Interactions of Pharmaceutical and Botanical Medicines

Francis J. Brinker, ND

Abstract

Plant medicines and their extracts present both advantages and disadvantages when used together with synthetic medicines. A beneficial "drug interaction" or synergism occurs when herbal remedies produce effects that are complementary to prescription drugs or reduce their toxicity. Examples of detrimental interactions include interference with the absorption or excretion of the prescription medicines. Additive effects are predictable complications when herbs are combined with similar or comparable pharmaceuticals. The use of herbs in conjunction with digitalis glycosides is explored as an example of the different types of considerations involved in mixing standard and phytotherapeutic medical care.

RESEARCH REVIEW

Introduction

As the medicinal use of herbs becomes more common, an understandable concern is the possible interference with prescription drugs. For doctors and pharmacists unfamiliar with the activities and effects of botanical products and their extracted components, a reluctance to recommend these agents to patients or customers may be attributed to a "fear of the unknown." Their concerns are multiple. Will components of botanical remedies interfere with the kinetics of their prescriptions, i.e., absorption, metabolism, and/or excretion, rendering them less available or more so? Or will the effects of the herbs alter the drug effect through metabolic changes, antagonism, or additive effects? Naturopathic physicians and others who use herbal products medicinally often face these same quandaries in prescribing for patients on drug maintenance therapies who wish to explore other approaches for the same or different conditions. This article addresses some of the concerns shared by those who administer or provide pharmaceutical and/or botanical medicines and discusses certain benefits of using botanical remedies and drugs together.

In herbs with primary active constituents whose pharmacology has been elucidated (e.g., *Ephedra sinica* with its alkaloids ephedrine and pseudoephedrine), a fairly straightforward assessment of potential interactions can be made by those with standard medical/pharmacological training. However, the case is not as simple with many herbs. Medicinal plants that have not attracted the attention of research scientists, as well as herbal remedies whose study has revealed a complexity that defies simplistic mechanistic explanations, can baffle even those clinicians who demonstrate an active interest in understanding the interplay of synthetic and natural medicinal agents. In an attempt to help bridge these gaps in knowledge, it is appropriate to address some general considerations and offer a variety of specific examples illustrating how botanical medicines may influence and modify the effects of common pharmaceuticals. Since the vast array of specific concerns cannot be addressed in a limited venue such as this, a practical reference source is needed. To supply this larger need the author has compiled a more complete reference text from the scientific and medical literature (1).

6417 E Hayne St
Tucson, AZ 85710-4638
520-747-1898
Fax: 520-881-4013 (attn: FB)

Complementary Combinations

In some circumstances the addition of botanical remedies to other medicines can improve the response or help protect from deleterious side effects of the pharmaceuticals (2). This adjunctive approach to prescribing blends the best of both systems in cases in

which the prescription drugs are deemed necessary for the patient's recovery or long-term maintenance. While the possibilities in this regard are many and varied, a few examples of how common medical prescriptions can be enhanced by the addition of botanical agents should suffice to illustrate such concomitant treatments.

The standard medical approach to treating infections that led to the dominant success of pharmaceuticals in this field is the administration of antibiotics. The extensive use of these agents has led to a growing crisis in developing new forms that overcome the increasing bacterial resistance to such compounds. The naturopathic approach, meanwhile, has relied heavily on strengthening the body's resistance to infections by employing natural means and substances that enhance the immune response. Foremost among such agents have been species of the American herb *Echinacea* (purple coneflower). European research on *Echinacea* spp. has identified a variety of nontoxic active constituents, among them high-molecular-weight polysaccharides, glycoproteins, isobutylamides, polyacetylenes, and caffeic acid derivatives, that together enhance replication, phagocytosis, and cytokine production by various white blood cells. In addition, individual components have shown some antibacterial, antimycotic, and antiviral activities (2). In a clinical study on recurrent candidiasis the recurrence rate after six months when using the topical antimycotic econazole nitrate alone for six days was 60.5% in 43 patients. Compared to the recurrence rate of 15.0% in 20 patients using both econazole and *Echinacea purpurea* herb pressed juice topically and 16.7% in 60 patients using econazole topically and *E. purpurea* juice orally, the econazole treatment alone was markedly less effective (3).

Other botanical remedies are also known for immunomodulating benefits that enhance antimicrobial effects in treating infections. Like *Echinacea*, the root of *Eleutherococcus senticosus* (Siberian ginseng) contains high-molecular-weight heteroglycan polysaccharides that enhance phagocytosis *in vitro* and *in vivo* (4). In addition, in a placebo-controlled study the alcoholic extract of *Eleutherococcus* root given in 10 ml doses three times daily to 36 healthy humans for four weeks drastically increased the number of immunocompetent cells, especially T-cells (helper/inducer, cytotoxic and natural killer cells), and generally enhanced the activation of T-lymphocytes with no side effects (5). A study of children aged 0-14 years suffering from dysentery caused by *Shigella* spp. and enterocolitis of *Proteus* etiology compared the use of monomycin and kanamycin together with *Eleutherococcus* and the related *Echinopanax elatum* in 157 patients, while using antibiotics alone in 101 patients. The periods of disease decreased for children using the herbs together with the antibiotics (6).

