https://doi.org/10.31925/farmacia.2022.5.3 **REVIEW**

DRUG-FOOD INTERACTIONS: THE INFLUENCE ON THE PATIENT'S THERAPEUTIC PLAN

KHALED ZIANI [1#], CAROLINA NEGREI [1#], CORINA-BIANCA IONIȚĂ-MÎNDRICAN [2]*, ADINA MAGDALENA MUSUC [2#], VALENTINA PATRICIA PREDOI [1], DENISA IOANA UDEANU [1], MAGDALENA MITITELU [1]

[1]*Faculty of Pharmacy, "Carol Davila" University of Medicine and Pharmacy, 3-6 Traian Vuia Street, sector 2, 020956, Bucharest, Romania*
[2]*"Ilie Murgulescu" Institute of Physical Chemistry, 202 Splaiul Independenței, 060021, Bucharest, Romania*

**corresponding author: corina-bianca.ionita-mindrican@drd.umfcd.ro*
[#]*Authors with equal contribution.*

Manuscript received: July 2022

Abstract

Diet influences tolerance to drugs and their effectiveness by attenuating, slowing down, or, on the contrary, reinforcing their effects. The interaction often involves drug absorption through the digestive tract, but some nutrients alter drug metabolism and elimination (e.g. grapefruit juice) interferes with the hepatic clearance of many drugs. This review will not be limited only to the interactions relating to absorption and will develop by highlighting the pharmaco-dynamic interactions, which cause the potentiation or antagonism of the pharmacological effect at the origin, of an increased risk of toxicity, in particular, in elderly patients, poly-medicated, transplant recipients, cancer patients, HIV-seropositive patients, malnourished patients, and those patients which are on enteral nutrition and theoretically are the most exposed. The present work offers the most exhaustive possible synthesis of the various drug-food interactions observed or demonstrated in clinical practice, their potential risk and the key messages for the internist ment on the major role of grapefruit, its derivatives, St. John's wort (*Hypericum perforatum*), and other medicinal plants in common drug-food interactions.

Rezumat

Dieta influențează toleranța la medicamente și eficacitatea acestora prin atenuarea, inhibarea sau, dimpotrivă, stimularea efectelor acestora. Interacțiunea presupune adesea absorbția medicamentului prin tractul digestiv, dar unii nutrienți modifică metabolismul medicamentului și eliminarea (de exemplu, sucul de grepfrut) interferând cu clearance-ul hepatic al multor medicamente. Acest review nu se limitează doar la interacțiunile legate de absorbție și evidențiază interacțiunile farmacodinamice, care cauzează potențarea sau antagonismul efectului farmacologic la origine, a riscului crescut de toxicitate, în special, la pacienții vârstnici, cu polimedicație, beneficiarii de transplant, pacienții cu cancer, pacienții HIV-seropozitivi, pacienții malnutriți, acei pacienți care urmează o nutriție enterală și, care teoretic, sunt cei mai expuși. Lucrarea de față oferă o sinteză exhaustivă a diferitelor interacțiuni medicament-aliment observate sau demonstrate în practica clinică, riscul potențial al acestora și mesajele cheie pentru specialiști cu privire la rolul major al grepfrutului, al derivaților săi, al sunătoarei (*Hypericum perforatum*) și alte plante medicinale în interacțiunile comune medicament-aliment.

Keywords: drug-food interactions; herbal medicines; P-glycoprotein; cytochrome P450 3A4; grapefruit juice

Introduction

Adverse drug reactions and drug interactions are main causes of excessive costs and mortality, but they are also preventable [1, 2]. In 2015, a US expert committee defined the expression drug interaction as "a clinically relevant modification of the effect of the drug that occurs due to the concomitant administration of another drug". This concomitant administration may cause side effects or alter the drug' therapeutic effect. A clinically harmful drug interaction is "the interdependence that outcomes in toxicity or in the loss of the therapeutic efficacy warranting the attention of a healthcare professional" [3].

In order to obtain a database that highlights possible drug interactions, many specialists are increasingly turning to scientific articles or specialized journals. Thus, while interactions between drugs [4] or adverse effects of a drug [5] are listed in databases such as DrugBank or Theriaque, other information, such as interactions between a drug and food, is scarcely present and often dispersed in heterogeneous sources. To provide an answear to the problems of updating or identifying this information, text mining methods are generally used [5-7].

A food-drug interaction can also be defined as a change in the pharmacokinetic and/or pharmaco-dynamic properties of a drug caused by one or more

foods [8, 9]. Therefore, the simultaneous administration of two or more drugs can result in pharmacokinetic interactions (changes of the drug in the body), pharmaco-dynamic interactions (changes in the action of the drug on its therapeutic target) or pharmaceutical interactions (physico-chemical incompatibility of two molecules administered orally, simultaneously). All drug interactions can be a source of therapeutic inefficiency or increased toxicity, sometimes endangering patients' lives [10].

Many mechanisms may be involved in DI: chelation, complexation, formation of physical barriers, stimulation of digestive secretions, modification of gastrointestinal transit times, modification of the pH of different segments of the gastrointestinal tract, induction or inhibition of enzymes, modification of blood flow, agonistic or antagonistic physiological effects. This may explain the relatively large number of possible classifications of different types of DI [11].

Within pharmacokinetic interactions, drug interactions can also be distinguished that will induce [7]: (i) delayed absorption of the drugs; (ii) decrease in the absorption of drugs; (iii) an increase in the absorption of drugs, sometimes accompanied by an increase in the degree of absorption.

When a number of drugs were administered at the same time, an increase in the risk of drug interactions appeared. Age, malnutrition, chronic liver disease and impaired renal function are other factors that increase the risk of drug interaction [12].

Based on the knowledge of the main pharmacological effects of the drugs involved, pharmaco-dynamic interactions are relatively predictable, being caused by the direct or indirect actions of receptors, transduction and/or effector systems, transporters or enzymes [13]. However, this type of interaction is more difficult to document, compared with the pharmacokinetic interactions, which are easily demonstrated by a variation in plasma concentration [14].

On the one hand, these changes can be correlated to an acceleration of the metabolism and the transport (enzyme induction), a rapid elimination and also under-dosing. However, they can be related to a decrease in the same metabolism or transport (enzyme inhibition), the source of overdose and toxicity. In the case of orally administered drugs, the human small intestine constitutes the first barrier against the penetration of xenobiotics into the body due to its richness in cytochromes P450 (CYP), the main detoxification enzymes in the body [15].

CYP expression varies from one patient to another, elucidating the differences observed in the bioavailability of specific drugs and, consequently, their efficacy and toxicity. The human liver and the small intestine are detoxification sites preferred by xenobiotics due to their abundance of CYPs, especially CYP3A4. Those represent the main metabolic pathway of more than 60% of the currently marketed drugs, their vasculature and anatomical location, defining the first-pass effect of the drugs. The small intestine importance during drug metabolism was also confirmed by the first descriptions of interactions with certain foods or beverages that are not metabolized in the liver [11, 12].

General information on drug-food interactions

Drug bioavailability is the main fraction of the administered dose that is actually absorbed in the small intestine and that escapes the first hepatic passage. Food-drug interactions (FDI) (Figure 1) are defined as changes in bioavailability that lead to variations in concentration (pharmacokinetics), efficacy or toxicity (pharmacodynamics) of a drug through food, plant extracts, dietary supplements [16].

