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CERTAIN FOODS, DRUGS, AND SUPPLEMENTS DON'T MIX

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Most patients know that dietary precautions should be observed when taking certain medications. Diuretics are more effective when you adhere to a low sodium diet. Such instructions are generally given by physicians and/or provided by printed information from pharmacists. These include warnings about the need to avoid other drugs or foods containing chemicals that could cause problems.

One example is Coumadin, a popular anticoagulant used to reduce clotting tendencies in patients who have suffered a stroke or heart attack due to a clot. Since sensitivity to Coumadin can vary considerably, patients must be monitored very closely and carefully.

Daily prothrombin time blood tests are required to insure that enough is being taken to provide protection, or to avoid taking too much, which could cause serious hemorrhage. Once a dosage regimen has been found to maintain prothrombin times within the proper levels, tests do not have to be performed as frequently - provided nothing else upsets the apple cart. That is why there are strong warnings not to take aspirin and other non-prescription and prescription pain medications that could prolong the clotting time to dangerous levels. However, many people are unaware that alcohol, vitamin E and garlic can cause the same problem. Conversely, patients are also advised to avoid eating large amounts of leafy green vegetables and other foods rich in Vitamin K that have the reverse effect. The PDR lists well over 100 drugs that can influence Coumadin's activities in some fashion.

Mixing some drugs with specific foods can result in strange and unanticipated reactions that could be very dangerous. Many of these go unrecognized until enough incidents are reported that finally identify the problem.

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Chocolates And Grapefruit Juice

Antidepressant medications such as phenelzine (Nardil) and tranylcypromine (Parnate) illustrate how dangerous drug interactions with different foods can be. It is essential that patients taking these and other monoamine oxidase inhibitors avoid consuming anything containing tyramine. Included in this list are beer, red wine, cheeses (American, cheddar, blue, brie, mozzarella and Parmesan), yogurt, sour cream, beef or chicken liver, cured meats (sausage and salami), game meat, caviar, dried fish, avocados, bananas, yeast extracts, raisins, sauerkraut, soy sauce, miso soup, fava and other broad beans, and caffeine in colas, chocolate, coffee and tea.

The problem here is not due to any increase or decrease in the efficacy of these medications, but rather a rapid and potentially fatal rise in blood pressure. Although monoamine oxidase inhibitors have been largely replaced by newer classes of drugs such as serotonin inhibitors and tricyclic antidepressants that are more effective and seem safer, they are still used when these fail to work.

This is what happened to one 49-year old male suffering from severe depression but who was otherwise healthy. He had been warned to avoid consuming any of the items listed above and had adhered to a tyramine-free diet for five months. There was a dramatic response to treatment during this period and as the depression diminished, his mood as well as his appetite improved. It's hard to keep remembering all the things you are supposed to avoid, and on one occasion, **he consumed a quantity of chocolate which would normally be considered safe because of its low tyramine content. He began to experience a headache that became so severe after two hours that he went to the Emergency Room of a local hospital. His blood pressure was found to be alarmingly high, and despite immediate vigorous treatment, he suffered a stroke and was pronounced dead 20 minutes later.**

In many instances, dangerous food-drug interactions are not recognized as the cause of symptoms, or are discovered only by accident. Canadian researchers were investigating a possible interaction between alcoholic beverages and felodipine (Plendene), a popular anti-hypertensive medication. This necessitated doing a double blind study in which neither the patient taking the drug nor the physician would know whether what was being consumed contained alcohol. The problem was that the patients could quickly detect if the beverage had alcohol since it was difficult to find a palatable way to mask its taste.

One of the researchers, Dr. David Bailey, a teetotaler, experimented at home with his wife by testing cola, orange and lemon juices, but these concoctions tasted awful. They finally found that grapefruit juice was the best-tasting way to disguise the presence of alcohol. The study found no important side effects or changes in the metabolism of the drug when taken with alcohol, but the grapefruit juice drinkers reported varied reactions, and their blood levels of felodipine were over three times higher than predicted. The manufacturer confirmed that the pills supplied were the proper dose, so Dr. Bailey checked further.