Benign prostatic hyperplasia (BPH) is a condition that involves a number of different processes that seem amenable to treatment with complementary pharmaceutical approaches. Therefore, the smooth-muscle relaxing α_1-adrenergic inhibitor terazosin (Hytrin), proven effective in relieving BPH symptoms, was combined with the 5α-reductase inhibitor finasteride (Proscar) in a clinical study. Though finasteride blocks conversion of testosterone to the more potent prostatic growth stimulator dehydrotestosterone, finasteride combined with terazosin proved no better than terazosin alone in treating BPH as documented by symptom scores in this study (7).

Several botanical remedies have been shown in clinical studies to be effective in treating early stages of BPH. Of greatest benefit are three whose concentrated solid and liquid extracts are commonly used phytomedicinals in Europe: *Serenoa repens* (saw palmetto) fruit, *Pygeum africanum* (African prune) bark, and *Urtica dioica* (stinging nettle) root (8). While their extracts have only a mild 5α-reductase inhibitory activity compared to finasteride (9), they impact the prostate by other means. *Serenoa* has shown some anti-androgenic effects (8), but it may be most useful due to its reduction of estrogen and androgen receptors in the nuclei of prostate cells (10). In addition to mild 5α-reductase inhibition, *Pygeum* and *Urtica* extracts both demonstrated *in-vitro* aromatase inhibition which reduces the conversion of androgens to estradiol, a contributing factor in BPH. While *Pygeum* was the more potent of the two when used alone, together these extracts had a significantly stronger, synergistic aromatase-inhibiting effect (11). It is possible that the combined effects of any one or all three of these effective plant remedies together with terazosin would produce better clinical effects than when terazosin is taken alone, based upon their different mechanisms of action from each other and from finasteride.

Botanical medicines can offer protective effects from some of the undesirable side effects associated with the use of pharmaceuticals. Flavanolignans from *Silybum marianum* (milk thistle) fruit have been shown to protect rodents from liver damage after exposure to a wide variety of xenobiotic hepatotoxins including deoxycholate, acetominophen, halothane, and ethanol due to their antioxidant and lipoxygenase-inhibiting activities (2). Clinical studies showed that using the flavanolignan extract called silymarin with patients suffering from alcoholic cirrhosis decreased mortality and helped normalize serum enzymes indicative of liver damage (2,12). Silymarin improves the metabolism of aspirin in cirrhotic rats, and may thereby help prevent or reduce side effects from other medications metabolized in the liver of patients with liver disease. In a woman with dilantin-induced hepatitis who required dilantin as a maintenance therapy, the liver enzyme changes normalized after silymarin was given (12). In a double-blind, placebo-controlled study involving 60 patients chronically receiving the psychotropic drugs butyrophenones or phenothiazines, silymarin reduced lipoperoxidative hepatic damage (13).

A number of botanically-derived isolated components have been used in a wide variety of ways in conventional medicine to enhance the medicinal effects of inadequate drugs. The cell-proliferant allantoin is found in yields of 1-2% in the leaves and roots of *Symphytum officinale* (comfrey). When used in 2% concentration topically in a lotion or cream base with 5% coal tar, allantoin increases the healing of psoriasis compared to coal tar alone. The immune-stimulant polysaccharide lentinan from the *Lentinus edodes* (shitake) mushroom when given by injection increased the mean survival time in 77 patients over 100% compared to 68 patients given placebo in advanced recurrent stomach cancer patients receiving chemotherapy (2). The combination of isolated

components from herbs with other pharmaceuticals is an established practice going back to the discovery of alkaloids. Using a more complex extract from a plant increases the number of interactive factors involved in combinations, but this type of botanical medicine is just as capable of increasing the therapeutic potential of other proven remedies.

Botanicals That Reduce Drug Availability

It is fairly obvious that if medicines, whatever their source, have antagonistic activities and are prescribed together, they will tend to hinder the effects desired from each one to a greater or lesser extent. The simultaneous prescription of antagonistic agents defies common sense and would be expected to occur only due to a lack of knowledge of the other medication being used. However, interference with medicinal effects not only occurs when two agents are directly antagonistic, but is more common when the absorption, metabolism, or excretion of a drug is compromised. In this regard there are several general categories of botanical medicines that need to be restricted when vital pharmaceutical drugs are being administered.

