THE INTERACTIONS OF HERBS AND DRUGS

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BACKGROUND

Until about 150 years ago, all medicines were derived from natural materials (1). Most of those early medicines are described under the broad heading "herbs," although that term may prove misleading. Even though people often think of herbs as plants or plant-derived materials, several commonly used items were obtained from animals and minerals. Further, although the term "herbs" suggests something that is beneficial and has little potential for harm, numerous toxic materials were used, such as foxglove, deadly nightshade, and jimson weed (datura). Herbalists sometimes processed the herbs to change them from their original form (2), and even isolated some active constituents, so that the end products were not as nature presented them. For example, aconite was processed extensively in China to reduce its toxicity so that it could more readily be used, and borneol, the active constituent found in a few tropical plants, was isolated centuries ago in relatively pure form, a translucent crystal, for both internal and external use. The use of potent and toxic substances and the intentional alteration of natural substances are characteristics of production of modern drugs. Thus, some issues that arise today about interactions of herbs and drugs may have already been encountered in earlier times when herbs were combined with each other.

In the formative period of traditional Chinese medicine, some concerns were raised about the intermixing of herbs (3). This could be considered the genesis of cautions about drug interactions (using the term "drug" here for medicines in general). In traditional herb pharmacies in China there is posted an ancient recitation of "18 incompatibles," namely three herbs (aconite, licorice, and veratrum) with 4–6 other specified drugs for each that are not to be combined because, according to this doctrine, their mixture would cause adverse effects. There is also a standard listing of "19 antagonistic drugs," namely, ten herbs that each impair the efficacy of one specified herb (with two types of aconite antagonizing rhino horn, to yield 19 items rather than 20). Some herbs were reported to interact with others in a beneficial way, such as by reducing the toxicity or other adverse effects that might be experienced (see Table 1).

Table 1: Chinese Herbal Concept of Interaction of Drugs. The common term used for interaction is *xiang*, literally, mutual or reciprocal action (that is, the drugs act upon one another).

Type of Interaction	Examples
Xiangfan (incompatibility): yields toxic reaction or side effects.	Raw aconite is incompatible with raw pinellia; licorice is incompatible with sargassum; veratrum is incompatible with scrophularia.
Xiangwu (antagonism): reducing the desired effect of one drug by combining with another drug.	Raphanus inhibits the action of ginseng; ginseng inhibits the action of pteropus; clove inhibits the action of curcuma.
Xiangsha (detoxification) or *Xiangwei* (inhibition): one drug reduces the toxicity or side effects of another.	Fresh ginger and alum each reduce the toxicity of pinellia and arisaema.

Xiangshi (enhancement): one drug enhances the effect of the other.	An herb that tonifies the spleen, when combined with an herb that is diuretic will enhance the diuretic action.
Xiangxu (synergism): drugs of similar nature reinforce each other's effects.	Rhubarb and mirabilitum are each purgatives that produce a more reliable and stronger purgative action when used together.

Isolated pharmaceutical drugs, in a form similar to those we rely on today, were first produced in Europe about 150 years ago. Except for the potent analgesics (e.g., morphine, cocaine) that were introduced first, pharmaceuticals only became a major force in medical practice during the past century. For the most part, these new drugs were viewed as direct replacements for herbs. Thus, rather than using willow bark or some other herb reputed to be helpful for arthritis, one would use the new drug aspirin. This chemical is derived from salicylic acid (similar to the salicin found in willow bark) by a simple transformation to yield acetylsalicylic acid (this form is less irritating to the stomach than salicylic acid).

Salicylic acid was obtained for drug manufacture from *Spiraea* plants (such as the European herb meadowsweet: *Spiraea ulmaria*), rather than willow bark, and given the common name spiric acid ("aspirin" came from *a*cetyl-*spiri*c-acid). Although acetylsalicylic acid was discovered in 1845, it was not marketed as a drug until 1900. In the interim, numerous "patent medicines," mostly fraudulent products made with alcohol and some herbal flavorings, were sold to the public as remedies for numerous ailments. When finally marketed, aspirin simply replaced any traditional herb or herbal combination or patent remedy that was used for the same purposes (e.g., alleviating pain, inflammation, and fever). The replacement took place almost everywhere in the world, including countries with well-established traditional medical systems, such as China and India, which simply produced their own aspirin rather than importing it. Aspirin became the most widely used drug in the world.

The transition from herbs to drugs was accelerated by the two World Wars that interrupted the international trade in herbs, making local manufacture of synthetics appear particularly attractive. The period from 1945 through 1975 was one of rapid development for advanced chemical technologies; there was an intensive effort made to produce new synthetic drugs, with the result that the majority of natural products declined in use. Although there are still about 25% of drugs that owe their active ingredients to plant materials in some way (a figure often cited by herb proponents to illustrate the value of herbs), increasingly, the relationship is remote: the drugs may have started out as isolates from herbs (or modified isolates, as with aspirin) but then became synthetic compounds. By 1975, the reliance on herbs in developed countries had declined to its lowest level. The development of new synthetic drugs continued.

The move from natural source to synthetic drugs was not necessarily any reflection of anti-herb bias by the medical profession or pharmaceutical manufacturers. Even the relatively new drug Taxol was originally extracted from yew trees. It was found in very minute quantities in the bark. The demand for Taxol (a drug widely used for treating breast and ovarian cancers, and increasingly tried for other cancers) grew so rapidly that the yew forests would have been decimated by now if it weren't for the development of a synthetic version, which was a very difficult process due to the complexity of the

molecule. Had Taxol been derived from an easily cultivated and renewable natural resource, the natural product would have been used instead.

