigue, nausea, renal impairment, cough, and hyperkalemia (elevated potassium levels in the blood). For pregnant women, ACE inhibitors can cause serious congenital malformations, still births, and neonatal death.



B.

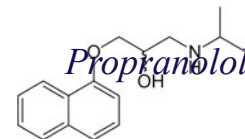
Calcium channel blockers (CCBs): nifedipine, diltiazem, amlodipine.

CCBs disrupt calcium channels and most CCBs decrease the force of myocardium (heart muscle) contractility making them valued for the treatment of hypertension. Many CCBs slow the electrical conduction within the heart are therefore used to treat atrial fibrillation and atrial flutter.

C.

Beta blockers: metoprolol xl, atenolol, propranolol.

This class of drugs is commonly used to treat cardiac arrhythmias and hypertension. They are also administered after MI (myocardial infarction, heart attack) for cardioprotection purposes.



Beta blockers are beta adrenergic receptor antagonists and therefore reduce the effects of endogenous catecholamines (including epinephrine 'adrenaline' and norepinephrine) on beta adrenergic receptors. The receptors are part of the sympathetic nervous system and therefore regulate the flight or fight response.

Beta blockers decrease melatonin release which may explain reports of sleep disturbances. They impair bronchial muscle relaxation and should therefore be avoided by asthmatics. Side effects include: nausea, diarrhea, bronchospasm, insomnia, fatigue, dizziness, hair loss, hallucinations, dyspnea, nightmares, depression, sexual dysfunction, and erectile dysfunction.

D.

ARBs (angiotensin receptor blockers): **Losartan, irbesartan, olmesartan.**

These are the "sartans". Losartan is available generically. They are also referred to as angiotensin II receptor antagonists and are often used to treat hypertension and congestive heart failure. New research suggests that ARBs may be associated with an increased risk of cancer.

Response to the various classes are individualized and are often dependent on the side effects profile.

Herb

Huang Qi (Radix Astragali Membranaceus) raises the Qi, encourages Qi to the surface and promotes wound healing.

Ren Shen (Radix Ginseng) strengthens source Qi.

Chai Hu (Radix Bupleuri) and **Sheng Ma** (Rhizoma Cimicifugae) raise Qi upwards. Chai Hu regulates Liver and GB Qi. Sheng Ma is stronger for raising the Qi upwards.

Dang Gui (Radix Angelicae Sinensis) promotes blood circulation and nourishes blood.

Lu Rong (Cornu Cervi Parvum) strengthens Kidney Yang and Jing.
Ge Jie (Gecko) strengthens Kidney and Lung Yang for treating asthma and impotence.

Suo Yang (Herba Cynomorii Songarici) is warm and astringes the Kidney Yang.

Yin Yang Huo (Herba Epimedii) and **Bai Ji Tian** (Rhizoma Bletillae Striatae) warm the Kidney Yang and expel wind damp cold Bi pain. Yin Yang Huo has a faster effective action. **Bai Ji Tian** is maintained in the bloodstream longer.

Bu Gu Zhi (Fructus Psoraleae Corylifoliae) warms the Kidney and Spleen Yang for treating morning diarrhea and strengthens the bone marrow.

Xian Mao (Rhizoma Curculiginis Orchiodis) warms Kidney Yang. Long term use is discouraged due to its toxicity.

Gou Ji (Rhizoma Cibotii Barometz) is warm and strengthens Kidney Yang, especially for spinal pain.

Xu Duan (radix Dipsaci Asperi) strengthens Kidney Yang and promotes blood circulation.

Gu Sui Bu (Rhizoma Drynariae) strengthens Kidney Yang and heals bone fractures.

Case I

A male patient with high blood pressure takes **losartan** to control it. The patient has stress, frustration and pain in the hypochondriac region. The tongue has red sides and the pulse is wiry.

Diagnosis:

Liver Qi stagnation with Yang uprising

After taking **Chai Hu** (Radix Bupleuri) his hands started mildly shaking like a person who drank a lot of coffee and therefore cannot be still or hold on to the cup.