Certain herbs that are high in water-soluble, hydrocolloidal fiber can delay gastric emptying. Their high viscosity can also produce a semi-permeable barrier over the gastrointestinal mucosa. These combined effects together can cause a delay in absorption of orally administered drugs and nutrients. Such fiber, commonly referred to as gum or mucilage, is insoluble in alcohol, so this effect is of greatest concern when certain powdered herbs, teas, juices, or dried aqueous extracts are taken orally in large quantities along with medications such as lithium salts, digoxin and penicillin. Examples of these different types of hydrocolloid preparations include powdered *Althaea officinalis* (marshmallow) root, cold infusion of *Ulmus fulva* (slippery elm) bark, *Aloe vera* (aloe) leaf gel, and alginate powder from brown algae. Many hydrocolloidal substances can be found in food items like okra and oats or as food additives such as carrageenan, guar gum, locust bean gum, and pectin that are known to adsorb cholesterol. Bulk laxative herbs that can also interfere with cholesterol and drug absorption include *Linum usitatissimum* (flax) seed, *Trigonella foenum-graecum* (fenugreek) seed, and *Plantago psyllium* or *P. ovata* (psyllium) seed (1).

Alkaloidal medications such as atropine, codeine, ephedrine and theophylline are susceptible to precipitation by binding with certain substances found in botanical medicines that can hinder absorption. Tannins are the most common cause of this problem, though salicylates will also cause alkaloids to precipitate. Since tannins are present in some herbal powders, are extracted in hot water, and are soluble in alcohol, herbs that contain significant quantities of tannins should be avoided in all forms administered orally while taking alkaloid-containing medicines by mouth simultaneously. Tannins can also precipitate proteins and minerals such as iron or copper that may be important factors or co-factors in drug or nutritional therapies. The most commonly consumed plant high in tannins is *Camellia sinensis* (black, green, or oolong tea), so a case history pertaining to the use of this recreational (and medicinal) beverage is important. Other common beverage and/or medicinal teas that contain high amounts (over 10%) of tannins include *Arctostaphylos uva-ursi* (bearberry) leaves, *Juglans nigra* (black walnut) leaves, bark, and rinds, *Geranium maculatum* (cranesbill) rhizome, *Rubus* spp. (raspberry) leaves, *Quercus* spp. (oak) bark, and *Hamamelis virginiana* (witch hazel) leaves and bark. Common salicylate-containing herbs that may precipitate alkaloids include *Filipendula ulmaria* (meadowsweet) flowers, *Populus* spp. (poplar) bark and buds, *Salix* spp. (willow) bark, and *Gaultheria procumbems* (wintergreen) leaves (1,14).

Besides reducing mucosal permeability and precipitating alkaloids, a third means by which botanical medicines can reduce absorption of medicinal agents is through their rapid elimination. Though not typically used as such by naturopathic physicians for their often-excessive cathartic effects, high doses of laxatives can lower absorption of orally-administered medicinal compounds by increasing peristalsis and reducing the bowel transit time. They effectively lower absorption by diminishing the amount of available time and mucosal contact necessary for diffusion or transport to occur across the intestinal mucosa. Prolonged maintenance of such bowel stimulation would best be termed abuse and is mostly encountered with self-adminstration of OTC laxatives by bulimic patients. In cases of anthranoid-containing botanicals, chronic overuse is evidenced by a black discoloration of the rectal mucosa. The more common laxative herbs yielding anthroquinones are *Aloe* spp. (aloe) leaf exudate, *Rheum* spp. (rhubarb) root, *Rhamnus purshiana* (cascara sagrada) bark, and *Cassia* spp. (senna) leaves and pods (1,14).

Many prescribed drugs are metabolized in liver microsomes. Herbs such as *Medicago sativa* (alfalfa) have been shown to increase hepatic xenobiotic-metabolizing enzymes such as mixed-function oxidase in rodents (1,2). Indoles produced enzymatically after consumption of glucosinolates found in various cruciferous vegetables and plants have a similar effects and enhance the glutathione S-transferase activity (15). For example, indoles from *Brassica* spp. crucifers (cabbage, broccoli, etc.) increase the liver's metabolism of estradiol. While increasing microsomal enzyme activity is useful as a means of detoxifying carcinogenic substances, the half-life of beneficial medications can also be decreased (2). In addition, the high vitamin K intake from regular consumption of cruciferous vegetables can produce resistance to the hypoprothrombinemic effects of warfarin (Coumadin) (16).

The aromatic compound eucalyptol, found in cough drops and in the essential oil of *Eucalyptus* spp. that is used in volatile inhalant preparations for steam humidifiers, has been shown to increase drug metabolism in rats and humans. Eucalyptol decreased plasma and/or brain levels of amphetamine, zoxazolamine, pentobarbital, and aminopyrine in rats exposed to eucalyptol aerosol for 2-10 minutes per day for four days. In humans exposed to the aerosol for ten minutes per day for ten days, the rates of disappearance of plasma aminopyrine and of urinary excretion of 4-aminoantipyrine (its metabolite) were increased (17). Eucalyptol was also shown to increase liver metabolism of *p*-nitro-anisol and aniline. Given as an aerosol to rats for four days for either 5-10 or 15-30 minutes daily, eucalyptol significantly decreased pentobarbital levels in

the brain and lowered the induced sleeping time when pentobarbital was given 18 hours after the last eucalyptol exposure (18). On the other hand, consumption of *Eucalyptus globulus* leaves increased the toxicity of pyrrolizidine alkaloid-containing *Senecio* spp. due to the increased metabolic activation of these toxic alkaloids by microsomal enzymes (19).