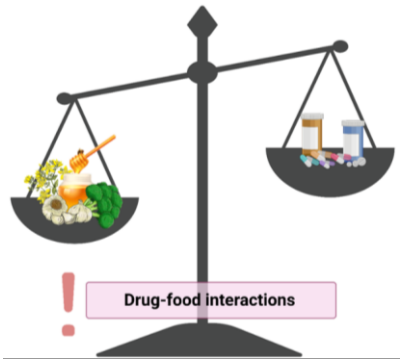

Figure 1.
Drug - food interactions. Created with BioRender

FDIs are commonly missed by physicians because the influence of mealtime on the absorption of a drug has long been neglected. This is because eating slows gastric emptying, increases the pH of the proximal small intestine, increases the hepatic blood flow, and also prolongs gastrointestinal transit time unlike fasting. Mealtime decreases plasma concentrations of isoniazid, rifampicin and ethambutol by 50%, which requires fasting and their administration at a distance from meals to preserve the effectiveness of these treatments [17]. The anticoagulant effect of antivitamin K drugs is reduced by repeated ingestion of cabbage, asparagus, lettuce, spinach, avocado or liver, that is, all foods rich in vitamin K [18]. For more than 15 years, it has been shown that certain foods can affect the pharmacokinetics of orally administered drugs by acting upon their intestinal metabolism, which remains poorly understood by prescribers. FDIs can lead to a decrease in plasma concentrations of the drug and a risk of therapeutic

failure or, conversely, to an increase in the concentrations and an increased risk of toxicity. Elderly patients with poly-medication (taking several drugs at the same time for several conditions), those with transplants, with cancer, seropositive, malnourished and those who benefit from enteral nutrition are, theoretically, the most exposed to drug-food interactions [13]. Four types of FDI (Figure 2) are usually recognized according to some specific mechanisms [19].

Type 1 "bio-inactivation *ex vivo*": the drug is rendered inactive by food due to its physicochemical properties and local intraluminal chemical reactions (hydrolysis, oxidation, neutralization, precipitation, complexation and chelation). Alendronate (etidronate), tetracyclines and didanosine, should be taken without meals because of the risk of the chelation and malabsorption. Other common medicines (ciprofloxacin, norfloxacin, avitriptan, indinavir, itraconazole syrup, levodopa, etc.) should be taken during meals. Levodopa, melphalan, perindopril, mercaptopurine also carry a risk of biochemical FDI. This type of FDI includes changes in drug ionization through food-induced physiological response, especially the secretion of the gastric acid, which can cause a decrease in the bioavailability of specific antibiotics (ampicillin, didanosine, erythromycin, azithromycin, and isoniazid). On the contrary, food (albendazole, isotretinoin, atovaquone, lovastatin, griseofulvin, tacrolimus, mefloquine, saquinavir) or gastric (itraconazole tablets) or biliary (griseofulvin, halofantrine) physiological acid secretions can increase the bioavailability of certain drugs by increasing their intestinal absorption [20].

Type 2: These are IMAs that affect intestinal absorption by at least one of the following mechanisms: altering gastric pH, intestinal transit time, drug dissolution, or by inducing or inhibiting intestinal metabolic enzymes (CYPs) or intestinal transporters. This type of FDI has been studied in particular with citrus juices, especially grapefruit juice, which will be detailed below [21].

Type 3: FDI that impairs the pharmacological effect of the drug once it has entered the systemic circulation. Examples include interactions with foods that affect the synthesis or activation of coagulation factors and may interact with some oral anticoagulants [21].

Type 4: FDIs that can affect biliary (enterohepatic cycle) or, less commonly, renal elimination of drugs. The complexity of the physiological and pathophysiological mechanisms involved in FDI, the great diversity of enteral nutrition meals or solutions, make information on the compatibility with commonly used drugs and the risk of FDI incomplete [21].

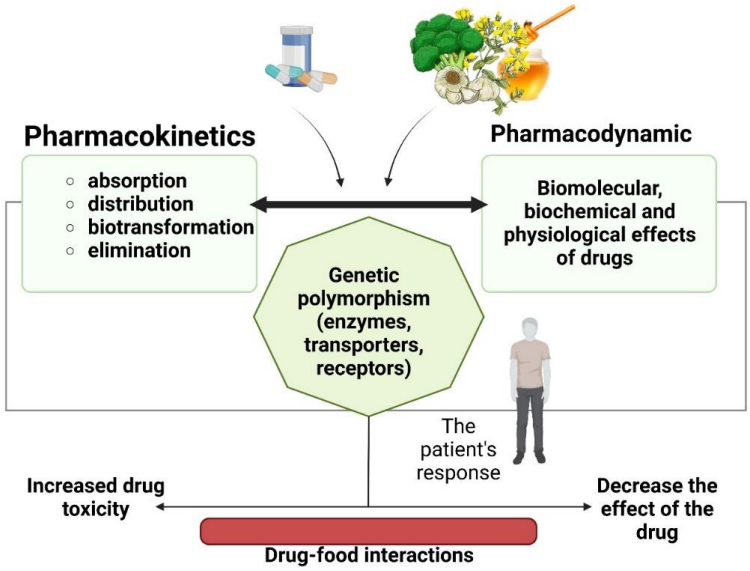

Figure 2.
IMAs can determine enzyme inhibition (increased drug toxicity) or enzyme induction (decreased drug effect). Created with BioRender

Intestinal metabolism and transport: the pathophysiological mechanism of drug-food interactions

Foods, vitamins and herbal dietary supplements or so-called "natural" products can alter the metabolism, distribution, absorption, and even elimination of the drugs through physical or physicochemical phenomena. Phenytoin, for example, bound to salts and proteins in enteral nutrition formulas, exhibits lower therapeutic efficiency [19].

First-pass intestinal effect

A main step in the first-pass effect is represented by small intestine and it constitutes a real barrier of the

diffusion of the drugs and the xenobiotics into the systemic circulation [22, 23]. Most CYPs and phase II enzymes (sulfotransferases, UDP-glucuronosyl transferases, N-acetyltransferase, glutathione-S-transferase) are transported at the mesenteric border of the small bowel [24]. The latter is principally responsible for the metabolism of various frequently used drugs, comprising verapamil, midazolam, nifedipine, amiodarone, ciclosporin, saquinavir, etc. [20,25] Associated with CYPs, efflux (which prevents xenobiotics from entering the body), influx (which favors the intestinal assimilation of drugs) or along the line separating the small intestine from the colon, bidirectional transporters are also stated. Among these, the small intestine-expressed ATP-dependent efflux pump P-glycoprotein (P-gp) serves as a barrier to the absorption of various medicines and xenobiotics [23, 26]. This enzyme and transport network, whose localisation is close to the enterocyte level and, which metabolizes most drugs via CYP3A4, are also substrates of P-gp, therefore represents a true barrier to the intestinal absorption of the pharmaceuticals and the xenobiotics, in upstream of liver, allowing, in principle, an optimal control the concentrations of plasma [27-29].

