HERBAL – DRUG – NUTRIENT – INTERACTIONS

PDF Correspondence

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Herbal-Drug-Nutrient Interactions

Welcome to the 2012 version of the Herb-Drug-Nutrient Interaction course. This is a complete upgrade from our last version written in spring of 2006. We have added many new features and well over 100 pages of information. The area of Herb-Drug-Nutrient Interaction is still in its infancy, with no real authority in the area. You still have two major camps of people contemplating the subject. One group, usually the naturalist Herbalist, that feels because herb are natural they have no interaction at all; and the second group, that is solid in the pharmaceutical/medical model, that fears any possible interaction.

I find my self closer to the naturalist group, having seen from clinical experience of over 35 years very little interaction problems. That does not mean there are none, as there clearly are. I have put this information together with as broad of a brush as I can, to list as many opinions as possible. But on a daily basis, in the clinic, I realize that well over 95% of this material is useless as most of it is based on “thought experiments”, not real cases. But there are always sensitive patients that push the realms of normal clinical experience, so I am including these thought experiments in this material so you could be aware of what others think could happen.

There still has not been a lot of scientific research on this topic after more than 15 years of study into this area. Even though there has been a flurry of academic papers written over this period of time, stating ‘that more research needs to be done,’ no real attempt has been made to clearly categorize this area. One of the obvious reasons is just a lack of funding for doing a comprehensive job, while accurate information on specific interactions is hard to find. The other reason is that even though it was thought that there was going to be a large number of interactions, this past 15 years has not proven that to be true. If there had of been a huge number of critical, or even fatal, interactions, funding would have been found. Here is a clear case of no news is good news. We can’t be as bold as to say that because the allopathic community has somewhat dropped this subject, we don't have to worry anymore. We still have to do our due diligence.
Most of the academic papers written since 2006 are just a repeat of information from earlier studies. There has been some new information, but most of these come out in the form of what I termed earlier as “thought experiments,” more than clinical data.

This course is an attempt to summarize the known information up to what is available to us in mid-2012.

We will give a brief introduction to the subject area and, more importantly, ways for you to be critical of information you find in the literature. This is meant so you can decide if the information you find is important to you, as a Herbal Practitioner.

This is the bias that this has been written in. What is important to a Clinical Herbalist? We are going to follow the research in the area, but look at it from a herbalist’s point of view, more than what is normally done from a pharmacist or medical doctor’s point of view.

Just because something could theoretically have an interaction, doesn’t mean it will happen. After we go through the theoretical material, we have an alphabetical list of currently known interactions. The alphabetical listing denotes whether the study was done on humans, animals, in vitro (test tube), or just a “thought experiment.”

With more and more people turning to botanical medicines and/or using both botanical and pharmaceutical supplements and medicaments, it is important for the alternative medicine practitioner to keep current with the latest findings.

This course is a good place to get a basic understanding of this area, but as new drugs are released daily, you cannot rely on this booklet as your only source of reference. It is your responsibility to seek out answers if you are in doubt about possible interactions.

Introduction

In North America we have entered an interesting crossroad where many patients are seeing more than one form of health care practitioner. It is not that uncommon for a patient to come to a Herbalist asking for advice for a
specific problem, while they are concurrently also seeing an allopath and taking pharmaceuticals for that same health issue. This is only to be understandable as approximate 40% of North Americans take some form of supplement on a regular basis, with approximately 50% taking at least one prescription drug. There is considerable crossover between these two groups. This is not to mention the numbers taking street drugs (estimated at 10% - 20% for 12 – 25 age group) and of course alcohol (60% on a weekly basis) and cigarettes (20%, varying by ethnicity) also thrown into the mix.

In a way this is good news, because if there were a large group of serious herb-nutrient-drug interaction, it would by now show up on radar screens in a significant way. Again just because they don’t, does not mean we can leave our guard down, as there are some very significant herb-nutrient-drug interactions and it is our job to understand what they are.

Safety has become a major issue for many in this area. Patients want to know about compatibility and possible interactions when taking herbs and prescription drugs simultaneously. Unfortunately such specific questions are often difficult (if not impossible) to answer. There are very few studies published to document the safety and effectiveness of combining herbs with prescription drugs. Most of the information is just thought experiments, not real clinical data. With some general insights into pharmacology, we should be able to foresee possible interactions and thus take precautions to avoid incompatibilities. This is the best we can do until clinical data is obtained. Your mission, if you so feel up to taking the job, is to collect data on your patients over the next several years and help increase the clinical data. You can always send the information to Wild Rose College, or your local Herbal Association, so we can collect it and send it out to various herbal associations around North America.

When we are looking at a possible interaction, we refer to the possibility that one substance may alter the bioavailability, or the clinical effectiveness, of another substance when two or more substances are given concurrently. This may result an increase or a decrease in effect of one or both substances. At first that might seem
funny as of course many herb should have benefits to the patient and help them reduce their need for the pharmaceutical. Isn’t that our goal? This is still an interaction and needs to be recorded. This is especially true if the cumulative effect might cause a new or additional health issue.

Most of the possible interactions may be classified into two major categories: pharmacokinetic and pharmacodynamic interactions. We will look at these two areas.

**Pharmacokinetic Interactions**

Pharmacokinetic interaction refers to the fluctuation in bioavailability of herb/nutrient/drug substances in the body as a result of changes in absorption, distribution, metabolism and elimination.

**Absorption**

Absorption is the passage of herbs, nutrients, or drugs from the outside to the inside of the body. The majority of all absorption occurs in the intestines, where herbs or drugs must pass through the intestinal wall to enter the blood. Several mechanisms may interfere with the absorption of drugs through the intestines.

Botanicals may be adversely affected when they are given together with some drugs due to binding in the G.I. tract: for example, *Questran* (cholestyramine), *Colestid* (colestipol), *Carafate* (sucralfate) may bind to certain herbs, forming an insoluble complex, thus decrease absorption because the size of the insoluble complex is too big to pass through the intestinal wall.

Herbs may be adversely affected when the herbs are given together with some drugs that change the pH of the stomach: for example, *Antacids: Tagamet* (cimetidine), *Pepcid* (famotidine), *Axid* (nizatidine), *Zantac* (ranitidine) and *Prilosec* (omeprazole) may neutralize, decrease or inhibit the secretion of stomach acid. With the subsequent decrease of stomach acid, herbs may not be broken down properly, leading to poor
absorption in the intestines. To minimize the risk of interaction, it is best if the drugs and the herbs are taken separately by approximately two hours and/or by taking digestive enzymes with the botanical if indicated.

**Drugs that affect G.I. motility** may affect the absorption of herbs. G.I. motility is the rate at which the intestines contract to push the content from the stomach to the rectum. **Slower G.I.** motility means the herbs stay in the intestines for a longer period of time and there will be an increase in absorption. Conversely, **faster G.I.** motility means the herbs stay in the intestines for a shorter period of time and there may be a decrease in absorption:

**Decreased G.I.** motility may increase absorption of herbs: for example, 
**Haldol** (haloperidol). Therefore, it may be necessary to decrease the dosage of herbs

**Increased G.I. motility** may possibly decrease absorption of herbs: for example, 
**Reglan** (metoclopramide) and **Propulsid** (cisapride);

**Distribution**

After absorption, herbs or drugs need to be presented to the affected area to exert their effect. This refers to the process in which herbs or drugs are carried and released to different parts of the body.

At the present time, most drugs and herbs do not appear to have any clinically significant interactions affecting distribution and can be safely taken together. Interactions occur during the distribution phase if the drug has a narrow range of safety index and are highly protein-bound. For example, **Coumadin** (warfarin) is an anticoagulant medication that is very highly bound to protein and has a very narrow range of safety index. Coumadin (warfarin) interacts with various drugs, vitamins, herbs and foods via different mechanisms.

**Known examples that interact with Coumadin** (warfarin) include aspirin, ibuprofen, vitamin K, some types of tea, green leaf vegetables, etc. These items interact with Coumadin (warfarin) by either enhancing its
effectiveness and thus leading to prolonged bleeding, or by decreasing its effectiveness and thus increasing the risk of blood clots in the vessels, both of which may be quite dangerous to the patient.

This is why patients who are taking Coumadin (warfarin) need to be exceedingly cautious when taking herbs concurrently. Unfortunately, it is extremely difficult to predict whether an individual herb will interact with Coumadin (warfarin), because there are very few tests or experiments documenting such interactions. The best precautionary measure is close observation of the patient's condition. If the patient shows abnormal signs of bleeding and bruises, then the dosage of herbs may need to be adjusted and the patient's medical doctor should be contacted immediately. Just because a herb is also is a ‘blood thinner’ does not mean it will have an interaction. This is an area that is rich in the ‘thought experiment’ literature, but that has not shown up at the clinical level. Again, this doesn’t mean that you don’t have to watch, you do! If there is a potential for an interaction, someone out there will have it. It also doesn’t mean you can not use that botanical or nutrient supplement, you just have to be way more responsible, with a keen eye to observation. It usually means starting with a lower dosage and slowly increasing it.

Metabolism

Most of the herbs, nutrients and drugs are metabolized by the liver to their inactive derivatives. The rate at which the liver metabolizes these determines the length of time they stay active in the body. If the liver were induced to speed up its metabolism (excessive), the substance would be inactivated at a faster pace and the overall effectiveness of ingested substances would be lower. On the other hand, if the liver is induced to slow down its metabolism (deficiency), the herbs and drugs would be inactivated at a slower pace and the overall effectiveness of the substances would be higher.

In general, drugs that induce liver metabolism do not exert an immediate effect. The rate of liver metabolism changes slowly over several weeks. Therefore, the effect of
increased liver metabolism is not seen until weeks after the initiation of drug therapy.

**Drugs that speed up liver metabolism:**
- *Dilantin* (phenytoin), *Tegretol* (carbamazepine), *phenobarbital* and *rifampin.*

Therefore, the herbs may be inactivated faster and their overall effectiveness may be lower. Under such circumstances, the patient may need a higher dose of herbs to achieve the desired effectiveness.

**Drugs which inhibit liver metabolism** have an immediate onset of action. The rate of liver metabolism may be greatly impaired within a few days. Therefore, there is a higher risk of herbs accumulating inside the body as the function of the liver to inactivate them is compromised.

**Drugs that slow down or inhibit liver metabolism** include, but are not limited to:
- *Tagamet* (cimetidine), *erythromycin, ethanol,*
- *Diflucan* (fluconazole), *Sporonox* (itraconazole) and *Nizoral* (ketoconazole).

Therefore, the herbs may be inactivated more slowly and the overall effectiveness may be prolonged. In this case, one may need to lower the dosage of herbs to avoid unwanted side-effects.

**Elimination**

The liver and the kidney are responsible for eliminating herbs and drugs from the body. If the kidney(s) are damaged, the rate of elimination by the kidneys would be slowed down, leading to an accumulation of herbs and drugs in the body.

**Drugs that damage the kidneys** include:
- *amphotericin B, methotrexate, tobramicin* and *gentamicin.*

As a safety precaution, it may be necessary to lower the dosage of herbs if warranted to avoid unnecessary and unwanted side effects.
### Table 1. Recognition of Drugs of Higher Risk of Interaction

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Type of Drugs</th>
<th>Effect of Interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin</td>
<td>amphotericin</td>
<td>anti-fungal</td>
<td>may reduce elimination of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Axid</td>
<td>Nizatidine</td>
<td>acid-reducer</td>
<td>may interfere with absorption of herbs</td>
<td>adjust herb doses according to patient</td>
</tr>
<tr>
<td>Carafate</td>
<td>Sucralfate</td>
<td>anti-ulcer</td>
<td>may interfere with absorption of herbs</td>
<td>separate taking herbs &amp; drugs by two hours</td>
</tr>
<tr>
<td>Cholestid</td>
<td>Colestipol</td>
<td>Anti hyperlipidemic</td>
<td>may interfere with absorption of herbs</td>
<td>separate taking herbs &amp; drugs by two hours</td>
</tr>
<tr>
<td>Courmmolin</td>
<td>Warfarin</td>
<td>anti-coagulant</td>
<td>Courmmolin effect may change with herbs</td>
<td>monitor Courmmolin effectiveness closely</td>
</tr>
<tr>
<td>Diffucan</td>
<td>Fluconazole</td>
<td>anti-fungal</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Dilantin</td>
<td>Phenytion</td>
<td>anti-convulsant</td>
<td>may increase the metabolism of herbs</td>
<td>increase dose of herbs if necessary</td>
</tr>
<tr>
<td>E-Mycin</td>
<td>Erythromycin</td>
<td>anti-biotic</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>EES</td>
<td>Erythromycin</td>
<td>anti-biotic</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Eryc</td>
<td>Erythromycin</td>
<td>anti-biotic</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Alcohol</td>
<td>Alcohol</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Haldol</td>
<td>Haloperidol</td>
<td>Antipsychotic</td>
<td>may interfere with absorption of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Maalax</td>
<td>Antacid</td>
<td>Antacid</td>
<td>may interfere with absorption of herbs</td>
<td>separate taking herbs &amp; drugs by two hours</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>methotrexate</td>
<td>anti-neoplastic</td>
<td>may reduce elimination of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Mylanta</td>
<td>antacid</td>
<td>Antacid</td>
<td>may interfere with absorption of herbs</td>
<td>separate taking herbs &amp; drugs by two hours</td>
</tr>
<tr>
<td>Nizoral</td>
<td>ketoconazole</td>
<td>anti-fungal</td>
<td>may slow the metabolism of herbs</td>
<td>decrease dose of herbs if necessary</td>
</tr>
<tr>
<td>Pepeid</td>
<td>famotidine</td>
<td>acid-reducer</td>
<td>may interfere with absorption of herbs</td>
<td>adjust herb doses according to the patient</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>phenobarbital</td>
<td>anti-convulsant</td>
<td>may increase the metabolism of herbs</td>
<td>increase dose of herbs if necessary</td>
</tr>
<tr>
<td>Prilosec</td>
<td>omeprazole</td>
<td>acid-reducer</td>
<td>may interfere with absorption of herbs</td>
<td>adjust herb doses according to the patient</td>
</tr>
<tr>
<td>Propulsid</td>
<td>cisapride</td>
<td>GI stimulant</td>
<td>may interfere with absorption of herbs</td>
<td>increase dose of herbs if necessary</td>
</tr>
<tr>
<td>Questran</td>
<td>cholestyramine</td>
<td>Antihyperlipidemic</td>
<td>may decrease absorption of herbs</td>
<td>separate taking herbs &amp; drugs by two hours</td>
</tr>
<tr>
<td>Reglan</td>
<td>metoclopramide</td>
<td>GI stimulant</td>
<td>may interfere with absorption of herbs</td>
<td>increase dose of herbs if necessary</td>
</tr>
<tr>
<td>Rifadin</td>
<td>rifampin</td>
<td>anti-biotic</td>
<td>may increase the metabolism of herbs</td>
<td>increase dose of herbs if necessary</td>
</tr>
</tbody>
</table>
Herb-Drug-Nutrient Interaction
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Summary of Pharmacokinetic Interactions

The pharmacokinetic interactions listed in this section include both theoretical and actual interactions. Though such interactions are possible, the extent and severity of each interaction will vary depending on the specific circumstances, such as dosage, sensitivity, body weight and metabolic rate.

Pharmacodynamic Interactions

Pharmacodynamic refers to the study of how drugs actually behave inside the human body. Pharmacodynamic interactions refer to the fluctuation in bioavailability of ingested substances as a result of synergistic or antagonistic interactions between herb/drug substances. These interactions are generally more difficult to predict and prevent than pharmacokinetic interactions. Most of the pharmacodynamic interactions known now are documented through actual cases-as opposed to laboratory experiments.

The best way to prevent pharmacodynamic interactions is to follow the patient closely and monitor all clinical responses including signs, symptoms and any abnormal reactions. Examples of pharmacodynamic interaction include additive or antagonistic interactions. An additive effect occurs when two drugs of similar properties show additive or exponential increase in clinical effects when given together. An antagonistic effect occurs when two drugs of similar properties show lessened or no clinical effect when given together.

Herb-to-Drug Interactions

The pharmacodynamics of herb-nutrient-drug interactions are best identified by analyzing the therapeutic effect of the
herbs and drugs. Concurrent use of herbs and drugs with similar therapeutic actions could risk a herb-to-drug interactions, but not always. The increase in treatment effect interferes with optimal treatment outcome as the desired effect becomes more unpredictable and harder to obtain with precision.

The highest risk of clinically significant interactions occurs between herbs, nutrients, or drugs that have sympathomimic effects, cardiovascular effects, diuretic effects, anticoagulant effects and anti-diabetic effects.

Herbs with sympathomimetic effects may interfere with anti-hypertensive and antiseizure drugs. The classic example of an herb with sympathomimetic effects is Ma Huang (Ephedra), which contains ephedrine, pseudoephedrine, norephedrine and other ephedrine alkaloids. Ma Huang may interact with many other drugs and disease conditions and should always be used with caution in patients who have hypertension, seizures, diabetes, thyroid conditions, etc.

Concomitant use of diuretic herbs and diuretic drugs may have additive or synergistic effects, making hypertension more difficult to control or hypotensive episodes more likely. The dosage of herbs and/or drugs must be adjusted to achieve optimal treatment outcome.

Herbs with anticoagulant effects include herbs that have blood-activating and blood-stasis-removing functions. Such herbs may interfere with anticoagulant drugs, such as Coumadin (warfarin), to prolong the bleeding time. Herbs that interfere with Coumadin (warfarin) include Salviae Miltiorrhizae (Dan Shen), Angelica Sinensis (Dang Gui), Ligustici Chuanxiong (Chuan Xiong), Persicae (Tao Ren), Carthamus Tinctorii (Hong Hua) and Hirudo seu Whitmania (Shui Zhi). The synergistic interaction between herbs and Coumadin (warfarin) may be advantageous for the patient as the dosage of both the herbs and the drugs can be reduced without compromising clinical effectiveness. The reduction in dosage will also decrease the frequency and severity of side effects of the drugs.
Optimal treatment, however, is directly dependent on careful titration of the herb and drug, cooperation from the patient, and communication between the doctors who prescribe the herbs and the drugs.

**Anti-diabetic** herbs may interfere with anti-diabetic drugs by enhancing hypoglycemic effects. The dosage of herbs and drugs must be balanced carefully to control effectively the blood glucose level without causing hyper- or hypoglycemia. Herbs with definite hypoglycemic effects include the following pairs of herbs: Anemarrhena Asphodeloidis (Zhi Mu) and Gypsum Fibrosum (Shi Gao); Scrophularia Ningpoensis (Xuan Shen) and Atractylodes (Cang Zhu); and Dioscorea Opposita (Shan Yao) and Astragalus Membranacei (Huang Qi).

**Teratogenic Herbs**

Teratogenic herbs are known to have the tendency or likelihood of causing danger or harm to the fetus during pregnancy and thus leading to birth defects or spontaneous abortion. Teratogenic herbs are classified into two categories: prohibited and use with caution.

**Prohibited herbs** are very potent and very toxic. The use of these herbs during pregnancy is prohibited to avoid possible harm to the fetus. Prohibited herbs include Semen Crotonis (Ba Dou), Semen Pharbitidis (Qian Niu Zi), Radix Euphorbiae (Da Ji), Mylabris (Ban Mao), Radix Phytolaccae (Shang Lu), Moschus (She Xiang), Rhizoma Sparganii (San Leng), Rhizoma Zedoariae (E Zhu), Hirudo seu Whitmania (Shui Zhi) and Tabanus (Meng Chong).

Herbs that should be used with caution are herbs that are pungent and warm in nature and have the functions to activate Qi, activate Blood circulation, and remove blood stasis. They are also very potent in nature and should be avoided during pregnancy whenever possible. The use of these herbs should be limited only to later stages of pregnancy and only when the benefits of using the herbs outweigh the risks.

Herbs that should be used with caution include Semen Persicae (Tao Ren), Flos Carthami (Hong Hua), Rz. et Rx. Rhei (Da Huang), Fructus Aurantii (Zi Shi), Radix Aconiti
Herb (Fu Zhi), Rhizoma Zingiberis (Gan Jiang), and Cortex Cinnamomi (Rou Gui).

Conclusion

Historically, herbs and drugs have been two very different treatment modalities, which have rarely, if ever, been used together. The line that separates herbs and drugs, however, has been blurred in recent times with the increased accessibility to the lay public of different treatment modalities. It becomes very difficult to predict whether the combination of all these medications will lead to unwanted side effects and/or interactions. It is imprudent to assume that there will be no interactions.

On the other hand, it is just as unwise to abandon treatment simply for the fear of possible interactions. The solution to this situation is in the understanding of drug-drug and drug-herb-nutrient interactions. With understanding of these mechanisms, one can recognize potential interactions and take proper actions to prevent their occurrence.

Herb Drug Interaction Quick Facts

- As previously addressed, most herbal-drug interactions are theoretical or are based on suspected pharmacologic activity or in vitro data. Although it is commonly felt that warfarin interacts with several herbals, actual documentation has only been reported for a few herbals.

- Statistics on the simultaneous use of drugs and herbs varies depending on what authority has published their findings. A study in the early nineties found that 18.4% of those surveyed were simultaneously using drugs and herbs. Prevention magazine published a report in 2000 stating that 31% prescription drugs and 48% OTC drugs were being simultaneously used with herbal supplements.

- The American Herbal Products Association’s Botanical Safety Handbook reviewed 540 popular herbs in depth
and found only 11 herb-drug interactions (five of which involved the Ephedra species.)

- Herb Contraindications and Drug Interactions lists 207 botanicals, with 79 botanicals having interactions. This includes 60 interactions with caffeine containing plants. Many of the interactions are theoretical and speculative.

- Most metabolic problems arise from liver metabolic pathways that have historically been classified as phase 1 and phase 2, in that a bottleneck can occur between phase 1 and 2. Phase 1 enzymes (a family of hemoproteins called cytochrome p450 (CYP)) oxidize relatively non-polar molecules, increasing their polarity, thus allowing them to be excreted in urine. An estimated 60% of drugs are metabolized and excreted via this pathway. Many of these get passed onto phase 2, which conjugates the chemical. As phase 1 works faster than phase 2, phase 2 can sometimes get overwhelmed. For example, acetaminophen is metabolized into a toxic intermediary chemical. If too much acetaminophen is consumed, then a build up of the toxic metabolite will occur, causing hepatic centrilobular necrosis. This is particularly true if taken concurrently with alcohol.

- Some botanicals (such as Hypericum) speed up phase 1 either eliminating the drug faster, or building up metabolite for phase 2.

- Warfarin is known to interact with many drugs and, owing to its narrow therapeutic index, interactions can result in potentially fatal consequences if either bleeding complications arise or if sub-therapeutic levels occur. Herbals can also interact with warfarin, but the risk of herbal-warfarin interactions is difficult to characterize because of the limited number and nature of existing case reports.

- Some botanicals (such as Grapefruit) slow down phase 1, thus increasing activity time in the body.