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When he took felodipine with grapefruit juice instead of water he became dizzy, turned red, and his blood levels were found to be four times higher than expected. Orange juice produced none of these effects and these findings were reported in 1991. Since then, Canadian and other researchers have intensively investigated this phenomenon. It has now been determined that **grapefruit juice contains specific bioflavonoids that can block essential enzyme systems in the liver and gastrointestinal tract that are needed for the metabolism of numerous drugs, including certain antihistamines, bronchodilators, tranquilizers, cholesterol lowering agents, calcium channel blockers and other cardiac medications, and immunosuppressants required by transplant patients to prevent rejection.**

One of the most dramatic grapefruit juice drug interactions can occur with the antihistamine terfenadine (Seldane). When Seldane was first introduced in 1985, it revolutionized the treatment of allergies because it didn't cause drowsiness and had no other apparent side effects. It quickly became the most popular allergy prescription and few problems were reported for the first five years. Doctors then started to become aware of severe heart rhythm disturbances in apparently healthy people, some of which proved fatal. In many instances, those affected had also been taking popular antibiotics like erythromycin or antifungal drugs. However, grapefruit juice proved to be the problem for one **healthy 29 year old male who had been taking terfenadine twice daily for a year to treat allergic rhinitis, and who usually drank grapefruit juice several times a week. One day he took his regular Seldane dose with two glasses of juice and began to mow the lawn, but quickly collapsed and could not be revived.** Seldane plasma levels were found to be in an elevated range known to cause seriously abnormal heart rhythms.

In a subsequent study, healthy subjects were given Seldane together with either water or grapefruit juice. None of the water group had detectable blood levels of Seldane, in contrast to everyone in the grapefruit juice group, all of whom also showed ECG changes.

In Australia, it is routine practice to add auxiliary labelling to prescriptions for Seldane that warn of grapefruit-juice drug interactions. Although it has not been studied, the same applies to Hismanal, an antihistamine of similar structure. Both of these drugs were available over-the-counter in Canada until 1997, when they were upgraded to prescription only. **Seldane was taken off the U.S. market in 1998, but it took 12 years to recognize that it was not as safe as originally claimed.**

Grapefruit juice has now been found to affect numerous other drugs because it interferes with enzymes responsible for their absorption and metabolism. These enzymes originally evolved to detoxify poisonous plants when primitive man was primarily a hunter/gatherer. It is therefore not surprising that a healthy food like grapefruit could contain powerful chemicals to block this. The problem is that in doing so, these protective systems are now not available to metabolize medications which they also regulate. One of the most important activities is cytochrome p450 oxidative metabolism in the intestinal wall and liver, utilized by benzodiazepines, (Valium, Xanax, Halcion), statin cholesterol lowering drugs (Lipitor, Zocor, Mevacor, Pravachol), calcium channel blockers (Adalat, Calan, Cardizem, Plendil, Vasocor), immunosuppressants (cyclosporine) and a host of popular medications like Quinidine, Amiodarone, Tegretol, Prilosec, Ethinyl Estradiol, and others given to treat everything from malaria and epilepsy to cancer.

Grapefruit juice can affect all of these, and in one study, increased Mevacor levels 15 times. Most tests are done in healthy young subjects with normal liver function. Older people may have impaired liver function and frequently take several of the above medications for hypertension, disturbances in heart rhythm, elevated cholesterol, etc. One patient taking Procardia and Hytrin for hypertension suffered a severe attack of low blood pressure after drinking grapefruit juice, and it seems doubtful that grapefruit is the only food that could interact with drugs.

Nutraceutical Snafus

Because they are considered to be "natural", nutritional supplements are readily available without a prescription and are generally assumed to be perfectly safe. While most of them are, some herbals containing ephedra and similar stimulants have been found to be dangerous and fatal, even in young, healthy individuals. There is little doubt that taking certain prescription medications or even ordinary over-the-counter cold remedies could aggravate these dangerous effects. Similar problems are now being increasingly reported for usually harmless herbals and other supplements if they are consumed in conjunction with specific drugs or foods.