Food-drug interaction

According to a scientific analysis from 2015, food delays the absorption of NSAIDs (non-steroidal anti-inflammatory drugs) with a T max (which represent the time to reach the maximum concentration) of less than 4 hours when not eaten. The delay will be more or less important depending on the NSAID, as shown in Table I [30].

Table I

Change in T max of NSAIDs in the presence of food

Molecule	T max on uneaten (h)	T max during meal (h)
Celecoxib	2.72	3.19
Diclofenac sodium	1.83	5.12
Ibuprofen	1.34	1.96
Ketoprofan	1.89	4.76
Meloxicam	9.30	7.10
Naproxen sodium	1.30	3.20

These results coincide with those of Klueglich et al. in which food intake delayed the T. max of ibuprofen and ibuprofen lysinate by 15 and 45 minutes, respectively, compared to the T. max on a fasted basis [31].

The absorption of paracetamol, a class I analgesic, is also delayed due to slower gastric emptying [32]. Food increases the T. max of paracetamol/sodium bicarbonate tablets by 20 minutes and that of paracetamol tablets by one hour [33]. In addition, a high-calorie meal has been reported to retain paracetamol in the stomach longer compared with a low-calorie meal. As with NSAIDs, the food-drug interaction for paracetamol reduces its maximum concentration but has no effect on the drug's AUC (area under the curve) (C. max). Although there is no proof that food has a barrier impact, these effects are still being thought about [30-32].

Regarding erythromycin, it is unstable in acidic environments. The lower the pH, the higher the rate of degradation. At the gastric level, the presence of food, through its buffering effect, will slow down this degradation. But at the same time, the increase in gastric emptying time exposes erythromycin to this phenomenon for a longer period [35, 36]. Another example, this time, chlorambucil is unstable inside the gastrointestinal tract because this molecule undergoes hydrolysis in an aqueous environment. Therefore, the additional time spent in the stomach will cause the early degradation of this anticancer drug. Although it is recommended to take the drugs with food, an increase in T. max and a decrease in C. max and AUC (area under the plasma concentration-time curve) have been reported when the drug was administered on an empty stomach. Therefore, patients should be advised to take chlorambucil in an empty stomach [37, 38].

Cefpodoxime proxetil (CP) and cefuroxime axetil (CA) are two orally administered cephalosporin esters. These prodrugs were designed to improve the permeability of the active ingredient. However, by increasing their lipophilicity, their aqueous solubility was reduced, thus being classified in group IV of the BCS (Biopharmaceutical Classification System). The higher the dose of CP prescribed, the greater the benefit of taking it with a meal [39, 40].

The administration of spironolactone with breakfast increases the C. max and AUC of spironolactone by 71% and 119%, respectively, without significantly changing its T. max. The same is true for its metabolites, though to a lesser extent. A prolonged intestinal transit time at the site of absorption, the beneficial effect of the presence of bile salts, as well as a decrease in the first-pass hepatic effect has also been suggested as mechanisms involved in this food-spironolactone interaction. However, this interaction does not appear to have a clinically significant long-term impact on blood pressure and heart rate in hypertensive patients. However, Overdieck *et al*. have questioned this [41, 42].

Protein-rich meals can increase the bioavailability of metoprolol and propranolol by 40% and 50 - 80%, respectively [43]. This type of mass is known to be an important factor in increasing splanchnic and hepatic blood flow. However, as mentioned above, these two drugs have high hepatic extraction coefficients. Therefore, it is possible that their simultaneous ingestion caused saturation of the first-pass hepatic effect, which led to an increase in the bioavailability of the drugs. However, this improvement in bioavailability was not observed with extended-release drugs. According to Jauregui *et al*., only this type of mass leads to this interaction. Indeed, taking propranolol with a high-carbohydrate or low-protein meal does not increase its bioavailability [44].

Consequences and implications for drug-food interactions

The consumption of so-called "natural" products (plant extracts, dietary supplements, St. John's wort) for the medicinal purposes is increasingly common worldwide [45]. Citrus juices are also widely consumed every day. The association of dietary supplements, citrus juices or herbs with drugs may therefore be a source of FDI due to changes in intestinal metabolism and transport [43, 46]. These changes in the first-pass intestinal effect are related to chemical compounds (most often called flavonoids) contained in fruits, vegetables, herbs and other beverages [43]. The drugs and foods detailed below are clinical examples of AMI in patients, and their mechanism is often multiple.

Drug interactions with fruits, vegetables and fruit juices

The low-calorie content of fruits and vegetables, which contrasts with a high intake of vitamins and dietary fibre, makes them essential diet staples. Nevertheless, several vegetables and fruits consumed as a whole or concentrated fruits can cause FDI among which some are lethal (Figure 3). More than 20 years ago, it was discovered that certain drugs could interact with grapefruit (fruit or juice) [47]. Grapefruit is known to interact or is likely to interact with more than 85 different usual drugs, due to the latter inhibition of their intestinal metabolism, with a consequent increased in the plasma concentrations and an increased risk of serious adverse events such as tachycardia, rhabdomyolysis, myelo-toxicity, respiratory depression, gastrointestinal haemorrhage, nephrotoxicity. Among 2008 and 2012, the number of drugs with severe complications were reported when grapefruit was co-administered increased threefold [47]. Furanocoumarins (bergamottin, 6,7-dihydroxyamottin), responsible for inhibiting the intestinal metabolism of drugs by grapefruit, do not cross the intestinal barrier and form a covalent bond with CYP3A4, inhibiting its activity in an irreversible and prolonged way until the synthesis of new enzymes active (approximately 24 hours). The absence of interaction at the hepatic level explains why the observed main changes are a major increase in the concentrations of plasma, especially the plasma peak of the drugs in question, without changing the accumulation time and the half-life elimination, which mainly depend on hepatic metabolism, by the renal elimination and by the tissue distribution. All forms of grapefruit, whether whole fruit, fresh concentrated juice or frozen, can cause FDI. A whole grapefruit or 200 mL of fresh grapefruit juice is enough to cause a clinically relevant drug interaction, even endangering patients' lives [48-51].

