11 Positive Drug–Nutrient Interactions

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Objectives

- Identify the drug–food and drug–nutrient interactions that result in enhanced positive drug effects
- Discuss the mechanisms of positive drug–food and drug–nutrient interactions
- Identify patient-specific clinical conditions that may benefit from positive drug–food and drug–nutrient interactions

Key Words: Bioavailability; drug effect; physicochemical; physiologic; toxicity

1. INTRODUCTION

Drug–nutrient interactions are often the result of physical and chemical interactions between drugs and nutrients. These interactions are influenced by factors of a physicochemical nature (e.g., pH, dissolution, disintegration, binding) or physiological determinants (e.g., absorption, elimination, gastrointestinal transit time, gastrointestinal secretions, splanchnic blood flow, liver enzyme inhibition or induction) *(1,2)*. Clinically significant negative drug–nutrient interactions may result in therapeutic failure, drug toxicity, or nutrient deficiency. Less commonly considered are drug–nutrient interactions that may significantly enhance drug effect, reduce drug toxicity, or reduce gastrointestinal drug intolerance. This chapter focuses on beneficial and clinically relevant drug–food and drug–nutrient interactions that improve serum drug concentrations, enhance therapeutic drug effects, or reduce or prevent severe drug toxicities (Table 1). Although data describing positive effects of food on drug absorption are commonly recognized, there are also examples of specific nutrients that improve drug absorption, enhance drug effect, and reduce drug toxicity.

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Table 1
Summary of Relevant Drug–Nutrient and Drug–Food Interactions that May Optimize Drug Effect (in the order they appear in the text)

Drug	*Diet/Nutrient*	*Proposed Mechanism of Interaction*	*Relevant Effects*	*Recommendations*
Albendazole	Fatty meal	Increased solubility and absorption	Increased plasma and tissue drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Mebendazole	Meals	Increased absorption	Increased target drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Cefuroxime	Meals	Increased absorption with decreased gastric pH	Increased plasma concentrations Bactericidal activity not affected	Suspension should be taken with food Tablets can be taken with or without food
Nitrofurantoin	Meals	Increased dissolution and absorption	Increased duration of urinary concentrations Reduced peak plasma concentrations Improved gastrointestinal tolerance	Should be taken with food
Griseofulvin	Fatty meal	Increased disintegration and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Itraconazole (capsules)	Meals, Acidic beverages	Increased solubility and absorption in acidic medium	Increased plasma concentrations Enhanced therapeutic effect	Capsules should be taken with food or an acidic beverage Oral solution should be taken on empty stomach
Posaconazole	Meals, Nutritional supplements	Increased absorption	Increased therapeutic effect	Should be taken with meals or nutritional supplement Otherwise, consider alternate therapy or monitor patient closely for breakthrough of fungal infection
Atovaquone	Fatty meal	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Nitazoxanide	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food (oral tablet and solution)
Atazanavir	Meals	Increased absorption and decreased gastric pH	Increased plasma concentrations	Should be taken with food
Darunavir	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food

Lopinavir (oral solution)	Meals	Increased absorption	Enhanced therapeutic effect	Oral solution should be taken with food
				Oral tablets can be taken with or without food
Nelfinavir	Meals	Increased absorption	Enhanced therapeutic effect	Should be taken with food
Saquinavir	Meals	Increased dissolution, disintegration, and absorption	Enhanced therapeutic effect	Should be taken with food or within 2 h after a meal
Fenofibrate	Fatty meal	Increased absorption	Enhanced therapeutic effect	Lofibra® and Lipofen® should be taken with food Tricor®, Triglide® and Antara® can be taken with or without food
Isotretinoin	Meals	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Mesalamine/ Olsalazine	Meals	Delays the presence of the active metabolite 5-aminosalicylic acid in the gut	Persistently high local therapeutic 5-aminosalicylic acid concentration in colon	Should be taken with food
Misoprostol	Meals	Reduced absorption rat Reduced peak plasma concentrations	Reduced frequency of diarrhea	Should be taken with food
Iron	Ascorbic acid	Inhibition of iron chelation to phytates Reduction of iron to the ferrous form	Increased iron absorption	Coadminister ascorbic acid (100–200 mg/day) with iron in patients who are poor absorbers
Fluorouracil (5-FU)	Folic acid	Increased levels of reduced folate metabolites	Possible reduction of 5-FU toxicity and modulation of 5-FU activity	Efficacy and safety not established
Methotrexate	Folic acid	Increased levels of reduced folate metabolites	Reduced low dose methotrexate toxicity in the treatment of rheumatoid arthritis	Weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg have been used with low-dose methotrexate regimens
Isoniazid	Pyridoxine	Increased pyridoxal phosphate availability	Prevention of isoniazid-induced peripheral neuropathy	Coadminister prophylactic pyridoxine to adults (50 mg/day) and children (1–2 mg/kg/day) receiving isoniazid
Docetaxel	Calcitriol	Possible enhanced antitumor activities	Improved patient survival, bone pain, and quality of life	Used mostly in clinical studies in patients with androgen-independent prostate cancer (AIPC)
Statins	Plant stanols	Blockage of cholesterol absorption	Reduced serum cholesterol and low density lipoprotein (LDL) concentrations	Use stanols 2–3 times/day in diet or as adjunct to lipid-lowering therapy

2. EFFECTS OF FOOD ON DRUG ABSORPTION

2.1. Anthelmintics

2.1.1. Albendazole

Albendazole is a broad-spectrum anthelmintic agent effective against larval and adult stages of trematodes and cestodes *(3)*. Albendazole is available commercially as oral tablets. Because of its low aqueous solubility, albendazole is poorly absorbed from the gastrointestinal tract. However, administration with a fatty meal enhances albendazole solubility and thereby increases its bioavailability.

Fatty meals increase the oral bioavailability of albendazole up to fivefold as compared with the fasting state. Maximal plasma concentrations of albendazole sulfoxide (the primary active metabolite) were achieved in 2–5 h with albendazole 400 mg doses during treatment of patients with hydatid disease *(4)*. In a study that assessed the bioavailability of albendazole in six patients with hydatid disease, mean plasma albendazole concentrations were 4.5 times higher when albendazole was administered with breakfast as compared with fasting *(5)*. In another study of adult patients with onchocerciasis, plasma albendazole sulfoxide concentrations increased fourfold when albendazole was administered with breakfast (43.1 g of fat) instead of on an empty stomach *(6)*. However, when albendazole was given with 20 mL of olive oil in 100 mL of milk to four adult volunteers, plasma albendazole sulfoxide concentrations increased 3.5-fold in one subject whereas only small changes occurred in the other three subjects *(7)*.

Albendazole absorption is significantly increased when taken with food. Albendazole should be administered with fatty meals to increase its concentrations within tissues and hydatid cysts *(4)*. However, administration of albendazole on an empty stomach is preferable when intraluminal effects are desired to treat susceptible intestinal parasites *(3,5)*.

2.1.2. Mebendazole

Mebendazole is a broad-spectrum anthelmintic agent that is available as oral chewable tablets. Mebendazole is poorly absorbed from the gastrointestinal tract, but its absorption is increased when administered with food *(3)*. When used for the treatment of echinococcosis, systemic bioavailability and intracystic mebendazole concentrations are essential to achieve therapeutic effect.

Administration of mebendazole 1.5 g with a fatty meal to three healthy volunteers resulted in an eightfold increase in plasma mebendazole concentrations. When administered in the fasting state, plasma mebendazole concentrations remained <17 nmol/L in two subjects and reached 17 nmol/L in the third subject. When the same dose was administered with a standard breakfast (2 slices of ham, 2 fried eggs, 10 g butter, jam, bread, and coffee), plasma mebendazole concentrations rose within 2–4 h to 91 nmol/L, 112 nmol/L, and 142 nmol/L in the three subjects, respectively *(8)*. Mixing mebendazole with olive oil also increased the drug's bioavailability to a greater level than giving the tablets or suspension with a standard breakfast *(9)*. A wide variability in mebendazole absorption was reported in

patients treated for hydatid cysts. Although plasma mebendazole concentrations were higher when mebendazole was given with food, the difference was not found to be significant *(10)*.

When taken with food, higher plasma mebendazole concentrations are achieved. This is a desirable effect for the treatment of hydatid cysts. Mebendazole tablets can be chewed, swallowed whole, or crushed and mixed with food *(11)*.

2.2. Antibiotics

2.2.1. Cefuroxime

Cefuroxime is a broad-spectrum beta-lactam antibiotic belonging to the second-generation cephalosporins. Cefuroxime has broad activity against susceptible bacteria that cause infections of the upper and lower respiratory tract, skin and soft tissues, and the genitourinary tract *(12)*. Cefuroxime is available as the prodrug cefuroxime axetil in oral suspension and tablet dosage forms and as crystalline cefuroxime for intravenous administration *(13)*. Due to the enhanced lipid solubility of the prodrug, oral cefuroxime axetil is rapidly absorbed from the gastrointestinal tract and is hydrolyzed to active cefuroxime once in the bloodstream *(12–14)*. However, the oral tablet and suspension forms of cefuroxime axetil are not bioequivalent and cannot be used interchangeably *(13)*. The safety and the efficacy of oral cefuroxime tablet and suspension were established in separate clinical trials, and the dosage forms have different therapeutic indications *(12,13)*. Since the cefuroxime axetil oral tablet first became available, it has been reformulated several times due to absorption problems *(14)*. Food *(15–17)* and milk *(18)* have been shown to enhance cefuroxime axetil bioavailability, but the exact mechanism of this effect remains unknown.

A randomized, crossover, open label study evaluated the effects of food and fasting on cefuroxime bioavailability in healthy volunteers. The mean cefuroxime absolute bioavailability during fasting was 32–35%. There was a 34% relative increase in bioavailability when cefuroxime axetil was taken with food (area under the plasma concentration-time curve, AUC: 50 μg·h/mL) as compared to fasting (AUC: 36.4 μg·h/mL). Food also resulted in increases of the peak plasma concentrations (C_{max}: 13.9 μg/mL vs. 9.9 μg/mL) and time-to-peak concentration (T_{max}: 2.7 h vs. 2.1 h, respectively) compared to fasting. Cefuroxime elimination half-life was not significantly changed *(15)*. In another study, similar effects of food on cefuroxime absorption were observed. A single 500 mg dose of cefuroxime axetil taken with food resulted in increased absolute cefuroxime bioavailability from 36 to 52%, corresponding to a 45% relative increase. A linear correlation was also observed between single doses of cefuroxime ranging from 125 to 1000 mg given with food and both the AUC ($r^2 = 0.958$) and C_{max} ($r^2 = 0.943$) *(16)*.

A study evaluated the effects of food and increased gastric pH (with administration of ranitidine and sodium bicarbonate) on cefuroxime absorption in six healthy volunteers. When cefuroxime was administrated with food, cefuroxime bioavailability increased despite the anticipated negative effects of a higher gastric pH on cefuroxime absorption. Cefuroxime AUC significantly increased with food as compared to fasting (39.8 ± 2.9 μg·h/mL vs. 23.4 ± 2.9 μg·h/mL, $p < 0.05$); T_{max} was significantly longer when cefuroxime was taken with food as compared to

fasting (13.6 ± 1.0 h vs. 7.3 ± 0.8 h, $p < 0.05$); and C_{max} was slightly higher in the fed state with a statistically significant difference as compared to fasting (1.5 ± 0.1 mg/L vs. 1.4 ± 0.152 mg/L, $p < 0.05$) *(19)*.

