

Considerations on Checking Chinese Herb-Drug Interactions

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1. Introduction

It is not unusual for a patient to seek herbal treatments while taking several prescription medications. According to a study in 1998 in the United States, botanical products are now a \$1.5 billion per year industry. It is estimated that 60% to 70% of the American population is taking botanical products, but less than one third of these persons inform their medical practitioners of such use ⁽¹⁾. According to Barnes' study, the 10 most commonly used CAM therapies during the past 12 months were use of prayer specifically for one's own health (43.0%), prayer by others for one's own health (24.4%), natural products (18.9%), deep breathing exercises (11.6%), participation in prayer group for one's own health (9.6%), meditation (7.6%), chiropractic care (7.5%), yoga (5.1%), massage (5.0%), and diet-based therapies (3.5%) ⁽²⁾.

In China Chinese herbs are very often prescribed together with conventional drugs. A survey done by Beijing Hospital of Chinese Medicine indicated that 57.34% of patients who are treated with conventional drugs are taking Chinese herbs simultaneously ⁽³⁾.

The clinical experience in China showed that combination of Chinese and western medicines is clinically safe and therapeutically desirable. The advantages of combining Chinese herbs and drugs include better therapeutic results than both

alone, lower doses of the drugs required, and fewer side effects of drugs due to a lower dose and herbal actions on counteracting the side effects of drugs ⁽⁴⁾. There is very few serious interaction reported. The most serious interaction that causes the death of a patient has never been reported. In one study on the safety of Chinese herbs the authors analyzed 484 deaths related to the use of Chinese herbs from 1950 to 1990 in China which involved 61 single herbs, 12 complex herbal formulas and 13 herbal extract injections.

All deaths have been caused by the toxicity due to unsupervised over dosages ⁽⁵⁾. However with so many patients are treated with conventional drugs and Chinese herbs together, the safety concern raised in general public and other health care providers. There are only a few studies published in English to document the safety and effectiveness of combining Chinese herbs with prescription drugs. Hospitals and pharmacies in western countries often rely on one of several popular databases to check herbs-drugs interaction, including Chinese herbs. However the information is often complicated and may sometimes give unnecessary cautions or warnings.

We believed with some general insights in pharmacology of conventional drugs and Chinese herbs; one can foresee possible significant interactions and thus take precautions to avoid incompatibilities and serious result.

1.1 Definition of herb-drug interactions

A possible interaction refers to the possibility that one substance may alter the bioavailability or the clinical effectiveness of another substance when two or more substances are given concurrently. The interaction may result in an increase or a decrease in effect of one (drug or herb) or both substances. Herb-drug interactions may be classified in two major categories: pharmacokinetic and pharmacodynamic

interactions. This paper focuses primarily on the alteration of bioavailability or clinical effectiveness of drugs due to concomitant use of Chinese herbs, although there may be cases of the alteration of bioavailability or clinical effectiveness of herbs due to concomitant use of drugs.

Many known drug-drug interactions are documented through actual cases, some, through laboratory experiments of pharmacokinetic studies. However many herb-drug interactions discussed are theoretical or documented through laboratory experiments. Therefore, professional judgment is often necessary when evaluating the clinical significance of a potential herb-drug interaction.

1.2 Clinically-significant interactions

Herb-drug interactions demonstrated through clinical trials, pharmacokinetic studies, or documented case reports involving specific herbs (supplements) and drugs are usually clinically significant.

Clinically significant interactions also include interactions of high risk that may result in an immediate, life-threatening adverse event even if their supporting data is not obtained through the above mentioned sources. These include interactions occurring between herbs and drugs that have sympathomimic effects, cardiovascular effects, diuretic effects, anticoagulant effects, anti-diabetic effects, antidepressant effect, anticonvulsant effects, or antipsychotic effects, interactions that may have a major impact to a patient's health and life, e.g., carcinogenic effects or failure of contraceptive pills. All potential high risk interactions should be monitored very carefully.

1.3 Definition of pharmacokinetic interactions

It refers to the fluctuation in bioavailability of herb-drug molecules in the body as a result of changes in absorption, distribution, metabolism and elimination.

1.4 Definition of pharmacodynamic interactions

Pharmacodynamic refers to the study the physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

Pharmacodynamic interactions refer to the fluctuation in bioavailability of ingested substances as a result of synergistic or antagonistic interactions between herb/drug molecules.

