Food and Drug Interactions

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Natural foods and vegetal supplements have recently become increasingly popular for their roles in medicine and as staple foods. This has, however, led to the increased risk of interaction between prescribed drugs and the bioactive ingredients contained in these foods. These interactions range from pharmacokinetic interactions (absorption, distribution, metabolism, and excretion influencing blood levels of drugs) to pharmacodynamic interactions (drug effects). In a quantitative respect, these interactions occur mainly during metabolism. In addition to the systemic metabolism that occurs mainly in the liver, recent studies have focused on the metabolism in the gastrointestinal tract endothelium before absorption. Inhibition of metabolism causes an increase in the blood levels of drugs and could have adverse reactions. The food-drug interactions causing increased blood levels of drugs may have beneficial or detrimental therapeutic effects depending on the intensity and predictability of these interactions. It is therefore important to understand the potential interactions between foods and drugs should and the specific outcomes of such interactions.

Key Words: Food, Drug, Pharmacodynamic interaction, Pharmacokinetic interaction

INTRODUCTION

Food is one of the most important components of a healthy lifestyle. Recent studies have focused on the active role of food products on health and longevity, specifically on preventing cardiovascular and malignant diseases. In this regard, the consumption of natural foods and vegetal supplements has increased spectacularly over the last few decades raising concerns over the potential interactions between food products and drugs particularly in patients undergoing chronic therapy. Therefore, this review briefly summarizes food-drug interactions focusing on recent findings. A food–drug interaction is the consequence of a physical, chemical, or physiologic relationship between a drug and a product consumed as food or a nutrient present in a botanically-derived food or dietary supplement [1]. The influence of dietary substances on drug effects depends on numerous variables ranging from physicochemical properties of the drug to host factors such as enzymes and transporters in the gastrointestinal (GI) tract [2] as well as in the entire body. The interactions may affect not only blood levels of drugs through pharmacokinetic change (absorption, distribution, metabolism and excretion, pharmacokinetic interactions), but also the actual effects of drugs (pharmacodynamic interactions).

PHARMACODYNAMIC INTERACTION

Some foods attenuate or enhance drug effects and toxicity by interfering with drug actions, mechanisms and the pharmacodynamics of the drug. Examples of pharmacodynamic interactions are as follows:

The anti-coagulant warfarin antagonizes vitamin K_1 recycling leading to the depletion of active vitamin K_1. However, green leafy vegetables or "greens" contain large amounts of vitamin K_1 reversing its depletion. Similarly, renin-angiotensin system inhibitors increase plasma potassium $[K^+]$ levels due to a reduction in aldosterone activity. However, foods rich in $[K^+]$ such as oranges and bananas may cause hyperkalemia resulting in cardiac arrest and death due to myocardial arrhythmia. In addition, a hypertensive crisis can result from the ingestion of tyramine-rich foods (fermented foods such as wine and cheese) in conjunction with monoamine oxidase inhibitors (MAOIs). MAOIs, used to treat depression, inhibit the breakdown of endogenous and dietary amines. Consequently, MAOIs reduce the breakdown of tyramine, a precursor of catecholamines (endogenous vasoconstrictors), and raise catecholamine biosynthesis causing a hypertensive crisis [3].

All these pharmacokinetic interactions of food and drug are relatively easy to predict and are recognized and examined during the drug development stage.

PHARMACOKINETIC INTERACTION

Pharmacokinetic interactions cause an increase or decrease in the blood levels of drugs and therefore, their effects and toxicities.

1. Pharmacokinetic interactions caused by physicochemical properties

The physiochemical properties of food products may cause changes in the pharmacokinetics of drugs by chemically binding to the drug and converting it into an insoluble salt that is not easily absorbed. For example, proteins in the food would bind to the antiepileptic agent, phenytoin, resulting in reduced phenytoin absorption and potentially inadequate seizure control [4]. Some tetracyclines and fluoroquinolones can bind to divalent cation-containing products (e.g., calcium in dairy) resulting in reduced drug absorption and potential therapeutic failure [5].

On the other hand, foods rich in fat can increase drug absorption by improving the solubility of lipid soluble drugs, such as some antiretroviral protease inhibitors (e.g., saquinavir and atazanavir) [6]. Food products may also affect drug absorption by delaying gastric emptying, stimulating/increasing bile or splanchnic blood flow, increasing/decreasing GI pH, or changing the gut flora through mechanical or physiological mechanisms.