Many whole herbs have remained in the Pharmacopoeias of nations that now rely on modern medicine, but the difficulties in procuring and handling the high-quality herbal materials has led to replacements by isolates and synthetics. Within the context of using intensively regulated, pure chemical drugs, medical doctors have correctly raised questions about the identity and variability of herbs that have been provided as alternatives without adequate clinical testing and without monitoring of adverse effects once on the market. On the other hand, herbs (as well as other natural healing approaches) were sometimes dismissed under the incorrect premise that modern medicine had already provided a satisfactory replacement for all the earlier health care practices that had been relied upon for centuries.

Beginning around 1975, and accelerating during the past few years, many people have turned to herbs. This often took the form of using beverage teas formulated so as to produce a good taste, and typically provided in convenient tea bags. However, as the popularity of herbs grew, a growing number of medicinal herbs have been sold in drug-like forms (capsules and tablets, increasingly with standardized or specified levels of one active ingredient). More people then turned to herbs in this drug-like form as an alternative to drugs (e.g., take echinacea instead of an antibiotic; take St. John's wort instead of an antidepressant). However, as the use of drugs has increased dramatically in recent years, especially among the elderly, herbs have been increasingly used *with* other drugs rather than in place of drugs, raising the concern about the interaction of herbs and drugs. From the perspective of the modern medical profession, if an herb or herbal mixture can have a therapeutic activity that is comparable to that of a drug, then it can interact with other drugs.

For the most part, the possibility of herb-drug interactions had been largely ignored during this revival of medicinal herb use. A strong impetus to look at the problem more closely came from the finding that grapefruit juice could impair drug metabolism and result in significant changes in the expected drug activity as a result. This observation, first published in 1989, did not come to public attention until several years later, when the use of herbs had become even more widespread. The question then immediately arises: if an ordinary food like grapefruit could cause this response, why not herbs? Among the other issues of herb-food interactions were these:

- it was recognized that certain foods interacted with a broad class of antidepressant drugs, making people wonder if it was safe to eat pizza while using the drugs (so, how safe could combining with herbs be?);
- it was noted that green vegetables could antagonize the effect of warfarin, the most commonly used blood thinner (many herbs appear no different than green vegetables);
- tetracycline absorption was markedly impaired by ingestion of milk or milk-based food products (perhaps herbs could impair the absorption of drugs as well).

During the past five years, a few herbs that had been widely popularized (partly because new labeling laws allowed medical use claims to accompany their sale), such as ginkgo, ginseng, and St. John's wort, were specifically cited as causing, or suspected of causing, interactions with drugs. The drugs of most concern for interactions with herbs were those that people took continuously, such as blood thinners prescribed after a heart attack or stroke, and antidepressants. However, interactions with anti-infection drugs, which might fail to work if their blood levels fell too low, could also present a

serious problem.

GRAPEFRUIT JUICE AND DRUGS

The discovery that grapefruit juice could alter drug metabolism was the serendipitous result of using the juice as part of a placebo preparation in a drug test conducted in Canada (4). The drug felodipine (vasodilator, diuretic; used for hypertension) was being evaluated for interactions with alcohol. Alcohol did affect the way the drug functioned, resulting in more side effects, mainly postural lightheadedness due to hypotension. The plasma concentrations of the drug in the placebo group that had received grapefruit juice rather than alcohol, were surprisingly high. The same researchers then performed a follow-up study (5) using either grapefruit juice or orange juice; the grapefruit juice increased the bioavailability of nifedipine (similar to felodipine; both are calcium antagonists) by an average of 284% (that is, there was nearly 3 times the amount in the blood of those who consumed grapefruit juice as those who consumed water). Orange juice had no such effect, indicating that it was a particular component of grapefruit juice that was responsible for this marked effect.

In the 10 years that followed, numerous drugs were found to respond the same way to grapefruit juice (100 medical journal articles around the world either described new findings of drug interaction or reviewed the growing number of cases). Adverse effects of combining grapefruit juice with drugs have been reported for calcium antagonists (used for lowering blood pressure), the benzodiazepines midazolam and triazolam (for depression), and terfenadine (antihistamine for allergies). The adverse effects are due to the greatly increased amount of drug in the bloodstream due to inhibited drug metabolism. The intentional combination of grapefruit juice and a lowered drug dose might yield a desired result of proper plasma levels of the drug with lower amounts ingested (hence, lower drug costs): this is an area of active research.

One of the main causative factors in the grapefruit juice effect on drug availability was identified as a group of furanocoumarins (6, 7) that inhibited a major drug metabolizing enzyme system, cytochrome P450 (known by the acronym CYP). In particular, CYP3A4 (3A4 gives the specific subtype) appears to be the enzyme most affected, though the entire CYP system is inhibited to some extent. CYP is mainly found in the small intestine and liver; it is believed that the major effect of grapefruit juice is to inhibit the small intestine CYP, thus preventing the drug from being metabolized before it enters the blood stream. In fact, the process has been described as more than simple inhibition: to a certain extent the enzyme is bound to the chemical compounds in the juice and washed away from the small intestine. Repeated administration of the juice increases its effect, rather than causing a rebound of enzyme levels (28). Thus far, the most potent of the CYP inhibitors found in grapefruit juice is bergamottin. This compound gets its name from its principal course, bergamot oil, the flavoring compound in Earl Gray Tea. Bergamottin, like the other furanocoumarins, is a photosensitizer.