1. Pharmacokinetic interactions

2.1 Absorption

- If taken orally the majority of all absorption occurs in the intestines, where herbs or drugs must pass through the intestinal wall to enter the blood.
- Several mechanisms may interfere with the absorption of drugs through the intestines, e.g., acidity, gastro-intestine motility, binding substance and the intestinal flora.
- Most of the interactions due to change in drug or herb absorption may be minimized if the drugs and the herbs are taken separately by approximately two hours or longer, except that due to intestinal flora.

2.1.1 Change of absorption due to change of acidity

The absorption of drugs that are sensitive to pH value may be adversely affected by herbs that may change the gastrointestinal acidity.

– Antacid herbs may increase the pH value of gastric juice. These herbs include Hai Gai Ke (clam shell), Hai Piao Xiao (cuttlefish bone), Mu Li (oyster shell), and Long Gu (dragon bone). Antacid herbs should not be used together with acid drugs such as Nitrofurantoin, 4-Aminosalicylic acid, aspirin, indomethacin, penicillin, Iodide, barbitol, Phenytoin Sodium, and Tetracycline. The gastric absorption of mentioned drugs may be decreased.

– Some herbs may increase the acidity and they are often high in organic acids. They include Shan Zhu Yu, Nu Zhe Zi, Jin Yin Zi, Fu Peng Zi, Qing Pi, Chen Pi, Wu Wei Zi, Wu Bei Zi, Bao Shao Yao, Jin Ying Hua, Wu Mei, Shan Za, Zhi Shi, Zhi Ke, and Mu Gua. Herbs that increase acidity should not be used together with antacid drugs.

2.1.2 Change of GI Motility

Chinese herbs that change of GI Motility may affect absorption of some drugs. Chinese herbs that slower GI motility may not significantly increase the absorption of drugs, Chinese herbs that promote peristalsis may significantly decrease the absorption of many drugs. These herbs include all herbs that purge (e.g., Da Huang, Fan Xie Ye, and etc.), and some herbs that promote digestion (e.g., Shan Zha, Lai Fu Zi, Ji Nei Jin, and etc).

2.1.3 Change of drug absorption due to the binding effect of herbs

Herbs that may interfere drug absorption due to their binding

effects include:

- Some gelatin products, e.g., E Jiao, Lu Jiao Jiao, Bie Jia and Gui Ban Jiao;
- Herbs that contain high in flavones which may be bound with drugs such as calcium carbonate, iron preparations, aluminums hydroxynate.
- Herbs that contain metal ions may cause binding problems: e.g., Hua Shi , Yang Qi Shi, and Hu Po (Magnesium), Ming Fan, Chi Shi Zhi (Aluminums), Dai Zhe Shi, Yang Qi Shi, Yu Yu Lian, Zhi Ran Tong, and Chi Shi (Iron)
- Herbs that contain tannins including: Di Yu, Wu Bei Zi, Hu Zhang, He Zi, Bian Xu, Da Huang, Shi Liu Pi, Huang Yao Zi, Jin Qian Cao, and Mu Gua. These tannin-containing herbs should not be used orally together with:
 - Enzymes such as, trypsin and pepsin
 - Drugs with metal ions such as Zn, Fe, or Calcium
 - Cardiac glycoside such as digoxin, digitalis to form salt products
 - Drugs with amidopyrine;
 - Vitamins B1 and B6
 - Any product with NaHCO₃
- 2. Some antibiotics such as tetracycline, sulfanilamide, erythromycin, chloramphenicol and rifampicin.

2.1.4 Change of drug absorption due to the effect of herb or drug's effect on intestinal flora

Alternation of bowel flora (e.g., by concomitant use of

antibiotics) by Chinese herbs can interrupt enterohepatic recycle and result in decrease of activity of some drugs (e.g., the oestrogen contraceptive pill), or increase of activity of some drugs (e.g., digoxin). Chinese herbs that have antibiotic effect are usually in the category of heat-clearing and detoxifying. Herbs such as Huang Lian, Huang Bai, Zhi Zi, and Ku Shen are high in berberine. They should be monitored carefully when used together with drugs whose intestinal absorption is related to the intestinal flora.