Melatonin, DHEA and androstenedione are also considered to be natural and thus exempt from government regulation, even though they have profound physiologic and endocrine effects that might influence the activities of hormones or medications with similar biological activities. Many of the above products are now banned from over-the-counter sales in certain states and countries because of such concerns and the lack of any need to satisfy regulatory requirements for either safety or efficacy.

Scientific studies, including double blind trials, have been conducted to support claims for St. John's wort, *Panax ginseng*, *Ginkgo biloba*, kava kava, echinacea and a few other popular herbals. However, much of this has been done abroad or has been limited to younger individuals without kidney or liver problems or other chronic conditions often found in the elderly that could affect their metabolism and excretion. More importantly, **relatively little is known about how any of these and other herbals react with drugs. Almost one in five Americans on prescription medications now takes some herbal or nutritional supplement, and countless others take multiple herbal preparations or combine them with non prescription drugs.** It is now clear that in some instances, the effects of certain medications are exaggerated, while in others they are blunted, which could lead to problems.

Fish oils make clots dissolve faster, and garlic, onion and vitamin E also inhibit clotting. St. John's wort and *Ginkgo biloba* interact with Coumadin and other blood thinners and ginseng influences the effects of Digoxin. There is great concern about how the use of these and other nutritional supplements, especially vitamin E, might affect patients undergoing major surgery. In one recent report, physicians surveyed 400 patients prior to cardiac bypass surgery or valve replacement. They found that 44 percent used one or more "alternative medicine" therapies, and when vitamins were included, this jumped to 75 percent. (The study also found that when asked about rating the benefits of alternative medicine on a scale of 1-10, users gave it a 7 for efficacy in fighting illness and improving their general health.)

Of particular concern to the researchers was the fact that **only 17 percent of those who used herbal preparations and other nutritional supplements on a daily basis had ever mentioned this to any of their physicians, and that doctors rarely inquired about this.** The vast majority also indicated that they would not want to discuss this with their surgeons. However, as the authors emphasized, "Regardless of their willingness to discuss this with their physicians, it is imperative that patients need to be aware of the potential dangerous interactions between alternative and conventional medicines because of the possible effects on surgical outcomes."

Ephedra is a particular problem. Although it, ma huang and similar compounds have been banned, they may be included in certain herbal products widely available whose contents are not completely disclosed since there is no control over labeling practices or regulations governing the contents of containers. Ephedra can cause serious elevations in blood pressure for those surgical patients who require general anesthesia. As a result, The American Society of Anesthesiologists and other groups recently issued a **warning to consumers using any herbal preparations to stop taking them at least two to three weeks before a scheduled surgical procedure.**

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A partial list of some of the other adverse interactions with popular herbals include:

- **Feverfew** (for migraine)
 - increased bleeding tendencies when taken with anticoagulants (Coumadin), aspirin and other non-steroidal pain relievers.
- **St. John's Wort** (for depression)
 - increased sedation, blood pressure and heart rate if taken with serotonin reuptake inhibitor antidepressants (Prozac, Zoloft, Paxil).
 - increased sensitivity to the sun when taken with tetracyclines and vitamin A derivatives like Renova and Retin-A that are used to treat skin problems.
- **Ginkgo biloba** (for improving memory and blood circulation)
 - increased bleeding with blood thinners and aspirin.
- **Ginseng** (for enhancing vitality)
 - increased bleeding with anticoagulants (Coumadin), as well as aspirin and NSAID's (Motrin, Naprosyn).
 - exaggeration of the blood sugar lowering effects of drugs used to treat diabetes resulting in hypoglycemia.
 - elevation of blood pressure when taken with monoamine oxidase inhibitor antidepressants.
- **Kava Kava** (for anxiety and stress)
 - increased sedation when taken in combination with tranquilizers, especially popular benzodiazepines like Xanax, Ativan, and Valium.
- **Echinacea** (for colds)
 - decreases the effects of cortisone and other drugs used to suppress immune system responses.
- **Valerian** (for relaxation, sleep aid)
 - increased sedation with monoamine oxidase inhibitors.