Furanocoumarins (also called furocoumarins and sometimes designated psoralens, after one of the best known furanocoumarins) and compounds of similar structure are found in several Chinese herbs (see Table 2). Therefore, the use of the herbs with the same drugs that interact with grapefruit juice could produce the same results, at least if the herb dosage yields a similar amount of the enzyme-inhibiting compounds as grapefruit juice. Further, other substances in herbs (as yet unidentified) could inhibit the same or other drug metabolizing systems, thereby causing the increase in drug absorption. Previously, it had been thought that flavonoids (e.g., naringin) in grapefruit juice were

responsible for its action on drug levels; however, it was found that the flavonoids were not present in sufficient quantity to account for the effects noted. High levels of flavonoids are provided in some herbal remedies, and might, in such cases, account for significant inhibition of CYP.

Table 2: Commonly Used Chinese Herbs with Furanocoumarins.

Herbs	Furanocoumarins
citrus varieties, including citrus, blue citrus, chih-shih, chih-ko, citrus seed	Bergapten
Angelica species; including angelica, chiang-huo, tu-huo, tang-kuei	psoralen, xanthotoxin, imperatorin, bergapten, angelin, marmesin, oxypeucedanin, isopimpinellin, phellopterin, byakangelicin
cnidium fruit	bergapten, isopimpinellin, columbianetin, cnidiadin
psoralea	Psoralens

Some herbs can increase drug metabolism rather than decrease it, resulting in lower drug availability. This effect was recently discovered with the use of St. John's wort by patients with HIV infection (8). It was found that the use of this herb resulted in much lower levels of the protease inhibitor drug Indinavir, with the possible consequence that the drug combination would not work and that resistant strains of HIV would emerge. A warning was issued by several agencies involved with AIDS treatment. St. John's wort was also blamed for a sharp drop in cyclosporin availability (30); since this drug is used to prevent transplant rejection, a lowered blood level could lead to initiation of the rejection reaction, which may be difficult to reverse. On the other hand, the herb has also been reported to inhibit CYP3A4 (31), which could result in some drugs being made available to the blood at elevated levels.

FERMENTED FOODS AND MAO INHIBITORS

A broad class of antidepressant, anti-anxiety drugs are the monoamine oxidase inhibitors (MAOIs). These drugs reduce the activity of the enzyme (MAO) that breaks down neurotransmitters that are monoamines (have one amino group), such as serotonin, dopamine, and norepinephrine. Monoamine oxidase is found in the outer membranes of mitochondria. The monoamines are constantly produced, released, and then inactivated, and changes in the rates of any of these actions affects the levels of the compounds and their effects on the nervous system.

Two well-known effects of having low levels of monoamines are depression and hypertension. If MAO activity can be inhibited, then the levels of the monoamines will rise and the symptoms of deficiency are likely to be alleviated. MAO inhibitor drugs, such as phenelzine (Nardil), are used to treat certain types of depression, mainly "situational depression." However, such drugs are often reserved for use when others fail because of the potential side effects, including reduced sexual function, hypotension, fluid retention, and nervous agitation. These MAO inhibitor drugs are powerful, and they often interact with other drugs, especially others that have as a secondary effect, inhibition of MAO, thus increasing the level of serotonin and other monoamines to harmful levels. Not only can the side effects increase with

such drug interactions, but the patient can experience episodes of mania that may not have occurred prior to drug use. High levels of serotonin can have immediate effects and, if prolonged, might have permanent damaging effects on the heart and kidney.

It was noted early on that certain foods could interact with MAOIs and, as a result, doctors worked towards developing MAOI diets that would be safe to consume. The primary concern is tyramine, an amino acid that is found in relatively high amounts in fermented and aged foods (e.g., aged cheeses, aged or cured meats, sauerkraut, tap beer, and soy sauce and other aged soybean products). Tyramine, a monoamine, is broken down by MAO; the inhibitor drugs thus increase tyramine levels and catecholamines (part of the group of "stress hormones"), sometimes to the point that serious adverse effects occur, such as hypertensive crisis. The medical literature is full of reports claiming that MAOI diets often went too far (9), being overrestrictive and preventing people from using the drug that would be most effective for them. Avoiding pepperoni pizza with beer from the tap is a reasonable restriction, but there are very low levels of tyramine in many foods that were being restricted under some dietary recommendations. Still, the fears of interactions with MAOIs ran high as a result of the overly strict dietary concerns, and when people on these limited diets thought about or mentioned to their doctors the use of herbs, the question arose: do the herbs also interact? Among Western herbs, it has been suggested that Scotch broom (*Cytisus scoparius*) should be avoided with MAO inhibitors due to its content of tyramine.