2.2 Distribution

Distribution refers to the process in which herbs or drugs are carried and released to different parts of the body. Protein binding is by far the biggest factor when determining interactions. Theoretically drugs or herbs with active ingredients that are highly protein bound are very susceptible to interactions. Serious interactions occur during the distribution phase if the drug has a narrow range of safety index and is highly protein-bound. For example, Coumadin (warfarin) is an anticoagulant medication that is very highly bound to protein and has a very narrow range of safety index. Other drugs that are highly protein bound include phenytoin, oral contraceptive pills and some NSAIDs. There is not much information about the protein binding of chemical components from herbs. The best precautionary measure is to monitor of medications on clinical observations of therapeutic effects and tolerability.

2.3 Metabolism

Drug metabolism is biochemical modification or degradation of the drugs, usually through specialized enzymatic systems. Drug metabolism often converts lipophilic chemical compounds into more readily excreted polar products. Its rate is an important

determinant of the duration and intensity of the pharmacological action of drugs and herbs.

Most herbs and drugs are metabolized by the liver. Metabolism, or biotransformation of substances, has a large potential for interactions. One of the biggest targets of interactions within the realm of metabolism is the cytochrome P450 (CYP) system. The most common reaction catalysed by CYP450 is a monooxygenase reaction.

Human CYPs are primarily membrane-associated proteins, located either in the inner membrane of mitochondria or in the endoplasmic reticulum of cells. CYPs metabolize thousands of endogenous and exogenous compounds. Most CYPs can metabolize multiple substrates, and many can catalyze multiple reactions, which accounts for their central importance in metabolizing the extremely large number of endogenous and exogenous molecules. Hepatic cytochromes P450 are the most widely studied.

Major human CYP isoforms in drug metabolism include CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5 and 3A7 ^(6, 7). The followings are some terms related to the discussion of CYP450 system and drug metabolism:

1. **Isoforms of CYP450**: Different subtypes of enzymes.
2. **Substrates**: In biochemistry, a substrate (a drug) is a molecule upon which an enzyme acts. The herb metabolism is not fully understood. Therefore the information on the herb as a substrate is very limited.
3. **Inhibitors**: A substance (a drug or herb) that decreases the enzyme's activity. Inhibitors affect the optimal level of metabolism of the substrate drug and the individual's response to that particular medication.
4. **Inducers**: A molecule (a drug or herb) that starts expression of the gene that encodes the enzyme.

The commonly used Chinese herbs that are identified as the

inhibitor or inducer of a CYP 450 isoform have been summarized in the following table. When a Chinese herb acts as an inhibitor, it will inhibit the activity of the affected CYP450 isoform and may decrease the metabolism of the drug on which the affected CYP450 isoform acts, thus may increase the bioavailability of the drug. When a Chinese herb acts as an inducer, it will increase the activity of the affected CYP450 isoform and may increase the metabolism of the drug on which the affected CYP450 isoform acts, thus may decrease the bioavailability of the drug.

Summary of CYP450 Isoforms and Herb-Drug Interactions

Note: If an herb is an inhibitor of an isoform, then the clinical effectiveness of the drug (substrate) metabolized by the isoform may increase due to the inhibited isoform activity and decreased decomposition of the drug in the body. The majority of current studies were performed in-vitro system. The results could be questionable. Results from in vivo studies and clinical trials would provide stronger evidence and better advice for treating patients with both drugs and herbs simultaneously.

Furanocoumarins are the active ingredient in grapefruit juice (GFJ) inhibiting intestinal CYP3A4 and thereby increasing the passage of drugs, such as felodipine, with extensive intestinal first-pass metabolism ⁽²⁹⁾. Chinese herbs that contain furanocoumarins include Qian Hu, Dang Gui, Chai Hu, Fang Feng, Du Huo, etc. Of them the inhibitory effect of Qian Hu on CYP1A1, 2E, 2C11, 2B, and the inhibitory effect of Bai Zhi on CYP2C, 3A, 2D1 have been confirmed ^(26,27). Although the effect of other herbs on CYP have not been confirmed in clinical or laboratory studies it may be advisable not to use these herbs together with drugs which are known substrates of

affected isoenzymes.