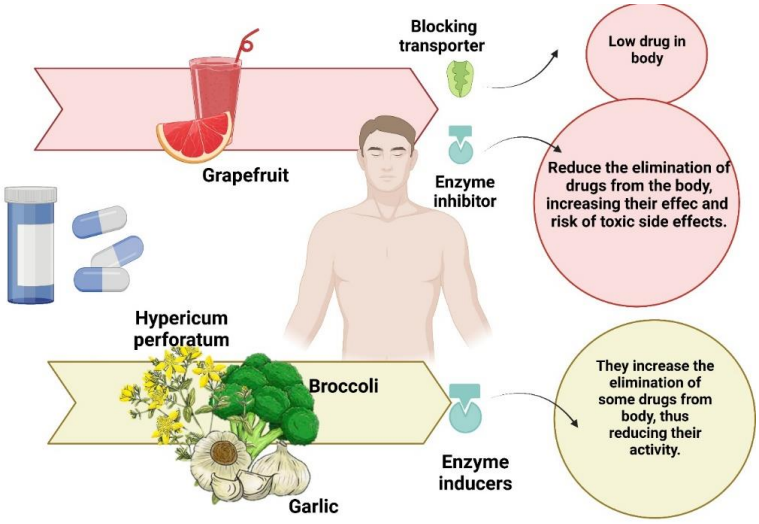

Figure 3.
The exemplification of drug – food interaction. Created with BioRender

The drugs in question which are mainly administered orally, have a low bioavailability (< 50%) due to a widespread intestinal metabolism caused by CYP3A4. The lower bioavailability is the more potentially dangerous interaction due to an increased concentration in the presence of grapefruit. Given that the drug's pharmacokinetic properties are detailed on its label, this could be anticipated by the clinician. In contrast, the amount of active CYP3A4 expressed in the intestine varies from one patient to another, but is not anticipated in practice [52]. In the presence of calcium channel blockers, a greater amount of active CYP3A4 has been observed in the gut, which caused a greater risk of interaction. When the period between the grapefruit consumption and the drug administration is less than 4 hours, the risk is high. Nevertheless, a 10-hour interval still has an interaction risk of approximately 50%, and a 24-hour interval has a 25% interaction risk [53]. If a period of three days passed between grapefruit ingestion and drug administration the risk is completely reduced, as this is the period required for a complete turnover of the CYP3A4 intestinal activity. In conclusion, patients over 45 years of age, those taking many medications (especially lipid-lowering drugs, sedatives, or cardiovascular treatments) and grapefruit consumers are most at risk of the interaction. Over the age of 70, interactions are very serious, even fatal [46].

Latest *in vitro* studies have shown that certain flavonoids (naringin, hesperidin, quercetin) contained in grapefruit, apples and oranges cause an inhibition on the activity of influx transporters expressed along the mesenteric border of enterocytes, thus inhibiting the entry of drugs and other xenobiotics into the body [54, 55].

Unlike the previously observed FDIs, the inhibition of these influx transporters by fruit juices, especially of OATPs (organic anion-transporting peptides), leads to a decrease in the plasma concentrations of drugs that are substrates of these transporters, there being a risk of loss of effectiveness. However, the number of drugs targeted by this type of FDI is small and includes fexofenadine (terfenadine analogue), not being used in France. The concentration of drugs decreases by 30 to 60% in the case of concomitant administration of orange or grapefruit juice). In the case of beta-blockers (atenolol, celiprolol, acebutolol), but also levofloxacin, ciprofloxacin, etoposide and aliskiren, drug concentrations decrease by 80% when grapefruit juice is administered simultaneously [52, 56, 57].

In contrast, not all OATP substrate drugs are affected by this type of interaction. Oral antidiabetics (glyburide, glyburide, repaglinide), as well as l-thyroxine, statins that are not metabolized by CYP3A4, and certain OATP substrates (pravastatin, rosuvastatin, fluvastatin, pitavastatin) are not affected by grapefruit, orange, or apple juice. Moreover, this type of FDI is transient; the effect of fruit juices on these transporters disappears within a few hours. Consequently, taking the drug at a distance of more than four hours after the ingestion of fruit juice will reduce the risk of interaction by more than 60% [54].

From a clinical perspective, to accurately observe a relevant drug-food interaction, large amounts (> 300 mL/day) of fruit juice must be consumed daily. FDIs involving cranberry juice seem to be correlated to the presence of flavonoids, and organic and phenolic acids that inhibit intestinal CYP2C9 and CYP3A4. To date, only 8 cases of FDI with warfarin (increased INR and bleeding) and one case with midazolam (somnolence) have been published. However, these two clinical examples of AMI occurred after consuming 250 to over 700 mL/day of cranberry juice over several consecutive days. Other drugs that may present a potential risk of FDI with cranberry juice include nonsteroidal anti-inflammatory drugs that are substrates of CYP2C9 and CYP3A4 (diclofenac, flurbiprofen), calcium channel blockers, immune-suppressants from the calcineurin inhibitor family that are substrates of CYP3A4 (cyclosporine) and certain antibiotics (amoxicillin, cefaclor) that require vigilance on the part of prescribers [58, 59].

Many other chemical compounds contained in significant amounts in apples, mangoes, guava, raspberries, garlic, broccoli, tomatoes (and tomato juice), carrots, avocados, celery have been extensively studied in vitro for their ability to modulate, at concentrations clinically relevant, the activity of many CYPs and transporters. To date, only garlic has been the main cause of drug-food interaction with anti-vitamin K drugs (increased risk of bleeding) and with antiretrovirals, causing loss of efficacy (saquinavir) [60, 61].

Interactions with other beverages

Green tea contains large amounts of polyphenols (especially catechins) that can interact with the first-pass effect of drugs. Only one case of FDI has been described to date in a 58-year-old patient with renal transplant, treated with tacrolimus, in whom tacrolimus concentrations doubled and returned to baseline after stopping green tea consumption [44].

Wine and beer are rich in polyphenols and flavonoids that can modulate intestinal activity of CYP. The only two clinically significant FDIs to date are for chlorzoxazone and cyclosporine, whose concentrations were reduced by 50% when red wine (rich in quercetin) was consumed concurrently. Because of the risk of graft rejection in patients on long-term ciclosporin treatment, such a combination should be avoided [62].

Drug interactions with herbal substances and vitamin supplements

Herbal medicines, nutritional supplements, nutrients or vitamins are commonly used globally [62-65]. More than 30% of Americans use at least one dietary supplement, one-third containing herbal medicine. One-third of Americans who take these herbal drugs and nutritional supplements also take an oral drug at the same time [66, 67]. Extracts of Gingko biloba rich in flavonoids ("ginkgolides"), recommended in the treatment of Meniere's vertigo, Alzheimer's disease or peripheral arterial disease, are mainly consumed by elderly subjects with polypathology and taking polymedication [59]. Unfortunately, the manufacturing and quality of these nutritional supplements and herbs are not controlled by any regulatory agency. Because they are sold without a prescription in supermarkets, pharmacies or over-the-counter, doctors are often unaware of their actual consumption, dosage (sometimes excessive or toxic) and timing of their use, especially in relation to the timing of drug administration, and, therefore, they cannot predict the risk of FDI or establish a causal relationship. This is particularly important in patients with multiple chronic conditions, who receive drugs with a narrow therapeutic index and who have one (or more) enzyme or transporter genetic polymorphisms involved in the first-pass effect of the drugs, the latter being rarely available and accessible in clinical practice outside therapeutic studies [61-63]. In the case of *Gingko biloba* extracts, the risk of AMI is low (except for certain drugs, due to the inhibition of platelet aggregation by "ginkgolide"), provided that daily doses below 250 mg are consumed. At higher doses (10 - 100 mg/kg/day), there may be significant inhibition of CYP3A4, CYP2C9, CYP2C19, P-gp, OATP2B1 at the intestinal level. In this article, only relevant AMIs are presented, which are probably observed in daily practice and have an impact on the life prognosis. Therefore, a distinction is needed between “potential”, *i.e.* un-proven, and “documented” interactions, illustrating for the latter that the combination should be avoided [64].