More importantly, doctors ask if the herbs also inhibit MAO. In fact, one of the positive advantages of "antiaging" Chinese herbs is considered by Chinese researchers to be their MAOI activity. This is because there is an increase in MAO activity with aging, leading to a decrease of the neurotransmitters: the result is impaired mental functions. In mice, it was found that MAO activity of brain mitochondria was much higher in senile mice than in young mice, thus providing a model for studying the changes that take place in humans when herbs are consumed (10). The antiaging "Essence-Restoring Decoction" was shown (11) to lower the MAO levels in senile mice brain mitochondria: the formula is comprised of herbs such as raw rehmannia, astragalus seed, cynomorium, cuscuta, ho-shou-wu, dipsacus, achyranthes, ligustrum, and morus fruit. Fortunately, regular administration of the formula to persons over age 60 for a year produced none of the typical MAO inhibitor drug side effects, but instead alleviated problems of fatigue, low appetite, insomnia, and night time urination. Still, one doesn't know the potential for problems if the herbs are combined with powerful MAO inhibitor drugs.

In another study (12), brain MAO activity of six month old mice was decreased by 50% and liver MAO activity decreased by 20% when oral administration of another essence nourishing formula was given for 90 days. The ingredients included astragalus, lycium, morus fruit, hoelen, euryale, codonopsis, polygonatum, ho-shou-wu, atractylodes, yu-chu, schizandra, placenta, rehmannia, cuscuta, mume, ophiopogon, lotus seed, salvia, biota, cornus, licorice, dioscorea, and longan. Herbs that are considered to have mental-rejuvenating properties were evaluated in a study (13) at Beijing University on mouse brain MAO. The strongest response was obtained from pantocrine (extract of deer antler) and processed ho-shou-wu (*zhishouwu*). These two substances yielded an 80% reduction of MAO activity. Crataegus, ginseng, polygonum, salvia, astragalus, and epimedium reduced MAO activity by 50%. Ganoderma, a famous longevity tonic, did not inhibit MAO. Ho-shou-wu was further studied in mouse liver and brain tissue (14): it was shown to inhibit activity of MAO in both organs and increase the content of monoamines in the brain. Such effects are more notable in old mice (which have higher

MAO activity) than in young mice.

A formula used in treatment of neurological and psychiatric diseases that is not classified as an essence tonic, Minor Bupleurum Combination, was tested on MAO of rat liver mitochondria (15). Not only did it inhibit MAO, but each of its ingredients used individually also inhibited MAO, with the highest activity in licorice, pinellia, bupleurum, and codonopsis. This formula was suggested to have interactions with interferon in persons treated for hepatitis C who have severe liver cirrhosis (see: *Update on hepatitis C treatments*).

As with the foods, the potential for the herbs to cause an unfavorable interaction with MAOI drugs is based on their dosage: if the amount is high enough, a reaction might occur; in lower dosage, no significant reaction is expected. One doesn't know, without extensive research, what dosage is necessary to cause a problem.

TETRACYCLINE AND MILK

Tetracycline is the most commonly used of a group of related antibiotic drugs that are labeled -cyclines. The significant inhibition (50–90%) of absorption of tetracycline by consuming milk was reported in 1976 (25). Patients were advised to avoid drinking milk within 3 hours of tetracycline ingestion. Because this drug is so widely used, the interaction with milk became one of the most widely cited cases of food-drug interactions.

However, few people outside the pharmaceutical field realize that the absorption problem of these cycline drugs with milk is actually a reflection of the drug's binding with polyvalent metals (that is, those that normally lose more than one electron to form an ion). The interaction with milk, in fact, is an interaction with calcium (Ca++) in the milk. The same type of interaction occurs with iron (Fe++), magnesium (Mg++), zinc (Zn++), and aluminum (Al++). The cycline antibiotic complexes with the mineral and becomes an insoluble salt that is not absorbed (26). The mycin antibiotics (such as kanamycin and neomycin) also form salts with polyvalent metals. Antacid preparations contain these metals, and are contraindicated when taking the antibiotics.

Inhibition of the drug's absorption can also occur when taking nutritional supplements that provide minerals (iron has a somewhat stronger effect than calcium) and, potentially, with any mineral rich food or herb. Chinese herbal formulas may be made with calcium-rich materials such as oyster shell, dragon bone, gypsum, haliotis, and mother of pearl. Oysters (the meaty portion) are rich in zinc; dried figs are rich in calcium; and raisins are rich in iron, and iron is a dominant component of the Chinese mineral compounds lapis, hematite, and magnetite. Laxative and mass-resolving Chinese herb formulas containing mirabilitum will provide considerable amounts of magnesium.

Fortunately, there are relatively few other drugs that are as sensitive to mineral chelation as the cycline antibiotics. However, similar concerns have been raised about substances other than metals binding up drugs that are administered in close temporal proximity and rendering the drugs unabsorbable. The main items mentioned are fiber (in foods and in supplements that are intended to provide fiber to promote a laxative effect), pectin (found in some fruits, such as apples and citrus, and added to some supplements to "bind toxins"), and tannins (found in tea and in astringent herbs). These substances have broad-spectrum binding actions, but the extent of binding that actually occurs depends mostly on the specifics of the drug and the binding agent. Thus, for example, tannins are particularly good at binding alkaloid drugs and

certain antibiotics; tannin-containing herbs include ilex, rosa, cynamorium, hu-chang, polygonum, gall, sanguisorba, terminallia, and pomegranate rind.

Ginger, used in Chinese and Western medicine to treat nausea, is postulated to have, as part of its action, the binding and inactivation of substances in the stomach that cause nausea. By this same mechanism, ginger might bind drugs (reducing their nauseant effect but, potentially, reducing their absorption as well). Recently, phytic acid, a significant component of corn that is also present in other grains and in some legumes, was promoted as a cancer inhibitor (under the name IP-6; see: *Questionable cancer therapies*). This substances is well-known as a chelator of minerals, and might also bind up drugs; phytic acid is one of the major binding agents in fiber.