Not all aromatic oils or terpenes induce microsomal enzyme activity. *Pinus pumilio* oil, guaiacol, menthol, α-pinene, and ß-pinene were shown to be without effect (18). Aromatic substances increasing microsomal metabolism of drugs include those found in cedarwood (*Juniperus virginiana, J. ashei*) oil such as cedrol and cedrene. The inhaled aromatic oil with these components reduced hypnotic effects of hexobarbitone in mice and enhanced the removal of bishydroxycoumarin (Dicoumarol) from the blood in rats. The enzymes enhanced by the cedarwood volatiles were aniline hydroxylase, suflanilamide acetylase, neoprontosil azoreductase, heptachlor epoxidase, and zoxazolamine hydroxylase (20).

Potentially Hazardous Additive Effects

Increasing the activity of a pharmaceutical drug is a significant risk due to the side effects or toxicities normally associated with many of these potent synthetic medicines. One means by which this can occur is through increasing the half-life of the drug by slowing its breakdown or excretion. For example, the suppressive effect of the glycyrrhetinic acid component of *Glycyrrhiza glabra* (licorice) on 5ß-reductase effectively delays the clearance of corticosteroids by the liver (21). As far as we know, this type of interference is fairly atypical. The most common way that mixing medicines accentuates their effects is by combining two agents with similar activities. There are a number of general categories of drugs for which this holds true. In many cases botanical medicines with the same or similar effects as pharmaceuticals can be used to reduce the dosage of a toxic drug or in some cases to replace a medicine that is not well tolerated. In either of these instances the gradual substitution of a botanical remedy for a prescription drug should only be done under a physician's close supervision and monitoring. Following are examples of serious over-medication resulting from combinations of medicines with comparable effects.

A number of cardiotonic botanical medicines were traditionally used in combination with, or in place of, *Digitalis* spp. (foxglove) and their extracts. Since *Digitalis* cardiac glycosides and their derivatives have become the standard agents for chronic treatment of cardiac insufficiency, the other botanical heart tonics, with the exception of *Strophanthus* spp., have been mostly confined to naturopathic and herbal practice. Most of these remedies share with *Digitalis* structurally-similar steroidal glycoside components with comparable activity. Botanicals containing the types of compounds that strengthen the heart's contractions include *Convallaria majalis* (lily-of-the-valley), *Adonis vernalis* (pheasant's eye), *Helleborus niger* (Christman rose), and *Urginea maritima* (squill) (1). *Selenicereus grandiflorus* (night-blooming cereus) lacks the steroidal glycoside components typical of this class of drug but acts as a cardiotonic agent nonetheless(1,2). Excessive amounts of these cardio-active medications alone or combined with digitalis could result in fatal arrhythmias or cardiac arrest (14).

Some botanical remedies contain natural coumarins which can result in a hemorrhagic diathesis with excessive consumption. These herbs can accentuate the effects of the prescription drug warfarin or other common anti-coagulants such as aspirin enough to be of concern. *Melilotus officinalis* (sweet clover), *Asperula odorata* (woodruff), and *Dipteryx odorata* (tonka beans) are among those plants which have contributed to clotting problems in the past. Bromelain, the proteolytic enzyme from pineapple (*Ananus comosus*), is also believed to potentiate coumarin's anticoagulant activity (22). Other botanicals that may enhance the effects of coumarin include *Aesculus hippocastinum* (horse chestnut), due to the antithrombin activity of its aesculin component, and *Cinchona* spp. (Peruvian bark) (1). Garlic (*Allium sativum*) has been shown to inhibit platelet aggragation (2), and excessive consumption of garlic has resulted in spontaneous (23) and postoperative bleeding episodes (24).

Anti-anxiety, sedative, and CNS depressant medications are prescribed with the warning that they should not be mixed with alcohol due to the deleterious combined effects. A number of botanical medicines have also been shown through research to increase the effects of pharmaceutical sedatives as demonstrated by increasing the sleeping time in animals induced by the drugs pentobarbital or hexobarbital. These herbs and their extracts include *Melissa officinalis* (lemon balm), *Eschscholtzia californica* (California poppy), *Humulus lupulus* (hops), *Passiflora incarnata* (passion flower), and *Valeriana officinalis* (valerian) (1,2). Excessive sedation could result from the combination of these herbs with standard depressant drugs.