Interactions with analgesics: examples of pharmacodynamic interactions

Nonsteroidal anti-inflammatory drugs, especially aspirin, interact easily with herbal nutritional supplements with platelet-aggregating activity (ginger, Gingko biloba, garlic, ginseng, chamomile, blueberry, willow, turmeric, rose hip) or coumarin-containing supplements (fenugreek, chamomile, red clover), which conduct to an increased risk of bleeding. Paracetamol can also interact with *Gingko biloba* and all the above mentioned herbs, increasing the risk of bleeding. Its hepatotoxicity and nephrotoxicity are potentially increased in the presence of willow or echinacea, all of which are hepatotoxic. The use of valerian, kava or chamomile nutritional supplements is not recommended in combination with opioid analgesics, alcohol, barbiturates, antidepressants and antipsychotics, as there is a risk of increased drowsiness and centrally induced respiratory depression. The analgesic effect of opioids can also be inhibited by Ginseng [62, 65].

Drug interactions with St. John's wort

At the liver and gut level, St. John's wort is also a potent inducer of the enzymes CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2E1 (alcohol hydrogenase), and P-gp [66, 68]. St. John's wort has many clinically relevant AMIs that are connected to routinely used medications. When St. John's wort teas or infusions are consumed, the interaction is always associated to induction of the drug's metabolism and excretion, with a significant risk of ineffectiveness and therapeutic failure. The dose required to induce this enzyme varies. As a result, FDI becomes more severe in a dose-dependent manner [62, 64, 65].

Drug-food interactions according to the main therapeutic classes frequently used

Antiarrhythmic and antihypertensive drugs

Because of complex metabolism and variable bioavailability, the therapeutic efficacy of antiarrhythmic drugs is heterogeneous among patients. According to a recent review of the literature, plasma concentrations of antiarrhythmic drugs, with the exception of beta-blockers, increase by at least 50% with a large meal. Grapefruit significantly increases the concentrations of plasma and the toxicity risk of dronedarone, disopyramide, amiodarone, verapamil, quinidine, propafenone and felodipine by inhibiting their intestinal metabolism (CYP3A4) [69].

In practice, in the case of long-term treatment, the consumption of grapefruit or its derivatives is not recommended for these patients. On the contrary, St. John's wort significantly decreases the plasma concentrations and efficacy of antiarrhythmic drugs by inducing CYP3A4 and intestinal and hepatic P-gp [69]. Glycyrrhizin (licorice) increases the arrhythmogenic potential of digoxin because of its hypokalemic effect. A clinical study in 17 healthy volunteers showed that plasma concentrations (especially peak) of quinidine were significantly decreased by the concomitant administration of dietary salt, without changing the metabolic activity of these patients [70].

A recent review on the main FDIs with antihypertensive treatments revealed that, apart from calcium antagonists (nifedipine, amlodipine, nicardipine, felodipine, nisoldipine, barnidipine,

isradipine, verapamil, diltiazem), which are CYP3A4 substrates and hepatic P-gp, no clinically relevant drug-food interactions have been demonstrated with the other classes, except for valsartan, furosemide, and hydralazine, which must be administered on an empty stomach due to a 50% and 70% reduction in bioavailability [71].

Anticancer drugs

Over the past 20 years, the number of anticancer drugs available for oral administration has increased with the advent of tyrosine kinase inhibitors (TKIs). Fatty and dairy-rich meals delay or even decrease the intestinal absorption and the plasma concentrations of alkylating agents (chlorambucil, melphalan, busulfant), vinorelbine, antimetabolites (5-fluorouracil, methotrexate, 6-mercaptopurine), rubitecan, topotecan and certain TKIs (gefitinib, ionafamib). In addition to the physico-chemical mechanisms involved in the effect of food on the intestinal absorption of antineoplastic agent, the role of flavonoids (quercetin, kaempferol, galangin) contained in fruits (grapefruit), vegetables (onions, etc.) and beverages (wine, tea) was stated, due their modulatory character of intestinal P-gp. These flavonoids can induce or inhibit CYP3A4 and intestinal P-gp. In the case of the last example illustrated above, flavonoids can increase the absorption of the cytotoxic agent (etoposide, vinblastine). Singh et al. summarized the recommendations for the administration of the main oral cytotoxic agents according to meals. Apart from agents whose absorption is reduced by a high-fat or dairy meal, the most cytotoxic agents must be administered immediately after a meal in order to optimize their intestinal absorption and to reduce variability [72].

Drug interactions with honey

As discussed above, the simultaneous administration of some drugs with products, especially of plant origin, may increase the possibility of drug-plant product interactions. About honey, there is little discussion about the possible interactions that can occur when taking it with some drugs. Honey is a natural product obtained by bees from the nectar of flowers, honey being a rich source of glucose, fructose, minerals, vitamins, oligosaccharides, flavonoids (luteolin, pinocembrin, quercetin, kaempferol, chrysin), these polyphenols are of great interest because they have the ability to induce or inhibit cytochrome P450 (CYP) enzymes, enzymes that play a role in the metabolism of endogenous and exogenous compounds [73, 74].

Due to its complex composition and multiple benefits, honey is a household product that is frequently used especially as a sweetener, therefore the possibility of interactions that may occur in the honey-drug relationship increases considerably when concomitant administration occurs (Figure 4). The enzymes most involved in food metabolism are CYP3A4, CYP2C19 and CYP2D6. Globally, the most widely used anti-epileptics are phenytoin and carbamazepine, therefore it is of great interest to research possible interactions that may occur when taking these drugs with other natural products. Thus, in a rabbit study evaluating the effect of honey on the kinetics of carbamazepine, it was observed that treatment with honey in both single and multiple doses showed a significant decrease in the area under the curve (AUC) compared with the control group treated with saline, instead pharmacokinetic parameters such as T max, T1/2 (half-life), C max, had no notable effect compared with the control group, the results highlight that honey may decrease the bioavailability of carbamazepine [75].

In the case of phenytoin, also in a study conducted on rabbits, it was observed that honey has the ability to increase the rate and degree of its absorption, a phenomenon explained by the increase of the following parameters: T max, C max, T1/2alpha, T1/2el, AUC (0-infinity) for phenytoin. To avoid the onset of toxicity when honey and phenytoin are administered concurrently, a reduction in the dose of phenytoin can be considered [76].

The effect of honey on the plasma concentration of diltiazem after oral and intravenous administration in rabbits was also studied. The results showed a reduction in AUC and C max and an increase in the volume of distribution and clearance, suggesting that honey has the potential to decrease the plasma concentration of diltiazem after oral or i.v. administration. in rabbits [77].

These animal experiments showed that repeated doses of honey induce CYP3A4 enzyme activity [76, 77] and inhibit CYP2C9 enzyme activity [76].

In an *in vitro* study evaluating CYP2C8-mediated amodiaquine N-deacetylase activity in the presence of Tualang honey, enzyme inhibition was observed, suggesting that Tualang honey, through this inhibition, may have the potential to cause the *in vivo* interaction with drugs metabolized by CYP2C8 (paclitaxel, imatinib, repaglinide, rosiglitazone, dasabuvir, amodiaquine, cerivastatin, enzalutamide, loperamide, montelukast, pioglitazone [78, 79].

It should be kept in mind that honey is not a standardized substance and thus there is a possibility that some types of honey may have effects on drug metabolism and other types may not, until more evidence is available it would be prudent to it is considered that the administration of

honey could generate a reduced therapeutic response of drugs metabolized by CYP3A4 and increase for those metabolized by CYP2C9.