In a study that evaluated the effects of food on cefuroxime serum concentrations and the minimum inhibitory concentration (MIC), serum cefuroxime concentrations were at or above the MIC of common respiratory pathogens for much of the dosing interval *(17)*. This suggests that administration of cefuroxime axetil with food achieves adequate serum concentrations for the effective treatment of susceptible organisms *(12–17)*.

Pharmacokinetic differences exist between the cefuroxime tablet and suspension forms to the point that they are not bioequivalent *(12–20)*. The AUC and C_{max} for cefuroxime suspension average 91 and 71% respectively, of that for the tablet *(12)*. When given with meals, cefuroxime had a significantly lower AUC for oral cefuroxime suspension as compared to the tablet (10.22 μg·h/mL vs. 14.02 μg·h/mL, respectively; $p = 0.001$). Food resulted in significantly lower C_{max} with cefuroxime suspension as compared to the tablet (2.48 μg/mL vs. 4.04 μg/mL, respectively; $p = 0.001$). Despite these differences, serum cefuroxime bactericidal activities were not affected and remained similar with both dosage forms *(20)*. Because bacteriological and clinical responses to cefuroxime axetil tablets are independent of food ingestion, tablets may be administered without regard to meals. Pharmacokinetic, efficacy, and safety studies of cefuroxime axetil suspension in pediatric patients were conducted in the fed state. No kinetic data on the suspension formulation are available when administered under fasting conditions in pediatrics *(13)*.

In summary, cefuroxime axetil tablets and suspension are not bioequivalent and cannot be substituted on a milligram-per-milligram basis. Oral cefuroxime axetil tablets can be administered with or without food. Oral cefuroxime suspension should be taken with food *(13)*.

2.2.2. Nitrofurantoin

Nitrofurantion is a broad-spectrum bactericidal agent that exerts its effects by possibly interfering with bacterial carbohydrate metabolism *(21,22)* or cell wall synthesis *(23)*. Nitrofurantoin is used for the treatment of uncomplicated urinary tract infections caused by susceptible microorganisms. Nitrofurantoin is available in different oral formulations including a combination formulation of nitrofurantoin monohydrate (75% of the drug) and macrocrystals (25% of the drug) in oral capsules (Macrobid®), nitrofurantoin macrocrystalline oral capsules (Macrodantin®), and microcrystalline oral suspension (Furadantin®) *(24–26)*. A tablet formulation of nitrofurantoin was previously manufactured but is no longer available.

Oral nitrofurantoin is absorbed in the small intestines. Because serum nitrofurantoin concentrations are usually low or undetectable in patients with normal renal function *(21,27,28)*, urinary nitrofurantoin levels are typically used to assess nitrofurantoin absorption *(29)*. Macrocrystalline nitrofurantoin has a slower dissolution and absorption rate than nitrofurantoin monohydrate. Food, however, increases the bioavailability of nitrofurantoin by about 40% *(24)* and substantially increases the duration of therapeutic nitrofurantoin urine concentrations *(21)*.

The effects of food on nitrofurantoin absorption in macrocrystalline and microcrystalline tablets were evaluated in a study of four healthy volunteers. Nitrofurantoin 100 mg single oral dose was administered either following an 8-h overnight fast or immediately after breakfast. Serial urinary specimens were collected to measure nitrofurantoin urine concentrations. Study results showed that food delayed nitrofurantoin absorption in the macrocrystalline form but did not have a significant effect on the rate of absorption of the microcrystalline form. Food also resulted in increased maximum urine excretion rate of macrocrystalline nitrofurantoin but did not have a significant effect on the rate of excretion of the microcrystalline form. Compared to fasting, food increased nitrofurantoin bioavailability by an average of 30 and 80% of the microcrystalline and macrocrystalline forms, respectively *(30)*.

Another study compared the effects of food on the oral bioavailability of nitrofurantoin in three different microcrystalline tablets, a macrocrystalline capsule, and an aqueous microcrystalline suspension. The percent of a single 100 mg oral dose recovered in the urine was significantly greater when administered with food as compared to the fasting state for the microcrystalline tablets ($p < 0.05$) and the macrocrystalline capsule ($p < 0.05$). Food increased the bioavailability of the tablets and the macrocrystalline capsule by 23–40 and 85%, respectively. Although the bioavailability of the microcrystalline suspension was also increased with food, it was not statistically significant. Compared to fasting, food also significantly increased the mean duration of therapeutic urinary concentrations of nitrofurantoin macrocrystalline capsules ($p < 0.05$). Food also increased the duration of therapeutic urinary concentrations of the microcrystalline suspension, but the difference was not statistically significant compared to the fasted state. Nitrofurantoin administration with food improved the uniformity of nitrofurantoin absorption and decreased the coefficients of variation. It was hypothesized that by decreasing the rate of gastric emptying, food increased nitrofurantoin residence in the stomach thereby increasing drug dissolution that makes nitrofurantoin more readily absorbed in the small intestines *(31)*.

In summary, food delays nitrofurantoin delivery to the intestines thereby increasing its absorption and reducing its peak plasma concentrations *(26,31)*. Nitrofurantoin macrocrystals are more slowly absorbed than the microcrystals *(29,32)*. Therefore, the macrocrystals are better tolerated and are associated with less nausea and vomiting *(33–35)*. Nitrofurantoin should be administered with food to enhance its absorption, increase the duration of nitrofurantoin urinary concentrations, and improve gastrointestinal tolerance *(24)*.

2.3. Antifungals

2.3.1. Griseofulvin

Griseofulvin is an oral antifungal agent used for the treatment of tinea infections. Because of its low aqueous solubility, griseofulvin absorption is slow, irregular, and incomplete, especially when taken on an empty stomach *(36)*. However, griseofulvin absorption increases twofold when taken with fatty meals *(37)*. Food increases griseofulvin absorption by increasing its disintegration and de-aggregation *(38)*.

In a study of 12 adult volunteers who each received a single dose of griseofulvin 500 mg tablet, there was a significant increase in griseofulvin bioavailability of

70 and 120% when taken with a low-fat (29.3% calories from fat) and high-fat (52.4% calories from fat) meals, respectively, compared to fasting ($p < 0.01$) *(39)*. However, one older study, using urinary excretion data, concluded that fatty meals increase the rate but not the extent of griseofulvin absorption, and that griseofulvin follows a circadian rhythm of absorption regardless of dietary fat content *(40)*.

Griseofulvin absorption also varies with the dosage form used. A crossover study of four healthy volunteers compared the absorption of two different dosage forms consisting of microsize and ultramicrosize griseofulvin tablets taken with or without food. When taken on an empty stomach, griseofulvin C_{max} of the ultramicrosize formulation was about 70% of the microsize formulation. When taken with food, griseofulvin C_{max} was 136% of the microsize formulation and about twice the C_{max} for the ultramicrosize formulation. The rate and the extent of griseofulvin bioavailability were similar for both formulations when taken with food *(38)*.

In summary, optimal plasma griseofulvin concentrations are attained when griseofulvin is administered with a high-fat meal. Taking griseofulvin with meals maximizes its absorption and enhances therapeutic drug effect.

2.3.2. Itraconazole

Itraconazole is a triazole antifungal used for treating superficial and systemic fungal infections. Itraconazole is available as oral solution and capsule formulations. Each oral itraconazole dosage form has specific indications *(41)*. Injectable itraconazole has been discontinued by the manufacturer for sales and distribution in the United States. Itraconazole is a highly lipophilic, extremely weak base that is almost insoluble in water and requires an acidic medium for optimal oral absorption *(42,43)*. The bioavailability of oral itraconazole also depends on the dosage form and the presence or absence of food. Whereas food enhances itraconazole capsule dissolution and absorption *(44,45)*, oral itraconazole solution is already in the dissolved form and is better absorbed when taken on empty stomach *(46)*.

In one study, the bioavailability of itraconazole capsules increased from 40% with fasting to 102% when administered with meals *(44)*. In another study of 27 healthy volunteers, a single dose of itraconazole 200 mg capsule was administered with or without food. Pharmacokinetic parameters were analyzed for itraconazole and its active metabolite hydroxyitraconazole. The AUC for itraconazole and hydroxyitraconazole was higher when the drug was administered with food (3423 $\pm$ 1154 ng·h/mL and 7978 $\pm$ 2648 ng·h/mL, respectively) as compared to fasting (2094 $\pm$ 905 ng·h/mL and 5191 $\pm$ 2489 ng·h/mL, respectively). The C_{max} for itraconazole with fasting was 59% of that with food (140 $\pm$ 65 ng/mL and 239 $\pm$ 85 ng/mL, respectively), and C_{max} for hydroxyitraconazole with fasting was 72% of that with food (286 $\pm$ 101 ng/mL and 397 $\pm$ 103 ng/mL, respectively) *(41)*.

The absorption of oral itraconazole capsules is decreased with increasing gastric pH such as in patients receiving gastric acid inhibitors (antacids, H_2-receptor antagonists, proton pump inhibitors). In patients with hypochlorhydria, coadministration of oral itraconazole capsules with an acidic beverage (e.g., cola) increased itraconazole bioavailability *(47,48)*. Following the administration of a single 100 mg dose of itraconazole capsules with 325 mL of water or an acidic cola beverage (pH = 2.5), the itraconazole AUC was significantly higher with cola (2.02 $\pm$ 1.41 μg·h/mL) than

with water (1.12 ± 1.09 μg·h/mL) ($p < 0.05$). Itraconazole C_{max} was also significantly higher with cola than with water (0.31 ± 0.18 μg/mL vs. 0.14 ± 0.9 μg/mL, respectively; $p < 0.05$), and T_{max} was significantly longer (3.38 ± 0.79 h vs. 2.56 ± 0.62 h; $p < 0.05$) *(48)*.

In contrast to itraconazole capsules, itraconazole oral solution does not require food or an acidic medium to increase its absorption. Significantly higher itraconazole and hydroxyitraconazole AUC and C_{max} and shorter T_{max} occur when itraconazole oral solution is taken on an empty stomach rather than with food *(42)*. Following administration of oral itraconazole solution at a dose of 200 mg/day, respective mean itraconazole and hydroxyitraconazole concentrations were 43 and 38% higher when the drug was taken with food as compared to fasting *(46)*. The AUC with a single 100 mg dose of itraconazole oral solution was significantly higher when administered during fasting (2379 ± 1353 ng·h/mL) as compared to the fed state (1713 ± 741 ng·h/mL). C_{max} was also significantly higher in the fasting state as compared to the fed state (349 ± 239 ng/mL vs. 147 ± 74 ng/mL; $p = 0.006$). Additionally, T_{max} was significantly shorter during fasting as compared to the fed state (1.7 ± 0.5 h vs. 3.8 ± 1.4 h; $p = 0.0001$) *(42)*.