Discussion:

The patient's personality is stressed. This is Liver Qi stagnation leading to Yang rising. **Chai Hu** (Radix Bupleuri) smoothes the Liver and GB Qi while lifting the Qi. The lifting the Qi function of Chai Hu is too strong for this patient at a normal dosage level. To avoid tremors, lower the dosage of Chai Hu and add calming and smoothing the Qi herbs.

Case II

An 80 year old male patient has high blood pressure. He has a blood clot in the brain and the left side of his body has partial paralysis. He is taking **warfarin**, a blood thinner, and the blood pressure medication **losartan (Cozaar)**. He complains after three months of taking the medications that his thinking is too slow. His tongue is dark red and the pulse is wiry and small.

Diagnosis:

Liver and Heart Yang uprising
Qi and blood stagnation

He is given **Huang Qi** (Radix Astragali Membranaceus), **Niu Xi** (Radix Achyranthis Bidentatae) and **Mu Li** (Concha Ostrae). Huang Qi promotes Qi flow, Niu Xi promotes blood circulation and descends blood circulation and Mu Li stabilizes the Yang.

After taking the formula for one month, his bodily range of motion improved by 30% on the impaired side. His mental responses are quicker and the blood pressure is controlled to a normal range by the herbs. The lifting, descending, and stabilizing effects of the herbs act to harmonize the patient's condition by restoring balance.

3. Anti-estrogenic drugs & breast cancer

Herbs that strengthen Qi, Blood, Jing and Kidney Yang should be used with caution because they may stimulate estrogen production. Careful diagnosis of the Yin and Yang balance and the Heart and Kidney communication is essential to treating patients who are taking anti-estrogenic drugs. It is recommended that these patients have their estrogen levels checked often.

Many tonic herbs have properties that reduce inflammatory responses, benefit the immune system, and encourage the production of red and white blood cells. These responses may be helpful for patients undergoing chemotherapy and radiation treatments.

Drug

***Breast tissue is stimulated by estrogen
Breast cancer cells need estrogen to grow***

Tamoxifen and **aromatase inhibitors** (Arimidex, Aromasin, Femara) are used to prevent recurrence of estrogen receptor-positive breast cancer in post-menopausal women.

Tamoxifen (Nolvadex, Istubal, Valodex) is an antagonist of estrogen receptors in breast tissue and is an agonist in the endometrium. It is used as a form of anti-estrogen therapy for breast cancer because some forms of breast cancer cells require estrogen to grow. Tamoxifen is an estrogen receptor agonist in bone and therefore inhibits osteoclasts. As a result, tamoxifen prevents osteoporosis.

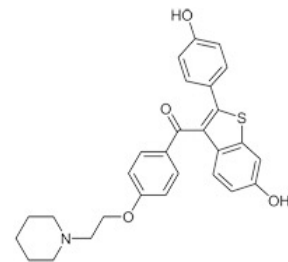


One of the most serious side effects of tamoxifen use

is uterine cancer due to its estrogen receptor agonist actions in the uterus. Tamoxifen may also cause cataracts.

Tamoxifen is estrogenic in the uterus
Raloxifene is anti-estrogenic in the uterus

Raloxifene (Evista) is often used in the treatment of breast cancer instead of tamoxifen because it has a lower rate of causing uterine cancer. Raloxifene is an oral selective estrogen receptor modulator that exerts anti-estrogenic actions in the breast and uterus but has estrogenic actions in bone. Therefore, raloxifene prevents osteoporosis but runs a lower risk of contributing to uterine cancer than tamoxifen. Raloxifene is contraindicated for pregnant women and may cause deep venous thrombosis and pulmonary embolism.



Aromatase inhibitors (AI) are often used to treat breast cancer and ovarian cancer in post-menopausal women. AIs block the synthesis of estrogen by inhibiting aromatase which is the enzyme which converts androgens into estrogens. Estrogen is largely produced in the ovaries in pre-menopausal women but is largely produced in the adrenal gland from the conversion of androgens in post-menopausal women.