- A component of Berberis (Mahonia) spp (5-methoxyhydnocarpin -- 5-MHC) inhibits bacteria efflux
pumps, thus reducing antibiotic resistance. This might also be true in case of cancer.

- Hypericum has had more drug interaction studies done than all other botanicals put together, as it affects CYP and of course its economic impact on pharmaceuticals sales.

- In looking at interactions between Hypericum and some drugs, there appears to be a significant difference between males and females.

- More study is needed to get a clear picture.

1 **Known Herb-Drug-Nutrient Interactions**

This alphabetical listing was last updated in May 2012. The omission of a herb or nutrient from this reference does not necessarily mean that an interaction with drugs has not been found. You are encouraged to do further research as new information is discovered daily.

It is important to understand that herb-drug-nutrient interactions are not always detrimental. In some cases the concurrent use of pharmaceuticals with herbs and nutrients creates a synergistic effect, meaning the efficacy of both the botanical and the pharmaceutical is enhanced. Or, in some cases, the use of a botanical can lessen unwanted side effects of pharmaceuticals, without lessening the pharmaceuticals efficacy on the targeted problem.

**Legend**

The following legend has been used to denote the type of study in which the following interactions were found. Of course in some cases, a reference can fit into more than one category.

- I – human study
- II – animal study
- III – in vitro (test tube) study
- IV – ‘thought experiments’
Definitions

**Empirical**: Relying on or derived from observation or experiment.

**Speculative**: Involving, based on, or constituting intellectual speculation.

**PO**: (per os) By way of the mouth, as in the administration of medication.

**IP**: (Intraperitoneal Injection) Administered by entering the peritoneum.

We have also included Lab results that might be alter with the use of a Herb-Nutrient. Again just because it could, does not mean it will; but if something is unexplained, this material might help you with those few patients that might produce most of these theoretical results.

As some Herbs and/or other nutrient might have an interaction, we have also included them. To an experienced Herbalist, most of these interactions are well expected, in fact they might be formulated to happen. These are included for non-herbalist to contemplate if they have have little experience in the area.

Foods also can have interactions. Most of these are again theoretical, not clinical, unless other wise stated.

If the interaction could be serious, we have highlighted it as major. Many of these are also theoretical and only might happen in sensitive people. We are including them without making value judgments. These potential major problems might not happen in 99% of the population, they could still be serious in the 1%.

**Aged cheese**

(brie, parmesan, cheddar and Roquefort), fava beans, sauerkraut, Italian green beans, some beers, red wine, pepperoni and overly ripe avocados should be avoided by
people taking MAO antidepressants. The interaction can cause a potentially fatal rise in blood pressure.¹³

**Alfalfa**

I Systemic lupus, while on prednisone may exacerbate symptoms after 9 - 30 months use.

II Increase metabolic rate of xenobiotics by liver.

III Warfarin activity can be reduced due to Vitamin K content (speculative). May increase activity of estrogen replacement therapy (speculative).⁷,⁸

IV Alfalfa seems to stimulate immune responses.⁹,¹⁰,¹¹ Theoretically, alfalfa might interfere with immunosuppressive therapy. Immunosuppressant drugs include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), corticosteroids.

IV Excessive doses of alfalfa may potentiate drug-induced photosensitivity.¹²

**Lab CHOLESTEROL**: Alfalfa seed might lower serum cholesterol concentrations and test results in individuals with type II hyperlipoproteinemia.⁴

**Herb VITAMIN E**: Alfalfa contains saponins, which interfere with the absorption or activity of vitamin E.

**Aloe**

I Increases hypoglycemic effect of glyburide (glibenclamide) with 1 Tbsp of Aloe.

I Aloe latex can reduce drug absorption of some drugs due to decreased GI transit time.¹³

I, IV There is a case of excessive intraoperative blood loss in a patient who took aloe 4 tablets/day for 2 weeks prior to surgery for hemangioma. The specific dose of aloe is unknown. Sevoflurane inhibits thromboxane A2 and therefore might decrease platelet aggregation and prolong bleeding time. Aloe vera also seems to inhibit thromboxane A2, prostaglandins, and therefore might also decrease platelet aggregation. Taking Aloe vera preoperatively might have contributed to excessive intraoperative bleeding.¹⁴ Advise patients to
avoid taking Aloe vera tablets at least 2 weeks prior to elective surgery.

II Improves anti-inflammatory action of hydrocortisone.

IV Preliminary research suggests aloe gel might lower blood glucose levels and have additive effects when used with antidiabetes drugs. This might increase the risk of hypoglycemia in some patients. Monitor blood glucose levels closely. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

IV Theoretically, overuse of aloe latex increases the risk of adverse effects from the cardiac glycoside drugs due to potassium depletion. Overuse of aloe, along with cardiac glycoside drugs, can increase the risk of toxicity.

IV Overuse of aloe latex might compound diuretic-induced potassium loss, increasing the risk of hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), hydrochlorothiazide (HCTZ, HydroDIURIL, Microzide), and others.

Lab BLOOD GLUCOSE: Preliminary research suggests aloe gel might lower blood glucose levels.

COLORIMETRIC DIAGNOSTIC TESTS: Aloe latex discolors alkaline urine (red) and can interfere with diagnostic tests that depend on a color change.

American Ginseng

III Increased the suppression of estrogen-dependent cancerous breast cell growth when used with tamoxifen, cytoxan, doxorubicin, taxol and methotrexate (in vitro).

IV American ginseng may lower blood glucose. Theoretically, concomitant use with antidiabetes drugs might enhance blood glucose lowering effects and possibly cause hypoglycemia. Monitor blood glucose levels closely. Some antidiabetes drugs
include glimepiride (Amaryl), glyburide (Diabeta, Glyburide PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

IV Theoretically, American ginseng may interfere with MAOI therapy. There is one case report of insomnia, headache, and tremors with concomitant phenelzine (Nardil) and unspecified ginseng use. There is also one case report of hypomania with concomitant phenelzine (Nardil) and unspecified ginseng use.

IV American ginseng can decrease the effectiveness of warfarin therapy. Healthy patients receiving warfarin 5 mg daily, who also take American ginseng 1 gram twice daily, seem to have a significantly reduced international normalized ratio (INR). To avoid this potential interaction, advise patients who take warfarin not to take American ginseng.

Lab BLOOD GLUCOSE: American ginseng may decrease postprandial blood glucose levels and test results.

Lab PROTHROMBIN TIME (PT): Theoretically, American ginseng may prolong thrombin time (TT) and activated partial thromboplastin time (aPTT), which is based on in vitro studies with the related species, Panax ginseng.

Ashwaganda

II Alcohol extract potentiated pentobarbital sleeping time. Speculative that it may enhance barbiturae sedative activity

IV Theoretically, ashwagandha might increase the effects of benzodiazepines. There is preliminary evidence that ashwagandha might have an additive effect with diazepam (Valium) and clonazepam (Klonopin). This may also occur with other benzodiazepines such as alprazolam (Xanax), flurazepam (Dalmane), lorazepam (Ativan), and midazolam (Versed).

IV Theoretically, ashwagandha might decrease the effectiveness of immunosuppressant therapy because of its potential immunostimulating effects. There is preliminary evidence that ashwagandha might decrease immunosuppression caused by cyclophosphamide. It might also decrease the
effectiveness of other immunosuppressant drugs such as azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), and other corticosteroids (glucocorticoids).

IV Theoretically, ashwagandha **might have additive effects when used with thyroid supplements.** There is preliminary evidence that ashwagandha might boost thyroid hormone synthesis and/or secretion.[22]

**Lab DIGOXIN SERUM ASSAY:** Ashwagandha contains withaferin A, which has a similar structure to digoxin.[25,26] Ashwagandha can **falsely elevate digoxin levels** when using fluorescence polarization immunoassays (FPIA), microparticle enzyme immunoassays (MEIA) or the Abbott Digoxin III assay.[25,26] The Beckman assay for digoxin seems to be only minimally affected.[25] The Roche Tina-Quant turbidimetric inhibition immunoassay is only affected by very high ashwagandha levels, equivalent to plasma levels after an overdose.[26]

**Lab THYROID FUNCTION TESTS:** There is some evidence that ashwagandha can **stimulate thyroid hormone synthesis or secretion.**[22] Theoretically, ashwagandha **might suppress thyroid stimulating hormone (TSH) or increase triiodothyronine (T3) or thyroxine (T4) values.**

**Astragalus**

I **Alpha interferon-1 and interferon-2 can be enhanced.**

II Acyclovir (Zovirax) antiviral effect against herpes simplex can be enhanced.

III Recombinant interleukin-2 can potentiate 10 fold (in vitro).

III **May be incompatible with immunosuppressive drugs** (e.g. cyclosporine, azathioprine and methotrexate).

IV Some evidence suggests astragalus might reduce immunosuppression caused by cyclophosphamide
IV Astragalus seems to stimulate immune function.\(^{27,29}\) Theoretically, taking astragalus might decrease the effects of immunosuppressive therapy. Immunosuppressant drugs include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), and other corticosteroids (glucocorticoids).

IV Astragalus is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, astragalus might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

**Barberry**

I 50 mg TID for 1-4 weeks helped to reverse leukopenia induced by benzene, cancer chemotherapy, or radiotherapy.

I 0.2% berberine has accumulative effect with local sulphacetamide, used as eye drops against Chlamydia.

IV There's very preliminary evidence that berberine, a constituent of European barberry, might inhibit cytochrome P450 3A4 (CYP3A4) enzyme.\(^{30}\) So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP3A4 in patients taking European barberry. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), indinavir (Crixivan), sildenafil (Viagra), triazolam (Halcion), and numerous others. Use European barberry cautiously or avoid in patients taking these drugs.

**Lab** **BILIRUBIN:** Theoretically, European barberry might increase bilirubin levels. This has been demonstrated with isolated berberine constituent, but not specifically with European barberry. Berberine displaces bilirubin from albumin and increases total and unbound bilirubin concentrations.\(^{31}\)
Bilberry

II 25% anthocyanoside inhibited gastric ulcer formation induced by phenylbutazone, indomethacin, reserpine, ethanol, and acetic acid (PO in rats).

IV Preliminary research suggests that anthocyanidin extracts from bilberry can inhibit platelet aggregation. Theoretically, combining bilberry with antiplatelet or anticoagulant drugs might increase the risk of bleeding. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.

II, IV Preliminary research in animal models suggests that bilberry leaf extract might have blood glucose lowering activity. Theoretically, concomitant use of bilberry leaf might require dosing adjustment of anti-diabetes drugs; monitor closely.

Lab BLOOD GLUCOSE: Theoretically, bilberry leaf might lower blood glucose and test results. Preliminary evidence suggests that a bilberry leaf extract might have blood glucose lowering activity.

Lab TRIGLYCERIDES: Theoretically, bilberry leaf might lower serum triglycerides and test results. Preliminary evidence suggests that a bilberry leaf extract might have triglyceride lowering activity.

Herb CHROMIUM-CONTAINING HERBS AND SUPPLEMENTS: Bilberry contains chromium and could increase the risk of chromium toxicity when taken with chromium supplements or chromium-containing herbs such as brewer's yeast, cascara, or horsetail.

Herb HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Theoretically, bilberry leaf might have additive effects with herbs that decrease blood glucose levels. Herbs with hypoglycemic potential include devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.
Bitter Melon

I Insulin dosage in diabetics may need adjusting.

III Additive effect with chlorpropamide (glucose lowering drug) in vitro

IV Bitter melon can lower blood glucose levels\textsuperscript{34,35,36} and might have additive effects when used with antidiabetes drugs. This might increase the risk of hypoglycemia in some patients. Monitor blood glucose levels closely. An additive effect of chlorpropamide (Diabinese) and bitter melon has been reported.\textsuperscript{37} Some antidiabetes drugs include glimepiride (Amaryl), glyburide (Diabeta, Glynase PresTabs, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

\textbf{Lab} \textbf{BLOOD GLUCOSE}: Bitter melon extracts, fruits, and fruit juice can lower blood glucose and test results in patients with type 2 diabetes.\textsuperscript{34,35,36}

\textbf{Lab} \textbf{GLYCOXYLATED HEMOGLOBIN (HbA1C)}: Bitter melon extract can lower HbA1C in type 2 diabetes patients after 7 weeks of treatment.\textsuperscript{36}

\textbf{Herb} \textbf{HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL}: Bitter melon can lower blood glucose levels\textsuperscript{34,35,36} and might have additive effects when used with other herbs and supplements that also lower glucose levels. This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic effects include alpha-lipoic acid, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

Black Pepper

I Phenytoin (Dilantin) absorbed more rapidly, being eliminated slower with piperine (PO). It increases intestinal cell permeability.\textsuperscript{13}

I Both propranolol (beta-blockers) and theophylline (asthma, chronic bronchitis, emphysema) were more completely absorbed with piperine.

I Black pepper and white pepper might increase levels of carbamazepine. Patients taking carbamazepine 300
mg or 500 mg twice daily had increased levels after taking a single dose of 20 mg purified piperine, which is a constituent of pepper. Piperine may increase absorption by increasing blood flow to the GI tract, increasing the surface area of the small intestine, or by cytochrome P450 3A4 (CYP3A4) inhibition in the gut wall. Absorption was significantly increased by 7-10 mcg/mL/hour. The time to eliminate carbamazepine was also increased by 4-8 hours. Although carbamazepine levels were increased, this did not appear to increase side effects.\(^{38}\)

II Increased bioavailability of vasicine when taken with sparteine and piperine (PO in rats). It is known to non-specifically inhibit cytochrome p450 clearing (in vitro).\(^{11}\) Pretreatment prolongs hexobarbital sleeping time and zoxazolamine (uricosuric and muscle relaxant) paralysis time (PO and IP in rats).\(^{13}\)

III Piperine is a non-specific potent inhibitor of drug metabolism due to oxidase and cytochrome p450 (in vitro).\(^{13}\)

IV Theoretically, black pepper and white pepper might increase levels of drugs metabolized by CYP3A4. The piperine constituent of pepper seems to inhibit CYP3A4 in vitro.\(^{39}\) Drugs that might be affected include some calcium channel blockers (diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), glucocorticoids, cisapride (Propulsid), alfentanil (Alfenta), fentanyl (Sublimaze), losartan (Cozaar), fluoxetine (Prozac), midazolam (Versed), omeprazole (Prilosec), ondansetron (Zofran), propranolol (Inderal), fexofenadine (Allegra), and numerous others.

IV Black pepper and white pepper are thought to have diuretic properties. Theoretically, due to these potential diuretic effects, black pepper and white pepper might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

IV Theoretically, black pepper and white pepper might increase levels of p-glycoprotein substrates. The piperine constituent of pepper seems to inhibit p-glycoprotein in vitro.\(^{39}\) Drugs that might be affected
include some chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir, saquinavir), H2 antagonists (cimetidine, ranitidine), some calcium channel blockers (diltiazem, verapamil), digoxin, corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, and others.

IV Theoretically, black pepper and white pepper might increase levels of rifampin. The piperine constituent of pepper seems to increase absorption and serum levels of rifampin.\(^{39}\)

IV Theoretically, black pepper and white pepper might increase levels of propranolol. The piperine constituent of pepper seems to increase absorption and slow elimination of propranolol.\(^{40}\)

IV Black pepper and white pepper might increase levels of phenytoin. The piperine constituent of pepper seems to increase absorption, slow elimination, and increase levels of phenytoin.\(^{41,42}\) Taking a single dose of black pepper (1 gram) along with phenytoin seems to double the serum concentrations of phenytoin.\(^{39}\) Consuming a soup with black pepper, providing piperine 44 mg/200 mL of soup, along with phenytoin also seems to increase phenytoin levels compared to consuming the same soup without black pepper.\(^{42}\)

**Lab** SERUM DRUG ASSAYS: Black pepper and white pepper can increase phenytoin, propranolol, and theophylline serum concentrations and test results.\(^{40,41}\)

**Herb** SPARTEINE: Piperine increases the bioavailability of sparteine, a constituent of scotch broom.\(^{13}\)

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**Bladderwrack**

I Lithium carbonate potentiates hypothyroid action of iodide (empirical).

III Bladderwrack seems to have anticoagulant effects.\(^{43}\) Theoretically, taking bladderwrack with antiplatelet or anticoagulant drugs might increase the risk of bruising and bleeding. Some of these drugs include aspirin; clopidogrel (Plavix); nonsteroidal anti-inflammatory
drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others); dalteparin (Fragmin); enoxaparin (Lovenox); heparin; warfarin (Coumadin); and others. Theoretically, concomitant use may result in additive hypothyroid activity, and may cause hypothyroidism. Some of these medications include methenamine mandelate (Methimazole), methimazole (Tapazole), potassium iodide (Thyro-Block), and others.

**Lab**

**ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT):** Theoretically, bladderwrack might increase aPTT test results due to the heparin-like activity of one of its constituents.

**Lab**

**ESTRADIOL:** In premenopausal women, bladderwrack seems to lower 17-beta-estradiol levels in a dose-dependent manner.

**Lab**

**PROGESTERONE:** In premenopausal women, bladderwrack seems to increase progesterone levels in a dose-dependent manner.

**Lab**

**RADIOACTIVE IODINE UPTAKE:** Theoretically, bladderwrack might interfere with the results of thyroid function tests using radioactive iodine uptake.

**Lab**

**THYROID STIMULATING HORMONE (TSH):** Theoretically, bladderwrack might increase serum TSH levels and test results.

**Lab**

**THYROXINE (T4):** Theoretically, bladderwrack might increase serum T4 levels and test results.

**Herb**

**ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS:** Theoretically, concomitant use of bladderwrack with herbs that might affect platelet aggregation might increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, fenugreek, feverfew, garlic, ginger, ginkgo, Panax ginseng, poplar, red clover, turmeric, and others.

**Herb**

**STRONTIUM:** Bladderwrack, also known as kelp, contains alginate, which binds strontium and reduces its absorption from the gastrointestinal tract. A 10% sodium alginate solution reduces strontium absorption 4-fold when taken at the same time. This effect has been used to reduce strontium absorption and toxicity in cases of poisoning, but could theoretically also
affect the absorption of strontium supplements.

**Bromelain**

1. Enhanced function of several antibiotics (PO).\(^{13}\)
2. Improved chemotherapy such as 5-fluorouracil (treatment of metastatic colon or rectum carcinomas) and vincristine (KS and non-Hodgkin’s lymphoma), (PO in humans).\(^{13}\)
3. Potentiated bleeding when used with anticoagulant (PO).\(^{13}\)
4. Increases plasma and urine levels of tetracycline (empirical).\(^{13}\)
5. Some evidence suggests that bromelain might increase levels of amoxicillin.\(^{48}\)
6. There is one case report of a patient experiencing minor bruising while taking bromelain with naproxen.\(^{49}\) Bromelain is thought to have antiplatelet activity.\(^{46,50}\) Theoretically, combining bromelain with other drugs that have anticoagulant or antiplatelet activity might increase the risk of bruising and bleeding. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.
7. Some evidence suggests that bromelain might increase absorption and levels of tetracycline antibiotics .\(^{51}\)

**Herbs**

**ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS**: Bromelain is thought to have antiplatelet activity.\(^{50,51}\) Theoretically, combining bromelain with other products that have anticoagulant or antiplatelet activity might increase the risk of bleeding. Some of these products include alfalfa, angelica, aniseed, arnica, asafoetida, bladderwrack, celery, chamomile, clove, fenugreek, feverfew, garlic, ginger, horse chestnut, licorice, meadowsweet, poplar, northern and southern prickly ash, quassia, red clover, and willow.

**Nutrients**

**ZINC**: Theoretically, metal ions such as zinc might inhibit the enzymatic activity of bromelain.\(^{52}\) However, there are no clinical reports of this
interaction.

**Food POTATO:** Potato contains a protein inhibitor of proteolytic enzymes. Theoretically, consuming potato might inhibit bromelain activity. 53

**Food SOYBEAN:** Soybean contains a protein inhibitor of proteolytic enzymes. Theoretically, consuming soybean might inhibit bromelain activity. 54

### Buckthorn

<table>
<thead>
<tr>
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<th>May reduce absorption of oral drugs due to increased bowel transit time (empirical). 13</th>
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<tbody>
<tr>
<td>IV</td>
<td>Concomitant use might compound fluid and electrolyte loss. 13</td>
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<tr>
<td>IV</td>
<td>Overuse of alder buckthorn might compound diuretic-induced potassium loss. 13 There is some concern that people taking alder buckthorn along with potassium depleting diuretics might have an increased risk for hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorothalidone (Thalitone), furosemide (Lasix), and hydrochlorothiazide (HCTZ, HydroDIURIL, Microzide), and others. 13</td>
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<tr>
<td>IV</td>
<td>Concomitant use of corticosteroids with alder buckthorn can increase the risk of potassium depletion. 55</td>
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<tr>
<td>IV</td>
<td>Theoretically, overuse or abuse of alder buckthorn can increase the risk of adverse effects from cardiac glycoside drugs. 13</td>
</tr>
<tr>
<td>IV</td>
<td>Alder buckthorn has stimulant laxative effects. In some people alder buckthorn can cause diarrhea. Diarrhea can increase the effects of warfarin, increase international normalized ratio (INR), and increase the risk of bleeding. Advise patients who take warfarin not to take excessive amounts of alder buckthorn.</td>
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</table>

**Lab COLORIMETRIC TESTS:** Alder buckthorn can discolor urine (pink, red, purple, orange, rust), interfering with diagnostic tests that depend on a color change, due to its anthraquinone content. 56,57,58

**Lab POTASSIUM:** Excessive use of alder buckthorn can cause potassium depletion, reducing serum potassium concentrations and test results. 56,57,7,13
**HORSETAIL**: Theoretically, concomitant use of alder buckthorn with horsetail can increase the risk of potassium depletion.

**LICORICE**: Theoretically, concomitant use of alder buckthorn with licorice can increase the risk of potassium depletion.

**STIMULANT LAXATIVE HERBS**: Theoretically, concomitant use of alder buckthorn with other stimulant laxative herbs can increase the risk of potassium depletion. Stimulant laxative herbs include aloe, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, yellow dock.¹³

**Bugleweed**

III May interfere with thyroid hormone (speculative) since it can block thyroxin to T3 conversion (in vitro, PO and IP in rat).

IV Theoretically, concomitant use of bugleweed can increase the risk of hypoglycemia.¹³ Blood glucose levels should be monitored closely.

**Lab RADIOACTIVE ISOTOPES**: Bugleweed can interfere with diagnostic procedures using radioactive isotopes.⁵⁵

**Lab THYROID FUNCTION TESTS**: Bugleweed might improve thyroid function and test results in mildly hyperthyroid patients.⁵⁵

**Herb THYROID-SUPPRESSING HERBS**: Theoretically, concomitant use of bugleweed with other thyroid suppressing herbs can have additive therapeutic and adverse effects.¹³ Herbs with thyroid-suppressing effects include balm leaf and the wild thyme plant.¹³

**Calamus**

II Alcohol extract increases sleeping time induced by pentobarbital (IP in rats), ethanol and ether (IP in mice), due to alpha-asarone, which potentiates pentobarbital.

