Food, dietary supplements and their components can have impact on the achievement of drug action and on the side effect profiles of various drugs. Upon entry into the stomach, food may alter the rate or the extent of drug absorption through a variety of direct and indirect mechanism. For certain drugs, food may enhance the rate of absorption, while it may reduce the rate of absorption of other drugs. The interactions are not always detrimental to therapy, but in some cases can be used to improve drug absorption or to minimize adverse effects. These interactions have received more interest recently (Fuhr, 1998). As new drug approvals occur there is less information available about their adverse effects, interactions and about the use of herbal medicines and dietary supplements. These products are not carefully monitored, and may contain little amount of ingredient mentioned on the label. Some of the herbs used can interact adversely with prescription drugs such as ephedra and feverfew. Ephedra is a stimulant that can cause hypertensive crises in patients under monoamine oxidase inhibitors therapy. Feverfew has anticoagulant properties that can enhance the effects of warfarin (Fleming, 1998; Lippman and Nash, 1990). Increased acidic environment of stomach results in the destruction of acid-labile drugs, such as penicillin G, ampicillin and dicloxacillin (Beverly et al., 2003). In other cases, food components such as calcium or iron, may form complexes with less easily absorbed drugs like tetracycline, sodium fluoride and ciprofloxacin (Shah et al., 1999). In many cases, the actual mechanism by which food interferes with absorption is not known, but interactions may occur through three methods: reduced rate or extent of absorption, increased rate or extent of absorption, or through chemical/pharmacologic effects (Alonso and Varela, 2000).

The bioavailability of some drugs may be enhanced by food, for example, an acid environment is necessary for the absorption of ketoconazole. The absorption of griseofulvin is increased by high fat diet. Fenofibrate, mebendazole, isotretinoin, tamsulosin, carbamazepine and labetalol are some examples of drugs that show better absorption while taken with food (Bennet and Brown, 2003; Sindhu et al., 2004). There is a common chemical or pharmacological interaction between alcohol and drugs that have sedative effects like opiates, benzodiazepines and antihistamines. The effect of these drugs are usually potentiated by the consumption of alcohol. Another alcohol-related
interaction is the competitive inhibition of the enzyme aldehyde dehydrogenase. Nausea, vomiting, flushing, dizziness and tachycardia may occur with exposure to alcohol in patients taking some cephalosporins, ketoconazole, metronidazole and sulfonylureas. In addition, chronic alcohol overuse can increase the toxicity of some drugs, as with acetaminophen and methotrexate, or reduce the drugs efficacy, as with phenytoin (Lieber, 1994).

Components of food may antagonize the desired effect of the drug, as in the case of warfarin. Vitamin K containing foods reduce the effectiveness of warfarin. Changing to a diet with increased consumption of leafy and/or dark green vegetables, such as spinach and turnip greens, could decrease the degree of anticoagulation effect of warfarin due to additional supply of vitamin K (Booth et al., 1997). Perhaps the most feared food-drug interaction is that between monoamine oxidase inhibitors (MAOIs) and tyramine, which is found in a variety of aged, fermented, overripe or pickled foods and beverages and, to a lesser extent, chocolate and yeast-containing foods. Tyramine is indirectly sympathomimetic, when its metabolism is suppressed as by MAOIs, it can cause a significant release of norepinephrine, resulting in markedly increased blood pressure, cardiac arrhythmias, hyperthermia and cerebral hemorrhage (Brown et al., 1989; Livingston and Livingston, 1996). There are variety of drugs that show interaction with flavonoids found in grapefruit juice that leads the inhibition of certain enzymes in the cytochrome P450 system, which results in reduced metabolism of drugs that are cleared by the same system (Bailey et al., 1998). Some examples of food and its components affecting drug absorption, disposition and their effect as given as under:

(1) Antibiotics

- **Cephalosporins, penicillin**: Acid secreted by gut after food destroy these acid labile drugs.
- **Erythromycin**: Fruit juice or wine consumption decrease the drug’s effectiveness.
- **Tetracycline**: Dairy products reduce the drug’s absorption and effectiveness.

