Drug Interactions with Food and Beverages

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Keywords

Alcohol · Caffeine · Drug metabolism · Cranberry · CYP3A4 · Garlic · Ginger · Grapefruit · Statins Tyramine

Key Points

- Acidic beverages aid in the absorption of antifungal drugs.
- Cranberry supplements may enhance the effects of warfarin.
- Dairy and calcium supplements can reduce drug absorption and effects.
- Grapefruit juice, alcohol, and caffeine may interfere with drug metabolism.
- Garlic enhances anticoagulant effects and reduces protease inhibitor levels.
- Vitamin K-rich foods impair anticoagulant effects of warfarin.

Introduction

Proper adherence to drug regimens is important for optimizing clinical outcomes and reducing the risk of adverse events. This is especially important for patients with chronic diseases, where adherence levels may be a low as 50%. For proper administration of medications, patients should always be encouraged

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to follow the label instructions carefully. In general, some medications should be taken with a full glass of water, some must be taken with food, while others should be taken on an empty stomach [1–3].

Patients should consult with a physician or pharmacist to determine if there are any foods that should be avoided while taking their medications [1–6]. Patients frequently ask about the best time to take their medicine relative to mealtime or whether they should take it with or without food? However, patients rarely ask about what specific foods should be avoided while taking their medications. In some instances, patients will be instructed to take their medication with a particular food or beverage to aid palatability (and hence compliance), minimize local irritation to the gastrointestinal tract, or aid in drug absorption. More importantly, there are many incidences when the consumption of specific foods in combination with certain medications presents a problem by interfering with the absorption, metabolism, or excretion of these drugs [1–6]. If these instances go unrecognized, therapeutic drug levels may become too high or too low leading to unmet therapeutic effects and possible drug-related adverse events.

This chapter highlights some of the main instances where concomitant ingestion of particular foods or beverages can interfere with medication action and then reviews how a better understanding of these interactions can sometimes be used to aid in patient management.

Medications to Be Taken on an Empty Stomach

Generally speaking, food slows absorption by reducing the drug's concentration as a result of simple dilution (see also Food–Drug interactions Table 26.1). However, in the majority of cases, the overall degree of final absorption is largely unaffected, with modest if any clinical effects. Food intake may have other effects on drug absorption: stimulation of gastric and intestinal secretions may aid drug dissolution, and fat-stimulated release of bile salts promotes the uptake of lipophilic compounds. However, in specific cases, for example, with levothyroxine, bisphosphonates, alendronate, and risedronate, the drugs should be taken first thing in the morning on an empty stomach with plain water.

While not technically a drug, iron supplements will also have much better absorption if taken on an empty stomach. However, while food typically cuts in half the amount of iron absorbed, it may be needed to minimize gastric irritation.

Specific Examples of Food–Drug Interactions

There are many examples of food–drug interactions. Some of the most important ones include the combination of grapefruit juice with many of the anticonvulsant, antihypertensive, antiarrhythmic, antihyperglycemic, and antipsychotic drugs. In addition, the anticoagulant, warfarin, interacts with many foods and beverages, with some foods increasing its anticoagulant effects, while others reduce the therapeutic effects of warfarin. Furthermore, dairy products and calcium can inhibit the adsorption of many drugs including antibiotics, and garlic products may reduce the therapeutic effects of antiretroviral drugs.

A more extensive list of specific food–drug interactions is described in Table 26.1.

Effects of Vitamin K on Warfarin Anticoagulation

With the increase in aging populations and cardiovascular diseases, the likelihood of thromboembolic events requiring the use of anticoagulants, such as warfarin, has also increased. Older patients often have comorbidities that require multiple drug therapy, thus increasing potential interactions with warfarin. The anticoagulant effect of warfarin is mediated through inhibition of the vitamin K-dependent coagulation factors II, VII, IX, and X. One key feature in the stability of the warfarin anticoagulant effect is week-to-week differences in the content of vitamin K in the patient's diet. Foods, particularly

Table 26.1 Drug–food interactions[a]