Therefore, when drug absorption is considered a critical matter, such as cases where a suboptimal dose of the drug has the potential to significantly influence the outcome of a disease, the drug should not be taken along with meals, nutritional supplements, or herbs. There are some exceptions, such as when small amounts of food are considered protective against irritant actions of the drug, or when there are specific foods are known to improve absorption of the drug (for example, a small amount of fatty food may enhance absorption of a drug that disperses more easily in fats). Although a 3-hour difference between the time of taking the drug and ingesting the other substances (as suggested for tetracycline and polyvalent metals) may be overly cautious, a period of at least one hour, and preferably one and a half hours, would be prudent (generally, a drug is fully absorbed during the first hour to hour and a half, and a meal is also digested in that time).

BLOOD THINNERS AND GREEN VEGETABLES

During the past decade, it has become standard procedure to place patients who have survived a heart attack or stroke on a regimen of daily use of "blood thinning" drugs (e.g., warfarin). These drugs are also used in other circumstances where it is feared that a clot may form, such as after leg surgery (a clot forming as a result of the surgical damage could release and migrate to the brain). The drugs don't actually make blood "thinner," but reduce the ability of its platelet component to clot (the clumped platelets represent a "thickening" of the blood). The drugs are administered with the intent of preventing a harmful or catastrophic clot. The dose of the anticoagulant must be adjusted carefully so that there is adequate clotting at the site of an injury, otherwise, the person could seriously bleed (even to the point of fatality) from a relatively minor cut or from a bleeding ulcer. Yet, there must be enough impairment of unnecessary clotting that a heart attack or stroke is unlikely to occur. One of the fears associated with use of blood thinning drugs is the possibility that the patient will suffer from a cerebral hemorrhage. This is a rare event, but unlike bleeding from a cut that might simply stop a little more slowly under the influence of the drug compared to normal, even the small amount of blood flow in a cerebral hemorrhage can be fatal. Usually, platelet aggregation rates of the patients on blood thinning regimens are measured weekly, so as to assure that the rate is within desired bounds; if it is not, the drug dosage can be changed or factors that are influencing it can be removed.

Green vegetables (especially broccoli, spinach, peas, cabbage, and cucumbers) were found to have a measurable impact on anticoagulant therapy. The usual advice given to deal with substances that interact with drugs—to avoid them—didn't seem an appropriate way out when the health benefits of green vegetables were so well established and so strongly promoted. Therefore, the solution offered was to avoid changing the amounts of green vegetables being consumed, so as to provide a stable environment

for the drugs to work in.

The main active ingredient in the green vegetables is vitamin K. It has coagulation promoting qualities that overcome the effects of the anticoagulant drug, thus making the therapy less effective (the drug dosage has to be increased). According to one recent literature review, it was suggested that patients try to limit their vitamin K intake from their diet to 65–80 micrograms (15). The current recommended daily requirement for adults not undergoing warfarin therapy, is 65 micrograms for women and 80 micrograms for men; thus, the recommendation is to avoid exceeding the levels suggested for normal nutritional needs. Vitamin K is produced by intestinal bacteria; use of antibiotics that inhibit intestinal bacteria can also change the vitamin K content of the patient's blood.

Teas, pills, and other forms of herbal preparations generally have low levels of vitamin K, due to the relatively small amount of leafy tops (the main source of this vitamin) that are consumed. Still, many herbs are reputed to have anticoagulant properties that were investigated because of the importance of anticoagulation therapy. The concern that arises is whether or not these herbs will further reduce platelet aggregation and, as a result, increase the chance of spontaneous hemorrhage, as can occur when two anticoagulant drugs are taken. In particular, the most commonly used Chinese herb for treating blood stasis in modern practice is salvia. It has been reported that salvia may enhance the warfarin effects and may cause significant changes in blood properties (16, 17). Tang-kuei was also mentioned as a possible cause of warfarin potentiation (16).

STEROIDS AND CHINESE HERBS

Many Chinese herbs have been reported to be useful in the treatment of autoimmune disorders. One mechanism of action is to enhance the circulating levels of corticosteroids by slowing their metabolism. This action will not only increase the amount of natural corticosteroids (hormones produced by the adrenal cortex), but also any steroids administered as drugs. When the steroid levels administered for treating inflammation are high enough to cause some side effects, elevation of the drug level by herb action could increase the side effects. The sex hormones are metabolized by both the same and by similar enzymes as the corticosteroids. Enhanced levels of sex hormones in aged individuals may be one of the mechanisms by which antiaging Chinese herbs are able to improve patient conditions. The enhancement may arise at the level of hormone production or by inhibition of hormone degradation. If hormone degradation is slowed, administered hormones may be present in amounts higher than expected. This situation is similar to that which arises with inhibition of the CYP enzyme system.

Bupleurum and Hoelen Combination (*Chai Ling Tang*) has been used extensively in Japan to aid withdrawal from corticosteroid therapy and then to serve as a replacement for that therapy in the treatment of rheumatoid arthritis, viral hepatitis, and nephritis (18, 19). By using this formula along with steroid therapy, the dose of the steroids can be reduced by two-thirds. It is also reported to reduce the withdrawal symptoms and relieve the arthritic, hepatic, or nephrotic inflammation. Part of the action is attributed to improvements in adrenocortical function, increasing the total production of the body's steroids. This formula contains, among other ingredients, saponins in ginseng, jujube, licorice, and bupleurum that are likely to contribute to this action. The formula is made from Minor Bupleurum Combination (mentioned previously), by adding cinnamon twig and four diuretic herbs (hoelen, alisma, atractylodes, and polyporus).