Although honey was and is often used by the population due to its exceptional therapeutic properties, its use in diabetics remains a controversial topic in modern medicine. It has been observed that honey is useful for diabetic patients because it contains fewer calories compared to sugar, also offering a varied palette of minerals (potassium, phosphorus, magnesium, iron, zinc, selenium), and vitamins (C, B2, B4, B5, B6, B11), polyphenols. Currently, the importance of carbohydrates is closely related to the value of the "glycemic index (GI)", honey has a variable content of glucose and fructose, content that is different from one type of honey to another, so acacia honey has a high concentration of fructose (lower GI), which may make honey consumption possible by diabetic patients [80].

In an attempt to answer to this controversy, a study was conducted on mice with streptozotocin-induced diabetes (STZ) where the effects of honey, metformin and their combination were analyzed over a period of five weeks. The results showed that both honey and the metformin-honey combination could prevent hyperglycemia, significantly improve glucokinase activity, and stimulate insulin secretion [81]. Another study in which tualang honey was administered concurrently with metformin or glibenclamide to STZ-induced diabetic rats was observed to have lower blood glucose levels compared with blood glucose levels obtained using glibenclamide or metformin alone. It can be suggested that a combination of honey and oral hypoglycemic agents may be a valuable adjunctive therapy to maintain glycemic control in diabetic patients. Thus, in the future it is desirable to evaluate whether the results obtained in animal studies can be extrapolated to human subjects [82].

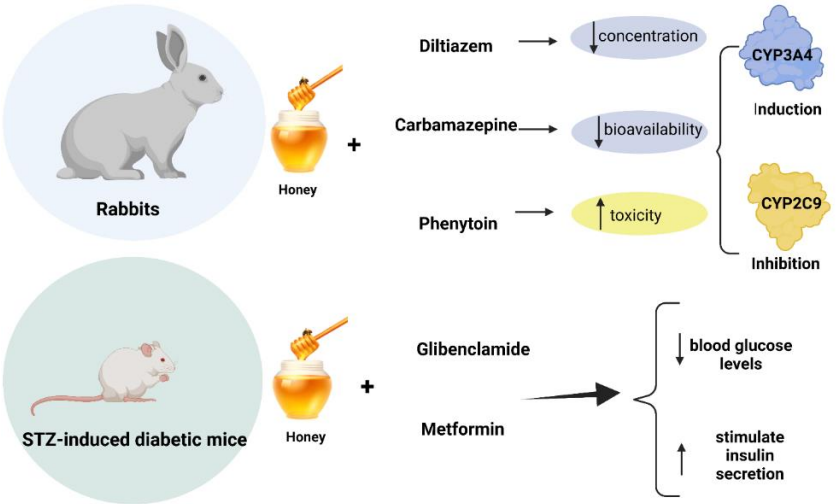

Figure 4.
Drug interactions with honey. Created with BioRender

Physiological effects related to gastrointestinal motility of food:

Gastrointestinal motility is influenced by the amount and composition of ingested food: volume, caloric content, temperature and viscosity. They determine the rate of gastric emptying, which is inversely proportional to the volume and energy content of ingested food. A sweet coffee, for example, will delay the absorption of caffeine, a hydrophilic molecule. High-calorie fats delay gastric emptying more than carbohydrates or proteins. Bioavailability will be two and a half times higher when Montelukast is taken after breakfast. Similarly, the absorption of Cefetamet-pivoxil and Cefuroxime-axetil is delayed, but their bioavailability increases from 41 to 78% if a meal is taken at the same time. This effect is due to the prolonged contact of these prodrugs with esterases of the gastric wall, during which the active substance is released [83]. The presence of food in the stomach stimulates the secretion of gastric juice and enzymes, temporarily neutralizing the pH. This results in different effects depending on the sensitivity of the drug to degradation and the action of acidity on its passage into the solution, as mentioned above (antiretrovirals, antifungals).

Bile acids increase the solubility of Halofantrine [Halfane] following micelle formation. A high-fat meal increases the bioavailability of the latter 12 times, which means increased toxicity. This antimalarial, used only in certain conditions, should therefore, under no circumstances, be taken with a high-fat meal because of the risk of potentially fatal arrhythmias (prolongation of the QT interval). Bile acids are also involved in other interactions

strongly influenced by the fat content of food, affecting fat-soluble drugs (eg, Ciclosporin).

Epithelial active transport: Drugs and foods can compete in the intestinal protein transport system. Thus, satiety effects were observed when Gabapentin was taken with protein-rich foods. Similarly, patients with Parkinson's disease should be warned of a decrease in Levodopa absorption when a large amount of protein is taken concomitantly [81].

Circadian cycle: In some cases, taking a drug at a certain time of day makes it possible to optimize its effect (chronopharmacodynamics) or influence its future in the body (chronopharmacokinetics). Indeed, various physiological parameters such as body temperature, heart rate, blood pressure, hormone levels, renal flow, gastric secretion follow a circadian rhythm. These principles are recognized for certain classes of once-daily drugs: antihypertensives, administered in the morning or antiulcer drugs, administered mainly in the evening. In the case of other classes of drugs, these principles are less justified (example: vitamins, antidepressants, etc.). Mealtimes can also influence these cycles. In all cases, a regular medication and meal schedule is desirable for consistency of effectiveness and tolerance.

Other factors such as dose and amount of food: Interactions depend on the dose administered and the amount of food in the digestive tract. Beyond a certain dose, depending on the involved mechanism, an interaction may become clinically insignificant. For example, the absorption of 700 mg (or more) Rifampicin is not influenced by food, while it is reduced at lower doses [84].

Beverages: Mildly acidic beverages (eg, Cola) enhance the poor bioavailability of Itraconazole and Ketoconazole in individuals with gastric hypochlorhydria [85].

Sustained release, delayed preparations: The release time, or even the amount released, is often influenced by both the physical properties of the medium (pH, motility) and the galenic formulation (hardness, adjuvants). In contact with food, certain forms of drugs can release their active substance too quickly ("dumping dose"), thus raising plasma levels to toxic values. This has been demonstrated with long-acting Theophylline preparations (over 24 hours), the absorption of which can fluctuate greatly depending on the substance and composition of food. In children with asthma, bioavailability has been shown to be reduced by 70% after multiple doses when the medication is taken 10 minutes after breakfast instead of before it. On the other hand, a laxative diet may accelerate transit to the point of faecal elimination before the full dose is released [85, 86].

Conclusions

This review brings to the attention of specialists involved in the process of prescribing and releasing drugs, on the possible interactions between them and the food products included in diets that can negatively affect the therapeutic efficiency of medicinal treatment.

Many times, these interactions are ignored or not given proper attention and the patient is the one who is most affected by these omissions of the specialists from the health domain. Unfortunately, in the last period, specialized literature has not considered the drug-food interactions, which has led to a secondary placement, an aspect that can often lead to the exacerbation of some adverse reactions or to a reduction of some therapeutic effects with negative consequences on the health of the patients.