Drug	Food interaction	References
Acebutolol	Grapefruit ↑ DE	[5, 6]
Acetaminophen	Alcohol ↑ AE	[5, 8]
	Caffeine ↑ DE	
Amiodarone	Grapefruit ↑ DE	[6]
Amlodipine	Grapefruit ↑ DE	[6]
Aliskiren	Grapefruit ↑ DE	[6]
Artemether	Grapefruit ↑ DE	[6]
Atenolol	Grapefruit ↑ DE	[6]
Atorvastatin	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	[5]
Barnidipine	Grapefruit ↑ DE	[6, 7]
Buspirone	Grapefruit ↑ DE	[6, 7]
Carbamazepine	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Celecoxib and other NSAIDs	Alcohol ↑AE	[5]
Cefotetan	Alcohol ↑ AE	[5]
Cilostazol	Grapefruit ↑ DE	[6]
Ciprofloxacin	Dairy, Ca, Mg, Fe ↓ DE	[1]
Clomipramine	Grapefruit ↑ DE	[6]
Clozapine	Caffeine ↑ AE	[5, 8]
	Alcohol ↑ AE	[5]
Cyclosporine	Grapefruit ↑ DE	[6, 9]
Diazepam	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	[5]
Disopyramide	Grapefruit ↑ DE	[6]
Doxycycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Ebastine	Grapefruit ↑ DE	[6]
Etoposide	Grapefruit ↑ DE	[6]
Felodipine	Grapefruit ↑ DE	[6, 9]
	Grape juice/red wine ↑ DE	[1]
Fexofenadine	Orange or grapefruit ↑ DE	[1, 6]
	Apple ↓ DE	
Fluvoxamine	Caffeine ↑ AE	[8]
Furafylline	Caffeine ↑ AE	[8]
Griseofulvin	Alcohol ↑ AE	[5]
Fe supplements	Food ↓ effect	[10]
Idrocilamide	Caffeine ↑ AE	[8]
Isocarboxazid	Tyramine ↑ AE	[10]
Isoniazid	Alcohol ↑ AE	[5]
	Tyramine ↑ AE	[10]
Isosorbide dinitrate	Alcohol ↑ DE	[5]
Isradipine	Grapefruit ↑ DE	[6]
Ketamine	Grapefruit ↑ DE	[6]
Levofloxacin	Dairy, Ca, Mg, Fe ↓ DE	[1]
Lithium	Caffeine ↓ DE	[8]
Loratadine	Grapefruit ↑ DE	[6, 7]
Linezolid	Alcohol, caffeine, tyramine ↑ AE	[5, 8]
Lovastatin	Grapefruit ↑ DE	[6]

(continued)

Table 26.1 (continued)

Drug	Food interaction	References
Methadone	Grapefruit ↑ DE	[6]
Mercaptopurine	Dairy, Ca, Mg, Fe ↓ DE	[1]
Metronidazole	Alcohol, ↑ AE	[5]
Mexiletine	Caffeine ↑ AE	[8]
Midazolam	Grapefruit ↑ DE	[6]
Minocycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Nicardipine	Grapefruit ↑ DE	[6]
Nifedipine	Grapefruit ↑ DE	[6]
	Grape juice ↑ DE	[1]
Nimodipine	Grapefruit ↑ DE	[6, 7]
Nisoldipine	Grapefruit ↑ DE	[6]
	Alcohol ↑ AE	[5]
	Grapefruit ↑ DE	[6]
Phenelzine	Tyramine ↑ AE	[5]
Pranidipine	Grapefruit ↑ DE	[6]
Propafenone	Grapefruit ↑ DE	[6]
Quinidine	Grapefruit ↑ DE	[6]
Quinolones	Caffeine ↑ AE	[8]
Saquinavir	Grapefruit ↑ DE	[1, 3, 4, 6]
	Garlic ↓ DE Grape juice↑ DE	
Sertraline	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Sildenafil	Grapefruit ↑ DE Grape juice↑ DE	[1, 6]
Simvastatin	Grapefruit ↑ DE	[6]
Sulfa drugs	Alcohol ↑ AE	[5]
Tacrolimus	Grapefruit ↑ DE	[6]
Terfenadine	Grapefruit ↑ DE	[6]
Tetracycline	Dairy, Ca, Mg, Fe ↓ effect	[1]
Theophylline	Caffeine ↑ DE	[8]
Thyroid hormone	Food ↓ effect	[10]
Tolvaptan	Grapefruit ↑ DE	[6]
Tranylcypromine	Tyramine ↑ AE	[10]
Triazolam	Grapefruit ↑ DE	[6]
Verapamil	Grapefruit ↑ DE	[6]
Warfarin	Vitamin K-rich foods ↓ DE	[3, 11, 12–15]
	Garlic ↑ DE Grapefruit ↑ DE	
	Cranberry ↑ DE	
	Green tea ↓ DE	
	Soy ↓ DE	
	Ginger ↑ DE	
Zaleplon	Grapefruit ↑ DE	[6]
Zolpidem	Alcohol ↑AE	[5]