2. Pharmacokinetic interactions related with enzymes and transporters

Most of the pharmacokinetic interactions occur when food alters the activities of the enzymes and/or transporters involved in drug pharmacokinetic processes. To investigate these pharmacokinetic interactions, the enzymes or transporters involved in the interaction and the active compounds contained in the food working on them must be clarified. However, food products contain too many compounds making it difficult to investigate all of them. Consequently, most studies focused firstly on the phytochemicals contained in the dietary supplements consumed for health, such as natural food, vegetal extracts, and commonly consumed fruit juices, teas, and alcoholic drinks. A number of studies have investigated the effects of phytochemicals on drug metabolism. It has however been challenging to conclusively indicate the effect of phytochemicals on drug metabolism because of the discrepancies observed between in vitro and in vivo studies [7]. The results obtained in vitro have frequently failed to be replicated in vivo probably because of the following reasons: (1) insufficient concentration(s) of causative ingredients at the enzyme or transporter active site, (2) metabolism of causative ingredients to inactive products, or (3) transport of causative ingredients out of target cells (e.g., enterocytes and hepatocytes) [8].

Recent reports have shown that dietary substances elicit a significant influence on drug absorption particularly in the GI tract, the primary portal for drugs and dietary substances. In this case, dietary substances do not have to be taken up by the body and therefore do not undergo metabolism. Attention is drawn to the modulation of the metabolizing enzymes, as well as uptake and efflux transporters located particularly in the GI tract [9]. Inhibition of metabolism and active efflux in the GI tract would be expected to increase systemic drug exposure enhancing the effect and toxicity of drugs while the inhibition of active uptake would produce a completely opposite result. Many phytochemicals have been shown to inhibit these processes held

in the GI tract in vitro. However, clinical applications remain insignificant or undetermined.

More details are discussed below regarding metabolic enzymes and transporters, and the actual influences on drug actions mediated by the enzymes and/or transporters affected by actual dietary substances.

3. Metabolizing enzymes and presence in the GI enterocyte

1) Cytochrome P450

Cytochrome P450s are a superfamily of enzymes (encoded by the gene CYP) involved in the phase 1 metabolism of xenobiotics and endogenous compounds [10]. The 3 families of CYP1, CYP2, and CYP3, and CYP3A4, CYP1A2, and CYP2C9 from these families constitute the major liver enzymes in the human body. The prevalence of these enzymes in human hepatic smooth endoplasmic reticulum is as follows: CYP3A4 (30%), CYP2C9 (20%), CYP1A2 (13%), CYP2E1 (7%), CYP2A6 (4%), CYP2D6 (2%), and CYP2B6 (1%) [11].

CYP3A4 is also a major CYP located in the villous tips of the enterocytes lining the duodenum to the distal jejunum. These destroy drugs before they reach the systemic circulation (pre-systemic metabolism, a sort of first pass metabolism). CYP3A is responsible for the oxidative metabolism of more than half of the pharmaceutical agents on the market [12].

2) Esterase

Esterases are enzymes that metabolize inactive biological compounds, known as prodrugs, to their active form in the body through hydrolytic cleavage of the ester bond to form the active species. Inhibition of enteric esterase activity by dietary substances in rats has been shown to increase stability of the ester in the lumen and enterocytes, resulting in higher absorption of the ester and higher exposure to active metabolites via rapid hydrolysis in the plasma [13]. The clinical significance of esterase inhibition by dietary substances remains under investigation.

4. Transporters and Presence in the GI enterocytes

Several types of transporters (transporting proteins) are involved in the absorption and distribution of macro-molecules including drugs in the body.

1) P-glycoprotein

P-glycoprotein (P-gp) is a membrane protein that protects cells by extruding toxic/unknown substances from cells. P-gp is highly expressed in tissues that have direct contact with xenobiotics such as the epithelium of the gastro-intestinal tract (the polarized apical membranes of enterocytes), the renal proximal tubule (at the brush border level), the canalicular surface of hepatocytes, and the endothelial cell surface of the blood brain barrier [14,15]. Cancer cells can often develop resistance not only to anti-cancer agents which they have been exposed to, but also to other drugs and chemicals that they have yet to come in contact with [15]. Some dietary supplements have a major influence on P-glycoprotein-mediated transport, thus interfering with anti-cancer therapies.