(2) Anticonvulsants

- **Dilantin, phenobarbital**: Increase the risk of anemia and nerve problems due to deficiency of folate and other B vitamins.
(3) Antidepressants
  - Lithium: A low-salt diet increases the risk of lithium toxicity; excessive salt reduces the drug’s efficacy.
  - MAO inhibitors: Foods high in tyramine (aged cheese, processed meats, legumes, wine and beer among others) can produce a hypertensive crisis.
  - Tricyclics: Many foods, especially legumes, meat, fish and foods high in Vitamin C reduce absorption of the drugs.

(4) Antihypertensives and heart medications
  - ACE inhibitors: Food lowers the absorption of the drugs.
  - Alpha blockers: Liquid or food avoid excessive drop in blood pressure.
  - Antiarrhythmic drugs: Caffeine increases the risk of irregular heartbeat.
  - Beta blockers: Food, especially meat, increases the drug’s effects and can cause dizziness and low blood pressure.
  - Digitalis: Milk and high fiber foods, which reduce absorption, increases potassium loss.

(5) Asthma drugs
  - Pseudoephedrine: Caffeine increase feeling of anxiety and nervousness.
  - Theophylline: High protein diet reduces absorption. Caffeine increases the risk of drug toxicity.

(6) Cholesterol lowering drugs
  - Cholestyramine: Increases the excretion of folate and fat soluble vitamins.
  - Gemfibrozil: Fatty foods decrease the drug’s efficacy in lowering cholesterol.

(7) Heartburn and ulcer medications
  - Antacids: Interfere with the absorption of many minerals.
  - Cimetidine, famotidine, sucralfate: High protein foods, caffeine and other items that increase stomach acidity.

(8) Hormone preparations
  - Oral contraceptives: Salty foods increase fluid retention. Drugs reduce the absorption of folate, vitamin B6 and other nutrients.
  - Thyroid drugs: Iodine-rich foods lower the drug’s efficacy.
(9) Laxatives
- Mineral Oils: Overuse can cause a deficiency of vitamins A, D, E, and K.

(10) Painkillers
- Aspirin and stronger nonsteroidal anti-inflammatory drugs: Food lowers the risk of gastrointestinal irritation. Alcohol increases the risk of bleeding.

(11) Sleeping pills, tranquilizers
- Benzodiazepines: Caffeine increases anxiety and reduce drug's effectiveness

(Sarah, 1998; Williams et al., 1996; Anonymous, 2003; Walker et al., 1996).

According to the Code of Federal Regulations, bioavailability is the rate and extent (fraction or the percentage of the dose) to which the active drug ingredient or therapeutic moiety is absorbed from a drug product and becomes available at the site of drug action (Lobenberg and Amidon, 2000). Oral bioavailability depends on a number of factors, primarily drug permeability, aqueous solubility, dissolution rate, presystemic metabolism, first-pass metabolism and susceptibility to efflux mechanisms. Among these factors low permeability and poor solubility stands as the most frequent causes of low oral bioavailability (Burnside et al., 2005).

