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Review Article

FOOD–DRUG INTERACTION AND THEIR CLINICAL IMPLICATIONS: SELECTED INVESTIGATIONS

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ABSTRACT

Food-drug interactions occur as a result of pharmacokinetic or pharmacodynamics mechanisms. Pharmacokinetic mechanisms include what the body does to a drug while Pharmacodynamics mechanisms involve what drugs do to the body. Many types of food have been shown to influence metabolism and the absorption of drugs. Large numbers of drugs are produced and introduced yearly. The interaction between Food and drug may cause negative effects in the nutritional status of the patient as well as safety and efficacy of drug therapy. Due to the possibility of unexpected or poor outcomes, generally, food-drug interactions, in this case, should be avoided. As the good clinical practice, drugs taken by mouth must be absorbed either through the lining of the stomach or the small intestine. Reduction in the absorbance of a drug might be influenced by the presence of food in the digestive tract. The avoidance of such interactions could be possible if the drug is taken 1 hour before or 2 h after eating the food. The effects of several types of food such as milk or milk products, grapefruit and grapefruit juice, bananas, oranges, legumes, fermented meats and pickled fish and some nutrient elements such as calcium, potassium, magnesium, iron, zinc, and vitamin K are highlighted in this paper including their clinical implications.

Keywords: Food-drug interaction, Medication, Clinical implications, Clinical practice

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INTRODUCTION

Many types of medicines can be useful because of their positive effects in treating and curing many health problems. To ensure that these medicines are safe and effective they must be taken properly. So, medications should have the same predictable effect for all patients, extremely specific in their effects, exhibit linear potency, never be affected by concomitant food or other medications, be totally non-toxic in any dosage and require only a single dose to affect a permanent cure [1]. Some types of food can sometimes have a significant impact on some drugs. Ayo *et al.* [2], revealed that a drug interaction is a situation in which a substance affects the activity of a drug, i.e. they produce a new effect that neither produces on its own or the effects are increased or decreased. Like drug-drug interaction (3), the interactions may also exist between foods and drugs (food-drug interactions) and could be possible between drugs and herbs (drug-herb interactions). The interactions between food and drugs may inadvertently reduce the absorbance of drug and also may increase the negative effect of the drug. However, due to the physiological response to food intake, particularly the gastric acid secretion, may increase or reduce the bioavailability of certain drugs [4]. Earlier (Schmidt and Dalhoff [5], reported that these may occur due to the lack of knowledge about the active ingredients that involved in the relevant substances. Several types of research have been dedicated with the objectives of investigating the effects of certain food-drug interaction systems [6-17]. The aim of the present was to investigate and highlight the effect of food-drug systems and their various clinical implications.

General food/some food components-drug interaction

Some specific types of foods can have unique influences on drug interaction and disposition. Within the gastrointestinal tract, an oral administration of a drug concurrent with meal alters may influence the rate or extent of drug absorption as well as the physicochemical conditions of the drug. Davit and Conner [18], claimed that a change in the rate of drug absorption is less clinically significant than a change in the extent of the drug absorption because due to the influences in bioavailability of both drug and meal. According to FDA [19], tested a meal contains about 800 to 1,000 kcal, with about 50% of calories as fat (eg, two strips of bacon, two eggs fried in butter, two slices of buttered toast, whole milk and brown potatoes and concluded that that such a meal will create the greatest perturbation on gastrointestinal physiology and be reflected in a meal's influence on drug bioavailability. Therefore, it is very important to test meal conditions used in any conducted study before making a clinical recommendation. Using data generated invitro studies can clearly predict food effects and drug disposition using the Biopharmaceutics Classification System [19-23]. Boullata *et al.* [9], suggested that based on drug solubility and intestinal permeability some drugs have low solubility but high permeability and are expected to have an enhanced extent of absorption when administered with food. On the other hand, some other specific foods have impaired the absorption of drugs with poor permeability when examined in several clinical studies.