IV Theoretically, calamus might potentiate the effects and adverse effects of monoamine oxidase inhibitor
drugs.\textsuperscript{7}

IV  Theoretically, concomitant use with drugs with sedative properties can cause additive effects and side effects.\textsuperscript{7}

IV  Theoretically, due to reports that calamus increases stomach acid, calamus might decrease the effectiveness of H2-blockers.\textsuperscript{13} The H2 blockers include cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid).

IV  Theoretically, due to reports that calamus increases stomach acid, calamus might decrease the effectiveness of PPIs.\textsuperscript{13} PPIs include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole (Nexium).

IV  Theoretically, due to reports that calamus increases stomach acid, calamus might decrease the effectiveness of antacids.\textsuperscript{13}

**Herbs**

**HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES:** Theoretically, concomitant use with supplements that have sedative properties might enhance therapeutic and adverse effects or calamus. Some of these include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, skullcap, valerian, yerba mansa, and others.

**Calendula**

II  Saponoside components increase hexobarbital sleeping time (in rats).\textsuperscript{13}

IV  Theoretically, concomitant use of calendula with drugs having sedative properties might cause additive therapeutic and adverse effects. A saponoside constituent in Calendula has been reported to increase hexobarbital sleep time in animals.\textsuperscript{13}
Cascara sagrada

IV Overuse or misused can cause potassium loss, thus increase toxicity of antiarrhythmic drugs and cardiac glycosides (empirical).13

IV May reduce absorption of oral drugs due to increased transit time (empirical).13

IV May aggravate potassium loss by thiazide diuretics.

IV Concomitant use of corticosteroids along with cascara can increase the risk of potassium depletion.55

IV Overuse of cascara might compound diuretic-induced potassium loss.13 There is some concern that people taking cascara along with potassium depleting diuretics might have an increased risk for hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), hydrochlorothiazide (HCTZ, Hydrodiuril, Microzide), and others.

IV Overuse of cascara might compound diuretic-induced potassium loss.13 There is some concern that people taking cascara along with potassium depleting diuretics might have an increased risk for hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), hydrochlorothiazide (HCTZ, Hydrodiuril, Microzide), and others.

IV Cascara has stimulant laxative effects. In some people cascara can cause diarrhea. Diarrhea can increase the effects of warfarin, increase international normalized ratio (INR), and increase the risk of bleeding. Advise patients who take warfarin not to take excessive amounts of cascara.

Lab COLORIMETRIC TESTS: Cascara can discolor urine (pink, red, purple, orange, rust), interfering with diagnostic tests that depend on a color change, due to its anthraquinone content.58

Lab POTASSIUM: Excessive use of cascara can cause potassium depletion, reducing serum potassium concentrations and test results.13
CARDIAC GLYCOSIDE-CONTAINING HERBS: Theoretically, concomitant use with other cardiac glycoside-containing herbs might increase risk of cardiac toxicity. Cardiac glycoside-containing herbs include black hellebore, Canadian hemp roots, digitalis leaf, hedge mustard, figwort, lily of the valley roots, motherwort, oleander leaf, pheasant's eye plant, pleurisy root, squill bulb leaf scales, and strophanthus seeds.\

CHROMIUM-CONTAINING HERBS AND SUPPLEMENTS: Cascara contains chromium and could increase the risk of chromium toxicity when taken with chromium supplements or chromium-containing herbs such as bilberry, brewer's yeast, or horsetail.

HORSETAIL: Theoretically, concomitant use of cascara with horsetail can increase the risk of potassium depletion.

LICORICE: Theoretically, concomitant use of cascara with licorice can increase the risk of potassium depletion.

STIMULANT LAXATIVE HERBS: Theoretically, cascara used concomitantly with other herbs that are stimulant laxatives can increase the risk of potassium depletion. Stimulant laxative herbs include aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, and yellow dock.

Cassia cinnamon

Can prevent ulcers by phenylbutazone and ethanol (IV and PO in rats).

Reduced absorption of tetracycline (speculative, in vitro).

Cassia cinnamon may lower blood glucose levels, and have additive effects in patients treated with antidiabetic agents; use with caution. Dose adjustments to diabetes medications might be necessary. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase...
PresTab, Micronase), insulin, metformin
(Glucomphage), pioglitazone (Actos), rosiglitazone
(Avandia), and others.

**Lab** BLOOD GLUCOSE: Cassia cinnamon might lower
blood glucose levels and test results in some
patients. 59

**Lab** LIVER FUNCTION TESTS: There is some concern
that ingesting large amounts of cassia cinnamon might
increase liver enzymes and cause hepatotoxicity in
some people. Cassia cinnamon contains coumarin
which can cause hepatotoxicity in animal models. 60 In
humans, very high doses of coumarin from 50-7000
mg/day can result in hepatotoxicity that resolves when
coumarin is discontinued. 61 Lower amounts might
also cause liver problem in susceptible people such as
those with pre-existing liver disease.

**Herb** HEPATOTOXIC HERBS AND SUPPLEMENTS:
There is some concern that ingesting large amounts of
cassia cinnamon might cause hepatotoxicity in some
people. Cassia cinnamon contains coumarin which
can cause hepatotoxicity in animal models. 60 In
humans, very high doses of coumarin, from 50-7000
mg/day, can result in hepatotoxicity that resolves when
coumarin is discontinued. 61 Lower amounts might
also cause liver problems in susceptible people
such as those with pre-existing liver disease.

Theoretically, concomitant use with other potentially
hepatotoxic products might increase the risk of
developing liver damage. Some of these products
include androstenedione, chaparral, comfrey, DHEA,
germander, kava, niacin, pennyroyal oil, red yeast,
and others.

**Herb** HERBS AND SUPPLEMENTS WITH
HYPOGLYCEMIC POTENTIAL: Cassia
cinnamon might lower blood glucose levels. 59
Theoretically, it might have additive effects when
used with other herbs and supplements that also lower
blood glucose levels. This might increase the risk of
hypoglycemia in some patients. Some herbs and
supplements with hypoglycemic effects include
alpha-lipoic acid, bitter melon, chromium, devil's
claw, fenugreek, garlic, guar gum, horse chestnut,
Panax ginseng, psyllium, Siberian ginseng, and other.
Cayenne

I 20 mg reduces gastric mucosal damage when taken 2 hour before aspirin (PO human).\(^{13}\)

I Concurrent use with ACE inhibitors can cause coughing if capsaicin cream is used topically.\(^{13}\)

I Antacids are antagonized (PO human).\(^{13}\)

II Theophylline (chronic asthma) absorption was enhanced and metabolism was inhibited (PO rabbits).\(^{13}\)

II Hexobarbital sleeping time enhanced with occasional capsicum use, decrease with chronic use due to p450 (IP rats).

II Reduce ethanol/acid-induced ulcer by 3 - 30 mg/K of capsaicin (PO in rats).

III Capsaicin inhibited metabolism of ethylmorphine (narcotic analgesic and antitussive) by microsome in liver (in vitro).

IV Theoretically, capsicum might increase the effects and adverse effects of antiplatelet drugs.\(^{62,63}\)

IV Theoretically, concomitant use of capsicum (including exposure to the capsicum in pepper spray) and cocaine might increase cocaine effects and the risk of adverse effects, including death.\(^{64}\)

Lab BLEEDING TIME: Capsicum has led to increased fibrinolytic activity and may lead to prolonged times in coagulation studies.\(^{65}\)

Herb ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs and supplements that affect platelet aggregation could theoretically increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, and others.

Herb COCA: Theoretically, concomitant use of capsicum (including exposure to the capsicum in pepper spray) and coca might increase the effects and risk of adverse effects of the cocaine in coca.\(^{64}\)
## Cinchona

<table>
<thead>
<tr>
<th>Classification</th>
<th>Interaction Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Potentiating of coumarin derivatives (empirical) or other anticoagulants due to rare platelet reduction (empirical).&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>I</td>
<td>Tobacco and rifampicin increases the clearance of quinine (PO human).&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Cinchona contains quinidine; concomitant use with cinchona can increase the therapeutic and adverse effects of quinidine.&lt;sup&gt;66&lt;/sup&gt; &lt;sup&gt;major&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Cinchona can increase serum drug levels of carbamazepine due to its quinine content.&lt;sup&gt;67&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Theoretically, due to reports that cinchona increases stomach acid, cinchona might decrease the effectiveness of antacids.&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
<tr>
<td>IV</td>
<td>Theoretically, due to reports that cinchona increases stomach acid, cinchona might decrease the effectiveness of PPIs.&lt;sup&gt;13&lt;/sup&gt; PPIs include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole (Nexium).</td>
</tr>
<tr>
<td>IV</td>
<td>Theoretically, due to reports that cinchona increases stomach acid, cinchona might decrease the effectiveness of H2-blockers.&lt;sup&gt;13&lt;/sup&gt; The H2 blockers include cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid).</td>
</tr>
<tr>
<td>IV</td>
<td>Cinchona can increase serum drug levels of phenobarbital due to its quinine content.&lt;sup&gt;68&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Herb: **ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS**

Theoretically, concomitant use of cinchona bark with herbs that might have anticoagulant or antiplatelet properties might increase the risk of bleeding in some people. These herbs include alfalfa, angelica, clove, garlic, ginger, Panax ginseng, horse chestnut, red clover, and others.
Coffee

I Iron absorption is inhibited (empirical human).\textsuperscript{13}

I Excessive caffeine should be avoided with MAOIs due to increased norepinephrine (PO human).\textsuperscript{13}

I Caffeine (within 12 hours) inhibits hemodynamics effects of adenosine (human).\textsuperscript{13}

I Reduction of effects of hypnotics.\textsuperscript{13}

I Antagonizes blood pressure medication.\textsuperscript{13}

I Decreases lithium levels with chronic but not acute use.\textsuperscript{13}

I Several drugs, including oral contraceptives, increase caffeine’s stimulative effect.\textsuperscript{13}

I Concomitant use of alcohol can increase caffeine serum concentrations and the risk of caffeine adverse effects. Alcohol reduces caffeine metabolism.\textsuperscript{69}

I Separate coffee ingestion and alendronate administration by two hours. Coffee reduces alendronate bioavailability by 60%.\textsuperscript{70}

I Coffee can reduce levothyroxine absorption in some patients, possibly by forming non-absorbable complexes. Several patients have an improved response to levothyroxine when they take it with water instead of their usual black coffee. A pharmacokinetic study in these patients found that 25-30 mL espresso coffee consumed with levothyroxine tablets delayed the time to peak plasma levels by 38-43 minutes, reduced the peak plasma level (Cmax) by 19% to 36%, and reduced the area under the curve (AUC) by 27% to 36%. Coffee consumed one hour after levothyroxine did not affect absorption.\textsuperscript{71} It is not known whether this interaction occurs with other types of coffee. Advise patients to avoid drinking coffee at the same time that they take their levothyroxine, and for up to an hour afterwards.

IV May reduce some oral drugs absorption.

IV Theoretically, caffeine in coffee might increase the risk of bleeding when used concomitantly with these agents. Caffeine is reported to have antiplatelet activity;\textsuperscript{72,73} however, this interaction has not been reported in humans. There is some evidence that caffeinated coffee might increase the fibrinolytic activity in blood.\textsuperscript{74} Antiplatelet agents include aspirin,
clopidogrel (Plavix), dipyridamole (Persantine), ticlopidine (Ticlid), and others. Anticoagulant agents include ardeparin (Normiflo), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, and warfarin (Coumadin).

IV Theoretically, concomitant use of coffee and diabetes drugs might interfere with blood glucose control due to the caffeine in coffee. However, data are conflicting. Reports claim that caffeine might increase or decrease blood sugar.\(^{75,76}\)

IV Theoretically, concomitant use of large amounts of coffee might increase cardiac inotropic effects of beta-agonists, due to coffee's caffeine content.\(^{77}\) Beta-adrenergic agonists include albuterol (Ventolin, Proventil), metaproterenol (Alupent), terbutaline (Brethine, Bricanyl), and isoproterenol (Isuprel).

IV Theoretically, concomitant use might increase serum caffeine concentrations and the risk of adverse effects, due to the caffeine contained in coffee. Cimetidine decreases the rate of caffeine clearance by 30%.\(^{78}\)

IV Theoretically, co-administration might acutely exacerbate psychotic symptoms, due to the caffeine contained in coffee. Caffeine can increase the effects and toxicity of clozapine. Caffeine doses of 400-1000 mg per day inhibit clozapine metabolism.\(^{79}\) Clozapine is metabolized by cytochrome P450 1A2 (CYP1A2). Researchers speculate that caffeine might inhibit CYP1A2. But there is no reliable evidence that caffeine affects CYP1A2. There is also speculation that genetic factors might make some patients more sensitive to the interaction between clozapine and caffeine.\(^{80}\)

IV Coffee contains caffeine. Concomitant use can increase caffeine serum concentrations, and the risk of adverse effects. Disulfiram decreases the rate of caffeine clearance.\(^{81}\)

IV Concomitant use might increase the effects of caffeine. Fluconazole decreases caffeine clearance by approximately 25%.\(^{82}\)

IV Use of ephedrine with coffee can increase the risk of stimulatory adverse effects of caffeine. There is evidence that using ephedrine with caffeine might increase the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizures, and
death.\(^{83,84,85}\) Tell patients to avoid taking coffee with ephedrine and other stimulants.

**IV** Concomitant use might increase the effects and adverse effects of caffeine in coffee. Mexiletine can decrease caffeine elimination by 50%.\(^{86,87}\)

**IV** Theoretically, concomitant intake of large amounts of coffee with MAOIs might precipitate a hypertensive crisis, due to the caffeine contained in coffee. This is based on the claim that intake of large amounts of caffeine with MAOIs might precipitate a hypertensive crisis.\(^{88}\)

**IV** The caffeine in coffee might negate the hypnotic effects of pentobarbital.\(^{89}\)

**IV** The tannins in coffee might cause precipitation of solutions of fluphenazine (Permitil, Prolixin), chlorpromazine (Thorazine), haloperidol (Haldol), prochlorperazine (Compazine), thioridazine (Mellaril), and trifluoperazine (Stelazine).\(^{90,91}\)

**IV** Concomitant use of phenylpropanolamine and coffee might cause an additive increase in blood pressure due to the caffeine in coffee.\(^{92}\) Phenylpropanolamine also seems to increase caffeine serum levels.\(^{93}\)

**IV** Theoretically, concomitant use might increase serum caffeine concentrations and the risk of adverse effects, due to the caffeine contained in coffee. Quinolones decrease caffeine clearance.\(^{94,95,96}\) Quinolones (also referred to as fluoroquinolones) include ciprofloxacin (Cipro), enoxacin (Penetrex), gatifloxacin (Tequin), levofloxacin (Levaquin), lomefloxacin (Maxaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), sparfloxacin (Zagam), and trovafloxacin (Trovan).

**IV** Theoretically, concomitant use might increase serum caffeine and riluzole concentrations and the risk of adverse effects of both caffeine and riluzole, due to the caffeine contained in coffee. Caffeine and riluzole are both metabolized by cytochrome P450 1A2, and concomitant use might reduce metabolism of one or both agents.\(^{97}\)

**IV** Theoretically, concomitant use might increase serum caffeine concentrations and the risk of adverse effects, due to the caffeine contained in coffee. Terbinafine decreases the rate of caffeine clearance.\(^{98}\)

**IV** Theoretically, concomitant use might increase serum theophylline concentrations and the risk of adverse
effects, due to the caffeine contained in coffee. Large amounts of caffeine might inhibit theophylline metabolism.99

IV The tannins in coffee might cause precipitation of solutions of amitriptyline (Elavil) or imipramine (Tofranil, Janimine).90,91

IV Theoretically, concomitant use might increase plasma caffeine concentrations and the risk of adverse effects, due to the caffeine contained in coffee. Verapamil increases plasma caffeine concentrations by 25%.99

Lab 5-HYDROXYINDOLEACETIC ACID: Coffee might increase urine 5-hydroxyindoleacetic acid concentrations and test results, due to its caffeine content. Caffeine can increase urine catecholamine concentrations.76

Lab BLEEDING TIME: Theoretically, coffee might increase bleeding time. Caffeine can prolong bleeding time and increase the results of a bleeding time test.100 Caffeine is reported to have antiplatelet activity.101,102 There is some evidence that caffeinated coffee increases fibrinolytic activity in blood.103 However, the significance of these effects in humans is not known.

Lab CATECHOLAMINES: Coffee might increase urine catecholamine concentrations and test results, due to its caffeine content. Caffeine can increase urine catecholamine concentrations.104

Lab CREATINE: Coffee might increase urine creatine concentrations and test results, due to its caffeine content.100

Lab DIPYRIDAMOLE THALLIUM IMAGING: Coffee might interfere with dipyridamole thallium imaging studies, due to its caffeine content. Caffeine attenuates the characteristic cardiovascular responses to dipyridamole and has altered test results.105

Lab GLUCOSE: Caffeine, a constituent of coffee, has been reported to cause increases and decreases in blood glucose.104

Lab LACTATE: The combination of ephedrine, a constituent of ephedra, and the caffeine in coffee can increase blood lactate levels.104

Lab NEUROBLASTOMA TESTS: Coffee (due to its caffeine content) might cause false-positive diagnosis of neuroblastoma, when diagnosis is based on tests of urine vanillylmandelic acid (VMA) or catecholamine
concentrations. Caffeine can increase urine catecholamine and VMA concentrations.  

**Lab PHARMACOLOGICAL STRESS TESTS:** The caffeine in coffee is a competitive antagonist for adenosine receptors. Caffeine attenuates the characteristic cardiovascular responses to dipyridamole and has altered test results. It is recommended that caffeine and caffeine-containing products be stopped 24 hours prior to pharmacological stress tests. However, caffeine appears more likely to interfere with dipyridamole (Persantine) than adenosine (Adenoscard) stress testing. The interaction between caffeine and dipyridamole is unlikely to be significant in stress testing if the heart rate increase is greater than 5% after dipyridamole infusion.  

**Lab PHEOCHROMOCYTOMA TESTS:** Coffee (due to its caffeine content) might cause false-positive diagnosis of pheochromocytoma, when diagnosis is based on tests of urine vanillylmandelic acid (VMA) or catecholamine concentrations. Caffeine can increase urine catecholamine and VMA concentrations.  

**Lab PULMONARY FUNCTION TESTS:** People may need to avoid caffeine and caffeinated beverages for at least four hours prior to lung function testing. Forced expiratory volume in one minute (FEV1) seems to show a small improvement up to two hours after caffeine use. Mid-expiratory flow rates may also improve with caffeine for up to four hours.  

**Lab THEOPHYLLINE:** Theophylline is a metabolite of caffeine. Caffeine in overdose can cause significant increases in theophylline serum concentrations. Theoretically very large amounts of coffee could cause measurable theophylline levels.  

**Lab URATE:** Coffee might falsely increase serum urate test results determined by the Bittner method, due to its caffeine content. Caffeine causes false elevations in serum urate test results determined by the Bittner method.  

**Lab URINARY CALCIUM:** Caffeine, a constituent of coffee, can increase urinary calcium levels.  

**Lab VANILLYLMANDELIC ACID (VMA):** Coffee might increase urine VMA concentrations and test results, due to its caffeine content. Caffeine can
increase urine VMA concentrations.\textsuperscript{76}

**WHOLE BLOOD FIBRINOLYSIS TIME (Fearnley method):** There is evidence caffeinated coffee may increase the whole blood fibrinolysis time.\textsuperscript{103}

**ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS:** Concomitant use of herbs and supplements that affect platelet aggregation could theoretically increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, and others.

**BITTER ORANGE:** Bitter orange in combination with caffeine or caffeine-containing herbs can increase blood pressure and heart rate in otherwise healthy normotensive adults, potentially increasing the risk of serious cardiovascular adverse effects.

**CAFFEINE-CONTAINING HERBS AND SUPPLEMENTS:** Concomitant use of coffee and caffeine-containing herbs/supplements constitutes therapeutic duplication (due to the caffeine contained in coffee) which increases the risk of caffeine-related adverse effects. Other natural products which contain caffeine include black tea, cocoa, cola nut, green tea, oolong tea, guarana, and mate.

**CALCIUM:** High caffeine intake from foods and beverages including coffee increases urinary calcium excretion.\textsuperscript{113}

**CREATINE:** There is some concern that combining caffeine or caffeine containing beverages and herbs with ephedra, and creatine might increase the risk of serious adverse effects. There is a report of ischemic stroke in an athlete who consumed creatine monohydrate 6 grams, caffeine 400-600 mg, ephedra 40-60 mg, and a variety of other supplements daily for 6 weeks.\textsuperscript{114} Caffeine might also decrease creatine's possible beneficial effects on athletic performance. Some researchers think caffeine can inhibit phosphocreatine resynthesis.\textsuperscript{115,116}

**EPHEDRA (Ma Huang):** Use of ephedra with coffee can increase the risk of caffeine stimulatory adverse effects. There is evidence that using ephedra with caffeine might increase the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizures,
and death.\textsuperscript{114,117,118} Tell patients to avoid taking coffee with ephedra and other stimulants.

**Nutri** MAGNESIUM: Consuming large amounts of coffee can increase excretion of magnesium.\textsuperscript{119}

### Cola

similar to coffee

### Cordyceps

<table>
<thead>
<tr>
<th></th>
<th>Reduces nephrotoxicity from gentamicin (aminoglycoside antibiotic), (PO human) and other drugs.\textsuperscript{13}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Improves cyclosorin A use in kidney transplants (PO human).\textsuperscript{13}</td>
</tr>
<tr>
<td></td>
<td>Increases effectiveness of asthmatic medication.\textsuperscript{13}</td>
</tr>
<tr>
<td>IV</td>
<td>Theoretically, cordyceps might reduce the immunosuppressive effects of cyclophosphamide.\textsuperscript{120,121}</td>
</tr>
<tr>
<td>IV</td>
<td>Cordyceps might stimulate the immune system.\textsuperscript{122,123,124,125} Theoretically, concurrent use of cordyceps might interfere with immunosuppressive therapy. Immunosuppressant drugs include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone (Deltasone, Orasone), corticosteroids (glucocorticoids), and others.</td>
</tr>
<tr>
<td>IV</td>
<td>Theoretically, cordyceps might reduce the immunosuppressive effects of prednisolone.\textsuperscript{124,126}</td>
</tr>
</tbody>
</table>

**Lab** LIVER FUNCTION TESTS: Cordyceps might improve liver function and test results in people with chronic hepatitis B.\textsuperscript{127}
Herb-Drug-Nutrient Interaction
By Terry Willard CIH, PhD

Crucifer

I Phenacetin, antipyrine, oxazepam (Serax) and acetaminophen (Tylenol) are metabolized more rapidly (PO human) due to enhancing p450 function.  

I Increase caffeine metabolism (PO human).  

I Estrone metabolism was increased by consuming 500 gm/day of crucifer (PO human).  

II Hexobarbital and 7-ethoxycoumarin are metabolized faster.  

