

Herbs and Foods that Alter Drug Metabolism

Clients have ready access to herbs in supermarkets, pet stores, and via websites. They've seen media coverage of the downside of drugs, while they may perceive herbs as natural, mild, and therefore, harmless. However, these same herbs may alter the metabolism of other drugs they give their animal, and veterinarians should be aware that the list of known drug-herb interactions is growing.

Some herb-drug interactions in humans have received widespread publicity (e.g., St. John's wort and oral contraceptives), but many are still awaiting verification and further study. The effects of these interactions on non-humans remain largely unknown. Food-drug interactions receive less attention, but are worth considering, in light of the creative mixtures of ingredients showing up in natural pet foods.

The body cannot discriminate between natural and synthetic chemicals. Thus, it deals with both the same way, recognizing these "xenobiotics" as foreign, and potentially deleterious. In its move to eliminate them, the body may metabolize herbs through enzymes, most notably via the cytochrome P450 pathway. This pathway is responsible for the metabolism of a wide variety of agents, including certain immunosuppressants (cyclosporine), antibiotics (erythromycin), antiepileptics (diphenylhydantoin), steroids (ethinylestradiol), antidepressants (imipramine), cardiovascular drugs (nifedipine), and cancer drugs (tamoxifen). Cytochrome P450 enzymes biotransform chemicals by structurally changing the functional groups responsible for their activity. Some chemotherapy drugs (cyclophosphamide, ifosfamide) enter the body as pro-drugs, whose structure must be altered by phase I enzymes in order to become active anti-cancer drugs. Other drugs enter the body already in their active forms, and are de-activated by Phase I enzymes as part of the clearance process.

Naturally occurring chemicals, even those at dietary levels of intake, can modulate the hepatic and extrahepatic expression of cytochrome P450 levels. When this happens, marked changes in the metabolism of drugs may occur, leading to adverse drug interactions, or clinically important alterations in plasma concentrations of the drug. This phenomenon takes on extra importance when considering drugs with a low therapeutic index. In these cases, plasma levels need to stay within a narrow range of concentration to ensure maximum benefits and minimum side effects. Elevating the activity of the cytochrome P450 system increases the metabolic rate and potentially decreases plasma drug concentrations, which may lead to subtherapeutic or even negligible drug effects. Herbs and certain foods can alter the activity of the cytochrome P450 system and cause plasma drug concentrations to change in unpredictable ways.

Herbs affecting the cytochrome P 450 system

The reduction in blood levels of drugs by St. John's Wort has probably received more attention than any other herb-drug interaction, and has raised awareness among clinicians and consumers of the potential impact of such interactions, as shown in Table 1, below.

Table 1, St. John's Wort (SJW) Interactions

Drug interacting with SJW	Blood levels
Antiretroviral drugs	↓
Coumarin anticoagulants	↓
Chemotherapy drug (active metabolite of irinotecan)	↓
Cyclosporine	↓
Benzodiazepines	↓
Digoxin	↓
Amitriptyline	↓
Theophylline	↓
Anticonvulsants: carbamazepine, Phenobarbital, phenytoin	↓
Oral contraceptives	↓
Antihyperlipidemic drugs	↓
Opioids	↓
Drug interacting with SJW	Serotonergic effects
Selective serotonin reuptake inhibitors	↑ (May cause central serotonergic syndrome: mental status changes, tremor, autonomic instability, GI upset, headache, myalgias, and motor restlessness. Central serotonergic syndrome can be fatal, especially in geriatric individuals.)

Several other herbal remedies also interfere with cytochrome P450 metabolism:

Milk thistle

The chemical silymarin, in milk thistle, suppresses cytochrome enzyme and also inhibits glucuronosyl transferase activity. This means that milk thistle could alter the metabolism of drugs by interfering with Phase I and II pathways of biotransformation.

Ginseng

In vitro red ginseng total saponins inhibit cytochrome P450 activity in rat liver microsomes. The effect of whole ginseng on drug-metabolizing enzymes is currently unknown.

Garlic

Organosulfate compounds in garlic undergo metabolism by a certain cytochrome P450 enzyme known as CYP2E1, and generate metabolites that interact irreversibly with and impair the activity of enzyme. CYP2E1 catalyzes the metabolism of volatile halogenated anesthetics such as enflurane and halothane. As such, garlic supplements may prolong the effect of gas anesthetics.

Licorice

Indications for licorice include gastric ulcers, arthritis, and viral infections. Ethanolic extracts of licorice inhibit the metabolism of certain chemicals by the cytochrome enzyme CYP3A4, potentially elevating drug levels. Certain licorice components, including glycyrrhizin, alter the hepatic expression of the cytochrome P450 activities.

Foods and the cytochrome P450 system

Vegetables can either enhance or impair cytochrome P450 activity. Cruciferous vegetables such as broccoli have been shown to up-regulate a number of cytochrome P450 enzymes in the livers and colons of rats.

Tea (normal-strength black and green tea) up-regulates cytochrome P450 expression, while decaffeinated tea does not. This led to the discovery that caffeine is the responsible for the metabolic alterations.

Apiaceous vegetables (carrots, parley, celery, and fennel) lead to lower P450 activity.

Grapefruit juice produces the most well-researched and clinically relevant (in humans) drug-food interactions by inhibiting intestinal cytochrome activity. The chemicals responsible for enzyme inhibition are furanocoumarins. This inhibitory effect is long-lasting, and requires the synthesis of new enzyme proteins for the "grapefruit juice effect" to disappear, and repeated juice intake amplifies the process. Thus, grapefruit juice ingestion can increase the absorption and blood levels of certain drugs, which can cause adverse effects, even overdose, to occur. On the other hand, drugs administered as pro-drugs may have less effectiveness, as the enzymes responsible for converting them into active metabolites are inhibited. While there are no current reports of "grapefruit seed extract" (touted as having antiparasitic and antimicrobial effects) causing similar alterations, this may change as more information becomes available.

With herbs in general, herb-drug interactions are no longer theoretical possibilities. The likelihood of clinically relevant interactions is high for herbs

given over long periods. Maintaining a high index of suspicion when animals are taking herbs and reporting adverse effects will help build the knowledge matrix currently lacking about the effects so many natural products have on animal drug metabolism.