This is only the tip of the iceberg, since there is little information on less popular herbals. As indicated, **little is known about what happens when several of these are taken simultaneously, and many individuals take five or more supplements on a daily basis.**

Functional Foods

Nutritional supplements are now being added to all sorts of foods, including: a butter-spread made with fish oil claimed to benefit the heart; soft drinks fortified with carotene "to support a healthy lifestyle"; a canned split pea soup that includes St. John's wort to "give your mood a natural lift"; chewing gum with phosphatidyl serine to "improve concentration". There is little doubt that certain food additives can provide significant health benefits. Iodized salt has essentially eradicated iodine deficiency goiter, orange juice with calcium improves bone strength, folate enriched flour prevents certain neurological birth defects and grain products fortified with oat bran or psyllium can help prevent heart attacks.

Such supplements have been shown to produce these benefits in scientific studies that satisfy FDA requirements to make these claims. **However, herbal supplements do not have to be tested for safety and can be added to various foods without violating any laws or regulations.** Beverages containing *Ginkgo biloba* are being marketed as "dietary supplements", and therefore are not subject to FDA regulations for foods. Last July, **the Center for Science in the Public Interest asked the FDA to ban the sale of more than 75 functional food products, claiming they are "spiked with illegal ingredients" and are labeled with "false and misleading claims".** This is a fuzzy area. It is unclear whether functional foods should be considered as conventional foods or dietary supplements in food form. Each category has a separate set of regulatory requirements, neither of which neatly fits functional foods.

St. John's wort sales increased 2800 percent last year after reports suggested it was an effective antidepressant. It is increasingly being added to foods **despite a long list of interference with other medications and adverse effects** ranging from decreasing the efficacy of HIV medications and promoting rejection of heart transplants to infertility and cataracts. Concerns have also been raised about the practice of adding caffeine to bottled water to boost energy levels and improve alertness.

What Mechanisms Are Involved?

Foods can influence the action of drugs and nutrients by effects on absorption, distribution, metabolism and excretion. Absorption is the process by which a drug or nutrient moves from the site of administration into the blood stream. Distribution refers to the movement of a drug or nutrient from one location to another. Metabolism is the process by which such substances are chemically altered by the action of enzymes, most often in the liver. The resultant metabolite may become more active, less active or as active as the parent compound. Excretion refers to the processes responsible for eliminating metabolites from the body, primarily by the kidneys.

• **Absorption:** The presence of food in the stomach may decrease the rate and/or extent of drug absorption. Absorption of the antihistamine Hismanal may be decreased by 60% when taken with food and a high fiber diet can decrease the absorption of tricyclic antidepressants like Elavil. Binding or chelation can occur when certain drugs come in contact with calcium, magnesium, and aluminum ions commonly found in antacid products. The antibiotic Cipro forms an insoluble complex when taken with some dairy products that are high in calcium, which reduces its absorption. Taking drugs with nutritional supplements can affect the absorption of either via varied mechanisms. Antiulcer drugs like Tagamet decrease the absorption of vitamin B₁₂, thiamine, and iron. Questran and bile acid sequestrants that lower cholesterol bind fat soluble vitamins A, D, E, and K so that less is available to be absorbed. Anti-cancer medications and other drugs that damage the mucosa of the stomach can cause decreased nutrient absorption.

• **Distribution:** When some drugs are absorbed, they become very highly bound to proteins in the blood. For Dilantin (90 percent) and Coumadin (99 percent), only a small fraction remains free to exert the desired effect. When serum albumin is significantly lowered there are fewer binding sites for these and other medications. Since more of the active free fraction is available, drug effects are magnified.