Monoamine oxidase (MAO) inhibitors given mostly as antidepressant agents have long been known to interact with other drugs and foods that can result in a hypertensive crisis. This is most common with adrenergic agents including the plant alkaloids ephedrine and pseudoephedrine obtained from *Ephedra* spp. (ephedra). Another familiar cause of this dangerous interaction are foods high in tyramine such as wine and cheese. The herb *Cytisus scoparius* (Scotch broom) also has a high tyramine content and can additionally aggravate high blood pressure due to the cardiac stimulant activity of its alkaloid sparteine. MAO inhibitors combined with excessive caffeine consumption from such sources as coffee (*Caffea* spp.), tea (*Camella sinensis*), cola (*Cola nitida*), and chocolate (*Theobroma cacao*) can also result in hypertensive episodes. Medicinal plants such as *Myristica fragrans* (nutmeg) and *Hypericum perforatum* (St. Johnswort) are known to act as MAO inhibitors (1). *Hypericum* extract is used effectively as an antidepressant in its own right (2). It not only performs as well as the standard tricyclic agents amitriptyline (25) and imipramine and the tetracyclic antidepressant maprotiline, but was actually shown to be safer than the latter two drugs (26,27). Due to its impressive clinical effects, it would be prudent to also avoid combining *Hypericum* with other antidepressants, especially MAO inhibitors and those such as fluoxetine (Prozac) that act as selective serotonin reuptake inhibitors.

Insulin-dependent diabetics must monitor their blood sugar carefully to avoid hypoglycemic episodes. The combined effect of exogenous

hypoglycemic agents with insulin treatment can disrupt the means by which diabetics maintain suitable blood sugar levels and avoid insulin shock. While plant remedies are used to help control Type II diabetes mellitus, those under medication for Type I disease must be concerned about ingesting herbs that can have a significant impact on serum glucose. Certain plants have a well-documented ability to lower blood sugar levels through a variety of mechanisms. Since many hypoglycemic plants are also used as remedies for conditions unrelated to diabetes, their concomitant additive effect with insulin therapy would likely be inadvertent. Foremost among these plants is *Momordica charantia* (bitter melon) which contains a number of hypoglycemic constituents including the steroidal glycoside charantin, proteins p- and v-insulin, alkaloids, and others (1,28,29). Other plants whose oral hypoglycemic activity has been confirmed and their active constituents identified include *Allium cepa* (onion) bulbs, *Allium sativum* (garlic) cloves, *Trigonella foenum-graecum* (fenugreek) seeds, *Vaccinium myrtillus* (bilberry) leaves (29), *Tecoma stans* (tronadora) leaves (29,30), and *Olea europaea* (olive) leaves (31). Other botanical remedies whose activity has been more or less confirmed without identifying the specific active constituents include *Arctium lappa* (burdock) roots, *Fatsia horrida* (devil's club) root bark, *Gymnema sylvestre* leaves, *Opuntia ficus-indica* (prickly pear) stems, *Syzygium jambolanum* (jambul) seeds, *Bidens pilosa* (aceitilla) plant, and *Turnera diffusa* (damiana) leaves (29,30). Hydrocolloidal fiber sources such as guar gum and psyllium taken in large quantities can delay gastric emptying and reduce the rate of absorption of dietary carbohydrates (1).

Plants in the Umbelliferae (carrot or parsnip) family typically contain components chemically categorized as furanocoumarins. These psoralen compounds can act as phototoxic agents by increasing the skin's senstivity to ultraviolet radiation. While occasionally problematic when used alone, the results are much more dramatic and damaging when these plants are taken simultaneously with 8-methoxypsoralen, prescibed to enhance UV therapy for hyperkeratotic conditions such as atopic eczema. Severe burns with swelling and blistering may occur. Umbelliferous plants containing natural psoralens include *Angelica* spp. (angelica), *Apium graveolens* (celery), *Ammi visnaga* (khella), *Heracleum* spp. (hogweed), *Lomatium* spp. (wild parsnip), and *Daucus carota* (Queen Ann's lace). Plants outside of the Umbelliferae family with components known to act as photosensitizers include *Ranunculus* spp. (buttercups), *Ruta graveolens* (rue), and *Hypericum perforatum* (1).

Herbs that lower blood pressure may have an additive effect with pharmaceuticals used for this purpose. Herbal diuretics that reduce fluid volume will also subsequently decrease cardiac output and blood pressure. Diuretic herbs include *Daucus carota, Agropyrum repens* (couch grass), *Galium aparine* (cleavers), and *Taraxacum officinale* (dandelion). Herbs used primarily for their hypotensive effects include *Crataegus oxycantha* (hawthorn), *Viscum album* (mistletoe), *Veratrum viride* (green hellebore), and *Rauwolfia serpentina* (snakewood). In an obvious example of avoiding antagonistic herbs, *Glycyrrhiza glabra* root and its extracts, unless they are deglycyrrhizinated, should not be used by patients on hypotensive medication due to its potential hypertensive effects (32).