Interaction of some vegetables with drugs

Some vegetables (broccoli, Brussels sprouts, kale, parsley, spinach, and others) had a high content of vitamin K. Earlier, Holt [24] was reported that making sudden changes in the amounts eaten or eating large quantities of these vegetables interferes with the safety and effectiveness of warfarin therapy. Great decrease in warfarin activity might be resulted from eating charbroiled food. However, Zikria [25], revealed that eating cooked onions may increase warfarin activity. On the other hand, it was reported that soy foods had both an increase and decrease effect on warfarin activity [25], but the author found that the combination of cranberry juice and warfarin administration appeared to be associated with an elevated international normalized ratio without bleeding in an elderly patient.

Fruit juice-drug interaction

Several juices were found to have an interaction with medication by metabolizing and altering transporters enzymes to a wider degree than initially described [26, 27]. Naringin, an ingredient in most citrus fruits has been shown to reduce aliskiren uptake [28]. Grapefruit juice was the first identified, but based on flavonoid and furanocoumarin content other juices have also been shown to interact with medication [29, 30]. It was found that furanocoumarins had significant inhibition on intestinal isoenzymes and can also

interfere with transporters, thereby increasing oral drug bioavailability. Grapefruit juice was found to have a significant effect on Aliskiren which is recognized as a direct renin inhibitor indicated for the treatment of hypertension. A clinical study conducted on 11 healthy volunteers administered using 200 ml single-strength of grapefruit juice (three times daily for five days) and 150 mg of aliskiren on day 3 showed that relative to water, grapefruit juice significantly reduced mean aliskiren by 61% [31]. A study with 28 healthy volunteers receiving 300 mg aliskiren and either water or grapefruit juice (300 ml) revealed a decrease of 38% by of the drug in the presence of grapefruit juice [28]. This decrease in the absorption of the drug was in a good agreement with the previous studies by several authors [30, 33-36]. However, some clinical studies with certain β-blockers, fexofenadine, and fluoroquinolones have demonstrated that orange juice can reduce systemic exposure by up to 83% [39-42]. Tapaninen *et al.* [31] investigated the effect of orange juice on aliskiren. In a randomized study, 12 healthy volunteers ingested 200 ml of orange juice, water or apple juice for a frequency of three times daily for a period of five days. On day 3, the volunteers ingested a single dose of 150 of aliskiren. The result showed that orange juice reduced aliskiren geometric mean by 62% relative to water while having no effect on elimination half-life. Apple juice was also investigated on drug metabolism *in vitro* and in human volunteers [26]. The evidence exists that apple juice inhibits organic anion transporting polypeptides activity which recognized as proteins that facilitate uptake of a number of endogenous compounds such as hormones and bile acids [41]. Apple juice intake on fexofenadine was evaluated in a randomized crossover study of 14 healthy volunteers [42]. Midazolam (5 mg) and fexofenadine (60 mg) with 300 ml of either normal-strength apple juice or water were orally taken. It was found that apple juice decreased fexofenadine mean 79% compared to water but it did not show significant effects on midazolam, indicating that apple juice had minimal effect on midazolam activity. Some other dedicated studies have shown the same effect of apple juice on fexofenadine [43-47].

Green tea-drug interaction

Green tea (GT) is well known among the most worldwide consumed beverages. It is obtained from the non-fermented leaves of the Camellia sinensis plant. It has promising health beneficial effects and it is considered as one of the most important nutraceuticals that used as new treatment approaches for oral cancer [48]. The polyphenols of GT (GTP), particularly catechin (−) epigallocatechin-3-gallate (EGCG), which has about 50–80% of the total catechins in GT, is reported to have an antioxidant effect [49]. It was investigated and reported that the anti-carcinogenic effect of tea catechins with EGCG being the most active.