• **Metabolism:** Concurrent ingestion of food may reduce the liver's ability to metabolize drugs like Inderal, resulting in higher levels. Alternatively, a high protein, low carbohydrate diet increases the metabolism of Theophylline, resulting in higher blood levels. Some medications can accelerate the metabolism of nutrients so that higher amounts are required to avoid signs and symptoms of deficiency. Anticonvulsants like phenobarbital and Dilantin increase the metabolism of folic acid as well as vitamins D and K. Isoniazid, which is used to treat tuberculosis, inhibits the conversion of pyridoxine (vitamin B₆) to its active form. This may cause peripheral neuropathy and other signs of vitamin B₆ deficiency unless B₆ supplementation is also administered during treatment.

• **Excretion:** Foods and nutrients can alter the kidney's excretion of drugs. Lithium and sodium compete for tubular reabsorption. A high sodium diet increases lithium excretion and low sodium intake raises blood levels in patients taking lithium for bipolar disorder. Drugs can increase or decrease the excretion of nutrients in complex ways. Loop diuretics like Lasix increase the excretion of sodium, potassium, chloride, magnesium and calcium. Thiazide diuretics such as Hydrodiuril decrease the excretion of calcium due to enhanced uptake by the kidney.

Nutritional supplements and foods can also interfere with drugs. Vitamin K and leafy green vegetables block the blood thinning effects of Coumadin. Drugs like Prozac may suppress appetite, while Mellaril and cortisone do the reverse. Elavil may cause dry mouth and a sour or metallic taste due to reduced salivary flow and Capoten may induce loss of taste. Antibiotics like Biaxin that are secreted in saliva cause a bitter taste and also suppress normal bacterial flora leading to oral fungus infections like those in the gut resulting from prolonged antibiotic treatment. Other prescription and non-prescription drugs can cause ulcerations and motility changes in the stomach that affect absorption. Caffeine aggravates the side effects of nervousness and tremors of Theophylline and other asthmatic medications, and can counteract the sedative action of tranquilizers. Indeed, it acts more like a drug than a mere food ingredient.

Alcohol, Caffeine And Nicotine

Wine and beer are usually viewed as foods, especially since they are often consumed while eating. However, as with other alcoholic beverages, they should be classified as drugs, since they can have powerful psychophysiologic effects and important interactions with medications. Western Europeans in the days of Columbus had few mind-affecting substances: no coffee, no tea, no tobacco, little opium or marijuana, no cocaine-like stimulants, and no sedatives or intoxicants except alcohol. They made use of alcohol in a variety of ways: as a social beverage, a before-meals aperitif, a thirst-quenching beverage during meals, an after-dinner drink, an evening drink, a nightcap, tranquilizer, sedative, religious offering, anesthetic, or a way to get drunk. Alcohol permeated every aspect of European culture, and still does.

European explorers, from Columbus and his successors, found other mind-affecting drugs, and brought them home. Tobacco was discovered on Columbus's first voyage. Cocaine was found in large areas of South America. Opium was imported from China. Caffeine and LSD-like drugs were found scattered all over the world. During the next two centuries, Europeans not only adopted nicotine and caffeine but spread them everywhere. In a remarkably short space of time, Western Europe was converted from an alcohol-only culture to a multidrug society.

Some food-drug interactions can provide strange benefits. A "Mickey Finn" is believed to be a generic name adopted when the Irish bars of New York City were rowdy and often dangerous places. It generally refers to "knock out drops" of a hypnotic like chloral hydrate used to high-jack sailors, who subsequently woke up on a ship from shore with no choice but to join the crew. According to one recent report, a gang of Mickey Finn artists that preyed on bar patrons was foiled by one potential victim who was protected from whatever they used because he had been drinking cranberry juice cocktails! Like grapefruits, cranberries contain chemicals that can inhibit drug metabolism and other constituents with mild diuretic actions.