In summary, oral itraconazole capsules should be taken with a full meal for maximal absorption. However, oral itraconazole solution is better absorbed when taken on empty stomach at least 2 h before or 2 h after a meal. Oral itraconazole solution provides an alternative to itraconazole capsules in patients who have difficulty swallowing the capsule or in those whose oral intake is restricted *(41,45)*. The optimal serum itraconazole and hydroxyitraconazole concentrations are not known; however itraconazole oral solution is associated with higher serum drug concentrations compared to oral capsules *(49)*. Administration of itraconazole with cola enhances itraconazole capsule absorption in patients receiving acid suppression therapy *(47)*. Patients receiving medications that alter gastric pH should take itraconazole oral capsules with a cola beverage.

2.3.3. Posaconazole

Posaconazole is a triazole antifungal agent that works by blocking the synthesis of ergosterol, one of the key compounds in the fungal cell membrane. Posaconazole is FDA labeled for the prophylaxis of invasive *Aspergillus* or *Candida* infections in patients who are at risk of developing systemic infections due to an immunocompromised state *(50)*. Posaconazole is insoluble in water and is commercially available as a suspension for oral administration. It is well absorbed from the gastrointestinal tract with a proportional increase in AUC and $C_{max}$with increasing doses up to 800 mg daily. Steady-state plasma posaconazole concentrations are reached after 7–10 days of therapy with a T_{max} ranging from 5.8 to 8.8 h *(51)*.

A study evaluated the difference in absorption of posaconazole oral suspension and tablet formulations and the effect of food and its fat content on posaconazole bioavailability *(52)*. In this randomized, open label, four-way crossover study, 20 healthy male volunteers received posaconazole 200 mg oral tablets administered with a high-fat breakfast (841 calories, 52% fat), or posaconazole 200 mg oral suspension administered with a high-fat breakfast, low-fat breakfast (461 calories, 0% fat), or after a 10-h fast. Absorption was significantly better with the oral

suspension compared to the tablets with a 37% increase in AUC ($p = 0.001$) and 23% increase in C_{max}($p = 0.004$). In addition, the AUC and C_{max} of the oral suspension were 4 times greater with the high-fat meal compared with the fasted state ($p < 0.001$). Administration with the low-fat meal also increased posaconazole absorption (2.6 times) and C_{max} (3 times) compared to the fasted state ($p < 0.001$). Pharmacokinetic profiles were similar between the high-fat and nonfat meals, suggesting that posaconazole should be administered with meals regardless of fat content and that the suspension should be used over the tablets to enhance absorption. A related study found that concomitant administration of antacids with posaconazole had no significant effect on posaconazole bioavailability under fasting or nonfasting conditions *(53)*.

Patients who receive posaconazole are often severely ill and may have difficulty eating. It would not be uncommon for these patients to receive their nutritional needs through enteral tube feedings. For this reason, a study evaluated the effect of a nutritional supplement (Boost Plus®, Novartis Nutrition Corp.) on the bioavailability of posaconazole *(54)*. In a randomized, crossover study, 20 healthy subjects received 400 mg of posaconazole oral suspension either after an overnight fast or with 8 ounces of the nutritional supplement (360 calories, 34% fat). Coadministration of posaconazole with the nutritional supplement resulted in a threefold increase in posaconazole C_{max} and a 2.6-fold increase in AUC compared to the fasted state. There was no difference in posaconazole T_{max} or half-life between the two groups.

In summary, posaconazole is a highly lipophilic compound for which administration with food results in a clinically significant increase in bioavailability. Posaconazole should always be administered with food regardless of fat content, or with a nutritional supplement to ensure adequate plasma posaconazole concentrations. If the patient cannot meet these feeding requirements, the manufacturer of posaconazole recommends that another antifungal agent be considered or that the patient be closely monitored for breakthrough fungal infections *(50)*.

2.4. Antiprotozoals

2.4.1. Atovaquone

Atovaquone is an antiprotozoal agent available as an oral suspension. It is used as a second-line agent for the treatment or prophylaxis of mild to moderate *Pneumocystis carinii* pneumonia in patients who are intolerant of trimethoprim-sulfamethoxazole (cotrimoxazole). Atovaquone is highly lipophilic with a low aqueous solubility making it slowly and irregularly absorbed on an empty stomach. Atovaquone bioavailability is enhanced when taken with a fatty meal. The previously marketed atovaquone tablet resulted in irregular absorption and subtherapeutic plasma concentrations. As such, manufacturing of atovaquone tablets (Mepron®) was discontinued once the suspension became commercially available. Atovaquone suspension exhibits double the bioavailability compared to the tablet *(55)*, resulting in increased atovaquone AUC and C_{max} *(56)*.

In a prospective, open label, crossover study of 10 healthy volunteers, the bioavailability of atovaquone (single 750 mg dose of suspension) was enhanced when administered following breakfast (fat content 21 g) or with an oral liquid nutrition supplement (Sustacal Plus®, Mead Johnson Nutritionals: fat content 28 g). The

AUC of atovaquone following breakfast (103.8 μg·h/mL) and Sustacal Plus® (118.8 μg·h/mL) was significantly higher when compared to administration under fasting conditions (43.4 μg·h/mL) ($p < 0.0001$). This corresponds to a mean increase in atovaquone bioavailability by 502 and 505% following breakfast and Sustacal Plus®, respectively *(57)*.

Two studies investigated the effect of food on the pharmacokinetics of atovaquone suspension in patients infected with HIV *(58,59)*. In an open label, dose escalation study including 22 HIV-infected patients, administration of atovaquone with breakfast (fat content 23 g) increased average atovaquone steady-state plasma concentrations by 1.3- to 1.7-fold as compared to fasting *(58)*. Similarly, a single- and multiple-dose pharmacokinetic study in HIV-infected patients showed food to increase atovaquone bioavailability by 1.4-fold. However, an increased incidence of rash was observed when higher plasma atovaquone concentrations were achieved with the 1000 mg twice daily dose taken with food *(59)*.

In summary, the rate and the extent of atovaquone absorption are significantly increased when taken with food, especially fatty meals. As such, atovaquone should be administered with meals to increase its absorption and improve its therapeutic effects *(55)*.

2.4.2. Nitazoxanide

Nitazoxanide is an antiprotozoal agent that is FDA labeled for the treatment of diarrhea associated with cryptosporidiosis (caused by *Cryptosporidium parvum*) and giardiasis (caused by *Giardia lamblia*). Nitazoxanide is practically insoluble in water. It is available in oral tablet (500 mg) and suspension (100 mg/5 mL) formulations which are not bioequivalent. The relative bioavailability of nitazoxanide suspension is 70% compared to the tablet. Although specific data on the bioavailability of nitazoxanide are lacking, nitazoxanide is metabolized in the gut wall, liver, and plasma. Nitazoxanide is rapidly converted to the active metabolite tizoxanide that is ultimately excreted in the urine, bile, and feces. About 67% of the parent nitazoxanide is excreted in the feces *(60)*.

Food significantly increases the absorption of nitazoxanide. Administration of nitazoxanide tablets with food resulted in a twofold increase in the AUC of tizoxanide and the metabolite tizoxanide glucuronide, and a 50% increase in C_{max}. Administration of nitazoxanide oral suspension with food resulted in a 45–50% increase in AUC of tizoxanide and tizoxanide glucuronide and an increase in C_{max} by up to 10% *(60)*. A study in 32 healthy volunteers evaluated the absorption of nitazoxanide following the administration of a single oral nitazoxanide dose of 1 g, 2 g, 3 g, or 4 g first under fasting conditions, and a week later with breakfast. Study results showed that food approximately doubled the plasma concentrations of tizoxanide and tizoxanide glucuronide irrespective of the administered dose *(61)*.

In clinical trials, nitazoxanide was administered with food that substantially increased drug absorption. Therefore, nitazoxanide oral tablets and suspension should be taken with food.

2.5. Antiretrovirals

2.5.1. Atazanavir

Atazanavir is an HIV-1 protease inhibitor that is indicated for the treatment of HIV-1 infection when used in combination with other antiretroviral agents. Atazanavir selectively inhibits virus-specific processing of HIV-1 infected cells, thereby preventing the formation of mature virons *(62)*.

Pharmacokinetic data supporting the effect of food on the absorption of atazanavir capsules are limited to information found in the product labeling, but are worthy of mention. Atazanavir is rapidly absorbed after oral administration. Steady-state plasma atazanavir concentrations are achieved after 4–8 days of continuous therapy. Absorption is significantly increased when atazanavir is administered with food as compared to the fasting state. This may in part be due to improved atazanavir solubility with decreasing pH. When a single dose of atazanavir 400 mg was administered with a light meal, the AUC of atazanavir increased by 70%, and C_{max} increased by 57% relative to fasting. When administered with a high-fat meal, the AUC of atazanavir increased by 35% with no change in C_{max} relative to the fasting state. In both cases (light meal or high-fat meal), there was a decrease in the coefficient of variation for AUC and C_{max} by approximately one-half compared to the fasting state *(62)*.

These data suggest that administration of atazanavir with food increases its bioavailability and reduces pharmacokinetic variability. Therefore, it is recommended that atazanavir be taken with food to enhance its absorption *(62)*.

2.5.2. Darunavir

Darunavir ethanolate (Prezista®), a protease inhibitor antiretroviral agent used for treatment of HIV-1 infection, is marketed as 300 mg oral tablets. The usual adult darunavir dose is 600 mg (two tablets) twice daily taken together with ritonavir 100 mg. Ritonavir, another anti-HIV protease inhibitor, is coadministered at a low dose with darunavir because it inhibits darunavir metabolism through the CYP3A4 isoenzyme and increases its plasma concentrations. Ritonavir increases the absolute systemic bioavailability of darunavir from 37 to 82% *(63)*.

Food increases the bioavailability of darunavir. Regardless of the type of meal (range 240 kcal with 12 g fat to 928 kcal with 56 g fat), taking darunavir with food along with ritonavir increased the AUC and C_{max} of darunavir by about 30% *(63)*. An open label, randomized, crossover study evaluated the effects of different meal types on the pharmacokinetic profile of darunavir in healthy adult volunteers who were given the darunavir/ritonavir combination. Darunavir was taken after a period of fasting for at least 10 h, immediately following a standard breakfast (533 kcal, 21 g fat, 67 g carbohydrate, 19 g protein), following a high-fat breakfast (928 kcal, 56 g fat, 65 g carbohydrate, 41 g protein), after a protein-rich nutritional drink (250 kcal, 8.4 g fat, 33.4 g carbohydrate, 10.5 g protein), or after coffee with croissant (240 kcal, 12 g fat, 28 g carbohydrate, 5 g protein). Study results showed that the AUC and C_{max} for darunavir were 30% lower under fasting conditions compared to when darunavir was taken with a standard breakfast. There were no significant differences in the AUC and C_{max} for darunavir when taken with the different types of meals *(64)*.

In summary, darunavir should only be used in combination with ritonavir. Food increases darunavir absorption regardless of the meal composition. Therefore, the combination of darunavir/ritonavir should be consistently taken with food, in order to achieve optimal therapeutic drug effects *(63)*.