Ca calcium, *Mg* magnesium, *Fe* iron, *AE* adverse effects, *DE* drug effects

[a]This list is not meant to be exhaustive but merely highlighting some of the main food and beverages that may give rise to a clinically significant interaction with particular drugs

those high in vitamin K, include vegetable oils, asparagus, broccoli, brussels sprouts, cabbage, lettuce, parsley, peas, pickles, and spinach. Many dietary supplements, including multivitamin preparations and herbal products, are also high in vitamin K which may also affect coagulation. While the clinical effect of increased dietary vitamin K can be overcome with increased warfarin, it is the variability of the clinical anticoagulant effect that is of greatest importance. Indeed, in cases where a patient's warfarin control is quite unstable, a supplement of modest daily vitamin K (e.g., 60–80 μg) may help in achieving a more stable warfarin effect.

Monoamine Oxidase Inhibitors and Tyramine

Monoamine oxidase (MAO) inhibitors are commonly used in the treatment of depression and phobic anxiety disorders. They are being increasingly replaced by safer alternatives due to a number of potentially dangerous interactions with foods containing high levels of tyramine (e.g., beer, ale, red wine, soy, aged cheeses, smoked or pickled fish or meat, anchovies, yeast, and vitamin supplements). Ingested tyramine is normally metabolized by the enzyme MAO in the bowel wall and liver. MAO inhibitors inhibit the metabolism of tyramine that can lead to a sudden and significant release of norepinephrine, resulting in a severe hypertensive crisis.

Calcium Impairs Absorption of Certain Antibiotics

Calcium-rich foods, such as dairy products and tofu, even milk added to tea or coffee, can deliver enough calcium to significantly impede the absorption of several antibiotics, including tetracycline, minocycline, doxycycline, levofloxacin, and ciprofloxacin [13]. To improve their absorption, these medications should be taken 1 hour before or 2 hours after calcium, magnesium, and iron supplements or dairy products.

Ginger Enhances Anticoagulant Effects

Ginger (the rhizome of *Zingiber officinale* Roscoe) is a widely used condiment, food, and herbal medicine. It is used as a digestive aid, to treat inflammation, for morning sickness, but it also has antiplatelet and antimicrobial effects. Ginger therefore has the potential to interact with anticoagulants. In the scientific literature, there are a few reports of an increase in the International Normalized Ratio (INR) in patients taking ginger root, ginger tea, and other herbal medicines containing ginger, in conjunction with warfarin [14–16]. The INR is an alternate measure of the common coagulation test known as prothrombin time (PT) and was introduced by the World Health Organization. A normal INR is approximately 0.9–1.1 and is elevated to between 2 and 3.5 when patients are on warfarin therapy, so an elevation following ginger supplementation indicates that ginger has anticoagulant effects. One longitudinal study showed that concurrent administration of warfarin with a ginger product resulted in a statistically significant increase in bleeding episodes [16].

It is well known that the cytochrome P450 (CYP450) isoenzymes are important for metabolizing a wide range of medications, including ginger and/or its chemical components This action may be due to mutual competitive inhibition, mechanism-based inhibition, or nonselective inhibition of CPYs. These effects of ginger on the activity of CPYs may result in alterations in the pharmacokinetics and pharmacodynamics of co-administered drugs [16].