Rehmannia has been shown to antagonize the suppressing effect of steroids on the hypothalamic-pituitary-adrenal axis: in rats treated with the drug dexamethasone, rehmannia was able to prevent the inhibition of corticosterone production by the adrenals (20). A combination of anemarrhena, raw rehmannia, and licorice was tested in rabbits that were administered dexamethasone, and the plasma cortisone levels rose (21). When nephritic patients were given anemarrhena, rehmannia, and licorice as well as low dose prednisolone, the proteinuria vanished in half the cases and the steroid side effects of "moon face," agitation, and insomnia were alleviated in most cases. These findings would suggest a positive effect of using the herbs along with corticosteroids, but they also indicate the potential for undesired effects in some treatment circumstances (for example, when the steroid administration is high and the body's own production is high). Thus, if the physicians administer a high rather than low dose of steroids and the patient receives herbs from another practitioner, the result could be adverse.

GENERAL CONCERNS

Some doctors have raised general concerns about using herbs, without being highly specific about the interaction that might occur. An anesthesiologist has raised the concern for his colleagues that herbal therapies might interact with the anesthesia, and has suggested, perhaps excessively, that herbal therapies be discontinued at least two to three weeks prior to surgeries that require anesthesia (22). Some medical doctors and pharmacists have advised that, until more is known, herbs not be mixed with drugs at all (23, 29), citing as examples several potential cases of interactions. A Chinese physician has expressed theoretical concerns about herb-drug interactions, especially with regard to antibiotics (27). For example, he suggested that antibiotics that are somewhat toxic to the liver, such as chloromycetin, erythromycin, tetracycline, riampicini, and rimifon, might become more toxic in the presence of hydrated tannins, as found in pomegranate rind, sanguisorba, gall (*webeizi*), and terminallia. The general concern is that the herbs have a mild liver toxicity that reinforces that of certain drugs. This might also apply to other herbs (without tannins) that are safe in normal usage but which become liver toxic in high dosage, such as xanthium. He also expressed concern over combining antibiotics with herbs rich in organic acids or alkaline substances (may change absorption characteristics of antibiotics), with herbs containing cyanosides (such as apricot and peach seeds; may cause respiratory inhibition), enzymes (as found in gallus, which may break down the drugs), licorice (decrease absorption), and blackened herbs (as used to stop bleeding, may decrease absorption of drugs). Table 3 provides a summary of some potential interactions for herbs used in the Chinese tradition; St. John's wort, though rarely used in Chinese medicine, is increasingly used in the West and the main herb for which drug interactions are reported..

Table 3: Some Herbs Recently Mentioned as Having Potential for Drug Interactions. According to modern journal reports, these "should not be used" with the drugs indicated. The herbs listed in this table are used in the Chinese tradition. Warfarin is the drug most often suggested to have interactions.

Herb	Source	Interactions Reported or Suspected
St. John's wort *tianjihuang*	*Hypericum perforatum* (tops)	warfarin (to cause bleeding); serotonin-uptake inhibitors (to cause mild serotonin syndrome); indinavir (increased bioavailability); digitoxin, theophylline, cyclosporin, phenprocoumon, and oral contraceptives (all with reduced bioavailability)

Herb	Source	Interactions Reported or Suspected
Ginseng *renshen*	*Panax ginseng* (root)	antidepressants such as phenelzine sulfate (to cause manic episodes, headaches); warfarin (to cause bleeding or to decrease effectiveness); corticosteroids (potentiation); estrogens (potentiation)
Ginkgo *yinxingye*	*Ginkgo biloba* (leaf)	warfarin (to cause bleeding)
Ginger *jiang*	*Zingiber officinale* (rhizome)	sulfaguanidine (enhance absorption)
Garlic *dasuan*	*Allium sativum* (bulb)	warfarin (to cause bleeding)
Tang-kuei *danggui*	*Angelica sinensis* (root)	warfarin (to cause bleeding)
Salvia *danshen*	*Salvia miltiorrhiza* (root)	warfarin (to cause bleeding)
Rhubarb *dahuang*	*Rheum officinale* (root)	cardiac glycosides and antiarrhythmic agents (potentiating by reducing potassium via laxative effect)
Aloe *luhui*	*Aloe ferox* (leaf sap)	cardiac glycosides and antiarrhythmic agents (potentiating by reducing potassium via laxative effect)
Ma-huang *mahuang*	*Ephedra sinica* (leaf)	MAO inhibitors (to cause hypertension); cardiac glycosides or halothane (to produce cardiac arrhythmia); caffeine (to intensify cardiovascular side effects)
Astragalus *huangqi*	*Astragalus membranaceus* (root)	cyclosporine, azathioprine, methotrexate (to impair intended immuno-suppressive effects).
Bupleurum *chaihu*	*Bupleurum falcatum* (root)	sedatives (potentiation)
Licorice *gancao*	*Glycyrrhiza uralensis* (root)	corticosteroids and thiazide diuretics (potentiation); digitalis or other cardiac glycosides (increased sensitivity)

