Part III. Herbal Medicine—Drug Interactions: The Role of the Pharmacist

Herbal medications have become increasingly popular both in the United States and in Europe. Recent data reveal that between 17% and 32% of adults in the United States have used at least 1 herb for medicinal purposes in the last year.[1] Herbs are rapidly becoming part of accepted mainstream medical practice. The vast majority of herbal products are unlicensed and are not required to demonstrate efficacy, safety, or quality.[2,3] Currently, only 9 herbs have been approved by the Food and Drug Administration as being safe and having effective therapeutic options.[4] More than 1400 herbs remain that are sold commercially and are promoted for various unproven medical uses.[4]

Traditionally, use of medications has been based on well-documented clinical trials. This justifies our use of chemotherapy, radiation modifiers, or immunomodulating therapy in the treatment of cancer. The use of herbal products (also known as *phytopharmaceuticals)* is controversial among health care providers. With a lack of clinical trials and evidence of efficacy and toxicity, predicting any outcome becomes very difficult. The Dietary Supplements Health and Educational Act of 1994 allowed dietary supplement manufacturers to make certain functional (not medical) claims in labels. This effectively shifts product responsibility to the regulator instead of the seller. Herbal products are considered food products under the Dietary Supplements Health and Educational Act of 1994 and are not subject to clinical testing as are pharmaceutical products. Currently, there are no manufacturing standards regulating the quality and production of herbal supplements.

In herbal medicine, product selection is usually based on testimonials and anecdotal evidence. Nevertheless, patients with cancer may be drawn to claims of safety, efficacy, and, most importantly, lack of toxicity or drug interactions. The danger is that these products may be neither safe nor effective and sometimes may contribute to catastrophic side effects[4a] and drug/herb interactions.

The National Cancer Institute, American Cancer Society, and Food and Drug Administration have published statements on the use of herbal products in an attempt to make substantiated recommendations in an unregulated market. Compiling scientific data continues to be problematic; how-

ever, in 1994 the Food and Drug Administration began requesting reports of drug/herb interactions, and more information regarding this issue is now available. Our task is to educate our patients and ourselves with the available data.

This chapter focuses on the most common or problematic interactions of herbs and drugs used by patients with cancer. An overview of the basic pharmacokinetic concept of drug interactions is essential. With a general insight and understanding to pharmacology, one can possibly foresee interactions and take the necessary precautions to avoid drug/herb incompatibilities.

Pharmacokinetic Interactions

Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolized, and excreted.

Absorption

A clear distinction needs to be made between those that decrease the *rate* of absorption and those that alter the *total amount* of drug absorbed. Concomitant administration of herbs and drugs may either increase or decrease absorption of herbs and drugs. The absorption of herbs may be affected when given together with drugs that bind the herbs in the gastrointestinal tract (ie, activated charcoal, questran, colestid, carafate). Effects of changes in gastrointestinal pH may alter the bioavailability of drugs and herbs. The passage of drugs through mucous membranes by simple passive diffusion depends on the extent to which they exist in the nonionized, lipid-soluble form. Absorption is therefore governed by the pK_a of the drug, its lipid solubility, the pH of the contents of gut, and various other parameters relating to the formulation of the drug. Many herbs/drugs may alter gastrointestinal pH (ie, antacids such as cimetidine, famotidine, nizatidine, ranitidine, omeprazole, and lansprazole).

The absorption of herbs may also be affected when given together with drugs that affect normal gastrointestinal motility. Medications such as metoclopramide (Reglan) and propulsid (Cisapride) increase gastrointestinal motility, resulting in decreased absorption of herbs. Other medications such as antipsychotics or narcotics decrease gastrointestinal motility, which may increase absorption of herbs.

The solution to interactions caused by improper absorption is to separate administration of herbs and drugs by at least 2 hours. This allows the stomach to return to an acidic environment, and the absorption of herbs/drugs will not be compromised.