2.5.3. Lopinavir

Lopinavir is a protease inhibitor antiretroviral agent used for the treatment of HIV-1 infection. It is only marketed in a co-formulation with ritonavir, a structurally related protease inhibitor. Ritonavir inhibits the principal isoenzyme CYP3A4 that metabolizes lopinavir; it is, therefore, combined with a low lopinavir dose to decrease lopinavir metabolism and increase its plasma concentrations, thereby enhancing its anti-HIV activity *(65)*.The lopinavir/ritonavir co-formulation is marketed as Kaletra® and is available as oral tablets (lopinavir 200 mg/ritonavir 50 mg) and oral solution (lopinavir 80 mg/ritonavir 20 mg per 1 mL) *(66)*. The main antiviral activity of Kaletra® is due to lopinavir.

Originally, the lopinavir/ritonavir formulation was available in oral soft gelatin capsules that required a daily dosing of six capsules taken with food. Because of patient compliance issues and storage requirements, the lopinavir/ritonavir oral capsules were replaced with a tablet formulation that was manufactured using a special melt extrusion technology that limits the excipient mass. The tablet formulation has significantly improved bioavailability under various meal conditions and is bioequivalent to the oral soft gelatin capsule when taken after a moderate fat meal. The tablet formulation also reduced the number of lopinavir/ritonavir doses to four tablets daily that can be easily stored at room temperature *(66,67)*. The absorption of Kaletra® oral tablets is not significantly affected by the presence of moderate or high-fat meals, but there is less variability and more consistent lopinavir and ritonavir absorption when administered with food compared to the fasted state *(67)*. However, the absorption of lopinavir in Kaletra® oral solution is substantially increased when taken with food. Compared to fasting, administration of Kaletra® oral solution with a moderate fat meal (500–682 kcal, 23–25% fat) increased lopinavir AUC by 80% and C_{max} by 54%. Taking Kaletra® oral solution with a high-fat meal (872 kcal, 56% fat) further increased lopinavir AUC by 130% and C_{max} by 56%, relative to fasting *(66)*.

Because the bioavailability of lopinavir oral solution is significantly increased when taken with moderate to high fat containing meals, Kaletra® oral solution must be taken with food to improve therapeutic drug effects. Kaletra® oral tablets can be taken with or without food.

2.5.4. Nelfinavir

Nelfinavir is a protease inhibitor antiretroviral agent used for treatment of HIV-1 infection. Nelfinavir is available as oral tablet (250 mg, 625 mg) and powder (50 mg/g) formulations that have similar bioavailability. Food increases nelfinavir absorption and decreases nelfinavir pharmacokinetic variability compared to the fasting state *(68)*.

A study in healthy volunteers evaluated the pharmacokinetics of a single nelfinavir dose of 1250 mg (5 × 250 mg tablets) taken under fasting conditions or with

three different meals. Study results showed that nelfinavir AUC, C_{max}, and T_{max} increased with higher caloric and fat intake. Compared to the fasting state, a low calorie and fat meal (125 kcal, 20% fat) caused an increase in the AUC and C_{max} of nelfinavir by 2.2- and 2-fold, respectively. Further increases in nelfinavir bioavailability occurred with a meal that provided higher calories (500 kcal, 20% fat) leading to a 3.1-fold increase in AUC and 2.3-fold increase in C_{max}. A meal with even higher calories and fat content (1000 kcal, 50% fat) was associated with a higher 5.2-fold increase in AUC and 3.3-fold increase in C_{max}. Similar pharmacokinetic results on nelfinavir absorption were obtained from another study in healthy volunteers that evaluated the effects of low (20%) vs. high (50%) fat meals with similar calorie intake (500 kcal) on *(68)*.

Although the effect of food on the pharmacokinetics of the 625 mg nelfinavir tablet has not been separately evaluated, a crossover study that compared the effects of food (standard breakfast at 820 kcal) on a single dose administration of nelfinavir 1250 mg (5 × 250 mg tablets vs. 2 × 625 mg tablets) showed that compared to fasting, food caused a six- and eightfold increase in nelfinavir absorption for the 250 mg and 625 mg tablet, respectively *(69)*.

In summary, nelfinavir bioavailability is higher when the drug is taken with high calorie or high-fat meals. For optimal absorption and enhanced therapeutic effects, nelfinavir should be taken with meals.

2.5.5. Saquinavir

Saquinavir is an antiretroviral agent used for treatment of HIV-1 infection. It is available in oral capsules as saquinavir mesylate (Invirase®) and in soft capsules as saquinavir (Fortovase®). The two dosage forms are not bioequivalent and cannot be used interchangeably. Fortovase® has better bioavailability as compared to Invirase®. Following administration of single 600 mg doses of saquinavir, the relative bioavailability of Fortovase® was 331% as compared to Invirase®. Food, however, substantially increases saquinavir absorption with either dosage form *(70,71)*. Administration of saquinavir with food was reported to increase saquinavir bioavailability by 1800% *(72)*.

In a study of six healthy volunteers who received saquinavir in a single 600 mg dose, a 6.7-fold increase in AUC was reported when saquinavir was administered with food as compared to fasting. Mean 24-h saquinavir AUC increased from 24 ng·h/mL with fasting to 161 ng·h/mL following breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein). The 24-h AUC and C_{max} were on average twofold higher following a higher calorie and fat meal (943 kcal, 54 g fat) than a lower calorie and fat meal (355 kcal, 8 g fat) *(70)*. In another study of 12 healthy volunteers who received a single dose of Fortovase® 800 mg, the mean 12-h AUC increased from 167 ng·h/mL with fasting to 1120 ng·h/mL when saquinavir was taken with breakfast (1006 kcal, 57 g fat, 60 g carbohydrate, 48 g protein) *(71)*.

In summary, food increases saquinavir bioavailability by increasing drug dissolution and disintegration *(73)*. As such, Fortovase® and Invirase®should be taken with food or within 2 h after a meal *(70,71)*. Due to its improved absorption, Fortovase® should be used as the saquinavir formulation of choice in an antiretroviral regimen.

2.6. Fenofibrate

Fenofibrate is a fibric acid derivative prodrug that is rapidly hydrolyzed to its major pharmacologically active metabolite, fenofibric acid. Fenofibrate reduces serum total cholesterol, low-density lipoprotein cholesterol (LDL), very low-density lipoprotein cholesterol (VLDL), and triglycerides, and increases high-density lipoprotein cholesterol (HDL) in patients with dyslipidemia. Fenofibrate also increases urinary uric acid excretion via a different mechanism, hence its off-label use in the treatment of hyperuricemia and gout *(74,75)*. The FDA-labeled indication of fenofibrate is for the treatment of hypercholesterolemia, hypertriglyceridemia, and mixed dyslipidemia (types IV and V) in adjunct to a low-fat diet *(76)*.

Fenofibrate is well absorbed from the gastrointestinal tract with C_{max} attained 6–8 h after oral administration. Fenofibrate is a neutral lipophilic compound that is practically insoluble in aqueous solution for injection, thus the lack of data on the drug's absolute bioavailability. The variable bioavailability and dissolution problems of fenofibrate have led to manufacturing innovations in oral fenofibrate formulations. Fenofibrate is available in various tablet and capsule formulations that have different bioavailability profiles and are not bioequivalent on a milligram-for-milligram basis. The bioavailability of the original non-micronized tablet was improved by micronization, conferring about a 30% increase in bioavailability. Fenofibrate capsules contain micronized fenofibrate particles that disperse and aggregate randomly to excipients. With the fenofibrate microcoated micronized tablet formulation, fenofibrate is coated directly into an inert excipient core which improved its in vitro dissolution by 46% owing to it its higher bioavailability over the non-microcoated micronized capsules. Plasma fenofibric acid concentrations that are achieved following administration of the 54 mg or 160 mg microcoated micronized tablets are equivalent under fed conditions to those achieved with the 67 mg or 200 mg micronized capsules, respectively. The extent of absorption of fenofibrate micronized capsules or micronized microcoated tablets is increased by about 35% under fed conditions compared to fasting *(74,77)*.

Commercially available fenofibrate products can be classified based on their formulation and whether they should be taken with or without regards to meals. Fenofibrate formulations that should be taken with food include micronized capsules (Lofibra® 67 mg, 134 mg, 200 mg), microcoated micronized tablets (Lofibra® 54 mg, 160 mg), and CIP-fenofibrate hard gelatin capsules (Lipofen® 50 mg, 100 mg, 150 mg) *(78–80)*. Fenofibrate formulations that can be taken with or without meals include nanoparticle tablets (Tricor® 48 mg, 145 mg), Insoluble Drug Delivery®-Microparticle (IDD-P) tablets (Triglide® 50 mg, 160 mg), and micronized capsules (Antara® 43 mg, 130 mg) *(76,81,82)*.

The CIP-fenofibrate formulation (Lipofen®) is a newly developed drug delivery technology (Lidose) that increased fenofibrate bioavailability by about 25% compared to the micronized form. The CIP-fenofibrate 150 mg capsule is bioequivalent to 160 mg micronized microcoated tablet (Tricor®) under low- and high-fat-fed conditions. When compared to fasting conditions, the extent of Lipofen®absorption increased by about 25% when taken with a low-fat meal and by 58% with a high-fat meal *(80)*. Similarly, the nanoparticle technology used in the reformulation of Tricor® allowed faster drug dissolution that improved its absorption and

allowed the drug to be taken with or without food. On the other hand, the formulation of the IDD-P tablets uses a technology of preparing fenofibrate microparticles that are stabilized with phospholipid-surface-modifying agents to prevent the re-aggregation of microparticles. This preserves the expanded drug surface area of microparticles and increases its dissolution for better absorption. Single-dose pharmacokinetic studies of the fenofibrate IDD-P formulation in healthy adults showed similar AUC for fenofibrate under fed or fasting conditions *(83)*. Although the micronized capsules in Antara® are better absorbed with a high-fat meal, the package insert states that Antara® capsules may be taken without regard to meals. When Antara® was administered with a high-fat meal, there was a 26% increase of the fenofibric acid AUC and a 108% increase in C_{max} compared to the fasting state. However, the AUC of fenofibric acid was unaffected when Antara® was taken with a low-fat meal or under fasting conditions. T_{max} was also unaffected in the presence of a low-fat meal. Although Antara® absorption was increased when taken with a fat-rich meal, the approval of Antara® to be administered without regard to meals was based on data from clinical studies that showed comparable outcomes on serum triglycerides and cholesterol concentrations when Antara® 130 mg was taken once daily with or between meals *(82)*. A study of an investigational sustained-release fenofibrate 250 mg capsule showed a significant increase in AUC (3.34-fold) and C_{max} (3.82-fold) when taken with a high-fat meal compared to fasting ($p < 0.01$). There was also a significant increase in AUC (2.45-fold) and C_{max} (2.89-fold) when the same formulation was given with a standard breakfast compared to fasting ($p < 0.01$) *(84)*.