II Interferes with iodine metabolism by thyroid gland (PO rats).  

IV Anticoagulant effect of warfarin may be inhibited or rendered ineffective (PO human).  

Lab INTERNATIONAL NORMALIZED RATIO (INR)/PROTHROMBIN TIME (PT): Theoretically, cabbage might decrease coagulation test results due to high vitamin K content.  

Lab THYROID STIMULATING HORMONE (TSH): Ingesting large quantities of cabbage juice might elevate TSH test results.  

Devil's Claw

I One case of pupura development with warfarin (PO human).  

IV There's preliminary evidence that devil's claw might inhibit cytochrome P450 2C19 (CYP2C19). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C19 in patients taking devil's claw. Some drugs metabolized by CYP2C19 include proton pump inhibitors including omeprazole (Prilosec), lansoprazole (Prevacid), and pantoprazole (Protonix), diazepam (Valium), carisoprodol (Soma), nelfinavir (Viracept), and others.  

IV There's preliminary evidence that devil's claw might inhibit cytochrome P450 2C9 (CYP2C9). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking devil's claw. Some drugs metabolized by CYP2C9 include
nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren), ibuprofen (Motrin), meloxicam (Mobic), and piroxicam (Feldene), celecoxib (Celebrex), amitriptyline (Elavil), warfarin (Coumadin), glipizide (Glucotrol), losartan (Cozaar), and others. Use devil's claw cautiously or avoid in patients taking these drugs.

**IV** There's preliminary evidence that devil's claw might inhibit cytochrome P450 3A4 (CYP3A4) enzyme. So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP3A4 in patients taking devil's claw. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use devil's claw cautiously or avoid in patients taking these drugs.

**IV** Theoretically, due to reports that devil's claw increases stomach acid, devil's claw might decrease the effectiveness of H2-blockers. The H2 blockers include cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axd), and famotidine (Pepcid).

**IV** Preliminary in vitro research suggests that devil's claw can inhibit the multi-drug transporter protein, P-glycoprotein. Theoretically, devil's claw might increase levels of drugs affected by P-glycoprotein. However, it is too soon to tell if this is clinically important. Some drugs transported by P-glycoprotein include etoposide, paclitaxel, vinblastine, vincristine, vindesine, ketoconazole, itraconazole, amprenavir, indinavir, nelfinavir, saquinavir, cimetidine, ranitidine, diltiazem, verapamil, corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, and others.

**IV** Theoretically, due to reports that devil's claw increases stomach acid, devil's claw might decrease the effectiveness of PPIs. PPIs include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole (Nexium).
Dong Quai

I Over 500 mg 1-2 times daily for four weeks with warfarin increased prothromin time, effect continued for four weeks after use. (PO human). No problem with single doses.\textsuperscript{13}

\textbf{Lab}

PROTHROMBIN TIME (PT), INTERNATIONAL NORMALIZATION RATIO (INR): Dong quai can enhance the effects of warfarin, resulting in increased PT and INR test results.\textsuperscript{132}

\textbf{Herb}

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs that have antiplatelet/anticoagulant effects could theoretically increase the risk of bleeding in some people.\textsuperscript{132} These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, panax ginseng, poplar, red clover, willow, and others.

Eleuthero

I Increased efficacy of several antibiotics (PO human).\textsuperscript{13}

IV There is preliminary evidence that suggests that Siberian ginseng root extract might have sedative effects.\textsuperscript{133} Theoretically, it might have an additive sedative effect with alcohol.

IV A constituent of Siberian ginseng, dihydroxybenzoic acid, appears to inhibit platelet aggregation.\textsuperscript{134} Concomitant use with anticoagulant or antiplatelet drugs might increase the risk of bleeding.

IV A constituent of Siberian ginseng, dihydroxybenzoic acid, appears to inhibit platelet aggregation.\textsuperscript{134} Concomitant use with anticoagulant or antiplatelet drugs might increase the risk of bleeding.

IV There is preliminary evidence that suggests that Siberian ginseng root extract may have sedative properties.\textsuperscript{131} Theoretically, concomitant use with drugs with sedative properties may cause additive effects and side effects.

IV Preliminary evidence suggests that standardized extracts of Siberian ginseng might inhibit cytochrome P450 1A2 (CYP1A2) in vitro and in animal models.\textsuperscript{132} Until more is known about the effect on CYP1A2, Siberian ginseng should be used cautiously in patients taking drugs that are metabolized by these
CYP450 enzymes. Some drugs metabolized by CYP1A2 include clozapine (Clozaril), cyclobenzaprine (Flexeril), fluvoxamine (Luvox), haloperidol (Haldol), imipramine (Tofranil), mexiletine (Mexitil), olanzapine (Zyprexa), Pentazocine (Talwin), propranolol (Inderal), tacrine (Cognex), theophylline (Slo-bid, Theo-Dur, others), zileuton (Zyflo), Zolmitriptan (Zomig), and others.

IV Preliminary evidence suggests that standardized extracts of Siberian ginseng might inhibit cytochrome P450 2C9 (CYP2C9) in vitro and in animal models. Until more is known about the effect on CYP2C9, Siberian ginseng should be used cautiously in patients taking drugs that are metabolized by these CYP450 enzymes. Some drugs metabolized by CYP2C9 include amitriptyline (Elavil), diazepam (Valium), estradiol (Estrace), tacrine (Cognex), verapamil (Calan), warfarin (Coumadin), zileuton (Zyflo), and others.

IV Preliminary evidence suggests that standardized extracts of Siberian ginseng might inhibit cytochrome P450 2D6 (CYP2D6) in vitro and in animal models. However, Siberian ginseng does not appear to inhibit drug metabolism by CYP2D6 in humans.

IV Preliminary evidence suggests that standardized extracts of Siberian ginseng might inhibit cytochrome P450 3A4 (CYP3A4) in vitro and in animal models. However, Siberian ginseng does not appear to inhibit drug metabolism by CYP3A4 in humans.

IV Siberian ginseng is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, Siberian ginseng might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

Lab BLOOD GLUCOSE: The effect of Siberian ginseng on blood glucose may vary. Some research suggests it might have hypoglycemic activity. Other research suggests it might increase blood glucose.

Lab DIGOXIN SERUM ASSAY: Siberian ginseng can interfere with some serum digoxin measurements. It falsely elevates serum digoxin concentrations when fluorescence polarization immunoassay (FPIA) or the Abbott Digoxin III assay are used, and falsely lowers digoxin concentrations when microparticle enzyme
immunoassay (MEIA) is used.\textsuperscript{138,139} This interference is likely related to the structural similarity of some Siberian ginseng eleutherosides to cardiac glycosides.\textsuperscript{138} Interference does not occur when digoxin levels are measured with an enzyme multiplied immunoassay (EMIT), the Randox digoxin assay, or a chemiluminescent assay (CLIA), or the Roche Tina-Quant turbidimetric inhibition immunoassay.\textsuperscript{138,139}

**ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS:** Concomitant use with herbs and supplements that affect platelet aggregation could theoretically increase the risk of bleeding in some people due to Siberian ginseng's possible effect on platelet aggregation.\textsuperscript{132} Some of these herbs and supplements include angelica, clove, danshen, fish oil, garlic, ginger, Panax ginseng, red clover, turmeric, vitamin E, others.

**HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL:** There is preliminary evidence that suggests Siberian ginseng might have hypoglycemic effects.\textsuperscript{131} Theoretically, concomitant use with other herbs and supplements that decrease blood glucose levels might increase the risk of hypoglycemia. Some of these products include bitter melon, ginger, goat's rue, fenugreek, kudzu, gymnema, and others.

**HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES:** There is preliminary evidence that Siberian ginseng root extract might cause dose-dependent sedation.\textsuperscript{131} Theoretically, concomitant use with herbs that have sedative properties might enhance therapeutic and adverse effects. These include calamus, California poppy, catnip, German chamomile, gotu kola, hops, Jamaican dogwood, kava, lemon balm, sage, St. John's wort, sassafras, skullcap, valerian, wild carrot, wild lettuce, and others.
Ephedra

I Thermogenic effect when combined with methyl xanthines and caffeine.\textsuperscript{13}

I Can adversely effect MAOIs (PO human).\textsuperscript{13}

I Increases function of several asthmatic drugs.\textsuperscript{13}

I Alkaloids of ephedra are excreted faster with urinary acidifiers such as ammonium chloride and reduced with urinary alkalinizers such as sodium bicarbonates (human).\textsuperscript{13}

IV Theoretically, concomitant use of ephedra might interfere with the effectiveness of anticonvulsant drugs. Ephedra is associated with seizure activity.\textsuperscript{140} Some anticonvulsant drugs include phenobarbital, primidone (Mysoline), valproic acid (Depakene), gabapentin (Neurontin), carbamazepine (Tegretol), phenytoin (Dilantin), and others.

IV Ephedra can raise blood glucose levels and might decrease the effectiveness of drug therapy. Monitor blood glucose concentrations closely.\textsuperscript{141} Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

IV Theoretically, concomitant use might reduce the effectiveness of dexamethasone, due to the ephedrine contained in ephedra. Ephedrine increases the clearance rate of dexamethasone.\textsuperscript{142}

IV Theoretically, concomitant use of ephedra and ergot alkaloids might cause hypertension, due to the ephedrine contained in ephedra.\textsuperscript{143}

IV Concomitant use of ephedra with MAOIs might increase the risk of hypertension.\textsuperscript{143}

IV Ephedra may have an additive effect with drugs that prolong the QT interval. This may increase the risk of ventricular arrhythmias.\textsuperscript{144} Drugs that prolong the QT interval include amiodarone (Cordarone), disopyramide (Norpace), dofetilide (Tikosyn), ibutilide (Corvert), procainamide (Pronestyl), quinidine, sotalol (Betapace), thioridazine (Mellaril), and many others. \textcolor{red}{major}

IV Use of ephedra with caffeine or other methylxanthines such as theophylline might increase the risk of stimulatory adverse effects.\textsuperscript{145} There is also some
evidence that using ephedra with caffeine might increase the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction (MI), stroke, seizures, and death.\textsuperscript{146,147,148} Tell patients to avoid taking ephedra with caffeine and other stimulants.\textsuperscript{major}

IV Theoretically, drugs with CNS stimulant properties, such as phenylpropanolamine, pseudoephedrine, and diethylpropion, and many others might increase the risk of hypertension and adverse cardiovascular effects of ephedra due to its ephedra content.\textsuperscript{143,146}

\textbf{Lab AMPHETAMINE/METHAMPHETAMINE:} Ephedra might cause false-positive urine amphetamine or methamphetamine test results. False-positive urine methamphetamine assays have been attributed to the use of herbal supplements containing ephedra.\textsuperscript{149,150}

\textbf{Lab CATECHOLAMINE:} Ephedrine, a constituent of ephedra, can increase plasma catecholamine levels.\textsuperscript{151}

\textbf{Lab EPHEDRINE:} Ephedra can cause a positive urine ephedrine test due to its ephedrine content. A case of an athlete whose urine tested positive for norpseudoephedrine was attributed to the use of an herbal supplement labeled to contain ephedra. However, the product might also have contained added norpseudoephedrine as an unlabeled ingredient.\textsuperscript{152}

\textbf{Lab GLUCOSE:} Ephedra can increase blood glucose levels and test results.\textsuperscript{153} Monitor blood glucose levels in diabetes patients closely.

\textbf{Lab LACTATE:} Ephedrine, a constituent of ephedra, can increase blood lactate levels.\textsuperscript{153}

\textbf{Herb ERGOT:} Theoretically, concomitant use might cause excessive vasoconstriction and hypertension due to the ephedrine contained in ephedra.\textsuperscript{143}

\textbf{Herb HERBS AND SUPPLEMENTS WITH STIMULANT PROPERTIES:} Use of ephedra and other stimulant herbs, such as those containing caffeine, can increase the risk of common side effects such as insomnia, jitteriness, tremulousness, dizziness, etc. Using ephedra with other stimulants might also increase the risk of more serious adverse effects such as hypertension, myocardial infarction (MI), stroke, and death. There are several reports of
serious life-threatening or debilitating adverse events in patients taking ephedra in combination with caffeine and other stimulants.\textsuperscript{145, 146, 147} Some herbs and supplements with significant caffeine content include black tea, coffee, cola nut, green tea, guarana, mate, and others.

**Herb** PANAX GINSENG: Panax ginseng can cause prolonged QT interval with initial use. It might have an additive effect with ephedra on the QT interval, increasing the risk for arrhythmias.\textsuperscript{154, 148}

**Food** COFFEE, TEA: Theoretically, concomitant use of large amounts of caffeinated coffee or tea might increase the stimulatory effects and adverse effects of caffeine and the ephedrine-associated adverse effects of ephedra.\textsuperscript{141}

### Eucalyptus

I Increase rate of metabolism and clearance of many drugs (inhaled human).\textsuperscript{13}

II Reduces effectiveness of pentobarbital, zoxazolamine (muscle relaxant) and amphetamine when given aerosol exposure (2-10 min) up to 24 hour before (rats).

II Increased toxicity of pyrrolizidine alkaloids when ingested together.\textsuperscript{13}

III There's preliminary evidence that eucalyptus oil might inhibit cytochrome P450 1A2 (CYP1A2).\textsuperscript{155} **So far, this interaction has not been reported in humans.** However, watch for an increase in the levels of drugs metabolized by CYP1A2 in patients taking eucalyptus oil. Some drugs metabolized by CYP1A2 include amitriptyline (Elavil), haloperidol (Haldol), ondansetron (Zofran), propranolol (Inderal), theophylline (Theo-Dur, others), verapamil (Calan, Isoptin, others), and others. Use eucalyptus oil cautiously or avoid in patients taking these drugs.

III There's preliminary evidence that eucalyptus oil might inhibit cytochrome P450 2C19 (CYP2C19).\textsuperscript{156} **So far, this interaction has not been reported in humans.** However, watch for an increase in the levels of drugs metabolized by CYP2C19 in patients taking eucalyptus oil. Some drugs metabolized by CYP2C19...
include proton pump inhibitors including omeprazole (Prilosec), lansoprazole (Prevacid), and pantoprazole (Protonix); diazepam (Valium); carisoprodol (Soma); nelfinavir (Viracept); and others.

III There's preliminary evidence that eucalyptus oil might inhibit cytochrome P450 2C9 (CYP2C9). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking eucalyptus oil. Some drugs metabolized by CYP2C9 include nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac ( Cataflam, Voltaren), ibuprofen (Motrin), meloxicam (Mobic), and piroxicam (Feldene), celecoxib (Celebrex), amitriptyline (Elavil), warfarin (Coumadin), glipizide (Glucotrol), losartan (Cozaar), and others. Use eucalyptus oil cautiously or avoid in patients taking these drugs.

III There's preliminary evidence that eucalyptus oil might inhibit cytochrome P450 3A4 (CYP3A4) enzyme. So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP3A4 in patients taking eucalyptus oil. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use eucalyptus oil cautiously or avoid in patients taking these drugs.

IV Preliminary research suggests eucalyptus leaf might have hypoglycemic activity, and might have additive effects when used with antidiabetes drugs. This might increase the risk of hypoglycemia in some patients. Monitor blood glucose levels closely. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

Lab **BLOOD GLUCOSE**: Preliminary research suggests eucalyptus leaf might have hypoglycemic activity and theoretically might lower blood glucose and test results.  

Herb **HEPATOTOXIC PYRROLIZIDINE ALKALOID (PA)-CONTAINING HERBS**: Eucalyptus can potentiate the toxicity of herbs that contain hepatotoxic pyrrolizidine alkaloids (PAs). Herbs
containing hepatotoxic PAs include alkanna, boneset, borage, butterbur, coltsfoot, comfrey, forget-me-not, gravel root, hemp agrimony, and hound’s tongue; and the Senecio species plants dusty miller, groundsel, golden ragwort, and tansy ragwort.\textsuperscript{157}

### Evening Primrose

**I** 20% of schizophrenic patents when given 4 grams of EPO and taking phenothiazine fluphenazine and chlorpromazine developed grand mall seizures (PO human). Other schizophrenics not on phenothiazines had hallucinations and increased frontal lobe activity.\textsuperscript{13}

**I** Faster response to tamoxifen with GLA in estrogen-dependent breast cancer (PO human).\textsuperscript{13}

**II** Reduced kidney damage by cyclosporine (PO rats).

**III** May potentiate anticoagulant (speculative).

**IV** There is a report of seizure in a patient taking evening primrose oil and receiving anesthesia; however, the patient was also taking other drugs. It is unclear if evening primrose or the other drugs were the cause.\textsuperscript{158}

**IV** Evening primrose oil, which contains gamma-linolenic acid (GLA), could have anticoagulant effects.\textsuperscript{159} Theoretically, taking evening primrose oil with other anticoagulant or antiplatelet drugs might increase the risk of bruising and bleeding. Some of these drugs include aspirin, clopidogrel (Plavix), nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, warfarin (Coumadin), and others.

**IV** There is some concern that evening primrose oil might prolong bleeding time. Evening primrose oil contains gamma linolenic acid (GLA), which can inhibit platelet aggregation.\textsuperscript{159}

**Lab** **BLEEDING TIME**: Evening primrose oil might affect cholesterol levels. Evening primrose oil contains gamma-linolenic acid (GLA), which can lower plasma triglycerides and increase high-density lipoprotein (HDL) cholesterol.\textsuperscript{159}
ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs that have constituents that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, red clover, turmeric, and others.

Fenugreek

May retard absorption of oral drugs (speculative), enhances cholesterol-lowering agent and potentiates or interferes with warfarin (speculative). Some drugs with anticoagulant or antiplatelet effects include aspirin, clopidogrel (Plavix), nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, and others.

Fenugreek may reduce blood glucose levels and might have additive effects on glucose levels when used with antidiabetes drugs. Monitor blood glucose levels closely. Medication dose adjustments may be necessary. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

Fenugreek can lower blood glucose and test results.

Fenugreek can cause a maple syrup odor in urine. Avoid confusion with "maple syrup urine" disease.

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs that have constituents that might affect platelet aggregation could theoretically increase the risk of
bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, red clover, turmeric, and others.

**Herbs and Supplements with Hypoglycemic Potential:** Theoretically, fenugreek might have additive effects with herbs that decrease blood glucose levels. Herbs with hypoglycemic potential include devil's claw, fenugreek, guar gum, Panax ginseng, and Siberian ginseng.

**Food Allergy to Fabaceae:** Chickpea, also a member of the Fabaceae family, has shown cross-reactivity in patients allergic to fenugreek. Theoretically, patients who are allergic to other Fabaceae plants including soybeans, peanuts, and green peas might also be allergic to fenugreek.

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**Feverfew**

IV Several speculative interactions including anticoagulants such as warfarin and aspirins.

IV There's preliminary evidence that feverfew might inhibit cytochrome P450 1A2 (CYP1A2). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP1A2 in patients taking feverfew. Some drugs metabolized by CYP1A2 include amitriptyline (Elavil), haloperidol (Haldol), ondansetron (Zofran), propranolol (Inderal), theophylline (Theo-Dur, others), verapamil (Calan, Isoptin, others), and others. Use feverfew cautiously or avoid in patients taking these drugs.

IV There's preliminary evidence that feverfew might inhibit cytochrome P450 2C19 (CYP2C19). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C19 in patients taking feverfew. Some drugs metabolized by CYP2C19 include proton pump inhibitors including omeprazole (Prilosec), lansoprazole (Prevacid), and pantoprazole (Protonix), diazepam (Valium), carisoprodol (Soma), nelfinavir (Viracept), and others.

IV There's preliminary evidence that feverfew might inhibit cytochrome P450 2C9 (CYP2C9). So far,
this interaction has not been reported in humans.
However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking feverfew. Some drugs metabolized by CYP2C9 include nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren), ibuprofen (Motrin), meloxicam (Mobic), and piroxicam (Feldene), celecoxib (Celebrex), amitriptyline (Elavil), warfarin (Coumadin), glipizide (Glucotrol), losartan (Cozaar), and others. Use feverfew cautiously or avoid in patients taking these drugs.

IV There's preliminary evidence that feverfew might inhibit cytochrome P450 3A4 (CYP3A4) enzyme.167 So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP3A4 in patients taking feverfew. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use feverfew cautiously or avoid in patients taking these drugs.

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Some evidence suggests that feverfew may inhibit platelet aggregation. However, this has not been demonstrated in humans. Theoretically, concomitant use of feverfew and herbs that affect platelet aggregation could increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, horse chestnut, red clover, turmeric, and others.

Flax

III, IV May reduce absorption of oral drugs (speculative).
III, IV Preliminary research shows that flaxseed decreases the permeability of acetaminophen in vitro.168 Theoretically, flaxseed might decrease absorption of acetaminophen. However, the clinical significance of this potential interaction is unknown.
IV Some potential benefits of flaxseed are thought to be due to its lignan content. Secoisolariciresinol
diglucoside (SDG), a major lignan precursor, is found in high concentrations in flaxseed. SDG is converted by bacteria in the colon to the lignans enterolactone and enterodiol. Antibiotics alter the flora of the colon. Theoretically, antibiotics might interfere with conversion of SDG to enterolactone and enterodiol, which could potentially alter the effects of flaxseed.

I, IV There is some evidence that the oil contained in flaxseed can decrease platelet aggregation. Theoretically, using flaxseed oil in combination with anticoagulant or antiplatelet drugs might have additive effects and increase the risk of bleeding. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

I, IV Some evidence suggests that flaxseed can lower blood glucose levels. Theoretically, flaxseed might have additive effects when used with antidiabetes drugs and increase the chance of hypoglycemia. Monitor blood glucose levels closely. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

III, IV Flaxseed contains lignans with mild estrogenic and possible antiestrogenic effects. The lignans seem to compete with circulating endogenous estrogen and might reduce estrogen binding to estrogen receptors, resulting in an anti-estrogen effect. Theoretically, taking flaxseed might decrease effects of exogenously administered estrogens including oral contraceptive drugs and estrogen replacement therapy.

III, IV Preliminary research shows that flaxseed decreases the permeability of furosemide in vitro. Theoretically, flaxseed might decrease absorption of furosemide. However, the clinically significance of this potential interaction is unknown.

III, IV Preliminary research shows that flaxseed decreases the permeability of ketoprofen in vitro. Theoretically, flaxseed might decrease absorption of ketoprofen. However, the clinical significance of this potential interaction is unknown.

III, IV Preliminary research shows that flaxseed decreases the permeability of metoprolol in vitro.
Theoretically, flaxseed might decrease absorption of metoprolol. **However, the clinical significance of this potential interaction is unknown.**

**Lab**

**GLUCOSE**: Flaxseed might lower blood glucose concentrations.\(^{170,171}\)

**Lab**

**PROSTATE SPECIFIC ANTIGEN (PSA)**: Some research shows that consuming flaxseed 30 grams daily can lower PSA in men with prostatic intraepithelial neoplasia (PIN), a precancerous proliferation of prostatic epithelial cells.\(^{173}\) However, flaxseed 30 grams daily does not seem to significantly reduce PSA levels in men with prostate cancer.\(^{174,175}\)

**Lab**

**TRIGLYCERIDES**: Partially defatted flaxseed, which is flaxseed without as much alpha-linolenic acid content, might increase triglyceride levels and test results.\(^{176}\)

**Herb**

**ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS**: There is some evidence that the oil contained in flaxseed can decrease platelet aggregation.\(^{177}\) Theoretically, concomitant of flaxseed and other herbs and supplements that affect platelet aggregation could increase the risk of bleeding. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, and others.