TABLE 1. Herbal supplement–drug interactions

Dietary supplement	Drug
Alfalfa *(Medicago sativa)*	Warfarin
Aloe species	Digoxin, diuretics
Black pepper *(Piper nigrum)*	Antiasthmatic drugs
Bovine cartilage	None reported
Cat's claw *(Uncaria guianensis)*	Antihypertensives
Chamomile	Anticoagulants
	Antispasmodics
Chaparral *(Larrea divaricata)*	MAO inhibitors
Cinnabar root *(Salviae multorrhizae)*	Warfarin
Coenzyme Q_{10} (Mitoquinone)	Oral hypoglycemic agents: acetohexamide, glyburide, tolazamide, phenformin
	HMG-COA reductase inhibitors: Lovastatin, pravastatin, Simvastatin
	Warfarin
Coltsfoot *(Tussilago farfara)*	Antihypertensive Cardiovascular
Dehydroepiandrosterone)	
Dong quai *(Angelica sinensis)*	Warfarin
Echinacea *(Echinacea augustifolia)*	Immunosuppressive drugs
(Echinacea pallida) (Echinacea purpurea)	Econazole Nitrate (Spectazole)
Feverfew *(Tanacetum sp)*	Aspirin, dipyridamole, warfarin
	NSAIDs
Flaxseed *(Linum usitatissinum)*	Laxatives, stool softeners
	Warfarin, Aspirin
	Cyclosporine
Garlic *(Allium sativum)*	Aspirin, dipyridamole, warfarin
	Hypoglycemic drugs
	Insulin
Ginger *(Zingiber officinale)*	Anticoagulants
Ginkgo *(Ginkgo biloba)*	Aspirin, dipyridamole
	Acetaminophen and ergotamine/caffeine
	Warfarin
	Thiazide diuretics
Ginseng, Panax *(Panax ginseng)*	Alcohol
	Furosemide
	Phenelzine
	Warfarin, hypoglycemia medications, caffeine

Distribution

After absorption, drugs are rapidly distributed around the body by the circulation. Some drugs are totally dissolved in the plasma, but many others are also bound to plasma proteins, particularly the albumins. The extent of this binding varies greatly, but some drugs are extremely highly protein bound (>95%). For example, warfarin (Coumadin) is very sensi-

	Anticipated effect
	Contains vitamin K, decreased INR.
	Hypokalemia enhances toxicity.
	Decreased metabolism.
	May potentiate effects.[5] Avoid concomitant use.
	May increase bleeding time.
	Decrease gastrointestinal transit time.[6]
	Interfere with MAO therapy.[7]
	Increased INR.
	Can reduce the effects of coenzyme Q-10.[8]
	Can reduce the effects of coenzyme Q-10.
	Decreased INR.[9]
	Reduces the effectiveness of antihypertensive medications.[10]
	None reported.
	Increased bleeding time.[4,5] Dong quai contains coumarins.
	Interferes with immunosuppressant therapy because of its immunostimulating activity.[10]
	Concomitant use of echinacea and topical econazole can decrease the recurrence rate of vaginal candidal infections.[11]
	Increased bleeding time.[11]
	NSAIDs can decrease the effectiveness of feverfew.[12]
	Increase laxative action of flax. Avoid concurrent use.[13]
	Increased bleeding time.[14]
	Can attenuate cyclosporine-induced hypertension in people with kidney or heart transplants.[15,16]
	Increased bleeding time.[5]
	May increase risk of bleeding.[10]
	Insulin dosage adjustment may be necessary because of hypoglycemic effect of garlic.[17]
	May enhance risk of bleeding.[17,18]
	Spontaneous hyphema.[19]
	Bilateral subdural hematoma.[20]
	Increased bleeding time, intracerebral hemorrhage.[21]
	Hypertension.[22]
	Increased alcohol clearance.[23]
	Decreased efficacy.
	Headache and tremor,[24] mania[25]; decreased INR.[26]
	Monitor blood glucose closely—ginseng may have possible hypoglycemic effects.[17] Long-term use of ginseng 3 g daily can lead to hypertension.[28]

continues

tive to changes in distribution because it has a high affinity to protein and a very narrow therapeutic range, therefore any slight change in its release from plasma proteins would greatly affect its clinical outcome.