A number of potent alkaloidal drugs are obtained from plant sources. The interactions of the mother plant should be taken as equivalent to those of the isolated alkaloids. Therefore, plants that contain anticholinergic tropane alkaloids such as atropine can potentiate synthetic drugs having sedative, antihistaminic, or antispasmodic activities, and these combinations should be avoided. Atropine-containing plants include *Atropa belladonna* (deadly nightshade), *Datura stramonium* (Jimson weed), and *Hyoscyamus niger* (henbane) (32). The α_2-adrenergic antagonism of yohimbine indicates that its parent plant *Pausinystalia yohimbe* (yohimbe) and extracts of the bark would be toxic combined with tricyclic antidepressants and phenothiazides and could reverse the effects of antihypertensive drugs (33). The adverse interactions that may occur with *Rauwolfia serpentina* are the same as for its biogenic amine-depleting alkaloid reserpine. In addition to enhancing antihypertensives as mentioned above, *Rauwolfia* can have a detrimental effect if used with depressants, MAO inhibitors, sympathomimetics, tricyclic antidepressants, or *Digitalis* glycosides (34).

DIGITALIS COMBINATIONS WITH DISSIMILAR BOTANICALS

Besides the cardiotonic herbs already mentioned (e.g., *Strophanthus, Convallaria, Adonis, Helleborus, Urginea,* and *Selenicereus*) that can have an additive effect with digitaloid cardiac glycosides, other herbal remedies can also affect the activity of *Digitalis* constituents or their derivatives. Digitaloids are much-prescribed drugs for atrial tachyrhythmias and congestive heart failure in our ever-aging population. Influencing the activity of these plant-derived medicines can have a profound impact on the life and health of the patient. *Digitalis* glycosides provide a useful example to illustrate the different types of interactions that may occur in conjunction with the use of herbs to the benefit and the detriment of those being medicated.

Besides cardiotonic effects, advantages that can be derived from phytotherapeutic agents in heart disease revolve mainly around the use of coronary vasodilators that improve the perfusion of the cardiac musculature and thereby enhance nutrient availability and metabolic waste removal. *Crataegus* spp. leaves, flowers, and berries and their extracts have been shown to act therapeutically as vasodilators in relieving angina pectoris, cardiac arrhythmias, and mild hypertension. A variety of active constituents including triterpene acids, procyanidins, and flavonoids help account for these benefits. *Crataegus* increased the cardiotonic activity of *Digitalis,* as well as *Convallaria* and *Adonis,* in tests on guinea-pigs. In cardiac failure *Crataegus* functions well in conjunction with *Digitalis* and digoxin. *Crataegus* extracts increase the response and reduce the toxicity to the cardiac glycosides digoxin and digitoxin, as well as g-strophanthin, allowing a reduction of their doses. *Ammi visnaga* is another botanical with coronary vasodilating components. The constituents khellin, visnadin, samidin and dihydrosamidin obtained from khella have all shown this activity, with visnadin also producing positive inotropic effects. Visnadin given orally decreases the acute and chronic toxicity of digitoxin in mice

by preventing bradycardia and reversing cardiac arrhythmias (2).

The absorption of digoxin is slowed by simultaneous consumption of guar gum which reduces the plasma level temporarily. However, a more threatening interaction with digitaloids involves the use of botanical products that reduce blood potassium levels. Low serum potassium potentiates *Digitalis* effects. The *Glycyrrhiza glabra* root component glycyrrhizin induces potassium excretion in conjunction with sodium and water reabsorption in the kidneys, resulting in hypokalemia and hypertension, if used in large amounts for prolonged periods (1). However, licorice extracts are safer than consuming an equivalent amount of pure glycyrrhizin, due to modified intestinal absorption and bioavailability of the glycyrrhizin when it is combined with other licorice components (35). Overuse of laxatives (e.g., *Aloe, Rheum, Rhamnus, Cassica*) can also diminish blood levels of potassium, particularly when combined with potassium-depleting diuretics (1,32). While some herbal diuretics such as *Equisetum* spp. (horsetail) plants lead to significant potassium excretion (36), *Taraxacum officinale* leaves compensate for the excretory loss due to their own high potassium content (37).

Since one of the uses of *Digitalis* is for slowing the contractile rate of the heart, plants with components that affect the autonomic control of this function can disrupt the digitaloid medication's influence. Anticholinergic atropine-containing botanicals (e.g., *Atropa, Datura, Hyoscyamus*) counteract the bradycardia, an effect that can be utilized in *Digitalis* toxicity (14). *Ephedra* spp. containing the sympathomimetic ephedrine can induce tachyrhythmias in patients on digoxin due to enhanced ectopic pacemaker activity. The reserpine in *Rauwolfia* depletes sympathetic neuotransmitters which may result in bradycardic arrhythmias for patients on digoxin (34).

Whether the botanical medicines are additive, complementary, reduce bioavailability, alter co-factors, or induce neurotropic influence, their modification of the action of *Digitalis*, its glycosides, or other medications warrants serious consideration. To safely prescribe botanicals for patients who are already taking other medicines not only requires a knowledge of the physiologic and pharmacologic effects of the herbal product, but, also, familiarity with the action of the other medications as well. All possible interactions can not be addressed in an article of this type. The considerations covered will help in recognizing general tendencies for combinations of drugs from particular categories. However, each medicine, botanical or otherwise, needs to be studied for its own distinctive patterns of activity and interplay. In any case, an informed, careful approach must be the rule in prescribing all medicines, but most especially when the patient is already taking other medication.