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**Garlic**

**I**

Enhanced fibrinolytic activity and diminished human platelet aggregative in 2 patients on warfarin (PO human).\(^{13}\)

**I, IV**

Clinical research suggests garlic oil can inhibit the activity of CYP2E1 by 39%.\(^{178}\) Use garlic oil cautiously in patients taking drugs metabolized by these enzymes. Some drugs metabolized by CYP2E1 include acetaminophen, chlorzoxazone (Parafon Forte), ethanol, theophylline, and anesthetics such as enflurane (Ethrane), halothane (Fluothane), isoflurane (Forane), methoxyflurane (Penthane).

**II**

**Prevents hepatotoxicity from acetaminophen (PO mice)**\(^{13}\)

**II**

Garlic powder protected the heart, liver and pancreas from damage induced by isoprenaline (used for low
cardiac output and hypotension). Even better when combined with hawthorn (PO rats). The effect of garlic preparations on the metabolism of contraceptive drugs may vary. Some garlic preparations containing allicin might decrease the effectiveness of contraceptive drugs by increasing the activity of the cytochrome P450 3A4 (CYP3A4) isoenzyme. However, other extracts, containing alliin and alliinase may not affect the activity of CYP3A4. Until more is known about this potential interaction, advise women taking garlic supplements and contraceptive drugs concurrently to use an additional or alternative form of birth control.

The effect of garlic preparations on the metabolism of cyclosporine may vary. Some garlic preparations containing allicin might decrease the effectiveness of cyclosporine by increasing the activity of the cytochrome P450 3A4 (CYP3A4) isoenzyme. However, other extracts, containing alliin and alliinase may not affect the activity of CYP3A4. Until more is known about this potential interaction, patients that are taking cyclosporine should avoid using garlic preparations.

There is inconsistent information about the effects of garlic on cytochrome P450 3A4 (CYP3A4) isoenzymes. Some garlic preparations containing allicin appear to induce activity of CYP3A4. This has been demonstrated in research showing a significant reduction in saquinavir levels, a CYP3A4 substrate, in patients taking garlic. However, other research suggests that other allicin-containing garlic products do not induce metabolism of CYP3A4 substrates. In one small study, taking a specific garlic product (GarliPure Maximum Allicin Formula, Natrolm Chatsworth) 600 mg twice daily, providing 3,600 mcg allicin per dose, for 12 consecutive days did not significantly affect the pharmacokinetics of docetaxel, a CYP3A4 substrate. Other research also suggests that garlic oil does not affect CYP3A4. Extracts containing alliin and alliinase also might not affect the activity of CYP3A4. Research in animal models also suggests that an aqueous garlic extract does not significantly affect pharmacokinetic parameters of rifampin, a CYP3A4 substrate. Until more is
known about this potential interaction, use caution when considering concomitant use of garlic and other drugs affected by this system. Drugs that might be affected include some calcium channel blockers (diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole,itraconazole), glucocorticoids, alfentanil (Alfenta), cisapride (Propulsid), fentanyl (Sublimaze), lidocaine (Xylocaine), losartan (Cozaar), fexofenadine (Allegra), midazolam (Versed), and others.

Research in animal models suggests that an aqueous extract of garlic can reduce isoniazid levels by about 65%. Garlic reduces both maximum concentration (Cmax) and area under the curve (AUC), but does not seem to affect half-life. This suggests that garlic extract might inhibit isoniazid absorption across the intestinal mucosa; however, the exact mechanism of this potential interaction is not known.

Some garlic preparations containing allicin may decrease plasma concentrations of the protease inhibitor saquinavir (Fortovase, Invirase). However, other extracts, containing alliin and alliinase may not affect the activity of CYP3A4. NNRTIs and protease inhibitors are metabolized through similar routes. Until more is known about this potential interaction, patients taking these medications should avoid using garlic. NNRTI-type antiretroviral drugs include nevirapine (Viramune), delavirdine (Rescriptor), and efavirenz (Sustiva).

**Lab**
- **BLOOD PRESSURE**: Garlic can lower blood pressure and blood pressure readings.
- **CHOLESTEROL**: Garlic can lower serum cholesterol concentrations and test results.
- **INTERNATIONAL NORMALIZED RATIO (INR), PROTHROMBIN TIME (PT)**: Garlic can increase INR in patients anticoagulated with warfarin (Coumadin). There are two case reports of increased INR associated with concomitant use of garlic products and warfarin.

**Herb**
- **ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS**: Concomitant use of herbs that have constituents that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include
angelica, clove, danshen, ginger, ginkgo, red clover, turmeric, vitamin E, willow, and others.  

**EICOSAPENTAENOIC ACID (EPA, Fish Oils):** Concomitant use of garlic can theoretically enhance antithrombotic effects.  

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**Ginger**

I Reduce nausea related to anesthetic if 1 gm given prior to surgery.  

I Increase absorption of some oral drugs (empirical).  

II Reduce gastric mucosal damage from alcohol, aspirins and indomethacin.  

III Speculative that it may enhance anticoagulant drugs like warfarin.  

I, IV Theoretically, excessive amounts of ginger might increase the risk of bleeding. Ginger is thought to inhibit thromboxane synthetase and decrease in platelet aggregation. Some anticoagulant or antiplatelet drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.  

III, IV Preliminary research suggests ginger might increase insulin levels. Theoretically, it could have an additive effect with antidiabetes drugs and cause hypoglycemia. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.  

IV Theoretically, ginger might have an additive effect with calcium channel blockers. Preliminary research suggests it might have hypotensive and calcium channel-blocking effects. Calcium channel blockers include nifedipine (Adalat, Procardia), verapamil (Calan, Isoptin, Verelan), diltiazem (Cardizem), isradipine (DynaCirc), felodipine (Plendil), amlodipine (Norvasc), and others.  

I, IV Phenprocoumon, a warfarin-related anticoagulant used in Europe, might increase the international normalized ratio (INR) when taken with ginger.  

There is one case report of a 76 year old woman
with a stable INR on phenprocoumon that increased to greater than 10 when she began consuming dried ginger and ginger tea.\textsuperscript{193}

**Ginkgo**

- 40 mg BDI of extract has caused spontaneous bleeding in chronic aspirin and antiplatelet drug use (PO human). \textbf{One human case on warfarin (5 years stable) had intracerebral hemorrhage after 2 month of ginkgo use.}\textsuperscript{13}
- Potential problem with heparin and NSAIDs (speculative).\textsuperscript{13}
- 200 mg daily offset sexual dysfunction of antidepressant in both males and females (more effective in women than men) (PO human).
- Ginkgo might decrease the effectiveness of alprazolam in some patients. Ginkgo extract 120 mg twice daily (Ginkgold), seems to decrease alprazolam levels by about 17\%. \textbf{However ginkgo doesn't appear to decrease the elimination half-life of alprazolam.} This suggests ginkgo is more likely to decrease absorption of alprazolam rather than induce hepatic metabolism of alprazolam.\textsuperscript{194}
- Several pharmacodynamic studies suggest that ginkgo inhibits platelet aggregation. It is thought that the ginkgo constituent, ginkgolide B, displaces platelet-activating factor (PAF) from its binding sites, decreasing blood coagulation.\textsuperscript{195,196} Several case reports have also documented serious bleeding events in patients taking ginkgo.\textsuperscript{197,198,199,200,201,202} Some evidence suggests that short-term use of ginkgo leaf might not significantly reduce platelet aggregation and blood clotting. One study shows that healthy men who took a specific ginkgo leaf extract (EGb 761) 160 mg twice daily for 7 days did not have reduced prothrombin time.\textsuperscript{203} However, single doses of ginkgo
plus cilostazol (Pletal) do seem to prolong bleeding time. It has been suggested that ginkgo has to be taken for at least 2-3 weeks to have a significant effect on platelet aggregation. But a meta-analysis of 18 studies (1985 patients) using standardized ginkgo extracts, 80-480 mg daily in studies lasting up to 32 weeks, did not find a significant effect on platelet aggregation, fibrinogen concentration, or PT/aPTT. Also, a single dose of ginkgo plus clopidogrel (Plavix) does not seem to significantly increase bleeding time. Similarly, a single dose of ginkgo extract 80 mg plus ticlopidine (Ticlid) 250mg does not seem to significantly affect bleeding time or platelet aggregation. Until more is known, use ginkgo cautiously patients who are taking antiplatelet or anticoagulant drugs. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.

Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves. Ginkgo leaf extract contains trace amounts of ginkgotoxin. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems unlikely to cause toxicity. However, there are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history of seizure disorder and in those with previously well-controlled epilepsy. Theoretically, taking ginkgo might reduce the effectiveness of anticonvulsants for preventing seizure. Some anti-epileptic drugs include phenobarbital, primidone (Mysoline), valproic acid (Depakene), gabapentin (Neurontin), carbamazepine (Tegretol), phenytoin (Dilantin), and others.

Ginkgo leaf extract seems to alter insulin secretion and metabolism, and might affect blood glucose levels in people with type 2 diabetes. The effect of ginkgo seems to differ depending on the insulin and treatment status of the patient. In diet-controlled diabetes patients with hyperinsulinemia, taking ginkgo does not seem to significantly affect insulin or blood glucose levels. In patients with
hyperinsulinemia who are treated with oral hypoglycemic agents, taking ginkgo seems to decrease insulin levels and increased blood glucose following an oral glucose tolerance test. Researchers speculate that this could be due to ginkgo-enhanced hepatic metabolism of insulin. In patients with pancreatic exhaustion, taking ginkgo seems to stimulate pancreatic beta-cells resulting in increased insulin and C-peptide levels, but no significant change in blood glucose levels in response to an oral glucose tolerance test. Theoretically, taking ginkgo might alter the response to antidiabetes drugs. Advise patients with type 2 diabetes to use ginkgo cautiously. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.

**IV** Ginkgo in combination with fluoxetine (Prozac), St. John's wort, melatonin, and buspirone might cause hypomania in patients with depression. Whether ginkgo alone or in combination with buspirone can cause hypomania is unknown.

**IV** There is preliminary evidence that ginkgo leaf extract can mildly inhibit cytochrome P450 1A2 (CYP1A2) enzymes. However, clinical research suggests ginkgo might not affect CYP1A2. Until more is known, use ginkgo cautiously in patients taking drugs metabolized by these enzymes. Some drugs metabolized by CYP1A2 include acetaminophen (Tylenol), amitriptyline (Elavil), clopidogrel (Plavix), clozapine (Clozaril), diazepam (Valium), estradiol, olanzapine (Zyprexa), ondansetron (Zofran), propranolol (Inderal), ropinirole (Requip), tacrine (Cognex), theophylline, verapamil (Calan, Covera-HS, Isoptin, Verelan), warfarin (Coumadin), and others.

**IV** There is some evidence that a specific ginkgo leaf extract (Remembrance, Herbs Product LTD, Hong Kong), 140 mg twice daily, can induce CYP2C19 enzymes and potentially decrease levels of drugs metabolized by these enzymes. Some drugs metabolized by CYP2C19 include amitriptyline (Elavil), carisoprodol (Soma), citalopram (Celexa), diazepam (Valium), lansoprazole (Prevacid), omeprazole (Prilosec), phenytoin (Dilantin), warfarin,
Herb-Drug-Nutrient Interaction
By Terry Willard CIH, PhD

and many others.

I, III, IV There is preliminary evidence that a specific standardized extract of ginkgo leaf (EGb 761) can significantly inhibit CYP2C9 in vitro.\textsuperscript{219,220,221} The terpenoid (ginkgolides) and flavonoid (quercetin, kaempferol, etc) constituents seem to be responsible for the enzyme inhibition. Most ginkgo extracts contain some amount of these constituents. Therefore, other ginkgo leaf extracts might also inhibit the CYP2C9 enzyme in vitro. \textbf{However, clinical research suggests that ginkgo might not have a significant effect on CYP2C9 in humans.} Ginkgo does not seem to significantly affect the pharmacokinetics of CYP2C9 substrates diclofenac or tolbutamide. Until more is known, advise patients to use ginkgo cautiously if they take any CYP2C9 substrate. Some of these drugs include warfarin (Coumadin), glyburide, glipizide, amitriptyline valdecoxib (Bextra), phenytoin (Dilantin), and many others.

I, III, IV There is preliminary evidence that ginkgo leaf extract can modestly inhibit CYP2D6 enzymes by about 9%.\textsuperscript{214,215,216} \textbf{This might not result in clinical significant changes in levels of drug metabolized by CYP2D6.}\textsuperscript{222} Preliminary clinical research also suggests that ginkgo does not significantly affect levels of donepezil, a CYP2D6 substrate.\textsuperscript{223} Other clinical research also suggests ginkgo does not inhibit CYP2D6.\textsuperscript{224} Until more is known, use ginkgo cautiously in patients taking CYP2D6 substrates. Some drugs metabolized by CYP2D6 include amitriptyline (Elavil), clozapine (Clozaril), codeine, desipramine (Norpramin), donepezil (Aricept), fentanyl (Duragesic), flecainide (Tambocor), fluoxetine (Prozac), meperidine (Demerol), methadone (Dolophine), metoprolol (Lopressor, Toprol XL), olanzapine (Zyprexa), ondansetron (Zofran), tramadol (Ultram), trazodone (Desyrel), and others.

I, III, IV There is conflicting evidence about whether ginkgo induces or inhibits CYP3A4.\textsuperscript{214,215,216,219} Ginkgo does not appear to affect hepatic CYP3A4.\textsuperscript{222} However, it is not known if ginkgo affects intestinal CYP3A4. Preliminary clinical research suggests that taking ginkgo does not significantly affect levels of
donepezil, a CYP3A4 substrate.²²³ Other clinical research also suggests ginkgo might not significantly inhibit CYP3A4.²²⁴ Until more is known, use ginkgo cautiously in patients taking drugs metabolized by CYP3A4. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), diltiazem (Cardizem), estrogens, indinavir (Crixivan), triazolam (Halcion), and others.

I,IV There is a single case report of decreased efavirenz concentrations and increased viral load in a patient taking ginkgo biloba. An HIV-positive male experienced over a 50% decrease in efavirenz levels over the course of 14 months while taking ginkgo extract. HIV-1 RNA copies also increased substantially, from less than 50, to more than 1500. It is suspected that terpenoids from the ginkgo extract reduced drug levels by inducing cytochrome P450 3A4 (CYP3A4) or p-glycoprotein.²²⁵ Monitor patients using this combination for therapeutic response and changes in viral load.

IV Ginkgo in combination with buspirone (BuSpar), St. John's wort, melatonin, and fluoxetine might cause hypomania in patients with depression.²¹³ Whether ginkgo alone or in combination with fluoxetine can cause hypomania is unknown.

I,IV There is a single case report of a patient experiencing hypertension after taking ginkgo along with hydrochlorothiazide.²²⁶ Monitor patient using this combination for potential hypertensive exacerbations.

IV A specific ginkgo leaf extract (Remembrance, Herbs Product LTD, Hong Kong), 140 mg twice daily, can induce CYP2C19 enzymes and decrease levels of omeprazole by about 27% to 42%.²¹⁸

IV Consumption of ginkgo seeds can cause seizures due to ginkgotoxin contained in the seeds. Large amounts of ginkgotoxin can cause neurotoxicity and seizure. Ginkgotoxin is present in much larger amounts in ginkgo seeds than leaves.²⁰⁷ Ginkgo leaf extract contains trace amounts of ginkgotoxin. The amount of ginkgotoxin in ginkgo leaf and leaf extract seems unlikely to cause toxicity.²²⁷ However, there are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history of seizure disorder and in those with previously well-
controlled epilepsy.\textsuperscript{228,229,230} Advise patients taking these drugs to avoid ginkgo leaf products. Some drugs that lower the seizure threshold include anesthetics (propofol, others), antiarrhythmics (mexitelitine), antibiotics (amphotericin, penicillin, cephalosporins, imipenem), antidepressants (bupropion, others), antihistamines (cyproheptadine, others), immunosuppressants (cyclosporine), narcotics (fentanyl, others), stimulants (methylphenidate), theophylline, and others.

\textbf{I,IV} Use of ginkgo leaf extract with trazodone has been associated with coma. In one case, an Alzheimer's patient taking trazodone 20 mg twice daily and ginkgo leaf extract 80 mg twice daily for four doses became comatose. The coma was reversed by administration of flumazenil (Romazicon). Coma might have been induced by excessive GABA-ergic activity. Ginkgo flavonoids are thought to have GABA-ergic activity and act directly on benzodiazepine receptors. Ginkgo might also increase metabolism of trazodone to active GABA-ergic metabolites, possibly by inducing cytochrome P450 3A4 (CYP3A4) metabolism.\textsuperscript{231}

\textbf{Herb} \textbf{ANTI COAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS:} Theoretically, concomitant use of ginkgo with other herbs and supplements that affect platelet aggregation could increase the risk of bleeding. \textbf{However, the extent of ginkgo's antiplatelet effects are questionable.} There is conflicting evidence about whether ginkgo inhibits platelet aggregation. Several pharmacodynamic studies suggest that ginkgo inhibits platelet aggregation. Several case reports have also documented serious bleeding events in patients taking ginkgo.\textsuperscript{232,233} \textbf{However, clinical trials and a meta-analysis evaluating standardized ginkgo leaf extracts show that the incidence of bleeding in patients taking ginkgo is not significantly higher than in those taking placebo.}\textsuperscript{234,235,236,237} Some other herbs and supplements that affect platelet aggregation include angelica, clove, danshen, garlic, ginger, glucosamine, Panax ginseng, and others.

\textbf{Herb} \textbf{SEIZURE THRESHOLD LOWERING HERBS AND SUPPLEMENTS:} Ginkgo seeds contain ginkgtoxin, which can cause seizures in high
doses. Theoretically, patients taking supplements that also lower the seizure threshold might be at greater risk. There are anecdotal reports of seizure occurring after use of ginkgo leaf both in patients without a history seizure disorder and in those with previously well-controlled epilepsy. Advise patients taking these supplements to avoid ginkgo products. Some of these supplements include butanediol (BD), cedar leaf, Chinese club moss, EDTA, folic acid, gamma butyrolactone (GBL), gamma hydroxybutyrate (GHB), glutamine, huperzine A, hydrazine sulfate, hyssop oil, juniper, L-carnitine, melatonin, rosemary, sage, wormwood, and others.

**ST. JOHN'S WORT: Ginkgo in combination with buspirone (BuSpar), fluoxetine (Prozac), melatonin, and St. John's wort might cause hypomania in patients with depression.** Whether ginkgo alone, or in combination with St. John's wort, can cause hypomania is unknown.

### Grapefruit

1. Increased bioavailability of several oral drugs including coumarin, benzodiazepine, midazolan, trazolam simvastins, simvastatin acid, lovastatin, saquinavir, quinidine estrdiol and ethinylestrodiols (PO human). This is due to slowing metabolism of p450. The increase in the blood can be 1.5 to 12 fold.

1. Oral half-life of caffeine is increased when consumed within 30 minute of each other.

1. Absorption and bioavailability of some drugs was reduced such as clarithromycin (antibiotic), fexofenadine (fevers and allergies).

1. Grapefruit juice can decrease aliskiren (Tekturna, Rasilez) levels by 60% by inhibiting organic anion transporting polypeptide (OATP). Grapefruit juice is thought to affect OATP for only a short time. Therefore, separating drug administration and consumption of grapefruit by at least 4 hours is likely to avoid this interaction.

1. Grapefruit juice inhibits metabolism and increases absorption of amiodarone (Cordarone). Grapefruit
juice increases levels by 50% and peak concentration by 84%.\textsuperscript{242,243} Advise patients to avoid grapefruit juice while taking amiodarone.\textsuperscript{major}

I Grapefruit juice increases the oral levels of artemether in healthy men by 90% to 250%.\textsuperscript{244,245} Watch for toxicity in patients combing artemether and grapefruit juice.\textsuperscript{major}

I Grapefruit juice increases absorption and plasma concentrations of buspirone.\textsuperscript{246} \textsuperscript{major}

I Some studies suggest grapefruit juice decreases caffeine clearance, possibly increasing the effects and adverse effects of caffeine.\textsuperscript{247}

I Grapefruit juice increases absorption and plasma concentrations of amlodipine (Norvasc),\textsuperscript{248} nifedipine (Procardia, Adalat),\textsuperscript{249} nicardipine (Cardene), diltiazem (Cardizem),\textsuperscript{249,251,252,247,253} and verapamil (Calan, Isoptin, Verelan).\textsuperscript{254,255} This interaction is likely the result of the inhibition of intestinal metabolism by CYP3A4.\textsuperscript{254,253} Extensive intake of grapefruit juice (1 liter per day) can increase steady state concentrations of verapamil by as much as 50%.\textsuperscript{255} Some references dispute the clinical relevance of the interactions with amlodipine, diltiazem, and verapamil.\textsuperscript{256,247} However, there is considerable inter-individual variability in the effect of grapefruit juice on drug metabolism, which might account for inconsistent study results.\textsuperscript{254,257,255}

In healthy older adults, the hemodynamic response to felodipine (Plendil) plus grapefruit juice might be influenced by altered autonomic regulation. In these adults, a single dose of grapefruit juice and felodipine enhanced the blood pressure lowering effects of felodipine. However, after a week of grapefruit juice and felodipine (steady state), the hypotensive activity was reduced, possibly due to compensatory tachycardia.\textsuperscript{258} Research indicates it is necessary to withhold grapefruit juice for three days to avoid interactions with felodipine and nicardipine.\textsuperscript{259,260,261} Watch for signs of toxicity such as flushing, headache, tachycardia, and hypotension in patients combining grapefruit juice and calcium channel blockers.\textsuperscript{major}

I Grapefruit juice increases absorption and plasma concentrations of carbamazepine.\textsuperscript{249} \textsuperscript{major}
Grapefruit juice is reported to increase the bioavailability of a single dose of carvedilol by 16%.\textsuperscript{262} Grapefruit juice increases absorption and plasma concentrations of cisapride. According to the cisapride prescribing information, grapefruit juice is contraindicated in patients taking cisapride.\textsuperscript{263,264,265} Grapefruit juice increases blood levels of clomipramine. Two cases are reported in which trough clomipramine blood levels increased significantly after adding grapefruit juice to the therapeutic regimen.\textsuperscript{266} Grapefruit juice increases absorption and plasma concentrations of cyclosporine.\textsuperscript{267,268} The mechanism of action is unclear. Advise patients taking cyclosporine to avoid grapefruit.