In summary, many different fenofibrate oral formulations are commercially available and they are not bioequivalent. The difference in bioequivalence should be considered when a patient is switched from one fenofibrate formulation to another. Lofibra® and Lipofen® should be taken with meals to improve absorption and optimize therapeutic effects. Tricor®, Triglide®, and Antara® can be taken with or without food.

2.7. Isotretinoin

Isotretinoin is a synthetic analog of vitamin A that is available in oral capsules and used for the treatment of cystic acne. Isotretinoin is a highly lipophilic drug with maximal isotretinoin absorption achieved when administered with a fatty meal *(85)*.

The effects of food and fasting on isotretinoin bioavailability were evaluated in a randomized, crossover study of 20 healthy, male volunteers. Isotretinoin 80 mg was administered either during a complete fast, 1 h before a standard breakfast, with a standard breakfast, or 1 h after a standard breakfast. Each treatment was separated by a washout period. Study results showed that isotretinoin bioavailability increased by about 1.5- to 2-fold when isotretinoin was administered 1 h before, with, or 1 h after breakfast, as compared to fasting. Mean isotretinoin C_{max} increased 1.6- to 2.4-fold in the presence of food. T_{max} was slightly delayed by 0.8–1.6 h. The investigators related the positive effects of food on isotretinoin absorption to the increased bile flow that enhances isotretinoin solubility *(86)*.

In summary, isotretinoin bioavailability is increased when taken with food. Consistent intake of isotretinoin with meals is recommended in order to optimize isotretinoin clinical effects.

2.8. Mesalamine/Olsalazine

Mesalamine (5-aminosalicylic acid) is an oral agent indicated for the treatment of chronic inflammatory bowel disease. The exact mechanism of action of mesalamine is unknown, but may be due to its local effects that decrease colonic inflammation by blocking the cyclooxygenase enzyme and inhibiting prostaglandin production in the colonic mucosa. Several different formulations of mesalamine are available on the market. Delayed-release tablets (Lialda®, Asacol®) and controlled-release capsules (Pentasa®) are minimally absorbed (20–30%). In addition, the delayed-release tablets are coated with an acrylic-based resin that only dissolves at a pH of 7 or higher, releasing mesalamine in the terminal ileum. When the delayed-release tablets are given with a high-fat meal, target exposure and absorption are delayed, and there is an increase in systemic exposure to mesalamine (91% increase in C_{max} and 16% increase in AUC) *(87)*. Despite enhanced absorption, the effects of mesalamine are believed to be due to its local effects in the colonic mucosa and not due to its systemic concentration.

Olsalazine (Dipentum®) is a prodrug containing two azo-bound molecules of mesalamine that is cleaved by bacteria in the colon to form mesalamine (5-aminosalicylic acid). Olsalazine is used for the maintenance of remission of ulcerative colitis in patients who are intolerant to sulfasalazine. The oral bioavailability of the olsalazine is limited at $<3\%$. Oral absorption of 5-aminosalicylic acid is also very slow, which leaves high local therapeutic drug concentrations in the colon. Of a 1 g dose of olsalazine, more than 0.9 g of 5-aminosalicylic acid reaches the colon where it exerts its effects *(88)*. Food does not affect the bioavailability of olsalazine or 5-aminosalicylic acid *(89)*. However, because the efficacy of olsalazine is dependent on the colonic concentration of 5-aminosalicylic acid and is independent of serum drug concentrations, taking olsalazine with food increases drug efficacy by prolonging the presence of 5-aminosalicylic acid in the gut *(88)*.

Because the pharmacologic action of mesalamine and olsalazine depends on the local effects of 5-aminosalicylic acid, they should be taken with food to maximize local colonic effects in patients with ulcerative colitis *(87,88)*.

2.9. Misoprostol

Misoprostol is a prostaglandin E_1 analog that is primarily used for preventing gastric ulceration in patients treated with nonsteroidal antiinflammatory drugs (NSAIDs). Misoprostol is available as oral tablets. Gastrointestinal side effects such as diarrhea and abdominal pain are common with misoprostol therapy. Diarrhea is dose-related and may sometimes require discontinuation of misoprostol therapy. The incidence of diarrhea with misoprostol 800 μg/day in patients treated with NSAIDs ranges between 14 and 40%. Administration of misoprostol after meals slows the rate of misoprostol absorption and thus reduces the frequency of diarrhea *(90)*.

In a randomized, open label, crossover study of 12 healthy volunteers, misoprostol absorption was studied when taken with a high-fat meal or during fasting. Study results showed that food decreases the rate of misoprostol absorption without significantly affecting the amount or extent of misoprostol absorption. Food significantly increased misoprostol T_{max} compared to fasting (64 ± 79 min vs. 14 ± 8 min; $p < 0.05$). Food, however, decreased misoprostol C_{max} (303 ± 176 pg/mL) compared to fasting (811 ± 317 pg/mL) ($p < 0.05$). Because achieving a rapid, high C_{max} of the active misoprostol metabolite (misoprostol acid) may result in increased side effects (diarrhea, abdominal pain), these effects can be minimized when misoprostol is taken with food *(91)*.

The effects of misoprostol on bowel motility were evaluated in a double-blind, crossover study of 12 healthy volunteers. Study results showed that oral-to-cecal transit time (measured by H_2 breath test following lactulose administration) was shortened by 57 and 18% when misoprostol was administered before and after meals, respectively. The mean oral-to-cecal transit time was significantly shorter when misoprostol 400 μg was taken before meals compared to after meals ($p < 0.001$) and to placebo ($p < 0.001$). Although other parameters such as stool frequency, fecal fat and bile acids, and fecal weight showed differences between treatments, these differences were not found to be significant *(92)*.

In summary, administration of misoprostol before or after meals decreases the C_{max} of the active metabolite misoprostol acid without affecting misoprostol bioavailability *(91)*. Misoprostol should then be taken with food to reduce the incidence of diarrhea *(90)*.

3. EFFECTS OF SPECIFIC NUTRIENTS ON DRUG ABSORPTION

3.1. Ascorbic Acid and Iron

Iron deficiency anemia can affect all age groups, especially children and women of childbearing age. There are two forms of iron found in the diet – heme iron from meat and non-heme iron from cereals, fruits, and vegetables. Heme iron accounts for about 10–15% of iron intake when consuming a meat-rich diet whereas most of the remaining dietary iron is in the non-heme form. Factors that increase (e.g., ascorbic acid) or decrease (e.g., phytates) non-heme iron absorption do not, however, affect heme iron absorption *(93)*. Ferrous iron (Fe^{2+}) is better absorbed than ferric iron (Fe^{3+}). Most dietary iron is in the ferric state, but factors such as gastric acidity, dietary ascorbic acid, and other reducing substances convert ferric iron to ferrous iron. When considering oral iron supplements, the amount of iron absorbed depends on the type of iron salt used (sulfate vs. fumarate vs. gluconate), iron dose administered, and body iron stores. For instance, 10–35% of an oral iron dose is normally absorbed, whereas up to 80–95% of iron is absorbed in patients with iron deficiency anemia *(94)*.

Iron absorption is significantly reduced by the presence of phytate in the diet. Phytates or hexaphosphates are natural components of vegetables and cereals that bind iron in the gastrointestinal tract to form insoluble and unabsorbable compounds. Ascorbic acid inhibits iron chelation to phytates and also reduces iron to the ferrous form, making it more available for absorption *(94)*. The amount of

ascorbic acid needed to inhibit phytate binding to iron depends on the amount of phytate present in the gastrointestinal tract *(95,96)*. The greater the amount of phytate that is present, the more ascorbic acid is required to reverse the inhibition. With meals containing no phytates, ascorbic acid increases iron absorption by about 60% *(97)*. When phytates were added into wheat rolls at 2 mg, 25 mg, and 250 mg, iron absorption was inhibited by 18, 64, and 82%, respectively. When coadministered with 50 mg of ascorbic acid, absolute iron absorption was highest when the rolls contained no phytates, and was lowest when the rolls contained 250 mg of phytates. It is estimated that about 80 mg of ascorbic acid is needed to counteract the effects of 25 mg of phytates, and a few hundred milligrams of ascorbic acid are required to counteract the effects of 250 mg of phytates *(98)*. The average North American person consumes about 750 mg of phytates daily, although wide individual and geographical variation exist *(99)*.

Iron absorption was increased two- to threefold when 50 mg of ascorbic acid was added twice daily to each meal *(93–96)*. The first 50–100 mg doses of ascorbic acid appear to have the most significant effects on iron absorption. Higher doses have little additional effects *(97)*. Administration of ascorbic acid at doses of 500 mg twice daily after meals for 2 months significantly improved iron status in strict vegetarians *(100)*. However, there was no significant effect on serum ferritin levels when higher ascorbic acid doses of 1 g twice daily were given to adults consuming a well-balanced diet. The lack of significant response with higher ascorbic acid doses may indicate that iron reserves are maintained under tight control regardless of the mechanisms that enhance iron bioavailability *(101)*. Also, ascorbic acid supplementation may have little effect on improving iron absorption in well-nourished, iron-replete subjects.

The effects of ascorbic acid on iron retention were also evaluated in a study of premenopausal women following induction of iron depletion by a low iron diet and phlebotomy. Women in this study consumed a low iron diet that provided 5 mg of elemental iron per 2000 calories for 67–88 days. At the end of the low iron diet period, subjects were divided into three groups to receive a diet containing either 13.7 mg of iron per 2000 calories, supplemental ascorbic acid 500 mg 3 times daily with meals, or a placebo supplement for a total of 5.5 weeks. Study results showed significant improvement in apparent iron absorption (defined as the difference between dietary and fecal iron) with ascorbic acid supplementation compared to placebo. Blood analysis at the end of 5 weeks showed ascorbic acid supplementation to have also improved hemoglobin, serum iron concentration, and erythrocyte protoporphyrins. Ascorbic acid had no effect on improving serum ferritin, transferrin saturation, hematocrit, or total iron-binding capacity *(102)*.

The effect of ascorbic acid on iron absorption was also reported in 54 preschool Indian children who had iron deficiency. Ascorbic acid supplemented at a dose of 100 mg twice daily given with meals for 60 days resulted in a significant improvement in hemoglobin ($p < 0.001$) and red cell morphology as compared with placebo ($p < 0.01$) *(103)*. In another study of 65 Chinese children with mild iron deficiency anemia who were consuming a predominantly vegetarian diet, daily ascorbic acid supplementation at 50 mg, 100 mg, and 150 mg had similar effects on improving iron status *(104)*.

The fraction of iron in ferritin and ferric hydroxide that enters the non-heme dietary iron is also influenced by diet composition. One study compared the absorption of iron from ferritin iron and ferric hydroxide in 35 multiparous women. When administered in water, the geometric mean iron absorption was 0.7 and 2.4% from ferritin iron and ferric hydroxide, respectively. With the presence of ascorbic acid 100 mg in dietary maize porridge, iron absorption increased to 12.1% for ferritin and 10.5% for ferric hydroxide, compared to 0.4% for both compounds with maize porridge without ascorbic acid *(105)*.