Metabolism

Most herbs and drugs are metabolized by the liver to active and inactive metabolites. The rate at which the liver metabolizes these herbs and drugs

TABLE 1. Herbal supplement–drug interactions–continued

Dietary supplement	Drug
Ginseng (Siberian) *(Acanthopanax senticosus)**	Digoxin
Grape seed *(Vitis vinefera)*	Warfarin
Hawthorn *(Crataegus* species)	Digoxin
	Coronary vasodilators
Kava kava *(Piper methysticum)*	Alcohol, sedatives
Licorice *(Glycyrrhiza sp)*	Agents that prolong QT interval: Loratadine, procainamide, quinidine, terfenadine, others.
	Corticosteroids (Prednisolone, hydrocortisone, topicals)
	Digoxin
	Diuretics
	Oral contraceptives
MaHuang *(Ephedra sp)*	Beta-blockers, MAOIs, methyldopa, caffeine, theophylline, decongestants, St John's Wort
Pau d'arco *(Tabebuia impetiginosa)*	Aspirin, Warfarin
Psyllium	Digoxin
Shark cartilage *(Squalus acanthias)*	None reported
St John's wort *(Hypericum perforatum)*	Antidepressants
	Alcohol, narcotics, MAO inhibitors, sympathomimetic, tyramine-containing foods, OTC and flu medications, ACE inhibitors, yohimbine
	SSRIs
	Photosensitizing drugs

INR, International normalized ratio; *HMG-COA,* 3-hydroxy-3-methyl-glutaryl-Coenzyme A; *MAO,* monoamine oxidase; *NSAIDs,* nonsteroidal antiinflammatory drugs; *CNS,* central nervous system; *AUC,* area under the curve; *MAOI,* monoamine oxidase inhibitor; *OTC,* over-the-counter; *ACE,* angiotensin-converting enzyme; *SSRI,* selective serotonin reuptake inhibitors.
*Medications for Panax Ginseng also apply.

determines the duration in which they remain active in the body. If the liver is induced to speed up its metabolism, herbs and drugs would be inactivated at a faster rate, and the overall effectiveness would be decreased. If drugs or herbs cause the opposite effect on the liver by inhibiting metabolism, then drugs/herbs would be inactivated at a slower rate, and the pharmacologic effect would last longer.

Examples of drugs that induce metabolism include phenytoin (Dilantin), phenobarbital, carbamazepine (Tegretol), and rifampin. Because these drugs speed up metabolism, the dosage of herbs may need to be increased. Examples of drugs that inhibit metabolism include cimetidine, erythromycin, ethanol, fluconazole, itraconazole, and ketoconazole. These medications may slow down or inhibit metabolism; therefore the dosage of herbs may need to be decreased to prevent overdosing.

Elimination

The rate of elimination is defined as the disappearance of the active

	Anticipated effect
	Increased digoxin level.[28]
	Increased bleeding time. Interaction caused by the tocopherol content of grape seed.[13]
	May potentiate digoxin effects; may require decreasing digoxin dose.[27,29]
	Hawthorne may cause additive vasodilatory effects.[29]
	CNS depression.
	May prolong QT interval and be potentially additive. Use together with caution.
	Decreased plasma clearance, increased AUC, glyrrhetinic acid potentiates cutaneous vasoconstrictor response.[30-32]
	May induce hypokalemia and increase risk for digoxin toxicity.
	May exacerbate hypokalemia.
	Hypertension, edema, hypokalemia.[33]
	Increased toxicity resulting from drug or disease state interaction.
	Increased bleeding time.[34]
	Impaired absorption.
	Avoid in hypercalcemia; reported to cause hypercalcemia.[35]
	Potential increase in adverse effects, serotonin syndrome.[10,34,36]
	May enhance MAO inhibition syndrome. Avoid concurrent use. Possible exacerbation of allergic reactions, hypertension, and serotonin syndrome.[37-40]
	Increased risk of serotonin syndrome. Concurrent use contraindicated.[41,42]
	Concomitant use can result in increased photosensitivity.[42]