Grapefruit juice can decrease the absorption and plasma concentrations of etoposide. There is some evidence that grapefruit juice coadministered with oral etoposide can reduce levels of etoposide by about 26%.\textsuperscript{269} Grapefruit juice seems to inhibit organic anion transporting polypeptide (OATP), which is a drug transporter in the gut, liver, and kidney.\textsuperscript{270,271,272} Grapefruit juice is thought to affect OATP for only a short time. Therefore, separating drug administration and consumption of grapefruit by at least 4 hours is likely to avoid this interaction.\textsuperscript{271,272}

Grapefruit juice inhibits metabolism and increases fluvoxamine (Luvox) levels and peak concentration.\textsuperscript{273} Watch for increased side effects such as nausea in people taking fluvoxamine with grapefruit juice.

Grapefruit juice can affect itraconazole absorption and might increase or decrease itraconazole levels.\textsuperscript{274,242} The clinical significance of this potential interaction is not known.

Concomitant use of grapefruit juice and losartan might reduce losartan effectiveness, but this requires further study. Losartan is an inactive prodrug which must be metabolized to its active form, E-3174, to be effective. In one human study, grapefruit juice reduced losartan metabolism, increased losartan AUC, and reduced the AUC of the major active losartan metabolite, E-3174.\textsuperscript{275}
I, IV Grapefruit juice inhibits metabolism and increases methadone levels and peak concentration. The clinical significance of this potential interaction is unknown.

I, IV Grapefruit juice can increase plasma concentration of orally administered methylprednisolone. Grapefruit juice, 200 mL three times daily, given with methylprednisolone, 16 mg, increased methylprednisolone half-life by 35%, peak plasma concentration by 27%, and total area under the curve by 75%. In some patients, consumption of large amounts of grapefruit juice with methylprednisolone might increase the risk of adverse effects; use cautiously. Some of these drugs include Adlone, A-Methapred, depMedalone, Depoject, Medrol, and Solu-Medrol.

I Grapefruit juice inhibits metabolism and increases absorption of nilotinib (Tasigna). Grapefruit juice increases levels by 29% and peak concentration by 60%. Advise patients to avoid grapefruit juice while taking nilotinib.

I Grapefruit juice increases absorption and plasma concentrations of terfenadine.

I, IV Grapefruit juice seems to modestly decrease theophylline levels when given concurrently with sustained-release theophylline. The mechanism of this interaction is unknown.

I, IV Grapefruit juice might increase warfarin effects. One case is reported of significantly increased international normalized ratio (INR) associated with consumption of 50 ounces of grapefruit juice daily. But smaller amounts of grapefruit juice might not be a problem. In a small clinical trial, consumption of 24 ounces of grapefruit juice daily for one week had no effect on INR in a group of men anticoagulated with warfarin.

Lab DRUG ASSAYS: Grapefruit juice decreases metabolism, and increases plasma concentrations and test results of amiodipine (Norvasc), nifedipine (Procardia, Adalat), nisoldipine (Sular), felodipine (Plendil), nimodipine (Nimotop), nicardipine (Cardene), diltiazem (Cardizem, Dilacor XR, Tiazac), verapamil (Calan, Isoptin, Verelan), buspirone (BuSpar), losartan (Cozaar), midazolam (Versed) and triazolam (Halcion), diazepam (Valium),
carbamazepine (Tegretol), cisapride (Propulsid),
cyclosporine (Sandimmune, Neoral), 17-beta-
estradiol, ethinyl-estradiol, lovastatin (Mevacor),
saquinavir (Fortovase, Invirase), simvastatin (Zocor),
atorvastatin (Lipitor), and terfenadine.

**Lab HEMATOCRIT:** Some clinical research suggests
that grapefruit may lower hematocrit count in people
with an elevated hematocrit. However, in people with
a low hematocrit, it may increase hematocrit. The
effect appears to be the same with one-half or a whole
grapefruit daily. The grapefruit constituent naringin
may be responsible for this effect.

**Herb RED YEAST:** Concomitant use of grapefruit with red
yeast increases the serum levels of lovastatin, a
constituent of red yeast.\(^{284}\) This effect is likely caused
by inhibition of cytochrome P450 (CYP450) enzymes
by grapefruit.

**Food TONIC WATER:** Grapefruit's inhibitory effect on
cytochrome P450 (CYP450) isoenzymes might
interfere with the metabolism of quinine in tonic
water. Grapefruit in combination with tonic water
containing quinine should be avoided in people with
cardiac rhythm disorders such as long QT syndrome
that may worsen with quinine.

**Food WINE:** Red wine, in combination with grapefruit
juice, appears to have an additive inhibitory effect on
CYP3A4, theoretically increasing the risk for
interactions with other drugs. White wine does not
appear to affect CYP3A4.

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**Guar Gum**

I Insulin needs can be lowered (PO human and rat).\(^ {13} \)

I Absorption of oral drugs is slower.\(^ {13} \)

I Concurrent use of guar gum with penicillin results in
decreased penicillin absorption and reduced penicillin
levels.\(^ {285} \)

I Concurrent use of guar gum with metformin may
decrease metformin absorption and lower antidiabetic
activity.\(^ {286} \)

I, IV There is some concern that guar gum can decrease
glucose levels and might have additive effects with
insulin and other diabetes medications. Monitor blood glucose levels closely. Dose adjustments may be necessary.

II Concurrent use of guar gum with ethinyl estradiol results in a decrease in ethinyl estradiol absorption. Ethinyl estradiol is in some oral contraceptives. Theoretically, guar gum might reduce the absorption of other estrogens.

Lab **CHOLESTEROL**: Guar gum can reduce serum total cholesterol and low-density lipoprotein (LDL) cholesterol levels and test results. 

Lab **GLUCOSE**: Guar gum can reduce postprandial serum glucose concentrations and test results.

Guarana

Similar to ephedra and coffee.

Gymnema

I Insulin requirements can be reduced, while hypoglycemic medication is enhanced.

Hawthorn

I Enhance action of digoxin; other studies showed it didn’t enhance.

III Inhibited concentration phenylephedrine in rat arteries (in vitro).

IV Theoretically, using hawthorn with beta-blockers such as atenolol (Tenormin), metoprolol (Lopressor, Toprol XL), nadolol (Corgard), and propranolol (Inderal) might cause additive effects on blood pressure and heart rate.

IV Theoretically, using hawthorn with calcium channel blockers such as verapamil (Calan, Covera-HS, Verelan), nifedipine (Procardia), and diltiazem (Cardizem, Dilacor, Tiazac) might cause additive coronary vasodilatory effects.

IV Using hawthorn with nitrates such as nitroglycerin (Nitro-Bid, Nitro-Dur, Nitrostat) and isosorbide (Imdur, Isordil, Sorbitrate) might cause additive coronary vasodilatory effects.
Theoretically, concurrent use of phosphodiesterase-5 (PDE-5) inhibitors and hawthorn might result in additive vasodilation and hypotension. PDE-5 inhibitors include sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra). Lab CHOLESTEROL: Theoretically, hawthorn might lower blood levels total and low density lipoprotein (LDL) cholesterol and test results. Herb HERBS AND SUPPLEMENTS WITH HYPOTENSIVE EFFECTS: Hawthorn might have hypotensive effects. Theoretically, concurrent use of hawthorn with other herbs and supplements that decrease blood pressure might increase the risk of hypotension. Some of these products include andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lycium, stinging nettle, theanine, others.

Kava

Reduces efficacy of levodopa in Parkinson’s disease, seemingly due to a dopamine antagonism (human). Benzodiazepine alprazolam may be enhanced. Intoxication seems to be enhanced with alcohol consumption (PO human). Concomitant use of kava and alcohol, barbiturates, benzodiazepines, or other CNS depressants can increase the risk of drowsiness and motor reflex depression. There is one report of an individual who was hospitalized due to lethargy and disorientation that occurred when alprazolam, cimetidine, terazosin, and kava were used concomitantly. Preliminary evidence suggests that kava significantly inhibits cytochrome P450 1A2 (CYP1A2), 2C19, 2C9, 2E1, 2D6, and 3A4; however, contradictory research suggests that kava has no significant effect on CYP1A2 and 3A4. Use kava cautiously or avoid in patients taking drugs metabolized through CYP450 pathways. There is some concern that kava can adversely affect the liver. Theoretically, concomitant use with
other potentially hepatotoxic drugs might increase the risk of developing liver damage. Some of these drugs include acarbose (Precose, Prandase), amiodarone (Cordarone), atorvastatin (Lipitor), azathioprine (Imuran), carbamazepine (Tegretol), cerivastatin (Baycol), diclofenac (Voltaren), felbamate (Felbatol), fenofibrate (Tricor), fluvastatin (Lescol), gemfibrozil (Lopid), isoniazid, itraconazole, (Sporanox), ketoconazole (Nizoral), leflunomide (Arava), lovastatin (Mevacor), methotrexate (Rheumatrex), nevirapine (Viramune), niacin, nitrofurantoin (Macrodantin), pioglitazone (Actos), pravastatin (Pravachol), pyrazinamide, rifampin (Rifadin), ritonavir (Norvir), rosiglitazone (Avandia), simvastatin (Zocor), tacrine (Cognex), tamoxifen, terbinafine (Lamisil), valproic acid, and zileuton (Zyflo).

Lab LIVER FUNCTION TESTS: There is some concern that kava can cause liver damage and increase liver function tests (LFTs) in some patients. Liver toxicity is primarily associated with prolonged use of high doses. However, in some patients, short-term use (3-8 weeks) of typical doses might result in liver damage and increase liver function tests. Liver function tests affected include aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyltransferase, lactate dehydrogenase (LDH), and total and conjugated bilirubin. Consider monitoring liver function tests in patients taking kava for more than one month or in patients with symptoms of liver problems such as fatigue, yellowing of the skin (jaundice), or dark urine.

Herb HEPATOTOXIC HERBS AND SUPPLEMENTS: There is some concern that kava can adversely affect the liver. Theoretically, concomitant use with other potentially hepatotoxic products might increase the risk of developing liver damage. Some of these products include androstenedione, chaparral, comfrey, DHEA, germander, niacin, pennyroyal oil, red yeast, and others.

Herb HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES: Theoretically, concomitant use with herbs and supplements that have sedative properties might increase the risk of
excessive drowsiness. Some of these supplements include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, skullcap, valerian, yerba mansa, and others.

**Kelp**

I Lithium carbonate potentiates the hypothyroid action of large amounts of iodine (empirical).³⁰³

III Bladderwrack seems to have anticoagulant effects.³⁰³ Theoretically, taking bladderwrack with antiplatelet or anticoagulant drugs might increase the risk of bruising and bleeding. Some of these drugs include aspirin; clopidogrel (Plavix); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others); dalteparin (Fragmin); enoxaparin (Lovenox); heparin; warfarin (Coumadin); and others.

IV Theoretically, concomitant use may result in additive hypothyroid activity, and may cause hypothyroidism.³⁰⁴ Some of these medications include methenamine mandelate (Methimazole), methimazole (Tapazole), potassium iodide (Thyro-Block), and others.

**Lab**

**ACTIVATED PARTIAL THROMBOPLASTIN TIME (aPTT):** Theoretically, bladderwrack might increase aPTT test results due to the heparin-like activity of one of its constituents.³⁰³

**Lab** **ESTRADIOL:** In premenopausal women, bladderwrack seems to lower 17-beta-estradiol levels in a dose-dependent manner.³⁰⁵

**Lab** **PROGESTERONE:** In premenopausal women, bladderwrack seems to increase progesterone levels in a dose-dependent manner.³⁰⁵

**Lab** **RADIOACTIVE IODINE UPTAKE:** Theoretically, bladderwrack might interfere with the results of thyroid function tests using radioactive iodine uptake.³⁰⁶

**Lab** **THYROID STIMULATING HORMONE (TSH):** Theoretically, bladderwrack might increase serum TSH levels and test results.
**Lab**  THYROXINE (T4): Theoretically, bladderwrack might increase serum T4 levels and test results.  

**Herb**  ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Theoretically, concomitant use of bladderwrack with herbs that might affect platelet aggregation might increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, fenugreek, feverfew, garlic, ginger, ginkgo, Panax ginseng, poplar, red clover, turmeric, and others.

**Herb**  STRONTIUM: Bladderwrack, also known as kelp, contains alginate, which binds strontium and reduces its absorption from the gastrointestinal tract. A 10% sodium alginate solution reduces strontium absorption 4-fold when taken at the same time. This effect has been used to reduce strontium absorption and toxicity in cases of poisoning, but could theoretically also affect the absorption of strontium supplements.

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**Kudzu**

I  **80% of alcohol abusers no longer desired alcohol after consuming kudzu for 2 - 4 weeks.**

I, II, IV Kudzu isoflavones are reported to have antiplatelet activity. Theoretically, kudzu might increase the risk of bleeding when used concomitantly with other drugs that have antiplatelet or anticoagulant effects. Antiplatelet agents include aspirin, clopidogrel (Plavix), dipyridamole (Persantine), ticlopidine (Ticlid), and others. Anticoagulant agents include heparin and warfarin (Coumadin).

I, IV Theoretically, kudzu might competitively inhibit the effects of oral contraceptives.

I, IV Theoretically, kudzu might competitively inhibit the effects of estrogen therapy.

II Preclinical research suggests that kudzu extract greatly reduces the elimination and increases the toxicity of methotrexate. Kudzu might inhibit organic anion transporters (OATs) that are responsible for hepatobiliary and renal excretion of anions, similar to the interaction between methotrexate and NSAIDs.

I, IV Theoretically, kudzu might interfere with tamoxifen...
because of its potential estrogenic effects. Tell patients taking tamoxifen to avoid kudzu.410

**Lab** **BLOOD GLUCOSE:** Theoretically, kudzu might decrease blood glucose levels and test results. Constituents of kudzu have hypoglycemic activity in animals.312,313

**Lab** **SERUM CHOLESTEROL:** Theoretically, kudzu might decrease serum cholesterol levels and test results. Constituents of kudzu reduce serum cholesterol levels in animals.312,314

**Herb** **ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS:** Theoretically, concomitant use of kudzu with herbs that might affect platelet aggregation might increase the risk of bleeding in some people.308,309 These herbs include angelica, clove, danshen, fenugreek, feverfew, garlic, ginger, ginkgo, Panax ginseng, poplar, red clover, turmeric, and others.

**Herb** **HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL:** Theoretically, kudzu might lower blood glucose levels,312,313 and have additive effects when used with other herbs and supplements that also lower glucose levels. This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic effects include alpha-lipoic acid, bitter melon, cassia cinnamon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

**Herb** **HERBS WITH ESTROGENIC ACTIVITY:** Theoretically, kudzu might have additive or antagonistic effects with other herbs that have estrogenic activity.314 These herbs include alfalfa, black cohosh, chasteberry, flaxseed, hops, ipriflavone, licorice, red clover, and soy.

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**Lemon Balm**

II Hydroalcoholic extraction (6mg/K) increase hypnotic effects of pentobarbital (IP mice) and volatile oils enhances hexobarbital sedative action (PO rats).13

I, IV Theoretically, concomitant use of lemon balm with drugs with sedative properties may cause additive effects and side effects.315
HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES: Theoretically, concomitant use with herbs that have sedative properties might enhance therapeutic and adverse effects. Some of these supplements include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, skullcap, valerian, yerba mansa, and others.

ETHANOL: Theoretically, lemon balm might increase the sedative effects of ethanol.

Licorice

I Potentiates toxicity of cardiac glycoside such as those in Digitalis (empirical) due to potassium reduction in the blood (PO human).
I Potentiate corticosteroid treatment (empirical).
I 7 grams of licorice, containing 0.5 grams of glycyrrhizin, reduced serum levels of testosterone in healthy males (PO human). It has been shown to increase levels of estradiol to testosterone in dosage range.
I DGL reduced gastric bleeding given with aspirin (PO human).
I Licorice with oral contraceptives induced hypertension and hypokalemia in a few cases.
I DGL increases bioavailability of nitrofurantoin by over 50%, while diminishing associated nausea (PO human).
I Licorice taken with thiazide (diuretic) can increase potassium loss.
II Licorice tincture significantly increased biliary and urinary excretion of acetaminophen (PO rats).
II Licorice or DGL reduced ulcer index when taken with ibuprofen.
I, IV Theoretically, licorice might reduce the effect of antihypertensive drug therapy. Licorice increases blood pressure in a dose dependent manner.
I, IV Theoretically, concomitant use might potentiate the duration of activity of corticosteroids, e.g., hydrocortisone. Concomitant use of licorice and
corticosteroids might also increase potassium loss and increase the risk of potassium depletion. Overuse or misuse of licorice can cause potassium depletion.

III There is preliminary evidence that licorice can inhibit the cytochrome P450 2B6 (CYP2B6) isoenzymes, 2C9 and 3A4 in vitro. Theoretically, licorice might increase levels of drugs metabolized by these enzymes; however, as of yet, these interactions have not been reported in humans. Use licorice cautiously or avoid in patients taking drugs metabolized in these pathways.

II, III, IV Theoretically, licorice might interfere with estrogen therapy due to estrogenic and anti-estrogenic effects.

IV Theoretically, ethacrynic acid and furosemide might enhance the mineralocorticoid effects of licorice by inhibiting the enzyme that converts cortisol to cortisone; however, bumetanide (Bumex) does not appear to have this effect. Licorice seems to increase metabolism and decrease levels of warfarin in animal models. This is likely due to induction of cytochrome P450 2C9 (CYP2C9) metabolism by licorice. Advise patients taking warfarin to avoid taking licorice.

Lab 17-HYDROXYPROGESTERONE: Licorice can increase serum 17-hydroxyprogesterone concentrations and test results in healthy volunteers who consume 7 grams of licorice per day.

Lab BLOOD PRESSURE: Excessive use of licorice can cause hypertension and increase blood pressure readings.

Lab POTASSIUM: Excessive use of licorice can cause hypokalemia, reducing serum potassium levels and test results.

Herb CARDIAC GLYCOSIDE-CONTAINING HERBS: Theoretically, the overuse or misuse of licorice can increase the risk of cardiotoxicity due to potassium depletion. Cardioactive herbs include digitalis, lily-of-the-valley, pheasant's eye, and squill.

Herb STIMULANT LAXATIVE HERBS: Theoretically, concomitant overuse or misuse of licorice with stimulant laxatives can increase the risk of potassium depletion. Stimulant laxative herbs include aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge,
gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, and yellow dock.

**Food** **GRAPEFRUIT JUICE**: Theoretically, grapefruit juice and its component naringenin might enhance the mineralocorticoid activities of licorice, by blocking the conversion of cortisol to cortisone.\(^{328,329}\)

**Food** **SALT**: A high salt diet can exacerbate adverse effects of licorice such as sodium and water retention and hypertension.\(^{330}\)

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**Lobelia**

I Lobelia alkaloid reduced the desire and addiction to tobacco. Used as a smoking deterrent.\(^{13}\)

IV Lobelia is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, lobelia might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.\(^{13}\)

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**Magnolia**

II Component honokiol at 0.2 mg/K for seven days enhanced anxiolytic effect of benzodiazepine diazepam (PO mice).\(^{13}\)

IV Theoretically, concomitant use of large doses of magnolia bark and alcohol might increase the risk of drowsiness and motor reflex depression.\(^{331}\)

IV Theoretically, concomitant use of large doses of magnolia bark and barbiturates might increase the risk of drowsiness and motor reflex depression.\(^{331}\) Some of these sedative medications include pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal), and others.

IV Theoretically, concomitant use of large doses of magnolia bark and CNS depressants might increase the risk of drowsiness and motor reflex depression.\(^{331}\)

**Herb** **HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES**: Theoretically, concomitant use with herbs and supplements that have sedative properties might increase the risk of excessive drowsiness. Some of these supplements include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, skullcap, valerian, yerba mansa, and others.\(^{331}\)
Maitake

II Protein-bound beta-glucan (D-fraction) inhibited metastasis of transplanted liver carcinomas by mitomycin C (powerful systemic DNA inhibiting anticancer agent) from 51 to 88% when given together. Compared to mitomycin C given together (mice).13

I, IV Some clinical research shows that taking maitake mushroom polysaccharide (MMP) can lower blood glucose levels in patients with types 2 diabetes.332 Theoretically, combining maitake mushroom with antidiabetes drugs might increase the risk of hypoglycemia. Monitor blood glucose levels closely.

IV There is some concern that maitake mushroom might increase the anticoagulant effects of warfarin. In a case report, a previously stable patient on warfarin developed an elevated international normalized ratio (INR) of 5.1 after taking maitake mushroom (Grifron-Pro Maitake D-Fraction) 1 drop/kg in three divided doses for one week. The elevated INR resolved after holding warfarin for two days and reducing the warfarin dose by 11%. It is thought that the beta-glucan constituent of maitake mushroom might cause warfarin dissociation from protein resulting in increased free warfarin and increased warfarin effects.333 Monitor INR levels closely in warfarin patients who take maitake mushroom.

Lab BLOOD GLUCOSE: Maitake mushroom might lower blood glucose and test results in patients with type 2 diabetes.13,334,332

Herb HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Maitake mushroom might lower blood glucose levels and might have additive effects when used with other herbs and supplements that also lower glucose levels.13,224,332 This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic effects include alpha-lipoic acid, bitter melon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut seed, Panax ginseng, psyllium, Siberian ginseng, and others.
Mate

Similar to coffee.

Meat, Grilled

Can lead to problems for those on asthma medications containing theophyllines. The chemical compounds formed when meat is grilled somehow prevent this type of medication from working effectively, increasing the possibility of an unmanageable asthma attack.13

Milk

Doesn't mix with laxatives containing bisacodyl (Correctol and Dulcolax). You might find the laxative works a little "too well" in the morning.13

IV Theoretically, use of whey protein with alendronate might decrease absorption. Whey protein contains minerals that might bind alendronate in the gut.335

IV Theoretically, concomitant use might decrease levodopa (Laradopa) absorption.336

IV Theoretically, use of whey protein with quinolones might decrease absorption. Whey protein contains minerals that might bind quinolones in the gut.335

IV Theoretically, use of whey protein with tetracyclines might decrease absorption. Whey protein contains minerals that might bind tetracyclines in the gut.335

Lab

**BLOOD UREA NITROGEN (BUN):** Whey protein in amounts of 2.3 g/kg/day or more, in addition to a normal diet, can produce twofold increases in BUN concentrations.335 However, whey protein does not change serum creatinine, indicating that the effect is due to protein loading, rather than reduced renal function.337
Milk Thistle

I 400 mg helps prevent liver damage from butyrophenones and phenothiazine. Reversing and preventing alcohol related cirrhosis (PO human).\textsuperscript{13}

II Alters metabolism of aspirins (IP rats). Protective of hepatotoxicity from acetaminophen (IV rats).\textsuperscript{13}

II Silybin prevented fatty liver induced by halothane; silibinin helped prevent nephrotoxic anti-tumor agent cisplatin (IV rats).\textsuperscript{13}

I, III, IV Preliminary evidence suggests that milk thistle constituents might inhibit cytochrome P450 2C9 (CYP2C9).\textsuperscript{338,339} \textbf{However, contradictory clinical research suggests that a milk thistle extract does not inhibit CYP2C9.}\textsuperscript{340} Until more is known, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking milk thistle. Some drugs metabolized by CYP2C9 include amitriptyline (Elavil), diazepam (Valium), verapamil (Calan), warfarin (Coumadin), zileuton (Zyflo), and others. Use milk thistle cautiously or avoid in patients taking these drugs.