Garlic Enhances Anticoagulant Effects and Reduces Protease Inhibitor Levels

Garlic, known scientifically as *Allium sativum* L., is both a food and a dietary supplement, and its beneficial effects on health are well documented [3, 4]. Garlic contains phytochemicals that may influence the pharmacokinetic and pharmacodynamic behaviors of prescription drugs, including warfarin and protease inhibitors. Clinical reports show a possible interaction between garlic (primarily as a dietary supplement) and warfarin [3, 4]. Some case studies reported that the ingestion of garlic with warfarin may increase the INR, while other reports showed no effect. However, since it is well known that garlic decreases platelet aggregation, there may be an increased risk of bleeding with warfarin [3]. In addition, garlic is well known to have antimicrobial activities and may prevent intestinal flora from producing vitamin K thus potentiating the effects of anticoagulants. Synergistic pharmacodynamic effects have been observed after the ingestion of garlic or garlic-containing supplements with fluindione, chlorpropamide, and NSAIDs, and pharmacokinetic interactions have been observed with both acetaminophen and lisinopril [3, 4]. In addition, garlic and garlic supplements have a significant impact on the efficacy of protease inhibitors used to treat human immunodeficiency virus (HIV). For example, there is a significant decrease in maximal plasma levels and the mean area under the curve (AUC) of saquinavir after co-administration of a garlic product for 3 weeks. However, no changes in the single-dose ritonavir pharmacokinetics were observed after 4 days [4].

Soy Reduces Anticoagulant Effects

Soy beans, known scientifically as *Gycine max* L., are fermented and then used as part of a wide array of Asian cuisine and soy-based products. These fermented products are well known to contain high levels of vitamin K that may interact with anticoagulants. Clinical reports and studies have shown that the administration of warfarin along with soy protein, soy milk, or other soy products may decrease the INR in patients [2, 17].

Specific Examples of Food–Beverage Interactions

Use of Acidic Beverages to Aid Drug Absorption

The absorption of the oral broad-spectrum antifungal drugs, ketoconazole and itraconazole, is dependent on an acidic environment. If gastric acid production is low (achlorhydria), either due to a manifestation of the patient's medical condition (e.g., AIDS gastropathy) or their use of acid-suppression therapy, then the absorption of these drugs is compromised [18]. These weakly alkaline drugs dissolve poorly in the relatively higher pH in the proximal small intestine and absorption is low. In such instances, patients should be advised to take their ketoconazole or itraconazole with an acidic beverage to boost drug availability by as much as 50% (Table 26.2) [19].

Citrus Juice Inhibits Drug Metabolism

Drug interactions with grapefruit juice (*Citrus paradisi*), and other fruits derived from grapefruits, were first characterized more than 20 years ago [9]. Both grapefruit and grapefruit juice, as well as *Citrus aurantium* (Seville oranges) and *C. grandis* (pomelo), interact with a number of prescription drugs, interfering with their metabolism and increasing the risk of dose-dependent side effects [6, 9]. It is estimated that > 85 drugs may interact with grapefruit due to an inhibition of their intestinal

Table 26.2 The pH of selected commercially available beverages that may affect drug absorption

Beverage[a]	pH	Beverage	pH
Coca-Cola Classic	2.5	Diet Coca-Cola	3.2
Cranberry juice	2.5	Diet Pepsi	3.2
Pepsi	2.5	Orange juice	3.3
Rockstar Energy Drink	2.5	Grape juice	3.3
Red Bull	2.7	Mountain Dew	3.3
Canada Dry Ginger Ale	2.8	Tropicana grapefruit juice	3.4
Dr. Pepper	2.9	7-Up	3.4
Sprite	2.9	Tropicana orange juice	3.8
Grapefruit juice	2.9	Black tea	4.1

[a]Those medications in the left column tend to aid in ketoconazole absorption

metabolism, causing an increase in their peak plasma concentrations and the risk of adverse events [9]. The compounds responsible for these interactions include the flavonoids and furanocoumarins.

Sufficient quantities of these compounds are present in a typical glass of grapefruit juice (or any part of the grapefruit) to irreversibly inhibit a key-metabolizing enzyme (CYP3A4) in the intestinal wall, although no effects are seen on the activity of CYP3A4 present in the liver [7]. Interestingly, oral antidiabetic medications including glybenclamide, glyburide, and repaglinide, as well as L-thyroxine, are not metabolized through CYP3A4 and therefore are not affected by the ingestion of grapefruit, orange, or apple juices. Furthermore, fruit juice–drug interactions appear to be transient, and the effect is significantly reduced within a few hours of ingestion, so that intake of the drug more than 4 hours after ingestion of the fruit juice reduces the risk of interaction by more than 60% [6]. In addition, large amounts of the juice, more than 300 ml/day, need to be consumed daily before such interactions are observed. However, it appears that orange juice may significantly interact with aliskiren, beta-blockers, fexofenadine, and fluoroquinolones by inhibiting the organic anion transporting polypeptide (OATP1A2 and 2B1) [9]. Furthermore, apple juice has been reported to decrease the concentrations of fexofenadine and atenolol in the plasma and may reduce oral bioavailability by up to 70% [6].