molecule from the bloodstream or body; this determines the duration of action for most drugs. Therefore knowledge of the time course of concentration in plasma is important in predicting the intensity and duration of effect for most drugs. This information is available for prescribed medications, but it is not readily available for herbal products. If renal function is compromised, the rate of elimination may decrease, which may lead to an accumulation of the drug/herb. If a patient has renal insufficiency, it is important that herbs are started at a low dose and that the prescribed medication is also appropriately dosed.

Table 1 lists some of the common herbs used by patients with cancer. This list is not all inclusive, but it does provide useful drug/herb interactions of which the provider should be aware.

Table 2 lists disease states at a higher risk of herb interaction, including the herbal supplement that should be avoided for each disease. Some herbal products may list the *genus* or *species* of the herb instead of the "common" known name, and therefore a possible interaction may be missed.

TABLE 2. Disease states at higher risk of herb interaction

Disease state	Herbal supplement
Cardiovascular diseases	*Aconitum sp*, Bitterroot (Apocynum), Khat *(Catha edulis)*, Lobelia *(Lobelia inflata)*, Ma Huang concentrates *(Ephedra sp)*, Licorice *(Glycyrrhiza sp)*, Coltsfoot *(Tussilago farfara)*
Autoimmune disease (SLE)	Alfalfa *(Medicago sativa)*
Renal insufficiency	*Acorus calamus, Aristolochia fangchi*, Gernanium supplements, pennyroyal *(Mentha pulegium)*, Rue *(Ruta graveolens)*
Hepatic insufficiency	*Borago officinalis*, Chaparral *(Larea tridentata)*, Coltsfoot *(Tussilago farfara)*, Germander *(Teucrium chamaedris)*, *Heliotropium sp*, Kombucha tea, Lobelia *(Lobelia inflata)*, Paraguay tea *(Ilex paraguayensis)*, pau d'Arco *(Tabebuia heptaphylla)*, *Petasites hybridus*, Rue *(Ruta graveolens)*, *Sencecio sp*
Seizures	*Sophora flavenscens*, pokeweed *(Phytolacca americana)*
Hematologic disorders	Ginkgo biloba, Ginseng *(Panax sp)*
Gastrointestinal diseases	Asafetida *(Ferula asafoetida)*, Bearberry *(Arctosphylos uvs-ursi)*, Black alder *(Rhamnus frangula)*, Buckthorn *(Rhamnus cathartica)*, Seneca snakeroot *(Polygala senega)*
Pregnancy	Dong quai *(Angelica archangelica)*, blessed thistle *(Cnicus benedictus)*, blue cohosh *(Cimicifuga racemosa)*, fenugreek *(Trigonella foenumgraecum)*, goldenseal *(Hydrastis canadensis)*, Kava kava *(Piper methysticum)*

SLE, Systemic lupus erythematosus.

Conclusion

Herbal supplements are being used by patients with cancer with increasing frequency. Health care providers should be concerned about the lack of scientific evidence present to make a solid decision about supplements. However, we do know that for the last 4 or 5 years, we have accumulated data on adverse reactions and drug/herb interactions. We must actively seek the information available to help guide clinical decision making. Currently there appears to be more information on toxic effects rather than on efficacy. The accessibility of a pharmacist trained in herb/drug interactions to patients with cancer should be widely considered.

At the Naval Medical Center San Diego, we have an herb/drug patient-oriented lecture once a month. Our patients bring their herbal supplements to the lecture, and the oncology pharmacist reviews each patient's prescription profile and herbal profile. Potential drug/herb interactions can be detected, and a possibly harmful event can be prevented. In addition, patients gain valuable information about their supplements and can make more informed decisions regarding their herbal purchases. This lecture is well received, and the concept is encouraged for other cancer institutions.

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