II, III, IV Theoretically, milk thistle might affect the clearance of drugs that undergo glucuronidation. Some preliminary evidence suggests that the silymarin constituent might inhibit beta-glucuronidase. Theoretically, this could increase clearance and decrease levels of glucuronidated drugs.\textsuperscript{341} Other preliminary research suggests that the milk thistle constituents silymarin and silibinin inhibit uridine diphosphoglucuronosyl transferase (UGT), the major phase 2 enzyme that is responsible for glucuronidation.\textsuperscript{342} Theoretically, this could decrease the clearance and increase levels of glucuronidated drugs. Until more is known, use milk thistle cautiously in patients who are taking glucuronidated drugs.

III Preliminary research in an animal model suggests that the milk thistle constituent silibinin might increase plasma levels of tamoxifen (Nolvadex) and alter its conversion to an active metabolite. The mechanism appears to involve inhibition of pre-systemic metabolism of tamoxifen by cytochrome P450 2C9 (CYP2C9) and cytochrome P450 3A4 (CYP3A4), and inhibition of P-glycoprotein-mediated efflux of
tamoxifen into the intestine for excretion. Whether this interaction occurs in humans is not known. Use milk thistle cautiously or avoid in patients taking tamoxifen.

**Nutmeg**

III May potentiate sympathomimetics and psychoactive drugs especially MAOIs (speculative).

II Theoretically, concomitant use may affect drugs metabolized by cytochrome P450 1A1(CYP1A1), 1A2, 2B1, 2B2 enzyme systems.  

IV Theoretically, concomitant use may decrease the therapeutic effects of phenobarbital. Studies suggest myristicin, a constituent of nutmeg and mace, acts as an inducer of cytochrome P450 enzyme systems.

**Herb SAFROLE-CONTAINING HERBS:** Avoid concomitant use with other safrole-containing herbs due to potential for additive toxicity. Other herbs that contain safrole include basil, camphor, and cinnamon.

**Oak**

I Reduce absorption of alkaloids (empirical) due to tannins.

III Tannins precipitate iron salts in vitro.

**Nutri IRON:** Theoretically, concomitant administration might precipitate iron salts due to tannin content.

**Herb TANNIN-CONTAINING HERBS:** Theoretically, herbs that contain high percentages of tannins such as oak bark may cause precipitation of alkaloids and other constituents of herbs.

**Oats**

I Reduction of desire for opium and tobacco (PO human).

**Lab BLOOD GLUCOSE:** Oat bran lowers postprandial blood glucose and test results.
CHOLESTEROL: Oat bran lowers blood levels total and low density lipoprotein (LDL) cholesterol and test results.\textsuperscript{348}

INSULIN: Oat bran lowers postprandial insulin levels and test results.\textsuperscript{347}

Oatmeal

Large amounts, as with other high-fiber cereals, should not be eaten when taking digoxin. The fiber can interfere with the absorption of the drug, making the act of swallowing the pill a waste of time.\textsuperscript{13}

However, don't stop eating your cereal right away, because that could cause digoxin levels in your system to soar to toxic levels. A professional should make the dietary changes after carefully examining the digoxin levels.

BLOOD GLUCOSE: Oat bran lowers postprandial blood glucose and test results.\textsuperscript{347}

CHOLESTEROL: Oat bran lowers blood levels total and low density lipoprotein (LDL) cholesterol and test results.\textsuperscript{348}

INSULIN: Oat bran lowers postprandial insulin levels and test results.\textsuperscript{347}

Orange juice

Shouldn't be consumed with antacids containing aluminum. The juice increases the absorption of the aluminum.

Orange Juice and milk should be avoided when taking antibiotics. The juice's acidity decreases the effectiveness of antibiotics, as does milk.

Taking ivermectin orally with sweet orange juice, 750 mL over 4 hours, seems to significantly reduce the bioavailability of ivermectin. This effect does not seem to be related to effects on p-glycoprotein. The effect on ivermectin is more pronounced in males compared to females.\textsuperscript{349,350,351}

Research shows that consuming sweet orange juice inhibits organic anion transporting polypeptides (OATP), which reduces bioavailability of oral drugs that are substrates of OATP.\textsuperscript{350,351} Fexofenadine (Allegra) is a substrate of OATP. Sweet orange juice decreases bioavailability of fexofenadine by about
Drinking large amounts of sweet orange juice, 200 mL three times daily, has also been shown to decrease the OATP substrate celiprolol by 80% to 90%. It is thought that sweet orange juice might affect OATP for only a short time. Therefore, separating drug administration and consumption of orange by at least 4 hours might avoid this interaction. Some drugs that are substrates of OATP include bosentan (Tracleer), celiprolol (Celicard, others), etoposide (VePesid), fexofenadine (Allegra), fluoroquinolone antibiotics, glyburide (Micronase, Diabeta), irinotecan (Camptosar), methotrexate, paclitaxel (Taxol), saquinavir (Fortovase, Invirase), rifampin, statins, talinolol, torsemide (Demadex), troglitazone, and valsartan (Diovan).

There is conflicting data about the effect of sweet orange juice on P-glycoprotein. In animal models and in vitro, an extract of orange juice seems to inhibit drug efflux by P-glycoprotein. Theoretically, this would increase absorption and blood levels of certain drugs that are transported by P-glycoprotein. But in humans, drinking large amounts of sweet orange juice seems to decrease absorption and blood levels of the P-glycoprotein substrate celiprolol. This suggests that orange juice actually induces drug efflux by P-glycoprotein or affects drug levels by another mechanism such as inhibiting the gut drug transporter called organic anion transporting polypeptide (OATP). Until more is known, sweet orange juice should be used cautiously in people taking P-glycoprotein substrates. Some of these drugs include some chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir, saquinavir), H2 antagonists (cimetidine, ranitidine), some calcium channel blockers (diltiazem, verapamil), corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, and others.

Consuming sweet orange juice, 800 mL over 3 hours, including before, during, and after taking pravastatin 10 mg significantly increases absorption of pravastatin, without affecting pravastatin elimination.
Sweet orange juice increased pravastatin levels by about 149%. The exact mechanism of this interaction is not known, but sweet orange juice appears to affect the drug transporter organic anion transporting polypeptide (OATP). Sweet orange juice does not seem to affect simvastatin (Zocor) levels, but it is not known if sweet orange affects any of the other statins.

Taking a quinolone antibiotic with calcium-fortified sweet orange juice can modestly reduce quinolone absorption. Sweet orange juice alone is unlikely to affect quinolone absorption. Quinolones (fluoroquinolones) include ciprofloxacin (Cipro), enoxacin (Penetrex), gatifloxacin (Tequin), levofloxacin (Levaquin), lomefloxacin (Maxaquin), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and trovafloxacin (Trovan).

**Papain**

Increased warfarin anticoagulation when taken concurrently (on PO case).

**Lab**

INTERNATIONAL NORMALIZATION RATIO (INR): Concomitant use of papaya extract (papain) and warfarin may increase INR.

**Herb**

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs that have constituents that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, turmeric, and others.

**Food**

FIG: Cross sensitivity to papain may occur in individuals sensitive to fig.

KIWI: Cross sensitivity to papain may occur in individuals sensitive to kiwi.

POTATO PROTEIN: May inhibit papain proteolytic activity.
Psyllium

I 1 tsp in water twice daily reduced the absorption of lithium (PO human case) and should be taken separately, at least 1 hour, from some oral drugs.13
I Black psyllium can reduce blood glucose levels in patients with type 2 diabetes363 and might have additive effects on glucose levels when used with antidiabetes drugs. Monitor blood glucose levels closely. Medication dose adjustments may be necessary. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (Diabeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), and others.
IV Black psyllium can reduce carbamazepine absorption.364
IV Concomitant use might reduce digoxin absorption, requiring dose adjustment.366
Lab BLOOD GLUCOSE: Theoretically, black psyllium might lower postprandial blood glucose levels and test results.365,367,368
Lab SERUM CHOLESTEROL: Black psyllium can lower total cholesterol and LDL cholesterol levels, LDL:HDL ratio, and test results.365,367,368
Food NUTRIENT ABSORPTION: The long-term use of black psyllium with meals can reduce nutrient absorption requiring vitamin or mineral supplementation.366

Reishi

I Reduces the stimulative effect of caffeine.13
I The effect of reishi mushroom on platelet aggregation is not clear. A dose of 1.5 grams daily does not seem to decrease platelet aggregation.369 But a higher dose of 3 grams/day does seem to decrease platelet aggregation.370 Theoretically, combining higher doses of reishi mushroom with drugs with anticoagulant or antiplatelet activity might increase the risk of bleeding. Some of these drugs include aspirin; clopidogrel (Plavix); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Voltaren, Cataflam, others), ibuprofen (Advil, Motrin, others), naproxen (Anaprox, Naprosyn, others); dalteparin (Fragmin); enoxaparin (Lovenox); heparin; warfarin...
(Coumadin); and others.

Reishi mushroom might have hypotensive activity. Theoretically, concurrent use of reishi mushroom with antihypertensive drugs might increase the risk of hypotension. These include captopril (Capoten), enalapril (Vasotec), losartan (Cozaar), valsartan (Diovan), diltiazem (Cardizem), Amlodipine (Norvasc), hydrochlorothiazide (HydroDIURIL), furosemide (Lasix), and many others.

Lab BLEEDING TIME: The effect of reishi mushroom on platelet aggregation is not clear. A dose of 1.5 grams daily does not seem to decrease platelet aggregation. But a higher dose of 3 grams/day does seem to decrease platelet aggregation. Theoretically, reishi mushroom use might prolong coagulation and bleeding time results.

Herb ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: The effect of reishi mushroom on platelet aggregation is not clear. A dose of 1.5 grams daily does not seem to decrease platelet aggregation. But a higher dose of 3 grams/day does seem to decrease platelet aggregation. Theoretically, combining higher doses of reishi mushroom with other herbs with anticoagulant or antiplatelet activity might increase the risk of bleeding. Some of these herbs with anticoagulant/antiplatelet effects include angelica, anise, arnica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, horse chestnut, red clover, turmeric, and others.

Herb HERBS AND SUPPLEMENTS WITH HYPOTENSIVE EFFECTS: Reishi mushroom might have hypotensive activity. Theoretically, concurrent use of reishi mushroom with other herbs with hypotensive effects might increase risk of hypotension. Some other herbs and supplements with hypotensive activity include andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lycium, stinging nettle, theanine, and others.

Rhubarb

I Overuse of rhubarb might cause potassium depletion, increasing the risk of digoxin toxicity.

IV Overuse of rhubarb might compound corticosteroid-induced potassium loss.
Overuse of rhubarb might compound diuretic-induced potassium loss. There is concern that people receiving rhubarb along with potassium depleting diuretics might be at an increased risk for hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), and hydrochlorothiazide (HCTZ, Hydrodiuril, Microzide), and others.

A rhubarb-containing supplement has been linked to one report of renal failure. Researchers speculate that the anthraquinone constituents of rhubarb contributed to the renal dysfunction; however, renal failure did not occur until two days after the patient also started taking the NSAID diclofenac, which is known to be a nephrotoxic drug. The combination of diclofenac plus rhubarb anthraquinones is thought to have led to renal failure. Until more is known, advise patients to avoid taking rhubarb if they are taking other potentially nephrotoxic drugs. Some potentially nephrotoxic drugs include cyclosporine (Neoral, Sandimmune); aminoglycosides including amikacin (Amikin), gentamicin (Garamycin, Gentak, others), and tobramycin (Nebcin, others); nonsteroidal anti-inflammatory drugs (NSAIDs) including ibuprofen (Advil, Motrin, Nuprin, others), indomethacin (Indocin), naproxen (Aleve, Anaprox, Naprelan, Naprosyn), piroxicam (Feldene); and numerous others.

Concomitant use might reduce absorption of drugs due to reduced gastrointestinal transit time.

Concomitant use might compound fluid and electrolyte loss.

Rhubarb has stimulant laxative effects. In some people, rhubarb can cause diarrhea. Diarrhea can increase the effects of warfarin, increase international normalized ratio (INR), and increase the risk of bleeding. Advise patients who take warfarin not to take excessive amounts of rhubarb.

Lab URINE TESTS: Rhubarb might discolor urine and interfere with diagnostic tests.

Herb Food CALCIUM: Concurrent use might decrease mineral absorption. Rhubarb contains oxalates, which
can bind multivalent metal ions in the gastrointestinal (GI) tract and decrease mineral absorption.  

**Cardiac Glycoside-Containing Herbs:** Overuse of rhubarb might cause potassium depletion, increasing the risk of cardiac toxicity. Cardiac glycoside-containing herbs include black hellebore, Canadian hemp root, digitalis leaf, hedge mustard, figwort, lily of the valley roots, motherwort, oleander leaf, pheasant's eye plant, pleurisy root, squill bulb leaf scales, and strophanthus seeds.

**Horse Tail:** Theoretically, concomitant use of rhubarb with horsetail increases the risk of potassium depletion.

**Iron:** Concurrent use might decrease mineral absorption. Rhubarb contains oxalates, which can bind multivalent metal ions in the gastrointestinal (GI) tract and decrease mineral absorption.

**Licorice:** Theoretically, concomitant use of rhubarb with licorice increases the risk of potassium depletion.

**Stimulant Laxative Herbs:** Theoretically, concomitant use with other stimulant laxative herbs may increase the risk of potassium depletion. Stimulant laxative herbs include aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, senna, and yellow dock.

**Zinc:** Concurrent use might decrease mineral absorption. Rhubarb contains oxalates, which can bind multivalent metal ions in the gastrointestinal (GI) tract and decrease mineral absorption.

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**Rosemary**

III Tincture increased intracellular accumulation of chemotherapeutic agent doxorubutin and vinblastine in human breast cancer cells by blocking the binding of these drugs to the P-glycoprotein transport pump (in vitro).
Senna

I Overuse or misuse can cause potassium loss, thus increase toxicity of antiarrhythmic drugs and cardiac glycosides (empirical). Overuse of senna might compound diuretic-induced potassium loss. There is some concern that people taking senna along with potassium depleting diuretics might have an increased risk for hypokalemia. Initiation of potassium supplementation or an increase in potassium supplement dose may be necessary for some patients. Some diuretics that can deplete potassium include chlorothiazide (Diuril), chlorthalidone (Thalitone), furosemide (Lasix), and hydrochlorothiazide (HCTZ, Hydrodiuril, Microzide), and others.

IV Senna has stimulant laxative effects. In some people, senna can cause diarrhea. Diarrhea can increase the effects of warfarin, increase international normalized ratio (INR), and increase the risk of bleeding. In one report, excessive use of senna for 3 weeks resulted in diarrhea, bloody stools, and an elevated INR of 11.9. Advise patients who take warfarin not to take excessive amounts of senna.

Lab COLORIMETRIC TESTS: Senna can discolor urine (pink, red, purple, orange, rust), interfering with diagnostic tests that depend on a color change, due to its anthraquinone content.

Lab POTASSIUM: Excessive use of senna can cause potassium depletion, reducing serum potassium concentrations and test results.

Herb HORSETAIL: Theoretically, concomitant use of senna with horsetail increases the risk of potassium depletion.

Herb LICORICE: Theoretically, concomitant use of senna with licorice increases the risk of potassium depletion.

Herb STIMULANT LAXATIVE HERBS: Theoretically, concomitant use with other stimulant laxative herbs increases the risk of potassium depletion. Stimulant laxative herbs aloe, alder buckthorn, black root, blue flag, butternut bark, colocynth, European buckthorn, fo ti, gamboge, gossypol, greater bindweed, jalap, manna, Mexican scammony root, rhubarb, senna, and yellow dock.
Soy

I Oral thyroxine dose to 3 infants with congenital hypothyroidism had to be reduce by 20% after discontinuation of soy-based formula (PO human).\textsuperscript{13}

III Antibiotics may decrease the action of isoflavones in soy, because intestinal bacteria are responsible in part for converting the isoflavones into their active forms. Antibiotics may decrease the ability of intestinal bacteria to convert the isoflavones.\textsuperscript{380}

IV Theoretically, soy might competitively inhibit the effects of estrogen replacement therapy.\textsuperscript{381}

IV Fermented soy products such as tofu and soy sauce contain tyramine. Tyramine is an amino acid that is involved in blood pressure regulation. Tyramine is metabolized by monoamine oxidase. MAOIs decrease the breakdown of tyramine. Consuming more than 6 mg of tyramine while taking a MAOI can increase the risk of hypertensive crisis.\textsuperscript{382} The amount of tyramine in fermented soy products is usually relatively small, often less than 0.6 mg per serving; however, there can be significant variation depending on the specific product used, storage conditions, and length of storage. Storing one brand of tofu for a week can increase tyramine content from 0.23 mg to 4.8 mg per serving.\textsuperscript{382,383,384} Advise patients taking MAOIs to avoid fermented soy products that contain high amounts of tyramine. Some MAOIs include phenelzine (Nardil), tranylcypromine (Parnate), and others.\textsuperscript{major}

II, III There is concern that soy might interfere with tamoxifen due to the estrogenic effects of soy isoflavones. Preliminary evidence suggests that soy isoflavones genistein and daidzen can antagonize the antitumor effects of tamoxifen under some circumstances;\textsuperscript{385,386} however, soy isoflavones might have different effects when used at different doses. A relatively low in vitro concentration of soy isoflavones such as 1 microM/L seems to interfere with tamoxifen. High in vitro concentrations such as those >10 microM/L might actually enhance tamoxifen effects. People on a high-soy diet have soy isoflavones levels ranging from 0.1-6 microM/L. Until more is known, advise patients taking tamoxifen
to avoid therapeutic use of soy products.

I, IV Soy milk has been reported to decrease the international normalized ratio (INR) in a patient taking warfarin. The mechanism of this interaction is not known. Soy may also inhibit platelet aggregation.387 Dosing adjustments for warfarin may be necessary.388

Lab PARATHYROID HORMONE: High intake of soy seems to lower parathyroid hormone levels in postmenopausal women.389

Lab PROSTATE SPECIFIC ANTIGEN (PSA): There is some evidence that men with prostate cancer who consume a specific bread containing 50 grams of soy and providing 117 mg isoflavones have significantly reduced PSA levels after about 3 weeks of use.390

Lab THYROID STIMULATING HORMONE (TSH): Theoretically, soy might increase TSH levels. Soy seems to inhibit thyroid hormone synthesis resulting in increased secretion of TSH in some postmenopausal women.391 There are also cases of hypothyroidism and goiter in infants fed soy formula.392 But this seems to occur primarily in people with low iodine levels.392 In postmenopausal women with normal levels of iodine, taking a soy extract for 6 months does not seem to significantly affect thyroid hormone levels.393

Food PLANT-BASED FOODS: Soy protein isolate reduces the absorption of non-heme iron from foods.394 Non-heme iron is found in plant-based foods.
St John’s Wort

- Four cases of elderly patients using SSRI setraline (Zoloft) and one case of nefazodone use (Serzone) (antidepressant) produced mild serotonin symptoms (2-4 days, PO human) Cases of reduction should be done under observation.\(^\text{13}\)

- Theophylline (chronic asthma) dose required an increase from 600 - 1600 mg to maintain same blood levels when taking 300 mg of St. John’s Wort (PO case).\(^\text{13}\)

- Concurrent consumption of proteinase inhibitors (indinvar) and St. John’s Wort reduced activity by 49 - 99 %\(^\text{13}\).

- Reduction in the amounts of digoxin has been observed after 10 days of consumption 900mg of St. John’s Wort.\(^\text{13}\)

- Reduction of heart transplant drug cyclosporine after three weeks of 900 mg of St. John’s Wort.

- Breakthrough bleeding has been observed in a small number of women on oral contraceptives.

- Oral anticoagulant phenprocoumon had reduced plasma concentrations when taken with a single dose of St John’s Wort.

- Midazolam (Versed, sleep anti-anxiety) blood levels reduced by 60% when given concordantly with 900 mg/day St. John’s Wort.\(^\text{13}\)

- St. John's Wort extract (Jarsin), 600 mg daily, significantly decreases tacrolimus serum levels. Dose increases of 60% may be required to maintain therapeutic tacrolimus levels in patients taking St. John's Wort concomitantly. St. John's Wort is thought to lower tacrolimus levels due to cytochrome P450 3A4 (CYP3A4) enzyme induction.\(^\text{395,396}\)

- St. John's Wort induces cytochrome P450 1A2, but to a lesser extent than CYP3A4.\(^\text{395,397}\)

- St. John's Wort can decrease the therapeutic effects of warfarin. Taking St. John's Wort significantly increases clearance of warfarin, including both the R-isomer and S-isomer of warfarin.\(^\text{398,399}\) This suggests that St. John's Wort induces CYP1A2 and CYP3A4, which metabolize R-warfarin and CYP2C9, which metabolizes S-warfarin.\(^\text{417}\) St. John's Wort can also
significantly decrease International Normalized Ratio (INR) in people taking warfarin. In addition, warfarin physically interacts with hypericin and pseudohypericin, active constituents of St. John's Wort. When the dried extract is mixed with warfarin in an aqueous medium, up to 30% of warfarin is bound to particles, reducing its absorption. Taking warfarin at the same time as St. John's Wort might reduce warfarin bioavailability.

III Hypericin has been shown to induce hepatic clearing of xenobiotic metabolic agents (in vitro).

III Concern of interaction with anesthetic drugs with taking St. John’s wort prior to surgery.

IV Theoretically, concomitant use of St. John's wort with selective serotonin agonists can increase the risk of serotonergic adverse effects and possibly serotonin syndrome. Concomitant use should be avoided. The "triptans" include frovatriptan (Frova), naratriptan (Amerge), rizatriptan (Maxalt), sumatriptan (Imitrex), and zolmitriptan (Zomig). Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome.

IV St. John's Wort may decrease the effect of alprazolam. Alprazolam, which is used as a probe for cytochrome P450 3A4 (CYP3A4) activity, has a two-fold increase in clearance when given with St. John's wort. St. John's Wort reduces the half-life of alprazolam from 12.4 hours to 6 hours.

IV Concomitant use with St. John's Wort extract may cause synergistic phototoxicity. Delta-aminolevulinic acid (an investigational drug used in oncologic diagnostic procedures) can cause a burning erythematous rash and severe swelling of the face, neck, and hands when taken with St. John's Wort.