Caffeine is contained in coffee beans, tea leaves (which also contain theobromine), cocoa, and kola nuts. Although not considered to be a drug in Western cultures, it is the most widely used central nervous system stimulant in the world. It is found in a wide variety of sodas, chocolate and other candy bars, cookies, ice cream as well as medications. Caffeine increases alertness and concentration; it may reduce depression, and improve headache, asthmatic bronchial constriction, and mood. However, its central nervous system stimulation effects can cause insomnia, nervousness and anxiety as well as disturbed heart rhythms, and can also augment or interfere with many medications.

Nicotine is not a food, although it can enter the blood stream through chewing tobacco and gum as well as smoking and skin patches. It is highly addictive, and although currently not approved for any medical condition, the incidence of colitis increases when people stop smoking; trials are underway to determine if a nicotine patch might reduce this. Nicotine can improve mood, memory, and cognitive function, and some studies suggest patches may benefit patients with Parkinson's and Alzheimer's. Many claim smoking has a relaxing effect, but much of this is due to a reduction of withdrawal symptoms when they are forced to abstain.

Nicotine can cause severe nausea initially, but this quickly disappears. It may also reduce appetite and cause fluid retention by stimulating the release of antidiuretic hormone. Cardiovascular effects include an increase in heart rate, blood pressure, and heart muscle contractility. It can precipitate angina or a heart attack in patients with coronary heart disease. Cigarette smokers are 5-19 times more likely to die of heart disease compared to nonsmokers, the higher rates being associated with preexisting hypertension or diabetes. Like caffeine, nicotine can minimize or magnify the effects of numerous drugs that are used to treat hypertension and heart disease, or certain central nervous system symptoms.

How To Avoid Problems And Get The Most Out Of Nutrients And Drugs

Although nutritional supplements cannot make medical claims without proof, advertisements contain carefully crafted statements that essentially serve the same purpose, especially when supplements are added to popular foods. This is an entirely new area of concern that was not even mentioned in a recent paper listing various food interactions that can occur with over 350 different drugs. This list will undoubtedly grow as previously unrecognized nutrient-medication-food glitches surface and new medications are introduced. Keeping abreast of all these possible interactions as they arise is almost impossible. To protect yourself, be sure to:

- Read the prescription instructions to determine whether the medication should be taken before or after meals and for how long. If this is not indicated, ask your physician or pharmacist.
- Scrutinize the warning and interaction precautions on all labels, inserts and packaging.
- Take medications with a full glass of water but never with alcoholic or hot beverages.
- Avoid mixing any drug into your food or taking capsules apart unless directed to do so.
- Avoid taking vitamins, minerals, or other supplements at the same time as any medicine.
- Find out at what hours medications should be taken if you travel to a different time zone.
- Ask if you should avoid certain foods, beverages, or nutritional supplements, what possible drug interactions you should be aware of, and where you can obtain more information about these items or additional material about your condition and the medicines you take.

The Web provides useful information at www.foodmedinteractions.com, including how to obtain the new 11th edition of Food Medicine Interactions, which has information on over 1000 drugs including 100 new ones, and an updated software program. Organizations like the American Dietetic Association (www.eatright.com) and the Food and Drug Administration (www.fda.gov) also deal with the effects of foods on medications. There are numerous sites that provide information about specific drugs and/or the disorders they are prescribed for, as well as one devoted solely to problems associated with drinking grapefruit juice.

However, there is also a lot of misinformation, since there is little control over the accuracy of medical claims and material on the Internet, as will be discussed in our next Newsletter. It is best to stick to sites sponsored by the government or recognized medical facilities and accredited organizations. There are always new developments and the best way to prevent problems is to keep informed about all the prescription and nonprescription products you take. Despite some of the horror stories cited, most drugs are not significantly affected by what you eat. There is no need to go overboard based on anecdotal reports or Internet warnings that don't apply to you. **Your physician is still the best person to guide you about what's probably safe and what might possibly prove to be a problem for your particular situation.** Stay tuned for more about this.

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