Food and its components interact with co-administered drugs and affect their availability across intestine. Several pharmacokinetic parameters are used to judge the clinical importance of food/drug interactions. The concept that botanical supplements could interact with conventional medications is understandable given that food-drug interactions have been recognized for a variety of fruits, spices and vegetables that constitute part of the normal human diet. Many food-drug interactions have phytochemical-mediated pharmacokinetic components. For example, furanocoumarins present in grapefruit juice inhibit intestinal CYP3A4 and have been shown to increase the oral bioavailability of medications that are CYP3A4 substrates e.g., felodipine, midazolam, cyclosporine. The human diet contains many different nutrients, several compounds that are not nutrients, and additives. According to studies where effects of carbohydrates, fat and proteins (macro-nutrients) were determined on drug absorption and metabolism, changes in micro- and macro-nutrient composition of the diet can affect absorption and/or elimination of drugs (Welling, 1996). The effects of non-nutrients and
additives in food may also exert an effect on bioavailability of drugs. Some drugs, which
normally are not interacting with food components, might interact during absorption with
the components of plant material, causing unexpected drug effects, such as several times
higher or lower drug concentrations in the circulation (Wallace and Amsden 2002).
Polyphenols (e.g. anthocyanins, coumarins, flavonoids, lignans and tannins), present in
herbs, vegetables, fruits, flowers, and leaves in many plants, are believed to be beneficial
to human health by exerting biological effects such as free radical scavenging.
Bioavailability of polyphenols has been studied in-vivo (Hollman et al., 1995; Miyazawa,
2000) and in-vitro (Kuo et al., 1998; Murota et al., 2000, 2002). Most dietary flavonoids
present in food exist as O-glycosides with glucose, glucorhamnose, galactose, arabinose,
or rhamnose (Heim et al., 2002). The β-linkage of these glycosides resist hydrolysis
caused by acidity in the stomach and the attack by pancreatic enzymes. However, β-
endoglucosidases present in small intestine are able to hydrolyse flavonoid glycosides
(Spencer et al., 1999). Additionally, colonic microflora hydrolyses the sugar moiety from
the flavonoid aglycone, thus increasing the absorption of flavonoids. During absorption,
the flavonoids may interact with metabolising enzymes and transport proteins, and thus
affect the uptake of co-administered drugs. Indeed, polyphenols are potent inhibitors or
inducers of CYPs, UGTs and transport proteins, if consumed in large amounts (Zhai
et al., 1998, Conseil et al., 1998, Ohnishi et al., 2000). Spices along with their components
may also effect drug absorption and metabolism.
Some natural compounds have demonstrated to increase the absorption and
bioavailability of co-administered drugs. Bioavailability and absorption enhancement
through co-administration of drugs with natural compounds from plants are considered to
be very simple and comparatively safe. Bioavailability enhancing activity of natural
compounds from medicinal plants may mainly be attributed to various mechanisms such
as P-gp inhibition activity, non-specific mechanisms promoting rapid absorption of drugs
such as increased blood supply to the gastrointestinal tract, decreased hydrochloric acid
secretion preventing breakdown of some drugs, non-specific mechanisms inhibiting
enzymes participating in metabolism of drugs. In many cases, bioavailability and
absorption-enhancing effect of natural compounds from medicinal plants were reported to
be attributed to inhibition of P-gp. Flavone, quercetin and genistein have showed a

Chapter I
Introduction

Ph. D Thesis

Jamia Hamdard
considerable P-gp inhibition activities. Additionally, naringin and sinomenine were also reported to be inhibitors for efflux transporters such as P-gp and breast cancer resistance protein (Tsai et al., 2001; Chan et al., 2006). Attenuation of physical barrier such as an increase in intestinal brush border membrane fluidity and inhibition of metabolic enzymes participating in biotransformation of drugs were reported to be absorption enhancing mechanisms of natural compounds (Khajuria et al., 2002). Many absorption enhancers are effective in improving the intestinal absorption, such as bile salts, surfactants, fatty acids, chelating agents, salicylates and polymers as shown in Table 1.1 (Lundin et al., 1990; Aungst et al., 1991). Surfactants including bile, bile salts and fatty acids act as absorption enhancers by increasing the solubility of hydrophobic drugs in the aqueous layer or by increasing the fluidity of the apical and basolateral membranes. Calcium chelators such as EDTA reduce the extracellular calcium concentration, leading to the disruption of cell-cell contacts. Chitosan, particularly trimethylated chitosan, was reported to increase drug absorption via paracellular route by redistribution of the cytoskeletal F-actin, causing the opening of the tight junctions (Schipper et al., 1997).

<table>
<thead>
<tr>
<th>Category</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile salts</td>
<td>Sodium cholate, sodium deoxycholate</td>
</tr>
<tr>
<td>Non-ionic surfactants</td>
<td>Polyoxyethylene alkyl ethers, polysorbates</td>
</tr>
<tr>
<td>Ionic surfactants</td>
<td>Sodium lauryl sulphate, Diocetyl sodium sulfosuccinate</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Sodium caprate, oleic acid, glycerides, natural oils, medium-chain glycerides, phospholipids, polyoxyethylene glyceryl esters, acyl carnitines and cholines, palmitoyl carnitine, lauroyl choline</td>
</tr>
<tr>
<td>Salicylates</td>
<td>Sodium salicylate, sodium methoxysalicylate</td>
</tr>
<tr>
<td>Chelating agents</td>
<td>EGTA, EDTA</td>
</tr>
<tr>
<td>Swellable polymers</td>
<td>Starch, polycarbophil, chitosan</td>
</tr>
<tr>
<td>Others</td>
<td>Citric acid</td>
</tr>
</tbody>
</table>