Table 1: Selected food-drug interaction and their clinical implication*

Food	Medicine	Type of effect	Clinical implications
Milk or milk products	Ciprofloxacin(Cipro) Levofloxacin (Levaquin)	Calcium in milk bind with these drugs inhibiting absorption of the drugs as well as calcium	Administer 2 h before or 2 h after milk or milk products
Grapefruit and grapefruit juice	Beta-adrenergic antagonists Labetalol Metoproplol Propranolol (Inderal)	Increased absorption by decreased first-pass metabolism; can slow heart rate and lower blood pressure	Avoid grapefruit or grapefruit juice 2 h before or 1 hour after administration of the drug
Bananas, oranges, legumes, and meats	Diuretics, potassium-sparing; Amiloride(Midamor) Spironolactone (Aldactone) Triamterene (Dyrenium)	Prevents kidneys from excreting potassium causing toxicity, slow heart rate, palpitations, and possibly cardiac arrest	Limit potassium-rich foods, such as bananas, oranges, and green leafy vegetables, and salt substitutes that contain potassium.
Foods that raise blood sugar, such as sweets and refined flour	Antidiabetic drugs, Sulfonylureas Chlorpropamide Glipizide (Glucotrol)	Reduces control of blood sugar Vitamin B12 deficiency and irreversible nerve damage	Avoid foods containing simple sugars and refined flour
Aged cheeses, fava beans, yeast extracts,	Monomine oxidase; inhibitors; Isocarboxazid Phenelzine (Nardil), Tranylcypromine	Potentially fatal spike in blood pressure	Avoid foods and beverages containing tyramine or tryptophan while taking medications and for 2 w after stopping this drug.
High-fiber products, such as bran, pectin, bulk laxatives	Cardiac glycosides	Decreases absorption of the drug	Administer before 1 hour or 4 h after ingestion of high fiber food products
Regular meal or snack	Anti-tuberculosis; Rifampin (Rifadin, Rimactance).	Delays or decreases absorption of the drug	Administer 1 hour before or 2 h after meal or snack
Dietary fiber and Fatty foods	Simvastatin (Zocor) Lovastatin (Mevacor) Lovastatin (Mevacor) Atorvastatin (Lipitor)	Decrease absorption of the drugs; cause headage and stomachage and muscle breakdown	Give with low-fiber foods or 1 hour after administration of drugs
Grapefruit juice	Drugs that prolong repolarization Amiodarone (Cordarone, Pacerone	Significantly enhanced toxicity	Give on an empty stomach, 1 hour before or 2 h after meal or snack
Fermented meats, pickled fish	Inhibitors; monomine oxidase	Potentially affect fatal spike in blood pressure	Avoid these foods after taking drugs for 2 w.
Soybean formulas	Thyroid supplements	Decreases absorption; increases fecal elimination	Avoid soybean formulas and Limit foods high in iodine, such as rutabaga, soybeans, or turnips.
High-carbohydrate meals	Respiratory medications	May cause nausea, vomiting, headache, irritability	Avoid high-carbohydrate meals or supplements and when necessary 2 h after dose
High-fat meals	Bronchodilators theophylline	Decreases absorption of the drug; May cause nausea, vomiting, headache, irritability	Avoid high-fat meals or supplements and when necessary hold enteral nutrition 1 hour before medication.

There are numerous investigations and reports in this regards [51-53]. GT was found to have high concentrations of catechins, including epigallocatechin (EGC), epicatechin (EC) and epicatechin gallate (ECG). Zaveri [53] studied the activity of predominant catechin extensively for health benefits on OATP1A2 (organic anion transporting polypeptide 1A2) and OATP1A2 (organic anion transporting polypeptide 2A1) and OATP2B1 have *in vitro*. He reported that both EGCand ECG at 100 μM inhibited OATP2B1-mediated estrone-3-sulfate uptake by ~70%. This finding agreed with that revealed by Roth *et al.* [54] and Fuchikami *et al.* [55]. However, ECG showed higher potency than EGCG (IC50 of 36 vs. 100 μM) [52]. Moreover, they reported that ECG at 100 μM also inhibited OATP1A2-mediated

estrone-3-sulfate uptake by ~75% but ECG again showed higher potency than (IC_{50} of 10 vs. 55 μM). The consumption of a cup of GT (e. g., 240–300 ml) or two cups of GT will result in inhibition of OATP activity due to high concentrations of ECG in intestinal line.