In the GI tract, P-gp is also expressed on the apical (luminal) membrane of enterocytes where drugs are pumped back into the intestinal lumen, lowering the systemic drug concentration [16]. It can therefore be postulated that the inhibition of enteric P-gp may increase systemic drug exposure. However, it has been difficult to establish an in vivo model to study intestinal P-gp largely because an ideal P-gp probe substrate has not been identified and several drugs transported by P-gp are also metabolized by CYP3A [17]. Therefore, it remains to be seen whether the increase in serum levels of CYP3A/P-gp substrates that occur after ingestion of dietary substances that inhibit both CYP3A and P-gp has an effect on CYP3A and P-gp individually or both.

2) Organic anion transporting polypeptide

In contrast to P-pg, organic anion transporting polypeptides (OATPs), a type of transmembrane transport protein, facilitate the uptake of a number of endogenous compounds (e.g., bile acids, hormones) and drugs [18]. Of the 11 human OATP family members, OATP1A2 and OATP2B1 have been reported to be expressed on the apical membranes of enterocytes [19]. A decrease in the drug concentration in systemic circulation could be attributed to the inhibition of an apically located intestinal uptake transporter.

PHARMACOKINETIC INTERACTIONS OF ACTUAL DIETARY SUPPLEMENTS

1. Grapefruit juice

Juice prepared from grapefruit (Citrus × paradisi Macfad.) is one of the most extensively studied dietary substances shown to inhibit CYP3A. Ingredients of grapefruit juice (GFJ) such as flavonoids, naringenin, and apigenin are reported to inhibit the liver enzymes CYP3A4 and CYP1A2 [20]. Since CYP3A is located in the liver as well as in the intestine, GFJ may influence its drug metabolism process in both sites. The main difference between these two interactions would lie in the changes in the half life ($T_{1/2}$) of the blood concentration of the drug. The inhibition of hepatic metabolism in the liver would increase $T_{1/2}$, but inhibition at the intestine would cause no change.

Co-administration of GFJ (250 mL daily for more than three months) with the anticancer drug docetaxel was reported to cause dermatologic toxicity in a patient. Two weeks after stopping GFJ administration, the area under the curve (AUC) in the blood concentration of docetaxel decreased by 60% with $T_{1/2}$ acceleration and the adverse reaction disappeared [21]. In another case study, the administration of amiodarone, an anti-arrhythmic drug, to a patient who regularly consumed GFJ (≥1-1.5 L/day) resulted in a marked QT prolongation associated with ventricular arrhythmia including an episode of torsade de pointes [22]. These two case reports are in line with previous findings that GFJ inhibits hepatic and intestinal cytochrome P450 enzymes, in particular CYP3A. Bailey et al. [23] also indicated that GFJ inhibits the drug pre-systemic metabolism mediated by CYP, particularly the isoform CYP3A4 in the bowel. On the other hand, Kupferschmidt et al. [24] did not observe any significant changes on the half-life of either orally or intravenously administered midazolam in a patient drinking GFJ regularly. Compelling evidence, therefore, indicates that GFJ indeed enhances systemic drug exposure by inhibiting CYP3A mediated pre-systemic (first-pass) metabolism in the intestine without changing $T_{1/2}$ [25].

The inhibition of CYP3A4 may be induced after consuming 200-300 mL of GFJ, while the effect of increasing the bioavailability and toxicity of the drugs may occur in the first 24 hours after consumption. Compounds known as furanocoumarins (e.g., 6',7'-dihydroxybergamottin, bergamottin), in aggregate, have been established as the major mediators of the 'GFJ effect' in humans. Modes of intestinal CYP3A inhibition include reversible and mechanism-based processes as well as degradation of the protein [26]. Similar effects were noted in several fruit juices in extensive studies held in vitro and in human participants.

It has also been demonstrated in vitro that GFJ flavonoids have esterase inhibitory activity and this concept provides an explanation of their plausible mechanism of interaction with ester prodrugs [27]. However, contributions of these effects in patients are not significant in the interactions of GFJ with drugs.

GFJ also acts on drug transporter proteins (such as P-gp) at the intestinal level. Unfortunately, however, it also inhibits hepatic P-gp, without affecting the activity of liver CYP3A4 [28]. Some of the flavonoid compounds present in grapefruit (quercetin and naringenin) also inhibit transporter proteins of organic cations (OCT) and organic anion transporters (OAT) from the basal membrane of intestinal epithelium [29].