2.4 Elimination

Factors that affect the GI elimination of herbs or drugs include GI motility and intestinal flora. GI motility is the primary factor in this regard.

Kidney elimination is another important factor of herb or drug excretion. Theoretically any substance that may change any of above factors may interfere the clearance of other substance (drugs or herbs) from the kidney. It depends on health of the kidneys, organ maturity, volume of distribution, perfusion of the kidneys and urinary pH.

In patients with impaired kidney function, the rate of elimination by the kidneys would be significantly slow down leading to an accumulation of herbs and drugs in the body. As a safety precaution, it may be necessary to lower the dose of herbs to avoid unnecessary and unwanted side-effects in following patients.

- Patients on dialysis
- Patients with transplant of kidney
- Patients taking some drugs that damage the kidneys such as amphotericin B, methotrexate, tobramycin and gentimicin.

The elimination of some drugs from kidneys is also associated with pH value of urine. There is no any clinical report about the association between urine acidity changes due to herbal use and changes of drug elimination and renal re-absorption. Generally when urine is acidic, weak acid drugs tend to be reabsorbed. Alternatively when urine is more alkaline, weak bases are more extensively. The renal clearance of drugs such as NSAIDs (pKa3-8) and morphine analogs and tricyclic antidepressants (pKa 6-12) is often dependent on urine pH.

The first group is the herbs that may decrease the acidity of urine. They include Hai Gai Ke (clam shell), Hai Piao Xiao (cuttlefish bone), Mu Li (oyster shell), and Long Gu (dragon bone). The renal re-absorption of some drugs may be increased in the alkalized urine, which may theoretically increase the risk of overdose toxicity. Alkaline urine (pH >6.0) increases crystal precipitation within tubular lumens from drugs such as indinavir, oral sodium phosphate solution, and ciprofloxacin^(30,31,32). The above mentioned herbs should not be used together with these drugs.

The second group of herbs may increase the urine acidity and they are often high in organic acids. They include Shan Zhu Yu, Nu Zhe Zi, Jin Yin Zi, Fu Peng Zi, Qing Pi, Chen Pi, Wu Wei Zi, Wu Bei Zi, Bao Shao Yao, Jin Ying Hua, Wu Mei, Shan Za, Zhi Shi, Zhi Ke, and Mu Gua. For example, acidic urinary pH (<5.5) increases crystal deposition with drugs such as sulfadiazine, methotrexate, and triamterene that are insoluble in a low pH environment^(30,31). These acidity-increasing herbs should not be used together with these drugs. The increased crystal deposition due to decreased pH of urine (acidic urine) may theoretically cause the damage of epithelium cells in urinary system, and causes the crystals in urine and hematuria.

Theoretically these acidity-increasing herbs should not be used together with aminoglycosides antibiotics such as streptomycin, neomycin, kanamycin, gentamicin, or other antibiotics such as lincomycin, clindamycin, and Polymyxin B. When these antibiotics are used to treat urinary infections, the antibiotic effect of these drugs may be decreased in an acidic urine environment (decreased pH).^(33,34)

Herbs that drain the dampness usually have diuretic effect; theoretically they may hasten renal clearance of the drugs.

3. Pharmacodynamic Interactions

The best way to prevent pharmacodynamic interactions is to exam the patient closely and to monitor all clinical responses including signs, symptoms and any abnormal reactions. Examples of pharmacodynamic interaction include additive and antagonistic interactions. Pharmacodynamic types of herb-drug interactions are best identified by analyzing the therapeutic effect of the herbs and drugs. Concomitant use of herbs and drugs with similar therapeutic actions will undoubtedly pose potential risk of herb-to-drug interactions. The increase in treatment effect interferes with optimal treatment outcome as the desired effect becomes more unpredictable and harder to obtain with precision. The highest risk of clinically-significant interactions occurs between herbs and drugs that have sympathomimic effects, cardiovascular effects, diuretic effects, anticoagulant effects, anti-diabetic effects, antidepressant effect, anticonvulsant effects, or antipsychotic effects. The results of these clinically significant interactions may be lethal, e.g., stroke, heart arrest due to serious arrhythmia, heart attack, serious bleeding, serious hypoglycemia or hyperglycemia, seizure, serious depression attack (suicide), etc. The following herbs and their interactions with drugs should be monitored more closely.