REFERENCES

1. Brinker F. *Herb Contraindications and Drug Interactions*, Eclectic Institute, Inc., Sandy, Ore., 1997
2. Brinker F. Botanical Medicine Research Summaries. *Eclectic Dispensatory of Botanical Therapeutics*, vol. 2, Eclectic Medical Pub., Sandy, Ore., 1995
3. Coeugniet EG, Kuhnast R. Recurrent candidiasis: adjuvant immunotherapy with different formulations of Echinacin. *Therapiewoche* 36:3352-8, 1986
4. Wagner H, Proksch A, Riess-Maurer, Vollmar A, Odenthal S, Stuppner H, Jurcic K, LeTurdu M, Fang JN. Immunostimulating Polysaccharides (Heteroglycans) of Higher Plants. *Arzneim.-Forsch.*, 35:1069-75, 1985
5. Bohn B, Nebe CT, Birr C. Flow-cytometric Studies with Eleutherococcus Senticosus Extract as an Immunomodulatory Agent. *Arzneim.-Forsch.*, 37:1193-6, 1987
6. Vereshchagin IA, Geskina OD, Bukhteeva RR. Increasing of antibiotic therapy efficacy with adaptogens in children suffering from dysentery and *Proteus* infections. *Antibiotiki*, 27:65-9, 1982 (*B.A.* 75:32108)
7. Lepor H, Williford WO, Barry MJ, Brawer MK, Dixon CM, Gormley G, Haakenson C, Machi M, Narayan PN, Padley RJ. The Efficacy of Terazosin, Finasteride, or Both in Benign Prostatic Hyperplasia. *New Eng. J. Med.*, 335:533-9, 1996
8. Brinker F. An Overview of Conventional, Experimental, and Botanical Treatments of Nonmalignant Prostate Conditions. *Eclectic Dispensatory of Botanical Therapeutics*, vol. 2, Eclectic Medical Pub., Sandy, Ore., 1995
9. Rhodes L, Primka RL, Berman C, Vergult G, Gabriel M, Pierre-Malice M, Gibelin B. Comparison of Finasteride (Proscar), a 5α–Reductase Inhibitor, and Various Commercial Plant Extracts in In Vitro and In Vivo 5α–Reductase Inhibition. *Prostate*, 22:43-51, 1993
10. DiSilverio F, D'Eramo G, Lubrano C, Flammia GP, Sciarra A, Palma E, Caponera M, Sciarra F. Evidence that *Serenoa repens* Extract Displays an Antiestrogenic Activity in Prostatic Tissue of Benign Prostatic Hypertrophy Patients. *Eur. Urol.*, 21:309-14, 1992
11. Hartmann RW, Mark M, Soldati F. Inhibition of 5α-reductase and aromatase by PHL-00801 (Prostatonin), a combination of PY 102 (*Pygeum africanum*) and UR 102 (*Urtica dioica*) extracts. *Phytomedicine*, 3:121-8, 1996
12. Fintelmann V. Toxic-Metabolic Liver Damage and its Treatment. *Zeit. Phytother.*, (3):65-74, 1986
13. Palasciano G, Portincasa P, Palmieri V, Ciani D, Vendemiale G, Altomare E. The Effect of Silymarin on Plasma Levels of Malon-Dialdehyde in Patients Receiving Long-Term Treatment with Psychotropic Drugs. *Curr. Ther. Res.*, 55:537-45, 1994
14. Brinker F. *Toxicology of Botanical Medicines*, rev. 2nd ed., Eclectic Medical Pub., Portland, Ore., 1996
15. Sparnins VL, Venegas PL, Wattenberg LW. Glutathione S-Transferase Activity: Enhancement by Compounds Inhibiting Chemical Carcinogenesis and by Dietary Constituents. *J. Nat. Canc. Inst.*, 68(3):493-6, 1982
16. Walker FB. Myocardial Infarction After Diet-Induced Warfarin Resistance. *Arch. Intern. Med.*, 144:2089-90, 1984
17. Jori A, Bianchetti A, Prestini PE, Garattini S. Effect of Eucalyptol (1,8-Cineole) on the Metabolism of Other Drugs in Rats and in Man. *Eur. J. Pharmacol.*, 9:362-6, 1970
18. Jori A, Bianchetti A, Prestini PE. Effect of Essential Oils on Drug Metabolism. *Biochemical Pharmacol.*, 18:2081-5, 1969
19. White RD, Swick RA, Cheeke PR. Effects of Microsomal Enzyme Induction on the Toxicity of Pyrrolizidine (*Senecio*) Alkaloids. *J. Toxicol. Environ. Health*, 12:633-40, 1983
20. Corrigan D. *Juniperus* Species. from *Adverse Effects of Herbal Drugs* 2, DeSmet PAGM et al (ed.), Springer-Verlag, Berline, 1993
21. Tamura Y, Nichikawa T, Yamada K, Yamamoto M, Kumagai A. Effects of Glycyrrhetinic Acid and its Derivatives on D^4-5α- and 5β-Reductase in Rat Liver. *Arzneim.-Forsch.*, 29:647-9, 1979
22. Hogan RP III. Hemorrhagic Diathesis Caused by Drinking an Herbal Tea. *JAMA*, 249:2679-80, 1983
23. Rose KD, Croisant PD, Parliament CF, Levin MB. Spontaneous Spinal Epidural Hematoma with Associated Platelet Dysfunction from Excessive Garlic Ingestion: A Case Report. *Neurosurg.*, 26:880-2, 1990
24. Burnham BE. Garlic as a Possible Risk for Postoperative Bleeding. *Plastic Reconstr. Surg.*, 95:213, 1995
25. Bergmann R, Nubner J, Demling J. Simple treatment of moderately serious depressions. *Therapie. Neurol./Psychitrie*, 7:235-40, 1993
26. Vorbach EU, Hubner WD, Arnoldt KH. Effectiveness and tolerance of the Hypericum extract LI 160 in comparison with imipramine: Randomized double-blind study with 135 outpatients. *J. Geriatr. Psychiatr. Neurol.*, 7(Suppl. 1):S19-S23, 1994
27. Harrer G, Hubner WD, Podzuweit H. Effectiveness and tolerance of the Hypericum extract LI 160 compared to maprotiline: A multicenter double-blind study. *J. Geriatr. Psychiatr. Neurol.*, 7(Suppl. 1):S24-S28, 1994