Table 1.1 List of compounds shown to have intestinal absorption enhancing effects
Phytoconstituents as bioenhancers

Quercetin

Quercetin is a flavonoid found in citrus fruits. It is reported that this flavonoid increase bioavailability, blood levels and efficacy of a number of drugs such as diltiazem (Choi and Li, 2005), digoxin (Wang et al., 2004) and epigallocatechin gallate (Anup et al., 2005). The absorption of epigallocatechin gallate has been enhanced with red onion supplementation, which is a rich source of quercetin. The AUC of epigallocatechin gallate determined over a period of 6 h increased from 1323 to 1814 ng.h/ml, when co-administered with quercetin.

Genistein

Genistein, well known as a phytoestrogen (Kurzer and Xu, 2003) inhibits P-gp, BCRP and MRP2 efflux function. The intestinal absorption of paclitaxel, a substrate for efflux transports such as P-gp, BCRP and MRP2 considerably increased when co-administered with genistein. It has been reported that the inhibition of the efflux transporters by genistein improve systemic exposure of paclitaxel (Li and Choi, 2007).

Naringin

Naringin is the major flavonoid glycoside found in grapefruits, that shows the inhibition of P-gp and CYP3A in rats (Zhang et al., 2000). AUC of paclitaxel is increased significantly in presence of naringin (49.1% for naringin at 10 mg/kg) (Lim and Choi, 2006).

Sinomenine

Paenoniflorin, bioactive monoterpenic glucoside has a poor bioavailability (3-4%) when administered orally (Takeda et al., 1995). Co-administration of paenoniflorin with sinomenine, an alkaloid extracted from Sinomenium acutum, significantly altered the pharmacokinetic behaviors of paenoniflorin in rats (Liu et al., 2005). The results of AUC obtained in the study demonstrated that oral bioavailability of paenoniflorin was enhanced by more than 12 times in rats treated with sinomenine.

Piperine

Piperine is a major alkaloidal component of Piper nigrum Linn. Piperine, or mixtures containing piperine, has been shown to increase the bioavailability, blood levels and efficacy of a number of drugs including vasicine, sparteine, sulfadiazine, rifampicin,
phenytoin and propranolol (Atal et al., 1981; Bano et al., 1987; 1991).

Glycyrrhizin
Glycyrrhizin is a triterpenoid saponin found in *Glycyrrhiza glabra* Linn. Glycyrrhizin showed a more potent absorption enhancing activity than caproic acid at the same concentration tested (Imai et al., 2005). The absorption-enhancing activity of sodium deoxycholate and dipotassium-glycyrrhizinate was much greater when coadministered with glycyrrhizin. The absorption enhancing activity of glycyrrhizin was increased by presence of other absorption enhancers (Sakai et al., 1999; Imai et al., 2005).

Nitrile glycosides
Nitrile glycosides and its derivatives are components derived from the pods of *Moringa oleifera* Lam. These glycosides enhanced the absorption of commonly used antibiotics such as rifampicin, tetracycline and ampicillin, vitamins and nutrients (Khanuja et al., 2005).

Cumin oil
*Cuminum cyminum* Linn. is an annual herb, its fruits are generally used as spice. Bioavailability enhancing activity of *C. cyminum* was revealed toward a number of drugs (Qazi et al., 2009). Various volatile oils and luteolin and other flavonoids seemed to attribute the bioavailability/bioefficacy enhancing activity. Especially luteolin has demonstrated to be a potent P-gp inhibitor in the literature (Boumendjel et al., 2002).

Peppermint oil
Peppermint oil extracted from mentha species increased cyclosporine maximum concentration (*C*<sub>max</sub>) and area under the concentration versus time curve (AUC<sub>0-a</sub>) from 0.60 to 1.6 µg/ml and 8.3 to 24.3 µg.h/ml respectively (Wacher et al., 2002).
References


Chapter 1

Introduction


Ph. D Thesis

Jamia Hamdard


Shah, A., Liu, M.C., Vaughan, D, Heller, A.H. (1999). Oral bioequivalence of three ciprofloxacin formulations following single-dose administration: 500 mg tablet compared with 500 mg/10 mL or 500 mg/5 mL suspension and the effect of food on