Multiple studies suggest that grapefruit and grapefruit juice inhibit the activity of CYP3A4, an enzyme that metabolizes >65% of drugs. The inhibition of CYP3A4 causes a range of dose-dependent effects, and both desirable and undesirable clinical effects can be observed. Grapefruit and other citrus juices also inhibit P-glycoprotein and a number of other metabolic enzymes and transporters. The extent to which individuals are affected by these juices is largely genetically determined and is related to the extent and relative distribution of isoforms of this enzyme in the intestine. Thus, the responses are often quite variable between individuals, with patients with the highest intestinal expression of CYP3A4 experiencing the greatest grapefruit juice–drug interactions. While there are broad ethnic differences, for example, African Americans are more affected than Caucasians, prediction of the scope of the effect in a particular individual is not yet possible in the clinic; however with increasing pharmacogenomic analyses, this may be possible in the future.

The drugs most affected by grapefruit juice include the dihydropyridine calcium antagonists: felodipine, pranidipine, nisoldipine, and nimodipine. Any possible interactions with other agents, such as amlodipine, cardizem, and verapamil, are not likely to be of clinical significance. The HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, and to a lesser extent atorvastatin, all have a significant interaction with grapefruit juice as they are all substrates for the CYP3A4 and P-glycoprotein (P-gp) [6, 9]. Other statins including fluvastatin, pitavastatin, pravastatin, and rosuvastatin are not substrates for CYP3A4 and do not appear to be affected. Lee et al. [20] have challenged the validity of medical advice suggesting that grapefruit juice should not be used in combination with statins. In their review of the clinical trials of grapefruit juice– statin interactions, they concluded that one daily

glass of grapefruit juice increases the blood simvastatin and lovastatin concentrations by ~260% when taken concomitantly, but by only about 90% if taken 12 hours apart, and grapefruit juice increases atorvastatin blood concentrations by ~80% (whenever taken). When grapefruit juice and statins are taken together, the reduction in LDL-cholesterol and risk of heart disease is significantly greater than when statins are given alone. Drinking grapefruit juice in moderation (one glass per day) may therefore be beneficial and not adverse to health [20]. The increased risk for rhabdomyolysis, the most serious and potentially fatal side effect of statin use, would only minimally increase when statins are administered with grapefruit juice. However, there are no studies to this effect [20]*;* therefore, until such studies are done, it might be prudent to err on the side of caution as most patients using statins may also be taking other drugs.

Other medications with a significant interaction with grapefruit juice include the immunosuppressants (cyclosporin and tacrolimus), the antihistamines (terfenadine, ebastine, and loratadine), the antimicrobials (artemether and saquinavir), the neuropsychiatric drugs (diazepam, midazolam, triazolam, buspirone, sertraline, carbamazepine, clomipramine, zaleplon, and methadone), cilostazol, and sildenafil. Interestingly, orange juice also appears to impact the oral effects of fexofenadine and celiprolol, both of which are substrates for the solute carrier organic anion transporter 1A2 (SLCO1A2). The flavonoids hesperidin and naringin have been identified as the compounds responsible for the effect on SLCO1A2. Naringin also modulates the activity of the organic anion transporting polypeptide and P-glycoprotein that causes a significant decrease in the oral bioavailability of pravastatin and pitavastatin [2, 21].

In summary, ingestion of grapefruit and other citrus fruits can significantly inhibit the metabolism of many medications spanning a variety of clinical fields. All forms of grapefruit (i.e., the whole fruit, fresh fruit juice, and frozen concentrate) are associated with the food–drug interactions. In general, the subset of patients in whom these juices may have the greatest effect are those who at baseline display the greatest amounts of intestinal metabolism and hence the lowest rates of drug bioavailability. In day-to-day practice, this group of patients is the most difficult to identify, and this inhibition of metabolism can lead to manyfold increases in circulating drug levels; this places these patients at risk for dose-dependent side effects. Unfortunately, due to a variety of both patient and grapefruit factors (perhaps explained by changes in the constituents of grapefruit with different crops and preparations), this effect is unpredictable and cannot be used clinically. Until these issues are defined, it seems prudent to dissuade patients from combining grapefruit juice with any of the abovementioned medications, particularly when they are taking them for the first time or in high doses.