Ascorbic acid in fruit juices and vegetables is as effective as equal amounts of synthetic ascorbic acid in enhancing iron absorption *(96)*. In a study that evaluated the effect of fruit and fruit juices on iron absorption from a rice diet containing 0.4 mg of iron, juices of citrus fruits with higher ascorbic acid content resulted in higher amounts of iron absorbed *(106)*.

Iron supplements are commercially available in different salt forms (gluconate, fumarate, sulfate) each providing different amounts of elemental iron *(107)*. Iron sulfate, the most widely prescribed oral iron supplement, is usually given in 1–3 daily doses. Most clinical evidence of enhanced iron absorption with ascorbic acid is with iron sulfate. *(94,108)*. Coadministration of ascorbic acid 100–200 mg/day with iron supplements enhances iron absorption, particularly in anemic patients *(94)*. Patients who absorb iron poorly, such as those with gastrectomy, would most benefit from ascorbic acid supplementation during oral iron therapy *(109)*. Various combinations of commercial iron and ascorbic acid formulations can be found, such as Fero-Grad-500® (timed release tablet containing ferrous sulfate 105 mg with sodium ascorbate 500 mg), Vitelle Irospan® (timed release tablet and capsule containing ferrous sulfate exsiccated 65 mg with ascorbic acid 150 mg), Hemaspan® (containing ferrous fumarate 110 mg with ascorbic acid 200 mg), and Cevi-Fer® (timed release capsule containing ferrous fumarate 20 mg with ascorbic acid 300 mg). Slow-release iron formulations may result in portions of the dose bypassing the intestinal sites of absorption.

4. EFFECTS OF SPECIFIC NUTRIENTS ON REDUCING DRUG TOXICITY

4.1. Folic Acid and Fluorouracil

Fluorouracil (5-FU) is a fluorinated pyrimidine antineoplastic antimetabolite used in the palliative management of colorectal, gastric, pancreatic, breast, ovarian, and head and neck cancers. 5-FU exerts its effects primarily through its active metabolite fluorodeoxyuridine monophosphate that inhibits thymidylate synthase, a key enzyme in pyrimidine synthesis. Leucovorin, a modulator of 5-FU activity, is typically administered intravenously in combination with 5-FU to enhance 5-FU activity. Leucovorin enhances thymidylate synthase inhibition through increasing the intracellular pool of folates that stabilize the thymidylate synthase–fluorodeoxyuridine monophosphate complex *(110,111)*. Because reduced folate metabolites enhance 5-FU antitumor activity, folic acid has been proposed as an alternative to leucovorin as long as it generates the same plasma metabolite levels. Animal studies

have shown potential modulating effects for folic acid in mice with lymphocytic leukemia treated with 5-FU *(112)*. However, human studies evaluating the role of folic acid as possible modulator of 5-FU activity are limited.

A crossover, randomized pharmacokinetic study evaluated the metabolism of folic acid and its ability to yield reduced folates. The study included 10 adult volunteers who were divided into two groups. One group received folic acid at doses of 25 mg/m^2 and the other group received 125 mg/m^2. After a 2-week washout period, the same group received the same folic acid dose by the alternative route. Serial blood samples were collected over 24 h following folic acid administration. Plasma samples were analyzed for folic acid and for reduced folate metabolite concentrations. Study results showed a twofold increase in plasma reduced folate concentrations with the higher oral folic acid dose as compared to the lower dose. In comparison with other studies using leucovorin, the same reduced folate metabolites were generated following folic acid administration. Folic acid at 125 mg/m^2 was at least as effective as leucovorin in increasing plasma reduced folate concentrations. However, folic acid metabolites accumulated at a slower rate and persisted longer than leucovorin metabolites. Based on these results and considering the short half-life of 5-FU, the study concluded that folic acid offers a potential therapeutic alternative to leucovorin in modulating 5-FU efficacy. It was also concluded that giving folic acid 4–6 h before 5-FU allows enough time for effective accumulation of reduced folate metabolites *(113)*.

A clinical study combining 5-FU and high-dose folic acid yielded disappointing results. The study included 22 patients with metastatic colorectal cancer who received a weekly dose of 5-FU 600 mg/m^2 (maximum 1 g) administered 1 h after an intravenous folic acid dose. The starting folic acid dose was 40 mg/m^2 intravenously escalated based on tolerance to the maximum dose of 140 mg/m^2. Study results showed a low response rate and severe toxicities with the combination therapy of folic acid and 5-FU, as compared to 5-FU alone. Only four patients had partial responses for a mean duration of 4 months; no patient had a complete response. Severe diarrhea requiring hospitalization was reported in 12 patients and also caused 3 patients to drop out of the study. Two patients developed leukopenia and later died from sepsis. The study concluded that the use of folic acid with 5-FU could not be justified and that further studies were still needed. There was no clear explanation for the low response rate and high toxicities encountered in this study. The 5-FU dose was within the usual recommended dose. Mean serum folate concentrations at 1 h after folic acid administration were 11 nmol/L higher than the in vitro optimal levels for stabilization of the thymidylate synthase–fluorodeoxyuridine monophosphate complex. However, interpretation of these levels is difficult because serum folate levels do not necessarily correlate with intracellular folate concentrations. Also, it was unknown whether folic acid or the folic acid dose could have contributed to these effects, or even if patients with colorectal cancer are more sensitive to the combination therapy *(114)*. For instance, severe gastrointestinal toxicities (e.g., stomatitis and diarrhea) are more commonly seen in patients with colorectal cancer who are treated with leucovorin and 5-FU, as compared to 5-FU alone. Additionally, it remains unknown whether reductase enzyme phenotype plays any

role in the findings. The C677T genotype codes for a poorly functional MTHFR that allows accumulation of 5,10-methylenetetrahydrofolate which increase the thymidylate synthase effects of 5-FU and drug-induced myelosuppression (115). For safety reasons, it is generally recommended that patients who develop gastrointestinal toxicity not be initiated or continued on leucovorin therapy with 5-FU and that patients should be monitored closely until diarrhea resolves *(116)*.

At present, intravenous leucovorin remains the agent of choice for modulation of 5-FU effect. The safety, efficacy, optimal dose, and dosing schedule for folic acid as a modulator of 5-FU activity remain unknown. Studies comparing leucovorin to folic acid are needed before folic acid can be recommended as a safe and effective modulator of 5-FU effect in the treatment of cancer.

4.2. Folic Acid and Methotrexate

Methotrexate is an antineoplastic antimetabolite used for the treatment of certain cancers. It is also used for treating psoriasis and rheumatoid arthritis (RA). Methotrexate use in RA is based on its antiinflammatory, immunosuppressive, and antiproliferative effects. A low methotrexate dose of 5–25 mg/wk is often used for short- and long-term treatment of adults with RA *(117,118)*. Higher methotrexate doses are exceptionally used when efficacy is not achieved at low doses. Significant toxicities, especially bone marrow suppression, occur at methotrexate doses exceeding 20 mg/wk *(119)*. Dose-related hematological, gastrointestinal, hepatic, and pulmonary toxicities frequently lead to cessation of methotrexate therapy *(120,121)*.

Methotrexate is structurally similar to folic acid. Methotrexate inhibits the dihydrofolate reductase enzyme that reduces folic acid to tetrahydrofolic acid. This results in decreased intracellular levels of reduced folates and inhibition of deoxyribonucleic acid (DNA) synthesis and cellular replication *(120,121)*. The resultant folate depletion and inhibition of folate-dependent enzymes contribute to methotrexate toxicities in nontarget tissues. Diarrhea, stomatitis, and leukopenia are manifestations of methotrexate toxicity that mimic the symptoms of folic acid deficiency *(122)*. Thus, adequate folate supplementation is crucial to reduce methotrexate toxicity.

Leucovorin (folinic acid) is a chemically active reduced folate derivative that is used clinically as a folate rescue to counteract methotrexate toxicity. Low oral doses of leucovorin at 2.5–5 mg/wk are used in combination with low-dose methotrexate *(123)*. Low leucovorin doses reduce methotrexate toxicity without altering its efficacy. However, higher leucovorin doses (45 mg/wk) may counteract methotrexate efficacy and result in worsening of RA *(124)*. As such, folic acid has been investigated as a possible substitute for leucovorin. Compared to methotrexate, folic acid has a lower affinity to the dihydrofolate reductase enzyme. This gives folic acid the advantage of reducing methotrexate toxicity without counteracting its efficacy.

Low plasma and erythrocyte folate and high homocysteine levels were reported in patients treated with methotrexate without folate supplementation *(125,126)*. Plasma homocysteine levels decreased following folic acid or folinic acid supplementation

(126). Reducing homocysteine levels may have long-term cardiovascular protective effect because hyperhomocysteinemia may be a risk factor for cardiovascular disease *(127)*.

The optimal dose and the timing of folic acid supplementation in relation to methotrexate therapy are still debatable. Although weekly folic acid doses of 1 mg *(128)* and 5 mg *(120)* were shown to reduce low-dose methotrexate toxicity, higher doses were suggested to sufficiently prevent methotrexate toxicity *(129)*. The effects of folic acid on reducing low-dose methotrexate toxicity were evaluated in a double-blind, placebo-controlled trial of 79 patients with RA. Oral folic acid doses of 1 mg/day (5 mg/wk) or 5.5 mg/day (27.5 mg/wk) were given 5 days a week on days not coinciding with methotrexate administration. Study results showed that either folic acid dose resulted in lower toxicity scores compared to placebo ($p < 0.001$). Neither folic acid dose interfered with methotrexate efficacy as assessed by joint indices and grip strengths *(121)*. However, results of another study using folic acid doses at 5 mg/day for 13 consecutive days along with weekly intramuscular methotrexate showed alterations in methotrexate pharmacokinetics. There was a significant decrease in plasma methotrexate concentrations and increased total methotrexate clearance. Study investigators concluded that decreased plasma methotrexate concentrations were possibly due to folic acid-induced increased cellular methotrexate uptake *(130)*. Based on these results, the question remains about the optimal folic acid dose that reduces methotrexate toxicity without interfering with its efficacy.

A meta-analysis of seven double-blind, randomized, controlled studies was conducted to evaluate the effects of folic acid or folinic acid on the toxicity of low-dose methotrexate (< 20 mg/wk) in patients with RA. Results of the meta-analysis showed a 79% reduction in methotrexate-induced mucosal and gastrointestinal toxicity with folic acid supplementation. A clinically, but not statistically, significant 42% reduction of the same side effects was seen with folinic acid. Similar effects were also achieved with low- and high-dose folic acid (1–27.5 mg/wk) or folinic acid (1–20 mg/wk). However, high folinic acid doses were associated with increased tender and swollen joint count, a possible indication of decreased response to methotrexate *(120)*. The protective effects of folic acid reported in the meta-analysis *(120)* were not, however, replicated in a later individual study *(131)*. In a 48-week, multicenter, randomized, double-blind, placebo-controlled study, folic acid 1 mg/day and folinic acid 2.5 mg/wk reduced the incidence of elevated liver enzymes without affecting the incidence, severity, or duration of other toxicities including mucosal and gastrointestinal side effects *(131)*.