Even if some natural food products are considered to have a beneficial effect on the health of consumers, it must not neglect the possible interaction with different drugs prescribed by the specialists for treating various diseases, an interaction that can sometimes seriously affect the patient's health.

During their practice, pharmacists regularly advise patients on how to administer their medications according to their main meals. The purpose of these tips is to improve the effectiveness of the treatment and/or its tolerance, as well as the patient's compliance (adherence to the treatment necessary to improve the patient's pathological condition). To this end, knowledge of food-drug interactions and their respective mechanisms is essential. Indeed, even though many medications can be taken without regard to meals, others are likely to be involved in FDI.

However, most of the time, pharmacists usually only have summary sources of information about FDI. In the "mode of administration" section of the leaflets, the time of day when the medicine must be administered with meals and/or the fact that certain foods must be avoided during treatment can be indicated. Early identification of drugs at risk of FDI during clinical use or development is essential for better dissemination of information to both clinicians and patients, and for optimizing interdisciplinary management in current internal medicine.

Acknowledgement

This research was financially supported by “Carol Davila” University of Medicine and Pharmacy Bucharest, Romania, through Contract no. CNFIS-FDI-2022-0253, funded by the Romanian Ministry of Education.

Conflict of interest

The authors declare no conflict of interest.

References

1. Sultana J, Cutroneo P, Trifirò G, Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother.*, 2013; 4(5): 73: 1-5.
2. Farcaș A, Bucșa C, Crișan A, Crișan I, Leucuța D, Mogoșan C, Knowledge, opinion and attitudes towards adverse drug reactions reporting, among pharmacy students in romania, *Farmacia*, 2021; 69 (3): 602-608.
3. Scheife RT, Hines LE, Boyce RD, Chung SP, Momper, JD, Sommer C, Abernethy DR, Horn J, Sklar SJ, Wong SK, Jones G, Brown M, Grizzle AJ, Comes S, Wilkins TL, Borst C, Wittie MA, Rich A, Malone DC, Consensus Recommendations for Systematic Evaluation of Drug - Drug Interaction Evidence for Clinical Decision Support. *Drug Safety*, 2015, 38(2): 197-206
4. Aagaard L, Hansen EH, Adverse drug reactions reported by consumers for nervous system medications in Europe 2007 to 2011. *BMC Pharmacol Toxicol.*, 2013;14: 30: 1-9.
5. Aronson JK, Ferner RE, Clarification of Terminology in Drug Safety. *Drug Safety*, 2005; 28(10)*:* 851-870.
6. Cohen KB, Hunter L, Getting Started in Text Mining. *PLoS Computational Biology*, 2008; 4(1): e20: 1-3.
7. RzhetskyA, Seringhaus M, Gerstein MB, Getting Started in Text Mining: Part Two. *PLoS Computational Biology*, 2009; 5(7): e1000411: 1-3.
8. Zawiah M, Yousef A-M, Khan AH, Al-Ashwal FY, Matar A, Alkhawaldeh B, Nassar R, Abduljabbar R, Abdo Ahmed AA, Food-drug interactions: Knowledge among pharmacists in Jordan. *PLoS ONE*, 2020; 15: e0234779: 1-12.
9. Petric Z, Žuntar I, Putnik P, Bursać Kovačević D, Food-Drug Interactions with Fruit Juices. *Foods*, 2021; 10: 33: 1-14.
10. Dresser GK, Bailey DG, A basic conceptual and practical overview of interactions with highly prescribed drugs. *Can J Clin Pharmacol.*, 2002; 9(4):191-198.
11. Segal EM, Flood MR, Mancini RS, Whiteman RT, Friedt GA, Kramer AR, Hofstetter MA, Oral Chemotherapy Food and Drug Interactions: A Comprehensive Review of the Literature. *Journal of Oncology Practice*, 2014; 10(4): e255-e268.
12. Goldberg RM; Mabee J, Chan L, Wong S, Drug-drug and drug-disease interactions in the ED: Analysis of a high-risk population. *The American Journal of Emergency Medicine*, 1996; 14(5): 447-450.
13. Allain H, Bentue-Ferrer D, Interactions médicamenteuses: Principes et mécanismes, Pharma: l'info pratique des pharmaciens d'officine. Les Editions Le Moniteur des pharmacies, 2006; 13: 55-58.
14. Barré E, Bisseux L, Chiadmi F, Toledano A, Cisternino S, Schlatter J, Champault G, Ratiney R, Fontan J-E, Interactions médicamenteuses dans une population âgée. *La Presse Médicale*, 2005; 34(12): 837-841.
15. Kaminsky LS, Fasco MJ, Small Intestinal Cytochromes P450. *Critical Reviews in Toxicology*, 1992; 21(6): 407-422.
16. Genser D, Food and Drug Interaction: Consequences for the Nutrition/Health Status. *Annals of Nutrition and Metabolism*, 2008; 52(1): 29-32.
17. Lin MY, Lin SJ, Chan SC, Lu YC, Impact of food and antiacids on the pharmaco-kinetics of anti-tuberculosis drugs: systematic review and meta-analysis. *Int J Tuberc Lung Dis.*, 2010; 14(7): 806-818
18. Butterweck V, Derendorf H, Gauz W, Nahrstedt A, Schulz V, Unger M, Pharmacokinetic Herb-Drug Interactions: Are Preventive -Screenings Necessary and Appropriate? *Planta Medica*, 2004; 70(9): 784-791.
19. Chan L-N, Drug-Nutrient Interactions *Journal of Parenteral and Enteral Nutrition*, 2013; 37(4): 450-459.
20. Schmidt LE, Dalhoff K, Food-Drug Interactions. *Drugs*, 2002; 62(10): 1481-1502
21. Lourenço R, Enteral feeding: Drug/nutrient interaction. *Clinical Nutrition*, 2001; 20(2): 187-193.
22. Thummel K, Enzyme-catalyzed processes of first-pass hepatic and intestinal drug extraction. *Advanced Drug Delivery Reviews*, 1997; 27(2-3): 99-127.
23. Hall SD, Thummel KE, Watkins PB, Lown KS, Benet LZ, Paine MF, Mayo RR, Turgeon DK, Bailey DG, Fontana RJ, Wrighton SA, Molecular and physical mechanisms of first-pass extraction. *Drug Metab Dispos.*, 1999; 27(2): 161-166.
24. Krishna DR, Klotz U, Extrahepatic Metabolism of Drugs in Humans. *Clinical Pharmacokinetics*, 1994; 26(2): 144-160.
25. Mouly S, Paine MF, *Pharmaceutical Research*, 2003; 20(10): 1595-1599.
26. Thiebaut F, Tsuruo T, Hamada H, Gottesman MM, Pastan I, Willingham MC, Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues. *Proceedings of the National Academy of Sciences*, 1987; 84(21): 7735-7738.
27. Zhang Y, Benet LZ, The Gut as a Barrier to Drug Absorption. *Clinical Pharmacokinetics*, 2001; 40(3): 159-168.
28. Watkins P, The barrier function of CYP3A4 and P-glycoprotein in the small bowel, *Advanced Drug Delivery Reviews*, 1997; 27(2-3): 161-170.
29. Neamtu M, Rusu RN, Ababeu DC, Bild W, Gavrilovici C, Stana B, Bild V, Review molecular backgrounds of individualised pharmacotherapy. *Farmacia*, 2020; 68(3): 396-405.
30. Moore RA, Derry S, Wiffen PJ, Straube S, Effects of food on pharmacokinetics of immediate release oral formulations of aspirin, dipyrone, paracetamol and NSAIDs - a systematic review. *British Journal of Clinical Pharmacology*, 2015; 80(3): 381-388.
31. Klueglich M, Ring A, Scheuerer S, Trommeshauser D, Schuijt C, Liepold B, Berndl G, Ibuprofen

Extrudate, a Novel, Rapidly Dissolving Ibuprofen Formulation: Relative Bioavailability Compared to Ibuprofen Lysinate and Regular Ibuprofen, and Food Effect on All Formulations. *The Journal of Clinical Pharmacology*, 2005; 45(9): 1055-1061.