Effect of Alcohol on Drug Action

Both acute and chronic excessive consumption of alcohol impart many effects on drug therapy [5]. Alcohol consumption may delay gastric emptying and thus slow the onset of absorption of many medications. Over time, heavy alcohol consumption may also lead to chronic altered bowel motility. Chronic consumption of excessive quantities of alcohol may result in cirrhosis and an associated impairment of hepatic drug metabolism. Alcohol is a known substrate for the cytochrome P450 isozyme CYP2E1, and, depending on the frequency of alcohol intake, it can also be either an inducer or inhibitor of CYP2E1. In the acute setting, alcohol competes for this enzyme and may reduce the metabolism of medications normally metabolized by CYP2E1 (e.g., warfarin, phenytoin, and rifampicin).

In chronic alcohol consumption, there is a five- to tenfold increase in CYP2E1 levels, which may increase the metabolism of these drugs over time [5]. CYP2E1 is also one of the minor pathways of acetaminophen metabolism, with the end product being a toxic metabolite. Therefore, chronic alcohol use greatly predisposes to acetaminophen toxicity. Cefotetan, griseofulvin, isoniazid, metronidazole, nitrofurantoin, and sulfa drugs mimic disulfiram by also inhibiting acetaldehyde dehydrogenase, a key

enzyme in the metabolism of alcohol. Hence, consumption of alcohol by many patients taking these antimicrobials is associated with greatly increased concentrations of acetaldehyde and symptoms of tachycardia, flushing, vomiting, confusion, and hypotension.

Red wine has also been shown to cause inhibition of intestinal CYP3A4, albeit to a lesser extent than grapefruit juice. Hence, a clinically significant effect of red wine on medications normally metabolized in the intestine by CYP3A4 would likely be uncommon. However, in rare patients (those with the highest intestinal CYP3A4 concentrations), red wine may carry the same risks as grapefruit juice for dose-dependent side effects.

In addition, alcohol intake is an independent risk factor for the exacerbation of GI bleeding in patients with concomitant use of NSAIDs [5]. The adverse effects may be due to degeneration of the gastric mucosa, development of esophageal varices, or a reduction in clotting factors due to chronic alcohol ingestion leading to chronic alcohol liver disease and cirrhosis. The risk of GI bleeding increases in individuals consuming three or more drinks per day, in combination with ibuprofen or aspirin, while hepatotoxicity may occur in these individuals when acetaminophen is consumed.

Effect of Caffeine on Drug Action

Caffeine is one of the most commonly used drugs worldwide and is most often consumed through coffee, tea, soda, energy drinks, and many other carbonated beverages [8]. These beverages are discussed in Chaps. 27, 28, and 31 of this book in greater detail. Acting as a central nervous system stimulant, caffeine ingestion leads to elevation in mood, a reduction in fatigue, and an increased facility for work [8]. Excessive caffeine intake can result in increases in heart rate, cardiac arrhythmia, delirium, and seizures. In addition to its stimulant action and effects on the cardiovascular system, caffeine has specific effects on drug metabolism by induction of the CYP1A2 enzyme system responsible for the metabolism of certain drugs [8]. However, it is likely that there are only a few medications that undergo a clinically significant interaction with usual doses of caffeine; of particular importance are medications with a narrow margin between when they are therapeutic and toxic (e.g., clozapine, lithium, and theophylline). The consumption of caffeine should be minimized in patients taking these medications. Clozapine, an atypical antipsychotic used in the treatment of schizophrenia, is one such medication. There are a number of reported cases of the presence of dose-dependent clozapine adverse events in patients consuming large quantities of caffeine (5–10 cups of coffee per day). It should be noted that psychiatric populations frequently have high caffeine consumption. Also noted is that ingestion of large quantities of caffeine may lead to a reduction in lithium levels and a decrease in its therapeutic effect.