Table 2: Selected nutrient-drug interaction and their clinical implication*

Nutrient in food	Medicine	Type of effect	Clinical implications
Calcium	Ciprofloxacin (Cipro)	Calcium binds with these drugs inhibiting absorption of the drugs	Hold enteral feeding 1 hour before and 2 h after administration of the drug.
Potassium	Diuretics, thiazide; Chlorthalidone (Hygroton)	Causes loss of potassium and magnesium; can cause rapid heart rate and arrhythmias	Administer potassium/magnesium supplement or foods such as apricots, bananas, cantaloupe, dairy foods, dried beans, lentils, oranges, and tomatoes.
Magnesium	Quinolones	Magnesium binds with this drugs inhibiting absorption of the drugs	Avoid meals contain magnesium and magnesium supplement
Vitamin D supplements	Gastrointestinal Medications	Calcium toxicity and kidney failure	Avoid milk; milk products and calcium supplement
Aluminum	Levofloxacin (Levaquin)	Aluminum binds with this drugs inhibiting absorption of the drugs	Avoid meals contain aluminum and aluminum supplement
Iiron	Norfloxacin (Noroxin)	Iron binds with this drugs inhibiting absorption of the drugs	Avoid meals contain iron and iron supplement
Zinc	Ofloxacin (Floxin	Zinc binds with this drugs inhibiting absorption of the drugs	Avoid meals contain zinc and zinc supplement
Vitamin B12	Proton-pump inhibitors	Vitamin B12 deficiency if used long term	Avoid foods rich in Vitamin B12
Meals that high in pyridoxine (B6)	Antiparkinson drugs	Decreases absorption of the drug, increases symptoms	Limit foods rich in pyridoxine such as chicken, fish, liver, and kidney.
Vitamin K	Medications affecting the blood and blood-forming organs anticoagulant such as warfarin (Coumadin)	increases chance of blood clots	Limit foods high in vitamin K such as broccoli, spinach, kale, and turnip greens.
High-dose itamin K	Medications affecting the blood and blood-forming organs anticoagulant such as	Prolongs clotting time and increases the risk of bleeding	Avoid foods rich or foods, such as leafy green vegetables, antagonize action; soy proteins; high doses of vitamin E (400 IU)
High-potassium supplements		Potassium toxicity can slow heart rate and possibly cause cardiac arrest	Avoid excessive potassium intake including salt substitutes that contain potassium.
Iodine	Metformin (Glucophage)	Decreases absorption; increases fecal elimination	Limit foods high in iodine, such as brussels sprouts, cabbage, rutabaga, soy beans.

*Harrington and Gonzales, 2004) [50]

CONCLUSION

Food-drug interaction is considered a critical issue and most studies in this regard are conducted to evaluate appropriate dosing, formulation of new drug candidates and intake timing. Commonly consumed foods could have inhibition effect on drug or either increase/decrease the absorption of certain drugs. Foods should be tested comprehensively before taking certain drugs to avoid the possibility of interaction with the drug. Therefore patients are advised to tell their doctors and pharmacists about their food intake and dietary supplements so that serious interactions between foods and drugs can be avoided. Carefully following the clinical implications in this article is highly suggested and recommended.

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ABBREVIATIONS

FDA (US Food and Drug Administration), GT (green tea), GTP (green tea polyphenols), EGCG (epigallocatechin-3-gallate), OATP1A2 (organic anion transporting polypeptide 1A2), OATP2B1 (organic anion transporting polypeptide 2A1), IC_{50} (the concentration of an inhibitor where the response (or binding) is reduced by half).

AUTHORS CONTRIBUTIONS

All the author have contributed equally

CONFLICT OF INTERESTS

No conflict of interest is declared

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