Based on available data, folic acid supplementation appears to reduce low-dose methotrexate toxicity *(129)* and results in less frequent interruption of methotrexate therapy *(131)*. Relying on dietary folic acid intake alone may not be sufficient to prevent methotrexate toxicity *(132)*. Because folic acid supplements are safe, effective, and less expensive than folinic acid *(133)*, weekly oral folic acid supplementation given on non-methotrexate days appears an appropriate substitute to leucovorin. Although there is no agreement on the optimal folic acid dose, clinical studies reported weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg to be safe and effective in reducing low-dose methotrexate toxicity *(120)*. Baseline patient folate status, methotrexate dose, duration of methotrexate therapy, and possibly

reductase (DHFR, MTHFR) enzyme phenotypes should play a role in determining the optimal protective dose of folic acid. Reports of possible liver protective effects of folic acid are encouraging and require further exploration *(134)*.

4.3. Pyridoxine and Isoniazid

Isoniazid is an antimycobacterial agent used for the treatment and prophylaxis of *Mycobacterium tuberculosis* infections. Peripheral neuropathy is the most common side effect of isoniazid therapy *(135)*. Peripheral neuropathy is dose-related and is most likely to occur in slow acetylators, chronic alcoholics, and malnourished, uremic, and diabetic patients. Signs and symptoms of peripheral neuropathy include paresthesias of the feet and hands, muscle weakness, and diminished or exaggerated reflexes. The mechanism of isoniazid-induced peripheral neuropathy is likely related to isoniazid-induced pyridoxine deficiency or to isoniazid blocking the effect of pyridoxal phosphate synthesis by inhibition of pyridoxine kinase activity *(136,137)*. Vitamin B_6 exists in the body as pyridoxine, pyridoxal, and pyridoxamine *(138)*. Pyridoxine kinase is the enzyme that converts pyridoxal to pyridoxal phosphate *(136,137)*. Pyridoxal phosphate is the active byproduct of pyridoxal metabolism that acts as a coenzyme in the metabolism of neurotransmitters. Reduced pyridoxal phosphate availability during isoniazid therapy is believed to cause a reduction in neurotransmitter synthesis (including gamma-amino butyric acid) that eventually leads to peripheral neuropathy *(137)*.

The incidence of peripheral neuropathy correlates with the isoniazid dose and the presence or absence of patient-specific factors. Peripheral neuropathy occurs in about 1–2% of patients treated with the usual isoniazid doses of 3–5 mg/kg/day *(135)*. The incidence of peripheral neuropathy increases to 40% with isoniazid doses of 20 mg/kg/day *(136)*. In malnourished patients, even low isoniazid doses of 4–6 mg/kg/day may cause peripheral neuropathy in up to 20% of patients *(137)*. Peripheral neuropathy does not usually appear until 6 months of isoniazid therapy *(135)*, but it could appear earlier in malnourished patients or those with preexisting pyridoxine deficiency *(139)*.

It is common practice to supplement pyridoxine at doses of 15–50 mg/day, during the course of isoniazid therapy. Higher pyridoxine doses of 100 mg/day are required in patients treated with hemodialysis. Increased pyridoxine requirements during hemodialysis likely result from reduced pyridoxine metabolism to active pyridoxal phosphate and increased dialysis clearance of pyridoxal phosphate *(140)*. Pyridoxine has also been used to prevent or treat isoniazid-induced psychosis *(138,141)* and seizures *(142,143)*. Seizures are the major toxic reactions of isoniazid overdose *(135)*. In case of isoniazid overdose, intravenous pyridoxine doses of 1 g for each 1 g of isoniazid dose ingested were used without evidence of pyridoxine toxicity *(143,144)*.

In summary, peripheral neuropathy rarely occurs in well-nourished patients treated with isoniazid doses up to 5 mg/kg/day *(145)*. Adult patients treated with isoniazid, especially those at high risk for peripheral neuropathy, should receive prophylactic oral pyridoxine doses of 50 mg/day *(135)*. Although high pyridoxine doses can possibly reduce isoniazid activity *(146)* or even cause neuropathy *(147)*, pyridoxine doses of 100–200 mg/day have been safely used to treat isoniazid-induced

peripheral neuropathy *(137,146)*. The practice of avoiding pyridoxine prophylaxis in children receiving isoniazid should be discouraged, especially in malnourished children *(148)*. Children treated with isoniazid may be supplemented with oral pyridoxine at a dose of 1–2 mg/kg/day *(149)*.

5. EFFECTS OF SPECIFIC NUTRIENTS ON ENHANCING DRUG EFFECT

5.1. Calcitriol and Docetaxel

Docetaxel is an antineoplastic mitotic inhibitor used in the treatment of breast, ovarian, head and neck, nonsmall cell, and hormone refractory androgen-independent prostate cancer (AIPC). In patients with AIPC, docetaxel-based therapy in conjunction with other chemotherapy agents improved patient survival, bone pain, and quality of life. The antineoplastic activity of docetaxel may be significantly enhanced when given in combination with calcitriol (1,25-dihydroxy-vitamin D). Calcitriol is the most biologically active form of vitamin D that exerts its antitumor activity at supraphysiologic concentrations. At the cellular level, calcitriol exerts its antitumor effects via a genomic pathway that is mediated by the vitamin D receptor present in many tissues and via cytoplasmic signaling pathways through protein kinases, lipases, and prostaglandins. Clinically, several mechanisms are proposed for calcitriol antineoplastic activities that varied with tumor and experimental models. These include induction of cell apopotosis, inhibition of differentiation and proliferation, and reduction in angiogenesis and invasiveness. In experimental and clinical studies, combining calcitriol with other cytotoxic agents (e.g., paclitaxel, docetaxel, cisplatin, carboplatin, mitoxantrone, and platinum compounds) has shown synergistic and/or additive antitumor effects in certain types of cancer. When combined with glucocorticoids, calcitriol-mediated inhibition of tumor cell growth and cycle cell arrest were also enhanced *(150,151)*.

The antineoplastic effects of calcitriol are dose dependent and occur at concentrations that exceed the physiologic calcitriol range. Calcitriol concentrations $\geq$ 1 nmol/L are required for in vitro antineoplastic activity. Clinically, achieving these high calcitriol concentrations with high daily calcitriol doses resulted in hypercalcemia, a limiting toxicity of intensive calcitriol regimen. Therefore, daily dosing was replaced with weekly oral calcitriol administration with the goal of avoiding hypercalcemia while still achieving high calcitriol concentrations. In a phase I study, weekly oral calcitriol dose escalation from 0.06 μg/kg to 2.8 μg/kg achieved higher blood calcitriol concentrations from 3.7 to 6 nmol/L without a dose-limiting toxicity. With weekly calcitriol dosing at 60 μg, self-limited hypercalcemia was observed. There was no dose-limiting toxicity observed with single calcitriol doses up to 165 μg *(150)*.

Data are emerging on the beneficial role of a weekly high calcitriol dose in combination with docetaxel for the treatment of patients with AIPC. Preliminary human data also show a possible beneficial effect of a combined regimen using calcitriol and docetaxel for improving the quality of life and pain relief of AIPC-treated patients *(152)*. A single center, phase II study evaluated the role of combining calcitriol and docetaxel in the treatment of 11 patients with AIPC. Oral calcitriol

was administered weekly at 0.5 μg/kg on day 1 followed by intravenous docetaxel 36 mg/m^2 on day 2 for 6 consecutive weeks of an 8-week cycle. The five patients who completed the 8-week cycle had at least a 50% reduction in prostate-specific antigen (PSA) *(153)*. Another phase II study of 37 patients with AIPC used a similar dosing regimen of calcitriol and docetaxel. The PSA response rate was 81% (30 of 37 patients); 59% of patients (22 of 37 patients) had > 75% reduction in PSA. Overall, 1-year patient survival was 89%, and treatment related toxicities were no different than with a single dose docetaxel *(154)*.

Because the commercial calcitriol (Rocaltrol®) formulation is available in 0.5 μg capsules, a large number of capsules (about 70–100) is required for each weekly high calcitriol dose. An investigational high-concentration calcitriol formulation (DN-101) was developed to overcome this limitation. A double-blind, randomized, international, multicenter, phase II study (Androgen Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere = ASCENT-1) of 250 patients with AIPC compared the effects of combining docetaxel with the DN-101 formulation or with placebo. Oral DN-101 45 μg or placebo was given on day 1 before intravenous docetaxel was administered on day 2 at weekly doses 36 mg/m^2 for 3 weeks of a 4-week cycle. The primary study endpoint was a 50% reduction in PSA confirmed 4 weeks later within 6 months. The primary endpoint was reached in 59% of DN-101-treated patients compared to 48% of placebo-treated patients ($p = 0.16$). At any time during the study, overall PSA response rates were 63% in DN-101-treated patients compared to 52% in placebo-treated patients ($p = 0.07$). An adjusted survival analysis showed improved survival in the DN-101 group compared to placebo (hazard ratio 0.67). The incidence of grade 3 and 4 adverse events (hematologic and non-hematologic) was significantly lower in the DN-101 group compared to placebo (58% vs. 70%, respectively; $p = 0.065$). In the DN-101 group, there were significantly fewer serious adverse events (2.4 % vs. 9.6%; $p = 0.02$) and thromboembolic events compared to placebo (1.6% vs. 7.2%; $p = 0.03$). Study investigators concluded that DN-101 treatment in combination with docetaxel does not increase docetaxel toxicity. Although the docetaxel and DN-101 combination improved survival of AIPC patients, this requires further confirmation in other studies because survival was not a primary endpoint of this ASCENT-1 study *(155)*. Currently, a phase III study (ASCENT-2) including 900 patients with AIPC is underway comparing weekly DN-101 with weekly docetaxel to the standard 3-weekly docetaxel 75 mg/m^2 with prednisone. Results of the ASCENT-2 study may better define the role of high-dose calcitriol in the treatment of AIPC. Calcitriol use as adjunctive therapy for specific malignancies primarily remains investigational at this time.

5.2. Plant Stanols and Statins

The management of dyslipidemia combines drug therapy with lifestyle modifications. HMG-CoA reductase inhibitors (statins) are the most widely prescribed agents to lower serum LDL concentration. Besides reducing saturated fat, trans fat, and cholesterol intake, an alternate or adjunct approach in managing hypercholesterolemia is inhibiting cholesterol absorption with dietary inclusion of plant sterols

and stanols. Plant sterols and stanols block dietary and biliary cholesterol absorption in the small intestines with subsequent reduction of serum cholesterol and LDL concentrations *(156,157)*.

Plant sterols (phytosterols) are naturally occurring plant constituents. They are 28-carbon (campesterol) and 29-carbon (sitosterol and stigmasterol) sterols found in edible oils, nuts, and seeds. Plant stanols are saturated derivatives of plant sterols, with sitostanol being the most common. Sitostanol is found mainly in wood pulp, tall oil, and to a lesser extent, in soybean oil.