There are several reports demonstrating the inhibition of OATP at the intestinal level. GFJ significantly reduced the mean AUC of aliskiren, a direct renin inhibitor, by 61% with no observable change in half-life, consistent with the inhibition of intestinal but not hepatic OATPs in 11 healthy volunteers who were administered GFJ (200 mL single-strength three times daily for five days) and aliskiren (150 mg on day 3) [30]. Similarly, the mean AUC decreased by 38% after GFJ in healthy subjects receiving 300 mg aliskiren and either water or GFJ (300 mL) [31]. In these cases, the average IC50 was well below the reported range of concentrations in grapefruit juice [31]. The clinical significance of the SLCO2B1*3 polymorphism has also been demonstrated in patients with asthma receiving the leukotriene receptor antagonist montelukast in adults [32] and children [33]. Unfortunately, the results regarding the influence of GFJ on the drug transporters (P-gp, OCT, and OAT) are premature, and larger trials are needed to demonstrate reproducibility of the clinical observations.

The most important drugs mentioned in the literature that interact with GFJ in terms of adverse events are calcium channel blockers (amlodipine, felodipine, manidipine, ni-

cardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, pranidipine, etc.), angiotensin II receptor blockers (losartan), beta-blockers (talinolol and acebutolol), some antiarrhythmic drugs (amiodarone, quinidine, disopyramide, and propafenone), anti-cancer agents (vinblastine), and some statins (atorvastatin) [10,34,35]. The increase in systemic drug exposure can be sufficient to produce adverse events such as muscle pain with some statins and severe hypotension with some calcium channel blockers.

Focusing on the adverse events of drugs, it is the current medical recommendation that individuals avoid grapefruit juice consumption while taking these types of drugs. Very recently, however, questions have been asked as to whether GFJ should be recommended rather than avoided [36] based on a report by Lee et al. [37]. Lee et al. [37] demonstrated that GFJ increased the blood levels of simvastatin and lovastatin by about 260% and hence enhanced their therapeutic effects by reducing LDL cholesterol levels by 37% and ischemic heart disease risk by 61%. The report indicated that increments in rhabdomyolysis risk after GFJ consumption were minimal compared to the greater benefit of preventing heart disease caused by statins. The report therefore suggested that GFJ juice should probably not be contraindicated in people taking statins.

As described above, there is compelling evidence that interactions between drugs and GFJ may have potential therapeutic benefits. However, more studies are needed to overcome the challenges hindering the exploration of these beneficial therapeutic effects such as the uncertainty regarding their intensity and interaction predictability [36].

2. Alcoholic beverages

Growing evidence supporting the cardio-protective benefits of alcoholic beverages has promoted moderate alcohol consumption as part of a healthy lifestyle. Alcoholic drinks such as wine and beer are rich in flavonoids and other polyphenols that have antioxidant properties [38] and can alter CYP activity through mechanisms that are independent of ethanol [39]. However, data on enteric CYP3A inhibition by teas and alcoholic beverages (e.g., wine, beer) are less abundant and their clinical significance remains to be determined [40].

1) Red wine

There have been many studies investigating the interactions between red wine, made from the common grape (Vitis vinifera L.), and clinical drugs. However, the findings from the studies have been inconsistent or clinically insignificant [41]. The magnitude of the effect of red wine on the pharmacokinetics of CYP3A substrates may depend on both the amount and type of red wine consumed. Differentiating the effects of ethanol and wine components also poses a challenge. The red wine components, trans-resveratrol and gallic acid, have been shown to inhibit hepatic CYP3A in vitro in a mechanism-based and non-competitive, reversible manner, respectively. However, enteric inhibition by red wine remains to be clearly elucidated [42].

2) Beer

Beer contains many types of phenolic acids and prenyl-flavonoids, some of which are used primarily for flavoring and preserving beer [43]. An evaluation of the inhibitory effects of a wide range of ales, lagers, specialty beers, ciders, and non-alcoholic lagers on CYP systems showed that some beers induced the inhibition of CYP3A4-mediated metabolism by up to 78%. However, there were wide variations in alcohol and hop acids contents. As a result, a definitive relationship between inhibition and hops constituent levels could not be established [44]. Further studies with individual compounds are warranted to support the clinical evaluation.