A review of interaction problems or potential problems was published recently in Herbalgram (24), citing reports in **Herb Contraindications and Drug Interactions** and **Botanical Safety Handbook** among other sources. In most cases, adverse reactions were described on the basis of laboratory animal studies showing variations in drug availability or metabolism, or on a small number of case reports that suggested involvement of the herbs. Caffeine-containing herbs were most often cited as the cause of documented interactions, usually with drugs that also affect the central nervous system. It has been repeatedly reported that caffeine, which is found in some drug products, interacts with ma-huang to produce more severe cardiovascular side effects than when ma-huang is used alone. Broad concerns were raised with regard to use of laxatives (see aloe and rhubarb in Table 3) because of the possibility of reducing potassium levels (when combined with drugs that act on the heart, which is sensitive to potassium levels) and also because speeding up intestinal transit time could reduce drug absorption: buckthorn bark, cascara sagrada bark, and senna were mentioned. Other concerns were raised about combining herbs with an effect that is similar to a drug therapy; for example, herbs reputed to treat diabetes (e.g., bitter melon and gymnema) were of concern in relation to the possibility of excessive hypoglycemic action when combined with diabetes drugs. If blood sugar levels drop too low, the patient can experience a hypoglycemic crisis. It was also pointed out that absorption of drugs could be impaired by herbs that are rich in fiber (e.g., flaxseed, psyllium seed), mucilage (e.g., marshmallow), or tannins (e.g., oak bark).

A total of 47 herbs and substances marketed as part of the general herb category were mentioned in the article as potentially problematic, including bromelain (enzyme from pineapple; may affect levels of drugs and may increase tendency to bleeding), brewer's yeast (possible interaction with MAO inhibitors), coffee charcoal (could bind up drugs), and chasteberry (possible interactions with dopamine-receptor antagonists). However, some of the possible interactions were merely favorable ones, such as eleuthero increasing the efficacy of antibiotics (the mycin drugs) in the treatment of colitis, or very broad cautions (e.g., under black current leaf: no interactions noted, but because it has diuretic properties, it should not be taken simultaneously with diuretics indicated for cardiac or renal insufficiency without medical advice) that seem excessively worrisome. Herbs can have significant positive effect when used as part of a program of drug therapy, such as reducing the side effects (see: *Counteracting side effects of modern drug therapies with Chinese herbs*), but the concerns being raised by doctors and patients are for the potential adverse responses.

ADVICE

Practitioners who prescribe herbal therapies must ask their patients about drug use and keep an updated record of the drugs. Drug interactions may be avoided entirely by not prescribing herbs, and may be minimized by having the patients take the herbs and drugs at different times (about one hour apart to avoid any direct interactions in the digestive tract; about 1.5 hours apart to avoid having maximum blood levels of the drug and herb occurring at the same time). The dosage of herbs that are aimed therapeutically at the same function as the drugs (e.g., both are sedatives; both are hypoglycemics; both are anticoagulants), should be reduced to alleviate concerns about additive or synergistic effects that are too great.

Patients that are taking multiple drug therapies are at greater risk of interactions between each of the

drugs, between drugs and foods, and between drugs and herbs. Therefore, greater caution must be exercised in considering use of herbs for these patients and, especially, herbs that may have a similar therapeutic action. Patients who are in fragile health and using multiple drug therapies should avoid most herbs. In order to more skillfully combine drug and herb therapies, it behooves the practitioner to learn as much as possible about the mechanisms of action of both the drugs and the herbs (pharmacological action, not the action in ancient terminology). Increasingly, this is the language used to describe potential interactions that might be avoided. When patients report that they have had an experience that they believe might be the result of an interaction between one or more drugs that they are taking and the herbs that have been prescribed, it is very helpful to be able to know the possibilities that are present for such interactions. It is reassuring to the patient if they know that the potential for any herb-drug interactions has been carefully considered in selecting or designing the herb therapy (see Table 4).

Table 4: Information for Practitioners to Relay to Patients about Interactions with Drugs. The interactions depicted here may involve foods, herbs, or nutritional and non-nutritional supplements; the information stated in terms of herbs should be applied to any substance with a potential for drug interactions.

Type of Interaction	Examples	Patient Information
Drug absorption inhibited by binding, resulting in low drug levels.	Tetracycline with minerals; alkaloids with tannins; pectins, resins, and fibers may bind several drugs.	Take herbs at least one hour apart, preferably 1.5 hours apart from taking drugs.
Drug absorption inhibited by rapid transit time, resulting in low drug levels.	Diarrhea or frequent bowel movements due to colitis or laxative intake speeds transit of all materials through the intestinal tract.	Treat diarrhea and avoid excessive use of laxatives. Induction of diarrhea is an intended treatment strategy in Chinese medicine for nephritis.
Drug absorption and/or elimination modified.	Saponins may improve absorption and elimination of drugs, altering the blood levels and rate of change of drug levels; strongly acid or alkaline herbs may alter absorption of drugs.	Take herbs at least 1.5 hours apart from drugs; avoid herbal preparations that have high saponin content.
Drugs metabolized too slowly resulting in elevated drug levels.	Grapefruit juice and herbs that inhibit CYP enzyme system can result in much higher levels of drugs in the bloodstream, and longer persistence of the drugs.	Take herbs at least 1.5 hours apart from drugs, preferably taking the drugs first (so that drug metabolism is already under way by the time the herbs can inhibit enzyme systems).
Potassium decreased when using cardiac drugs, resulting in adverse cardiac conditions.	Laxative and diuretic herbs may reduce potassium; these types of herbs are often given together for weight loss.	Avoid any strong laxative or diuretic action while using cardiac drugs. To compensate for mild diuretic or laxative treatments, consume high-potassium foods.
Drug action is intensified by similar effect of herbs.	Blood vitalizing herbs and blood thinning drugs may prevent adequate clotting; hypoglycemic herbs and hypoglycemic drugs may lower blood sugar too far; caffeine or ephedrine containing herbs and CNS stimulants disturb nerve functions.	When the drug therapy is already addressing a particular therapeutic goal, avoid adding an herbal therapy with the same goal. Intensify monitoring of blood conditions affected by the drugs.