The Western diet provides about 100–300 mg/day of plant sterols and 20–50 mg/day of plant stanols. Plant stanols and sterols have been incorporated into various food products, including margarine and salad dressing. They are more commonly used in Europe than in the United States. Although plant stanols and sterols have been shown to be equally effective in reducing serum cholesterol concentrations *(156)*, the compounds have inherent differences. For instance, plant stanols are preferable over plant sterols because they are relatively unabsorbed from the gastrointestinal tract. Although plant sterols are poorly absorbed, daily sterol intake of 3.24 g increases serum sitosterol and campesterol by 40 and 70%, respectively. Because of concerns that plant sterols and their byproducts may initiate the development of atherosclerosis, plant stanols appear safer substances, especially during long-term consumption *(158)*.

Plant stanols have been used as adjunctive therapy with statins to manage hypercholesterolemia. Because statins inhibit cholesterol synthesis and stanols block cholesterol absorption, an additive effect of combining the two agents would be anticipated to further lower serum cholesterol concentrations. The combined effects of statins and plant stanols are equivalent to a one- to twofold increase in statin dose *(159)*. A double-blind, placebo-controlled study evaluated the effects of adding dietary plant stanol esters (esterified plant stanols) to statin therapy *(160)*. One-hundred-sixty-seven adults with serum LDL cholesterol concentrations $\geq$ 130 mg/dL and total cholesterol concentrations $\leq$ 350 mg/dL who had been receiving a stable dose of a statin for at least 90 days were included in the study. Subjects were randomized to receive either dietary canola oil-based spread in three servings that provided 5.1 g/day of plant stanol ester (equivalent to 3 g/day of plant stanols) or placebo for a period of 8 weeks. Study results showed plant stanols in combination with statins significantly reduced serum total cholesterol (12% vs. 5%, $p < 0.0001$) and LDL concentrations (17% vs. 7%, $p < 0.0001$) compared to placebo. There were no changes in serum triglyceride or HDL concentrations. Plant stanols were well tolerated *(160)*.

Plant sterols have also been studied. A double-blind, randomized, multicenter study evaluated the effects of plant sterol ester margarine on serum LDL cholesterol concentrations when combined with a statin drug in subjects with hypercholesterolemia (baseline LDL cholesterol $\geq$ 97 mg/dL) *(161)*. The study design used four parallel treatment arms with four daily treatment options of placebo with regular margarine 25 g ($n = 38$), placebo with sterol ester margarine 25 g (2 g of plant sterol; $n = 39$), cerivastatin 0.4 mg with regular margarine 25 g ($n = 38$), and cerivastatin 0.4 mg with sterol ester margarine 25 g ($n = 37$). Study results at the end of 4 weeks showed that cerivastatin significantly reduced serum LDL cholesterol by 32%

compared to placebo ($p < 0.0001$). Sterol ester margarine reduced serum LDL cholesterol concentrations by 8% compared to regular margarine ($p < 0.0001$). There was an additive effect of sterol ester margarine with cerivastatin that resulted in a 39% reduction in serum LDL cholesterol concentrations. All treatments were well tolerated. Study investigators concluded that adding sterol ester margarine to statin therapy reduces serum LDL cholesterol that is equivalent to doubling the statin dose *(161)*.

The effects of plant sterols were also investigated in patients with familial hypercholesterolemia. Patients with heterozygous familial hypercholesterolemia have markedly elevated serum cholesterol concentrations and require lifelong intensive dietary and lifestyle modifications with intensive lipid-lowering drug therapy for hypercholesterolemia. A double-blind, randomized, placebo-controlled, crossover study with two consecutive periods of 8 weeks compared the effects of plant sterol intake at 2.5 g/day in fat spread to placebo on plasma lipid and lipoprotein concentrations *(162)*. Thirty patients with heterozygous familial hypercholesterolemia were concurrently treated with a statin drug, and 32 patients with type IIa primary hypercholesterolemia with total serum cholesterol concentrations > 250 mg/dL were not being treated with lipid-lowering agents. Because of possible carryover effects at the end of the two 8-week study periods, data analysis was limited to the first phase of treatment. At the end of the first 8 weeks, serum LDL cholesterol concentrations had significantly decreased by 10% with sterol treatment compared to no decrease in the placebo group ($p < 0.0001$). There was no difference in response between patients receiving or not receiving concomitant statin therapy *(162)*. The lack of combined effects between plant stanols and sterols with statins in patients with heterozygous familial hypercholesterolemia was replicated in another study of children with heterozygous familial hypercholesterolemia. Combined inhibition of cholesterol absorption by plant stanol ester intake at 2 g/day and inhibition of cholesterol synthesis with pravastatin therapy (40 mg/day) in these patients did not significantly improve serum cholesterol concentrations, especially in patients with the highest serum cholesterol concentrations *(163)*. It was postulated that high baseline serum cholesterol concentrations, possible enhanced cholesterol absorption by statins as detected by increased cholesterol absorption markers, and reduced biliary secretion of plant sterols may be contributing factors to the lack of significant combined effects between plant stanol esters and statins in patients with heterozygous familial hypercholesterolemia *(163)*.

Maximum lowering of serum LDL concentrations appears to be achieved with plant stanol esters at 2 g/day; higher doses are unlikely to provide additional efficacy *(164)*. When considering statin therapy alone or in combination with stanols, doubling the statin dose would reduce serum LDL concentrations by an additional 6%, whereas a 10% reduction in LDL concentrations is achieved when statins are combined with stanols. Also, doubling the statin dose carries the risk of hepatic and muscle toxicity. Therefore, adding plant stanols to statin therapy appears a safer alternative *(159,160,164)*. A possible limiting factor to stanol efficacy alone is related to liver upregulation of its LDL receptor activity to increase LDL synthesis in response to decreased cholesterol levels in liver cells *(165)*. The magnitude of this compensatory effect remains unknown.

Because plant sterols are not water-soluble but dissolve better in fat, most clinical studies of sterol-containing foods have been brands of stanol-enriched margarine. However, patients with hypercholesterolemia commonly avoid using margarine products to limit their fat intake, and using stanol-containing margarine is not convenient when eating out at a restaurant. A placebo-controlled study evaluated the effect of a daily dispersible tablet formulation containing a 1.8 g dose of soy stanols on serum LDL cholesterol in 26 subjects who were already eating a heart-healthy diet and taking statin drugs. To help them dissolve in water and get to their targets in the intestines, stanols were combined with lecithin and compressed into the investigational tablet formulation. Following 9 weeks of therapy, study results showed that the addition of plant stanols in a tablet decreased serum LDL cholesterol concentrations by an additional 9.1% and serum total cholesterol by 12.2 mg/dL *(166)*.

Currently, a commercial product of plant stanol esters (Benecol®) is available in spreads (regular and light) and Chews. Benecol®spread is taken with meals in 2–3 daily servings (1 serving = 1 tablespoon = 0.85 g of plant stanol esters). Benecol®Chews are usually taken as two Chews twice daily with meals and snacks (1 Chew = 0.85 g of plant stanol esters). There are also several multi-ingredient products available as nutritional supplements that contain plant stanols and sterols. However, the exact quantities of ingredients in these products are less well defined. The overall efficacy of plant stanols and sterols on lowering serum cholesterol remains modest, especially with the associated compensatory increase in liver cholesterol synthesis *(165)*. Also, stanol-enriched diets do not appear to have any significant effects on lowering serum triglyceride concentrations *(167)*.

The relatively high cost of plant stanol and sterol products and the need to consume them several times daily make them less appealing to the consumer. However, data are emerging on the cost-effectiveness of dietary supplementation of plant stanol and sterols. A European study evaluated the cost-effectiveness in Euros per quality adjusted life years (€/QALY) of the daily intake of dietary plant stanol ester spread in combination with and without statin drugs in preventing coronary heart disease (CHD). This was based on conducting two meta-analyses of randomized, placebo-controlled clinical studies: one meta-analysis evaluated the reduction of total serum cholesterol concentrations with the use of stanol esters alone and another meta-analysis evaluated reduction of total serum cholesterol concentrations with the use of stanol ester spread in combination with statin therapy. Health-care data from Finland were used to determine age- and gender-specific CHD risk factors. Study results showed that regular use of plant stanol ester spreads alone (assuming consumption of 2 g stanol/day) and in combination with statins reduced serum total cholesterol concentrations by about 14 mg/dL and 15 mg/dL, respectively. Regular use of plant stanol ester spreads was found to be cost-effective in preventing CHD in adult males and older age women with total serum cholesterol concentrations $\geq$ 194 mg/dL. Based on the assumption that changes in serum cholesterol concentrations are converted to changes in the incidence of CHD events using the CHD risk equations, the base case cost (€/QALY) gained ranged from €7,436 to €20,999 in men and from €34,327 to €112,151 in women *(168)*.

6. CONCLUSIONS

6.1. Limitations of Current Data

Data on clinically beneficial drug–nutrient and drug–food interactions are scarce. Well-designed clinical studies of positive drug–nutrient interactions are few, and mainly focused on certain drugs and nutrients. A limitation to the available data on beneficial drug–food and drug–nutrient interactions is that many studies were performed in healthy individuals and/or with small sample size populations. Because disease states may alter the normal physiology of organ functions that ultimately affect drug and nutrient disposition, data from healthy subjects may not always be replicated in sick individuals.

6.2. Research Needs

The list of commonly recognized positive drug–nutrient and drug–food interactions that optimize drug effects is limited, considering the extensive number of drugs available and their potential interactions with various nutrients and foods. Future avenues should include research that focuses on identifying the potential benefits of nutrients that enhance therapeutic drug effect and prevent drug toxicity, determining the populations that may benefit from these positive interactions, and defining the appropriate nutrient intake and drug dosing to achieve the clinically desired beneficial effects. Prospective randomized controlled studies in patients with different disease states and consuming different nutrients are needed to further explore the arena of clinically beneficial drug–nutrient interactions.

6.3. Clinical Recommendations

Drug–nutrient and drug–food interactions can cause increased or decreased drug effects. Beneficial drug–nutrient and drug–food interactions can enhance therapeutic drug effect and reduce or prevent drug toxicity. Clinicians should be aware of these positive drug–nutrient and drug–food interactions and should apply them to patient-specific clinical conditions when clinically indicated. Clinicians should also counsel patients about the appropriate nutrient or food intake to improve the safety and efficacy of drug therapy.

DISCUSSION POINTS

Drug–nutrient and drug–food interactions are often the result of physical and chemical interactions between drugs and nutrients.

- Discuss the factors that can influence drug–nutrient and drug–food interactions.
- Discuss the mechanisms of positive drug–nutrient and drug–food interactions.

Positive drug–nutrient interactions can improve serum drug concentrations, enhance therapeutic drug effects, or reduce or prevent adverse drug events.

- Discuss which nutrients can have a positive influence on drug effects.
- Discuss how nutrients can reduce drug toxicity.

Certain foods can enhance the absorption of certain drugs.

- Discuss how a fatty meal can affect the absorption of certain drugs to enhance their therapeutic effect.

Several of the antiretroviral drugs should be administered with food.

- Discuss the advantages of administering these antiretroviral drugs with food.

Plant stanols and sterols have been used in patients with hypercholesterolemia.

- Discuss the differences, including advantages and disadvantages, of plant stanols vs. plant sterols for the management of hypercholesterolemia.
- Discuss the rationale behind using plant stanols in combination with statin therapy.

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