3) Tea

Tea is the most widely consumed beverage in the world, second only to water. The processing technique for the leaves of the tea plant (Camellia sinensis (L.) Kuntze) dictates the level of fermentation and type of tea — white, green, black, oolong, etc. [45]. Green tea undergoes minimal oxidation during processing, ensuring high polyphenol content [46]. The predominant polyphenolic compounds are catechins, which are presumed to prevent and/or treat cancer, cardiovascular disease, and obesity [47]. The majority of controlled clinical studies evaluating the effect of repeated green tea administration (given as an extract) on CYP activity have failed to demonstrate clinically significant interactions to date [48].

Green tea has gathered attention due to its potential effects on OATPs. Green tea contains catechins including epigallocatechin gallate (EGCG), epicatechin (EC), epigallocatechin (EGC), and epicatechin gallate (ECG) in high concentrations. In vitro studies have shown that both EGCG and ECG inhibited both OATP2B1- or OATP1A2-mediated estrone-3-sulfate uptake by ~70% and ~75%, respectively [49]. Interestingly, their concentrations (IC50 < 100 μM) were much lower than the concentrations in typical green tea (average ~450 μM). Consumption of a cup (e.g. 240-300 mL) or two of green tea would result in intestinal concentrations of ECG and EGCG within the range that inhibits OATP activity. However, no clinical studies have reported on the significance of intestinal OATP inhibition by green tea except for several case reports on rats [50] and humans [51]. Again, larger clinical studies are needed to determine the clinical significance of these observations.

POLYPHENOLS: ANTIOXIDANTS BECOMING PRO-OXIDANTS

Antioxidant activity of polyphenols or flavonoids is believed to be the central mechanism involved in the health promoting effects of natural foods and vegetal supplements [52-54]. Flavonoids are natural polyphenols, best known as pigments responsible for a diversity of colors found in vegetables (yellow, orange, red, etc.—their name being derived from the Latin word flavus meaning yellow).

There are some problematic issues that are linked to the use of vegetal supplements and vegetal components of diet, especially when associated with classical medicines. Several reports revealed the possibility of pro-oxidant effects induced by polyphenols, which were generally known for their antioxidant effects. We should be aware that flavonoids (like many other antioxidants), can act, under certain circumstances, as pro-oxidants, for example in systems containing redox-active metals (copper, iron, etc.) [55]. The pro-oxidant activity is linked to the total number of hydroxyl groups in a flavonoid molecule. As the total number increases, the hydroxyl groups increase the risk for production of radical/nonradical reactive species (hydrogen peroxide and hydroxyl radicals) in Fenton reactions [56-59]. The flavonoid pro-oxidant function could be related to their beneficial functions: one example being epigallocatechin gallate which reduces O_2 to yield H_2O_2 to promote apoptosis and exert cytotoxic activity against bacteria [60].

Flavonoid pro-oxidant functions could have potentially toxic effects. Some individual flavonoids, for example quercetin, particularly at high-dose levels, are able to induce toxic effects, including pro-oxidant activity, which could be related to mutagenicity and mitochondrial toxicity. For example, quercetin efficiently protects against H_2O_2- induced DNA damage in rat lung epithelial (RLE) cells, but this protection results in a reduction in GSH levels, an increase in LDH leakage, and an increase in cytosolic free calcium concentration [61]. Ultimately, quercetin acts as a toxicant. This phenomenon has been defined as "the quercetin paradox" (the conversion of quercetin into a potential toxicant while offering protection by scavenging ROS) [61,62]. It is surmised that oxidized quercetin is generated intensely in subjects with elevated oxidative stress associated with pathological conditions (diabetes mellitus, obesity, malignancies, etc.). In the event that these subjects have low levels of GSH, quercetin used for antioxidant reactions may become toxic making them even more susceptible to damage by quercetin oxidation metabolites [52,61]. However, this kind of toxicity would require very high concentrations (>several hundreds of mM) [63,64], indicating that quercetin use is indeed rather safe [65]. The extent to which flavonoids are able to act as anti- or pro-oxidants in vivo is still poorly understood [59].

Subjects usually consuming a rich polyphenols diet are characterized by concentrations of respective compounds ranging between 2.5 and 10 μM. Subjects using natural supplements can reach blood levels of over 20 μM polyphenols [66-68].

CONCLUSION

Interactions between drugs and food products occur in various ways and in various steps ranging from ingestion, absorption, metabolism, and excretion of both the drug and food product. Some of the effects induced by food-drug interactions, such as an increase in the blood drug level, may have potential therapeutic benefits while some interactions may result in detrimental physiological effects. It is there-

fore important to understand and examine the potential interactions between foods and drugs and their specific effects at an individual level.

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