28. Raman A, Lau C. Anti-diabetic properties and phytochemistry of *Momordica charantia* L. (Cucurbitaceae). *Phytomed.*, 2:349-62, 1996
29. Bever VO, Zahnd GR. Plants with Oral Hypoglycaemic Action. *Quart. J. Crude Drug Res.*, 17:139-96, 1979
30. Perez G. RM, Ocegueda Z. A, Munoz L. JL, Avila A. JG, Morrow WW. A Study of the Hypoglucemic (sic) Effect of Some Mexican Plants. *J. Ethnopharm.*, 12:253-62, 1980
31. Gonzalex M, Zarzuelo A, Gamez MJ, Utrilla MP, Jimenez J, Osuna I. Hypoglycemic Activity of Olive Leaf. *Planta Med.*, 58:513-5, 1992
32. D'Arcy PF. Adverse reactions and interactions with herbal medicines. Part 2 - Drug interactions. *Adverse Drug React. Toxicol Rev.*, 12:147-62, 1993
33. DeSmet PAGM, Smeets OSNM. Potential risks of health food products containing yohimbe extracts. *Br. Med. J.*, 309:958, 1994
34. Barnhart ER (pub.). *Physicians' Desk Reference,* 45th ed., Medical Economics Data, Oradell, N.J., 1991
35. Cantelli-Fort G, Maffei F, Hrelia P, Bugamelli F, Bernardi M, D'Intino P, Maranesi M, Raggi MA. Interaction of Licorice on Glycyrrhizin Pharmacokinetics. *Environ. Health Perspec.*, 102(Suppl. 9):65-8, 1994
36. Perez Gutierrex RM, Yesca Laguna G, Walkowski A. Diuretic Activity of Mexican Equisetum. *J. Ethnopharmacol.*, 14:269-72, 1985
37. Racz-Kotilla E, Racz G, Solomon A. The Action of Taraxacum Officinale Extracts on the Body Weight and Diuresis of Laboratory Animals. *Planta Med.*, 26:212-7, 1974

Biography

Francis J. Brinker, ND, received his doctorate from the National College of Naturopathic Medicine, after earning bachelor degrees in biology from the University of Kansas and human biology from Kansas Newman College. He teaches botanical medicine at the Southwest College of Naturopathic Medicine & Health Sciences. Dr. Brinker also works as a writer and consultant for Eclectic Institute, Inc. In addition to his new book, *Herb Contraindications and Drug Interactions,* he is known for his published writings in the *Eclectic Dispensatory of Botanical Therapeutics,* vol. I and II, including *The Toxicology of Botanical Medicines* and *Formulas for Healthful Living.*

A Fertile Ground for Lawsuits?

As your professional field grows so does your professional liability exposure.

From complications arising from allergic reactions, to failure to refer a patient to a medical specialist when appropriate, you may be sued for the professional services you provide.

Defend yourself with a professional liability insurance program designed exclusively for nutritionists and naturopathic consultants.

Call Gillingham & Associates, Inc.,
at (970) 879-9633,
Fax (970) 879-2891, or write to:
1495 Pine Grove Road, Suite A101
Steamboat Springs, CO 80487