Herb

Ren Shen (Radix Ginseng) strengthens the source Qi and calms the Shen. Ren Shen enhances the immune system and strengthens patients undergoing chemotherapy who suffer from leukopenia. It is

used to strengthen the patient so that they may endure the chemotherapy.

Ren Shen is known to be an immunostimulant and raises the total count of IgM. IgM (Immunoglobulin M) is an antibody and appears early in response to infections. Antibodies are produced by the immune system when foreign antigens are introduced into the body. The antibodies kill or neutralize the antigen.

Shu Di Huang (Radix Rehmanniae Glutinosae Conquिताe) and **Sheng Di Huang** (Radix Rehmanniae Glutinosae) nourish the blood, Yin and Jing. Shu Di Huang is stronger at nourishing. Shen Di Huang cools the heat in the blood. Sheng Di Huang increases levels of adrenocortical hormone which may be partially responsible for its anti-inflammatory effects.

Dang Gui (Radix Angelicae Sinensis) promotes blood circulation and nourishes the blood. Combined with **Huang Qi** (Radix Astragali), it helps to raise the RBC (red blood cell) and WBC (white blood cell) counts in patients undergoing chemotherapy.

Lu Rong (Cornu Cervi Parvum) strengthens the Kidney Yang and Jing. Lu Rong increases levels of RBCs when used for a long duration.

Ge Jie (Gecko) warms the Kidney Yang and nourishes Kidney Jing. Ge Jie increases levels of adrenocortical hormone and white blood cells. Ge Jie increases the phagocytic activity of macrophages.

Suo Yang (Herba Cynomorii Songarici) warms the Kidney Yang and restrains the Kidney Yang and Qi.

Yin Yang Huo (Herba Epimedii) and **Bai Ji Tian** (Rhizoma Bletillae Striatae) warm the Kidney Yang and expel wind damp Bi pain. Yin Yang Huo tends to increase libido. Bai Ji Tian has a slower effective action and is maintained in the bloodstream longer.

Bu Gu Zhi (Fructus Psoraleae Corylifoliae) warms the Kidney and Spleen Yang and strengthens the bone marrow.

Xian Mao (Rhizoma Curculiginis Orchiodis) warms the Kidney Yang and penetrates through the channels.

Gou Ji (Rhizoma Cibotii Barometz) warms the Kidney Yang and expels wind damp Bi pain, especially in the spine.

Xu Duan (Radix Dipsaci Asperi) warms the Kidney and promotes blood and menstruation. Xu Duan strengthens the Yang, tonifies the Liver and Kidneys, benefits the tendons and bones, calms the fetus, and promotes blood circulation.

Gu Sui Bu (Rhizoma Drynariae) warms the Kidney Yang and heals bone fractures.

Case I

A 53 year old patient has breast cancer and had surgery. She is taking an **aromatase inhibitor (Arimidex)**. She was complaining of fatigue, cold hands and feet, and her eye lids were pale. Her tongue is purple with white coating and the pulse is weak and empty.

Diagnosis:

Liver blood deficiency

Qi and blood stagnation

The patient took **Xue Ge Gao** (Oviductus Ranae from Rana Chensinesis) which are dried asiatic frogs' fallopian tubes. It is often made into sweet soups which are served as desserts in parts of China. The Xue Ge Gao lubricates Kidney Yin and the patient consumed it for several months. Although the patient felt less dry and depleted, it raised her estrogen levels slightly. Therefore, use with caution and monitor estrogen levels carefully.

Case II

A 45 year old cancer patient is taking **Arimidex** and is suffering from fatigue, loose stools, low appetite, and palpitations. She has a teeth-marked tongue and a weak pulse.

Diagnosis:
Spleen and Heart Qi deficiency

The patient was given **Ren Shen** (Radix Ginseng) for one month and there was no more loose stool, fatigue, or palpitations. Her estrogen levels were checked regularly and did not rise due to Ren Shen use. The patient had Spleen Qi deficiency so **Ren Shen** was indicated to strengthen Qi and balance general health. However, as with all tonics, it was important to monitor the patient's estrogen levels to ensure that the herbs did not raise them.



Sheng Di Huang

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