Type of Interaction	Examples	Patient Information
Drugs cause adverse reaction to occur when certain substances are ingested.	MAO inhibitors can cause hypertension when an ordinary food component, tyramine, is ingested; some drugs can cause severe nausea when alcohol is ingested.	Learn the known reactions and take reasonable steps to avoid problematic herbs. It may be unnecessary to have total abstinence from an herb that reacts with a drug.
Miscellaneous: reported drug interactions.	St. John's wort decreases bioavailability of indinavir.	Learn the known reactions and avoid using the combination.
Desired drug effect is counteracted by herb effect.	Immune-enhancing herbs may counteract intended immunosuppressive action of drugs in autoimmune disorders, including transplant rejection reactions.	If herbs with known immune-enhancing actions are to be used, limit the dosage to avoid counteracting the drugs.

A well-reasoned analysis of the potential for drug-herb interaction will often permit the use of drugs and herbs together, but with some limitations. For example, if one wishes to prescribe a formula that contains a small amount of salvia to a patient who is taking warfarin, the only precaution necessary may be to continue the normal monitoring of blood coagulation that is routinely carried out as part of the prescribing of this drug. On the other hand, if one wishes to use a Chinese anticoagulant therapy with a high dose of salvia (usually with other herbs having a similar blood-vitalizing property), that would be contraindicated. If one wished to prescribe a spleen-tonifying formula to improve digestion in a patient requiring immunosuppressive therapies, a low-dose pill sufficient for improving digestion need not be avoided, whereas a high-dose decoction aimed at boosting immune functions would be contraindicated, even if both formulas contain similar ingredients.

As a more specific example, a formula for promoting digestion might include the herb astragalus, which is used in clinical practice both as a means of promoting digestive functions and as an immune enhancing agent. A few pills of *Buzhong Yi Qi Wan* or *Guipi Wan* might effectively promote digestive functions, but would have little effect on immunity; the total daily dose of astragalus when using these pills could be about 1 gram. By contrast, an immune enhancing formula aimed at counteracting the side effects of cancer therapies might be made with a decoction that included astragalus at 15 grams per day. Although it is not always possible to directly compare the dosage used in decoctions versus pills (due to differing availability of active constituents in the two preparation methods), the large difference in dosage suggests that there will be a difference in therapeutic effects. Further, by studying the other ingredients in the formulas, one will find an additive effect on digestion for the aforementioned pills, and an additive effect on immune functions for the decoction to be used with cancer therapies. Therefore, one can expect the treatment for digestive functions to be unlikely to cause an undesired effect on the drug therapy for suppressing immune functions. However, one would be concerned about the possibility that the immune-enhancing prescription at full dosage would counteract the desired immunosuppressive drug therapy. It is important for practitioners to know the ingredients of the formulas they prescribe (not just what the formulas are indicated for) and to know the dosing patterns common to Chinese medical practice (so as to distinguish low and high dosage ranges).

There are far too many variations in the conditions of individuals and the contents of herbal preparations to be able to guarantee a desired outcome or to guarantee absence of an undesired outcome. However, the incidence of adverse herb-drug interactions reported thus far is quite small and could easily be minimized by following prudent measures such as avoiding taking herbs and drugs at the same time and avoiding matching a strong drug therapy with a strong herb therapy aimed at the same physiological action.

If the patient or the patient's doctor (who has prescribed the drug) indicates that there is a substantial worry about herb-drug interactions, then it is best not to prescribe herbs. It is likely, in such cases, that any apparent adverse event would first be blamed on the potential interaction, with interruption of the planned herbal therapy anyway. By contrast, it is normal for a patient or doctor to simply raise a question about this matter, and, if the herb prescriber has taken the possibilities of interactions into account, one can usually proceed with an herbal therapy under the guidelines described here. One way to assess the reasonable degree of concern for any herb-drug interactions is to consider what the consequences might be of a small, but significant, increase or decrease in the level of the drug(s) that the

patient is taking. Changes in drug levels appear to be the most common outcome of herb-drug interactions and might still occur to a limited extent while taking the above-mentioned precautions. If the result of the modest change in drug levels is something that is easily reversed by ceasing use of the herbs or by altering the dose of the drugs, then the risk is low and one can proceed to utilize the herb therapy; if the consequence of change is irreversible or potentially catastrophic, then the risk is high and it is better to avoid the herb therapy. It is fairly common that persons with serious heart disease will take three or more cardiac drugs (e.g., an antihypertensive, an anticoagulant, and an antiarrhythmic or heart stimulant). Since even small changes in the activity of these drugs could lead to serious consequences, one would have to consider the situation one of high risk and uncertainty, and avoid the use of herbs.

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