1 Herbs with aristolochic acid are banned in most countries due to their potentially nephrotoxicity.

2 Herbs that have the effect of blood thinning should be avoided in patients who are also treated with blood thinning drugs such as aspirin, Coumadin, heparin, and plavix. These herbs include: Zi Cao, Yin Xing, Shui Zhi, Dan Shen, Chi Shao Yao, Dang Gui, Ji Xue Teng, Chuan Xiong, Hong Hua, Yi Mu Cao, Yan Hu Suo, Wu Ling Zhi, and San Leng. When a patient is using regular blood thinning drug(s), the above mentioned herbs should be avoided.

3 Herbs that may increase the blood pressure should be avoided in patients who are treated with drugs that lower blood pressure. Herbs that may increase blood pressure include Fu Zi, Ma Huang, Kuan Dong Hua, Qin Pi, Ren Shen, Se Xiang, Zhi Shi and Gan Cao (especially in higher dosage). Those herbs should be avoided in all hypertensive patients. There is no much concern on herbs that lower the blood pressure such as Che Qian Zi, Da Ji, Di Gu Pi, Di Long, Du Zhong, Gou Teng, Huai Hua, Huang Lian, Ju Hua, Jue Ming Zi, Shan Zha, Xi Xian Cao, Xia Ku Cao, Xuan Shen, Yin Yang Huo, and Ze Xie. Monitor the blood pressure carefully when those herbs are used in patients who are treated with anti-hypertension drugs.

4 Some herbs may have estrogen-like effect. They should be used very cautiously in patients diagnosed with gynecological cancers, such as breast cancer, uterine cancer and ovarian cancer. According to studies in mice, it has been discovered that Bu Gu Zhi, Yin Yang Huo, Rou Cong Rong, Tu Si Zi, Dong Cong Xia Cao, Nu Zhen Zi, Gou Qi Zi, Dan Shen, Niu Xi, Bai Guo, Xiao Hui Xiang, She Chuang Zi, Bai Ji Li, Ge Gen, Xiang Fu and Sheng Ma have estrogen-like effects. ^(35,36)

⁵ Many herbs contain polysaccharides. The mechanism of digestion and actions of polysaccharides in Chinese herbs are not well understood. Currently there is no evidence indicating that polysaccharides in Chinese herbs will increase patients' blood sugars dramatically like other simple sugars. Herbs that lower blood sugar should be used carefully in diabetic patients who are using anti-diabetic drugs. The synergetic hypoglycemic effect of herbs and drugs may cause a serious result of low blood sugar. Pharmacological studies suggest that the following herbs may lower blood sugar in diabetic patients: Huang Jing, Huang Lian, Bai Jiang Can, Nu Zhen Zi, Huang Qi, Dan Shen, Gou Qi Zi, Sheng Di Huang, Yu Mi Xu (corn silk), Zhi Mu, Chi Shao Yao, Dang Gui, and Ge Gen. In Chinese hospitals those herbs are used often in diabetic patients who are also taking diabetic drugs. No serious hypoglycemic result

has been reported. However we still recommend more frequently and careful monitoring of patients blood sugars to prevent the hypoglycemia.

Several steps of checking and handling herb-to-drug interactions:

- 1 Establish a complete pharmaceutical and neutraceutical list of the patient;
- 2 Understand the pharmaceutical and neutraceutical products used by the patient;
- 3 Draft herbal prescription and research each Chinese herb in your formula, or check the ingredients in the patent products;
- 4 Understand the Chinese herbal medicines (both their traditional properties and application and their chemical, pharmaceutical and pharmacologic studies);
- 5 Research and evaluate any known potential pharmacokinetic and pharmacodynamic herb-drug interactions;
- 6 Evaluate the potential severity and level of evidence of an interaction by using the ratings, such as those included in Natural Medicines Comprehensive Database (insignificant, mild, moderate and high);
- 7 Adjust herbal formula by using substitute herb(s) or deleting the suspected herb(s) that are known to cause clinically significant interactions;
- 8 Monitor the patient closely when potential herb-drug interactions are not clinically significant or very mild (blood drug concentration may be affected, but a clinical significant interaction is not likely, or the interaction may cause only mild impairment or mild discomfort); and

9 Adjust formula further if necessary.

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