III, IV Concomitant use can reduce serum concentrations of amitriptyline by 22% and its metabolite, nortriptyline, by 42%. St. John's Wort induces intestinal and hepatic CYP3A4 and intestinal P-glycoprotein/MDR-1, a drug transporter, which increases amitriptyline clearance. P-glycoprotein is a carrier mechanism responsible for transporting drugs and other substances across cell membranes. When P-glycoprotein is induced in the gastrointestinal (GI)
tract, it can prevent the absorption of some medications. In addition, induction of p-glycoprotein can decrease entry of drugs into the central nervous system (CNS) and decrease access to other sites of action. Concomitant use can reduce serum concentrations of amitriptyline by 22% and its metabolite, nortriptyline, by 42%. Concomitant use can lead to increased adverse effects and increase the risk of serotonergic side effects, including serotonin syndrome. Although this effect has only been reported with nefazodone (Serzone), paroxetine (Paxil), and sertraline (Zoloft), it might also occur with other antidepressants. Use of St. John's Wort with other antidepressants should only be done with close supervision. Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome. St. John's Wort can decrease barbiturate-induced sleep time. Some of these sedative medications include pentobarbital (Nebutal), phenobarbital (Luminal), secobarbital (Seconal), and others. Taking St. John's Wort with clopidogrel seems to increase the activity of clopidogrel. In clopidogrel non-responders, taking St. John's Wort seems to induce clopidogrel metabolism to its active metabolite and therefore increase clopidogrel's antiplatelet activity. Theoretically, in clopidogrel responders, this might lead to an increased risk of bleeding. St. John's Wort induces cytochrome P450 3A4. Use caution when considering concomitant use of St. John's Wort and other drugs affected by these enzymes. Drugs that might be affected include some calcium channel blockers (diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vinorelbine), antifungals (ketoconazole, itraconazole), glucocorticoids, cisapride (Propulsid), alfentanil (Alfenta), fentanyl (Sublimaze), losartan (Cozaar), fluoxetine (Prozac), midazolam (Versed), omeprazole (Prilosec), ondansetron (Zofran), propranolol (Inderal), fexofenadine (Allegra), and numerous others. Taking St. John's Wort, 900 mg/day, decreases serum
levels of imatinib by 30% in healthy volunteers. This is most likely due to St. John's Wort's inducing effect on cytochrome P450 3A4 (CYP3A4).\textsuperscript{418} Advise patients not to take St. John's Wort if they are taking imatinib. major

I, IV Concomitant use with St. John's Wort can decrease serum levels of irinotecan by at least 50%. Clearance of the active metabolite of irinotecan, SN-38, is increased, resulting in a 42% decrease in the area under the concentration curve.\textsuperscript{419} St. John's Wort is thought to lower drug levels by inducing cytochrome P450 3A4 (CYP3A4).\textsuperscript{420} major

I, IV Preliminary clinical research in healthy males shows that taking St. John's Wort for 14 days induces cytochrome P450 2C19 (CYP2C19) and significantly increases metabolism of mephenytoin (Mesantoin). In patients with wild-genotype 2C19 (2C19*1/*1), metabolism was almost 4-fold greater in subjects who received St. John's Wort compared to placebo. In contrast, patients with 2C19*2/*2 and *2/*3 genotypes did not demonstrate a similar increase in metabolism.\textsuperscript{421} Theoretically, St. John's Wort might increase metabolism of other CYP2C19 substrates. Use St. John's Wort cautiously in patients taking drugs metabolized by CYP2C19. major

I, III, IV There is contradictory research about the effect of St. John's Wort on CYP2C9. Some in vitro research shows that St. John's Wort induces CYP2C9, but to a lesser extent than CYP3A4.\textsuperscript{395,410,411} St. John's Wort also induces metabolism of the S-warfarin isomer which is a CYP2C9 substrate.\textsuperscript{422} Other research shows that taking St. John's Wort, 300 mg three times daily for 21 days, does not significantly affect the pharmacokinetics of a single 400 mg dose of ibuprofen, which is also a CYP2C9 substrate.\textsuperscript{423} Until more is known, use St. John's Wort cautiously in patients who are taking CYP2C9 substrates.

I, II Concomitant use can decrease serum levels of NNRTIs. St. John's Wort can increase the oral clearance of nevirapine (Viramune) by 35%. Subtherapeutic concentrations are associated with therapeutic failure, development of viral resistance, and development of drug class resistance. St. John's Wort induces intestinal and hepatic cytochrome P450 3A4 (CYP3A4) and intestinal P-glycoprotein/MDR-1,
a drug transporter.\textsuperscript{424,425,426} Other NNRTIs include delavirdine (Rescriptor), and efavirenz (Sustiva).

IV Concomitant use with St. John's Wort can increase the risk of serotonergic side effects and serotonin syndrome-like symptoms. St. John's Wort, 600 mg per day, with fenfluramine can cause nausea, headache, and anxiety.\textsuperscript{427}  

I Concomitant use has been associated with serotonergic side effects, including nausea, vomiting, and restlessness.\textsuperscript{428}

II, IV Theoretically, concurrent use with meperidine might cause additive serotonergic effects and increase the risk of serotonin syndrome.\textsuperscript{429,430,431} Also, concurrent use might theoretically cause cerebral vasoconstriction disorders such as Call-Fleming syndrome.\textsuperscript{432}

I A single dose of St. John's Wort can decrease the clearance of fexofenadine, resulting in increased plasma concentration of fexofenadine. However, with continued dosing, more than 2 weeks, St. John's Wort does not appear to affect fexofenadine levels.\textsuperscript{433} Patients taking fexofenadine and who start taking St. John's Wort should be monitored for possible fexofenadine toxicity.

IV Theoretically, because St. John's Wort might affect serotonin similar to conventional antidepressants,\textsuperscript{429,434} concurrent use might cause additive adverse effects, including hypertension, hyperthermia, agitation, confusion, coma, etc. St. John's Wort should be avoided in patients taking MAOIs and for 14 days after MAOI discontinuation.

I, IV St. John's Wort can increase narcotic-induced sleep time\textsuperscript{435} and might also increase analgesic effects.\textsuperscript{436}

IV St. John's Wort may increase the metabolism of phenobarbital and phenytoin, resulting in loss of seizure control. Plasma concentrations of phenobarbital should be monitored carefully. The dose of phenobarbital may need to be increased when St. John's Wort is started and decreased when it is stopped.\textsuperscript{437}

II Preliminary research in an animal model shows that taking St. John's Wort extract increases the bioavailability of procainamide, but does not increase
its metabolism. Whether this interaction is clinically significant in humans is not known.

**St. John's Wort can antagonize the effects of reserpine.**

**Lab**

**PROTHROMBIN TIME (PT)/INTERNATIONAL NORMALIZED RATIO (INR):** St. John's Wort can decrease PT/INR test results in patients treated with warfarin (Coumadin).

**Lab**

**THYROID STIMULATING HORMONE (TSH):** Some preliminary research suggests that St. John's Wort might elevate TSH levels.

**Herb**

**CARDIAC GLYCOSIDE-CONTAINING HERBS:** Concomitant use might reduce the therapeutic effects of digitalis. The St. John's Wort extract, LI 160, decreases digoxin serum levels in healthy people. St. John's Wort seems to lower digoxin serum concentrations by approximately 25%. St. John's Wort seems to induces the activity of the carrier protein P-glycoprotein, which increases the clearance of digitalis.

**Herb**

**HERBS AND SUPPLEMENTS WITH SEROTONERGIC PROPERTIES:** Theoretically, St. John's Wort might increase the effects and adverse effects of products that increase serotonin levels; including 5-hydroxytryptophan (5-HTP), Hawaiian baby woodrose, L-tryptophan, and SAMe.

**Herb**

**RED YEAST:** St. John's Wort induces cytochrome P450 3A4 enzyme and can lower serum levels of the statin drug lovastatin. Red yeast contains statin-like drugs such as lovastatin. Theoretically, St. John's Wort might reduce serum levels of lovastatin from red yeast.

**Herb**

**TRYPTOPHAN:** Combining St. John's Wort with tryptophan might increase the risk of serotonin syndrome. There is a case report of serotonin syndrome in a patient who took tryptophan and high doses of St. John's Wort.

**Stinging Nettles**

**I** 50 gm of stewed leaves enhanced anti-inflammatory effect of 50 mg of diclofenac (making it as effective as 200 mg) (PO human).

**IV** There is some evidence that stinging nettle can
decrease blood glucose levels. Theoretically, concomitant use of excessive amounts of stinging nettle might interfere with blood glucose control.\textsuperscript{9}

**IV** There is some evidence that stinging nettle might have blood pressure lowering effects. Theoretically, concomitant use of excessive amounts of stinging nettle might have additive effects with antihypertensive drugs on blood pressure.\textsuperscript{9}

**IV** There is some evidence that stinging nettle preparations might have CNS depressant activity. Theoretically, concomitant use of excessive amounts of stinging nettle might have additive effects with CNS depressant drugs.\textsuperscript{9}

**IV** Stinging nettle is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, stinging nettle might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.

**IV** There is some concern that stinging nettle might decrease the effects of anticoagulant drugs such as warfarin (Coumadin). Stinging nettle contains a significant amount of vitamin K;\textsuperscript{13} use cautiously. Dose adjustment of anticoagulants may be needed.

**HERBS AND SUPPLEMENTS WITH HYPOTENSIVE EFFECTS**: Stinging nettle is thought to have hypotensive effects. Theoretically, combining stinging nettle with other herbs or supplements with hypotensive effects might increase the risk of hypotension. Some of these herbs and supplements include andrographis, casein peptides, cat's claw, coenzyme Q-10, fish oil, L-arginine, lycium, and others.

**Spinach**

**IV** Monitor blood glucose level closely due to claims that spinach leaves have hypoglycemic effect.\textsuperscript{13}

**IV** Spinach contains vitamin K. Individuals using anticoagulants should consume a consistent daily amount to maintain the effect of anticoagulant therapy.\textsuperscript{13}

**INTERNATIONAL NORMALIZED RATIO (INR)/PROTHROMBIN TIME (PT)**: Theoretically, spinach might decrease coagulation test results due to high vitamin K content.\textsuperscript{443}

**CALCIUM**: Concurrent use might decrease
mineral absorption. Spinach contains oxalate,\textsuperscript{444,445} which can bind multivalent metal ions in the gastrointestinal tract and decrease mineral absorption.

**Herb Food IRON:** Concurrent use might decrease mineral absorption. Spinach contains oxalate,\textsuperscript{444,445} which can bind multivalent metal ions in the gastrointestinal tract and decrease mineral absorption.

**Herb Food ZINC:** Concurrent use might decrease mineral absorption. Spinach contains oxalate,\textsuperscript{444,445} which can bind multivalent metal ions in the gastrointestinal tract and decrease mineral absorption.

**Strawberries, Raspberries, Spinach, and Rhubarb:**

These contain oxalic acid, which can aggravate kidney and bladder stones in susceptible people, and reduce body's ability to absorb iron and calcium.\textsuperscript{13}

**Tea**

1. Reduces absorption of Iron in young children.\textsuperscript{13}

1. Reduces anticoagulation after stabilization on warfarin (0.5 - 1 gallon of green tea daily).\textsuperscript{13}

**Lab 5-HYDROXYINDOLEACETIC ACID:** Black tea might increase urine 5-hydroxyindoleacetic acid concentrations and test results, due to its caffeine content. Caffeine can increase urine catecholamine concentrations.\textsuperscript{446}

**Lab BLEEDING TIME:** Theoretically, black tea might increase bleeding time. Caffeine is reported to have antiplatelet activity.\textsuperscript{447,448} However, the significance of these effects in humans is not known.

**Lab CATECHOLAMINE:** Caffeine can increase plasma catecholamine levels.\textsuperscript{449}

**Lab CREATINE:** The caffeine in black tea can increase urine creatine levels.\textsuperscript{450}

**Lab DIPYRIDAMOLE THALLIUM IMAGING:** Black tea might interfere with dipyridamole thallium imaging studies, due to its caffeine content. Caffeine attenuates the characteristic cardiovascular responses to dipyridamole and has altered test results.\textsuperscript{451}

**Lab FERRITIN:** Drinking black tea may cause a
reduction in serum ferritin in iron-deficient people.\textsuperscript{452,453}

**Lab GLUCOSE**: Caffeine, a constituent of black tea, has been reported to cause increases and decreases in blood glucose.\textsuperscript{454}

**Lab HEMOGLOBIN**: Drinking black tea may cause a reduction in hemoglobin in iron-deficient people.\textsuperscript{452,453}

**Lab IRON**: In people with iron deficiency, black tea may further reduce the concentration of serum iron.\textsuperscript{452,453}

**Lab LACTATE**: The combination of ephedrine, a constituent of ephedra, and caffeine, a constituent of black tea, can increase blood lactate levels.\textsuperscript{454}

**Lab NEUROBLASTOMA TESTS**: Black tea (due to its caffeine content) might cause false-positive diagnosis of neuroblastoma, when diagnosis is based on tests of urine vanillylmandelic acid (VMA) or catecholamine concentrations. Caffeine can increase urine catecholamine and VMA concentrations.\textsuperscript{446}

**Lab PHARMACOLOGICAL STRESS TESTS**: The caffeine in black tea is a competitive antagonist for adenosine receptors.\textsuperscript{455} It is recommended that caffeine and caffeine-containing products be stopped 24 hours prior to pharmacological stress tests.\textsuperscript{456}

However, caffeine appears more likely to interfere with dipyridamole (Persantine) than adenosine (Adenocard) stress testing.\textsuperscript{455} The interaction between caffeine and dipyridamole is unlikely to be significant in stress testing if the heart rate increase is greater than 5% after dipyridamole infusion.\textsuperscript{457}

**Lab PHEOCHROMOCYTOMA TESTS**: Black tea (due to its caffeine content) might cause false-positive diagnosis of pheochromocytoma, when diagnosis is based on tests of urine vanillylmandelic acid (VMA) or catecholamine concentrations. Caffeine can increase urine catecholamine and VMA concentrations.\textsuperscript{446}

**Lab PULMONARY FUNCTION TESTS**: People may need to avoid caffeine and caffeinated beverages such as black tea for at least four hours prior to lung function testing. Forced expiratory volume in one minute (FEV1) seems to show a small improvement up to two hours after caffeine use. Mid-expiratory flow rates may also improve with caffeine for up to four hours.\textsuperscript{458}
THEOPHYLLINE: Theophylline is a metabolite of caffeine. Caffeine in overdose can cause significant increases in theophylline serum concentrations.\(^{459}\) Theoretically, very large doses of black tea might produce measurable theophylline levels.

URATE: Black tea might falsely increase serum urate test results determined by the Bittner method, due to its caffeine content. Caffeine causes false elevations in serum urate test results determined by the Bittner method.\(^{460}\)

URINARY CALCIUM: Caffeine, a constituent of black tea, can increase urinary calcium levels.\(^{461}\)

VANILLYLMANDELIC ACID (VMA): Black tea might increase urine VMA concentrations and test results, due to its caffeine content. Caffeine can increase urine VMA concentrations.\(^{446}\)

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs and supplements that affect platelet aggregation could theoretically increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, and others.

BITTER ORANGE: Bitter orange in combination with caffeine or caffeine-containing herbs, such as black tea, can increase blood pressure and heart rate in otherwise healthy normotensive adults, potentially increasing the risk of serious cardiovascular adverse effects.\(^{462}\)

CAFFEINE-CONTAINING HERBS AND SUPPLEMENTS: Concomitant use can increase caffeine therapeutic and adverse effects. Natural products that contain caffeine include coffee, black tea, green tea, oolong tea, guarana, mate, and cola.

CALCIUM: High caffeine intake from foods and beverages including black tea increases urinary calcium excretion.\(^{463}\)

CREATINE: There is some concern that combining caffeine, a constituent of black tea, with ephedra, and creatine might increase the risk of serious adverse effects. There is a report of ischemic stroke in an athlete who consumed creatine monohydrate 6 grams, caffeine 400-600 mg, ephedra 40-60 mg, and a variety of other supplements daily for 6 weeks.\(^{464, 465}\) Caffeine might also decrease creatine's possible beneficial
effects on athletic performance. Some researchers think caffeine can inhibit phosphocreatine resynthesis.\textsuperscript{466,467}

**Herb EPHEDRA (Ma huang):** Use of ephedra with black tea can increase the risk of stimulatory adverse effects due to its caffeine content. There is evidence that using ephedra with caffeine might increase the risk of serious life-threatening or debilitating adverse effects such as hypertension, myocardial infarction, stroke, seizures, and death.\textsuperscript{468,469} Tell patients to avoid taking black tea with ephedra and other stimulants.

**Nutri IRON:** Black tea appears to reduce absorption of non-heme iron from foods.\textsuperscript{470} Infants given tea to drink have an increased risk of microcytic anemia.\textsuperscript{471} Theoretically, black tea might reduce the absorption of iron supplements. For most patients, this effect will not be clinically significant. Advise patients with iron deficiency to consume tea between meals rather than with meals to lessen this interaction.\textsuperscript{470}

**Nutri MAGNESIUM:** Consuming large amounts of black tea can increase excretion of magnesium.\textsuperscript{472}

**Food IRON:** Black tea can interfere with the absorption of iron in the diet. People who are iron-deficient should avoid drinking black tea. Black tea doesn't seem to affect iron status in people with normal iron stores.\textsuperscript{471,473}

**Food MILK:** Adding milk to black tea appears to reduce some of the beneficial cardiovascular effects of drinking tea.\textsuperscript{474,475} Milk might bind and prevent absorption of the antioxidant flavonoids in tea. However, some contradictory evidence suggests that this interaction does not occur.\textsuperscript{476} More evidence is needed to determine the clinical significance of this potential interaction.

See Coffee for caffeine action.

**Tomato**

Contains small quantities of a toxic substance known as solanine that may trigger headaches in susceptible people. A relatively common cause of allergies. An unidentified substance in tomatoes and tomato-based products can cause acid reflux, leading to indigestion and heartburn.
Individuals who often have digestive upsets should try eliminating tomatoes for 2 to 3 weeks to see if there is any improvement.\textsuperscript{13}

**Turnips**

Contains two goitrogenic substances, progoitrin and gluconasturtin, which can interfere with the thyroid gland’s ability to make its hormones. Although moderate consumption of goitrogens is not a hazard for healthy people, the consumption of goitrogens can promote development of a goiter (an enlarged thyroid) in persons with thyroid disease.\textsuperscript{13}

**Turkey Tail**

I Prevents rapid drop in white blood cells after chemotherapy treatment of vincristine, cyclophosphamide and 4'epidoxorubicin (PO human case studies).\textsuperscript{13}

**Turmeric**

II Reduced frequency of gastric and duodenal ulcers induced by indomethacin (PO rats).\textsuperscript{13}

III High doses with anti-platelet drugs should be avoided (speculative).\textsuperscript{13}

IV Concomitant use of turmeric with these drugs might increase the risk of bleeding due to decreased platelet aggregation. Turmeric has been reported to have antiplatelet effects;\textsuperscript{477} avoid concomitant use. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

**Herbs Anticoagulant/Antiplatelet Herbs and Supplements:** Concomitant use of turmeric with herbs that might affect platelet aggregation could theoretically increase the risk of bleeding in some people.\textsuperscript{477} These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, willow, and others.
Uva Ursi

II Urinary acidifiers inhibits conversion of arbutin to active hydroquinone.\textsuperscript{13}

II Enhances anti-inflammatory action of prednisolone (PO mice).\textsuperscript{13}

IV Uva ursi is thought to have diuretic properties. Theoretically, due to these potential diuretic effects, uva ursi might reduce excretion and increase levels of lithium. The dose of lithium might need to be decreased.\textsuperscript{13}

Lab \textbf{COLORIMETRIC URINE TESTS}: Theoretically, uva ursi can interfere with colorimetric urine tests and can turn urine greenish-brown.\textsuperscript{9}

Valerian

I Helps with withdrawal from benzodiazepine drug (empirical).\textsuperscript{13}

II Valpotriate reduces diazepan withdrawal (IP rats).

IV Theoretically, valerian might have an additive sedative effect with alcohol.\textsuperscript{478} major

I, IV Taking valerian extract, 1000 mg/day (providing 10 mg valerenic acid), seems to increase alprazolam levels by about 19\%. This is most likely due to valerian's inhibitory effects on cytochrome P450 3A4 (CYP3A4).\textsuperscript{479} \textbf{Although this increase is statistically significant, it might not be clinically significant.}, major

II, IV Theoretically, concomitant use with benzodiazepines may cause additive therapeutic and adverse effects.\textsuperscript{480,481} Some benzodiazepines are alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), midazolam (Versed), temazepam (Restoril), triazolam (Halcion), and others. major

II, IV Theoretically, concomitant use of valerian and drugs with sedative and anesthetic properties may cause additive therapeutic and adverse effects.\textsuperscript{480,481} Some CNS depressants are benzodiazepines, pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal), thiopental (Pentothal), fentanyl (Duragesic, Sublimaze), morphine, propofol (Diprivan), and others. major
There is preliminary evidence that valerian might inhibit the cytochrome P450 3A4 (CYP3A4) enzyme. However, clinical research suggests that valerian might not significantly inhibit CYP3A4 at relatively low doses of 375 mg/day, but might have modest effect at higher doses of 1000 mg/day. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), and numerous others. Use valerian cautiously or avoid in patients taking these drugs.

**Herbs and Supplements with Sedative Properties:** Use of valerian with other herbs and supplements with sedative properties might enhance therapeutic and adverse effects. Some of these products include calamus, California poppy, catnip, hops, Jamaican dogwood, kava, L-tryptophan, melatonin, sage, SAMe, St. John's wort, sassafras, skullcap, and others.

**Food Alcohol:** Theoretically, valerian might have an additive sedative effect with alcohol.

### Yohimbe

I Hypertension has occurred if given with tricyclic antidepressant such as imipramine (IV and PO human) and amitriptyline (SC in mice).

I Toxicity of yohimbe is increased when used with phenothiazines such as chlorpromazine (IV human case study) and promazine (SC mice).

I Concomitant use of yohimbe can interfere with blood pressure control and should be used with caution.

I Avoid concomitant use; yohimbine antagonizes the effect of clonidine.

I Avoid concomitant use; yohimbine antagonizes the effect of guanabenz.

II MAOIs increases yohimbe toxicity.

IV Concomitant use with Naloxone can have additive therapeutic and adverse effects.

**Herbs Caffeine-Containing Herbs and Supplements:** Theoretically, concomitant use of yohimbe with large amounts of caffeine-containing...
herbs or products can increase the risk of hypertensive crisis. 

**Caffeine-containing herbs include coffee, cola, guarana, mate, and tea.**

**Herb EPHEDRA:** Theoretically, concomitant use of large amounts of ephedra can increase the risk of hypertensive crisis due to ephedrine content.

**Food TYRAMINE-CONTAINING FOODS:** Avoid concomitant consumption of large amounts of tyramine-containing foods, due to the risk of hypertensive crisis. Tyramine-containing foods include aged cheeses, fermented meats, red wines, and others.

**Food VASOPRESSOR-CONTAINING FOODS:** Avoid concomitant consumption of large amounts of vasopressor-containing foods due to the risk of hypertensive crisis. Vasopressor-containing foods include overripe fava beans, coffee, tea, colas, and chocolate.

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