Green Tea Reduces Anticoagulant Effects

Beverages and dietary supplements that contain green tea also contain vitamin K and may therefore reduce the effect of warfarin and other anticoagulants. Green tea leaves contain high levels of vitamin K; however, the vitamin K levels in brewed beverages are much lower; thus only large amounts (1500–3500 mL/day) are reported to decrease the INR [9].

Cranberry Increases Anticoagulant Effects

Cranberries, known scientifically as *Vaccinium macrocarpon*, are very popular worldwide as a food or beverage, as well as an herbal supplement for treatment of digestive disorders and urinary tract infections. In the scientific literature, there are a few reports of an interaction between cranberry and

warfarin, but this interaction remains controversial [9, 11, 22–24]. In one case report, administration of cranberry together with warfarin increased the International Normalized Ratio and caused significant bleeding [9]. There is also one report of a very serious interaction in which a patient drinking approximately two cups of cranberry juice daily for 6 weeks purportedly died as a consequence of this interaction [11]. Increases in the INR (up to 28%) have been reported when cranberry is administered with warfarin. However, it is important to remember that the case studies have not been supported by controlled clinical trials. For example, Lilja et al. [22] investigated the effects of cranberry juice on simultaneous administration of R- and S-warfarin, tizanidine, and midazolam as drug probes for the CYP liver isozymes CYP2C9, CYP1A2, and CYP3A4 in a randomized crossover study. Ten healthy volunteers were administered 200 mL of cranberry juice or water three times daily for 10 days. On day 5, they ingested 10 mg of racemic R- and S-warfarin, 1 mg tizanidine, and 0.5 mg midazolam, with juice or water, followed by monitoring of drug concentrations and thromboplastin time. The results show that for a one-time dose of these three drugs, cranberry juice did not increase the peak plasma concentration or area under concentration–time curve (AUC) of any of the drugs or their metabolites, but slightly decreased (7%) the AUC of S-warfarin. Thus, cranberry juice did not change the anticoagulant effect of warfarin. Daily ingestion of cranberry juice for 10 days did not inhibit the activities of any of the liver enzymes responsible for drug metabolism. The study concluded that a pharmacokinetic mechanism for the cranberry juice–warfarin interaction seems unlikely [22]. However, the limitations of this study are that it does not take into account repeated daily drug administration or the suggestion that many food–drug interactions may take 2–4 weeks to be observed. It has been suggested that consumption of 1–2 L of cranberry juice per day or the equivalent of cranberry juice concentrate in supplements for an extended time period (~3–4 weeks) may temporally alter the effect of warfarin; however, the complete avoidance of cranberry juice by warfarin users may not be justified based on the current published studies [23, 24].

Conclusion

This chapter has reviewed some of the most common drug interactions with food and beverages. In general, patients should carefully follow the the label instructions for proper administration of all medications. Some medications should be taken with a full glass of water, some must be taken with food, while others should be taken on an empty stomach. Patients should consult with a physician or pharmacist to determine if there are any foods that should be avoided while taking their medications. Patients often ask what time of the day to take their medications, and if they should take them with food, but need to be informed if there are specific foods that they should avoid when taking some medications. In some instances, patients will be instructed to take their medication with a particular food or beverage to aid palatability (and hence compliance), to minimize local irritation to the gastrointestinal tract, or to aid in drug absorption. However, importantly, there are many incidences when the consumption of specific foods in combination with certain medications presents a problem by interfering with the absorption, metabolism, or excretion of these drugs. If these instances go unrecognized, there may be significant divergence of therapeutic drug levels and hence therapeutic effects and possible drug-related adverse events.

By acting on gastric motility, pH, and drug metabolism, food and beverages can have a variety of effects on the absorption and metabolism of medications, as well as on many vitamins and minerals, with the clinical significance ranging from passing interest to concern for significant reductions in drug action, as is seen with garlic and saquinavir, as well as serious adverse events, as seen with cranberry and warfarin. For some food–drug interactions, such as grapefruit juice, that affect drug metabolism through the cytochrome P450 isoenzymes, there is huge variability from one person to the next

and the risks of dangerous interactions are only present in a few. With further understanding and perhaps profiling of patients for their gene expression of metabolic enzymes, it may be possible to identify those most at risk for both beverage–drug and drug–drug interactions. In the meantime, it is best for patients to take their medications with a glass of water unless otherwise advised.

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Suggested Further Readings

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