32. Bekersky I, Dressler D, Mekki QA, Effect of Low- and High-Fat Meals on Tacrolimus Absorption following 5 mg Single Oral Doses to Healthy Human Subjects. *The Journal of Clinical Pharmacology*, 2001; 41(2): 176-182.
33. Rostami-Hodjegan A, Shiran MR, Ayesh R, Grattan TJ, Burnett I, Darby-Dowman A, Tucker GT, A New Rapidly Absorbed Paracetamol Tablet Containing Sodium Bicarbonate I A Four-Way Crossover Study to Compare the Concentration-Time Profile of Paracetamol from the New Paracetamol/Sodium Bicarbonate Tablet and a Conventional Paracetamol Tablet in Fed and Fasted Volunteers. *Drug Development and Industrial Pharmacy*, 2002; 28(5): 523-531.
34. Bartholomé R, Salden B, Vrolijk MF, Troost FJ, Masclee A, Bast A, Haenen GR, Paracetamol as a Post Prandial Marker for Gastric Emptying, A Food-Drug Interaction on Absorption. *PloS One*, 2015; 10(9): e0136618: 1-9.
35. Kim Y-H, Heinze TM, Beger R, Pothuluri JV, Cerniglia CE, A kinetic study on the degradation of erythromycin A in aqueous solution. *International Journal of Pharmaceutics*, 2004; 271(1-2): 63- 76.
36. Voigt M, Savelsberg C, Jaeger M, Identification of Pharmaceuticals in The Aquatic Environment Using HPLC-ESI-Q-TOF-MS and Elimination of Erythromycin Through Photo-Induced Degradation. *J Vis Exp.*, 2018; (138): 57434: 1-11.
37. Newell D, Calvert A, Harrap K, McElwain T, Studies on the pharmacokinetics of chlorambucil and prednimustine in man. *British Journal of Clinical Pharmacology*, 1983; 15(2): 253-258.
38. Ganta S, Sharma P, Paxton JW, Baguley BC, Garg S, Pharmacokinetics and pharmacodynamics of chlorambucil delivered in long-circulating nanoemulsion. *Journal of Drug Targeting*, 2010; 18(2): 125-133.
39. Borin MT, Driver MR, Forbes KK, Effect of Timing of Food on Absorption of Cefpodoxime Proxetil. *The Journal of Clinical Pharmacology*, 1995; 35(5): 505-509.
40. Borin MT, Forbes KK, Effect of food on absorption of cefpodoxime proxetil oral suspension in adults. *Antimicrobial Agents and Chemotherapy*, 1995; 39(1): 273-275.
41. Overdiek HWPM, Merkus FWHM, Influence of food on the bioavailability of spironolactone. *Clinical Pharmacology and Therapeutics*, 1986; 40(5): 531-536.
42. Sivakumar B, Malta D, Mak S, Dash S, Newton GE, Arcand J, Evaluating the confounding effects of medical therapies on potassium intake assessment in patients with heart failure. *Nutrition, Metabolism and Cardiovascular Diseases*, 2020; 30: 1005-1013.
43. Wisher D. Stockley's Drug Interactions. 9th ed and Stockley's Drug Interactions 2010 Pocket Companion. *J Med Libr Assoc.*, 2011; 99(2): 174-175.
44. Jáuregui-Garrido B, Jáuregui-Lobera I, Interactions between antihypertensivedrugs and food. *Nutr Hosp.*, 2012; 27(6):1866-1875.
45. Aszalos A, Role of ATP-Binding Cassette (ABC) Transporters in Interactions Between Natural Products and Drugs. *Current Drug Metabolism*, 2008; 9(10): 1010-1018.
46. Won CS, Oberlies NH, Paine MF, Mechanisms underlying food-drug interactions: Inhibition of intestinal metabolism and transport. *Pharmacol Ther.*, 2012; 136(2): 186- 201.
47. Petric Z, Žuntar I, Putnik P, Bursać Kovačević D, Food-Drug Interactions with Fruit Juices. *Foods*, 2020; 10(1): 33: 1-4.
48. Bailey DG, Malcolm J, Arnold O, David Spence J, Grapefruit juice-drug interactions. *British Journal of Clinical Pharmacology*, 2002; 46(2): 101-110.
49. Kane GC, Lipsky JJ, Drug-Grapefruit Juice Interactions. *Mayo Clinic Proceedings*, 2000; 75(9): 933-942.
50. Lohezic-Le Devehat F, Marigny K, Doucet M, Javaudin L, Jus de pamplemousse et médicaments: une association à surveiller? *Thérapie*, 2002; 57: 432-445.
51. Bailey DG, Dresser G, Arnold JMO, Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? *Canadian Medical Association Journal*, 2012; 185(4): 309-316.
52. Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD, Thummel KE, Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. *J Pharmacol Exp Ther.*, 1997; 283: 1552-1562.
53. Greenblatt D, Time course of recovery of cytochrome p450 3A function after single doses of grapefruit juice. *Clin Pharmacol Ther.*, 2003; 74(2): 121-129.
54. Dresser GK, Bailey DG, The effects of fruit juices on drug disposition: a new model for drug interactions. *European Journal of Clinical Investigation*, 2003; 33(s2): 10-16.
55. Hanley MJ, Cancalon P, Widmer WW, Greenblatt DJ, The effect of grapefruit juice on drug disposition. *Expert Opin Drug Metab Toxicol.*, 2011; 7(3): 267-286.
56. Seden K, Dickinson L, Khoo S, Back D, Grapefruit-Drug Interactions. *Drugs*, 2010; 70(18): 2373-2407.
57. Dolton MJ, Roufogalis BD, McLachlan AJ, Fruit Juices as Perpetrators of Drug Interactions: The Role of Organic Anion-Transporting Polypeptides. *Clin Pharmacol Ther.*, 2012; 92(5): 622-630.
58. Rodríguez-Fragoso L, Martínez-Arismendi JL, Orozco-Bustos D, Reyes-Esparza J, Torres E, Burchiel SW, Potential Risks Resulting from Fruit/Vegetable-Drug Interactions: Effects on Drug-Metabolizing Enzymes and Drug Transporters. *Journal of Food Science*, 2011; 76(4): R112-R124.
59. Srinivas NR, Cranberry juice ingestion and clinical drug-drug interaction potentials; review of case

studies and perspectives. *J Pharm Pharm Sci.*, 2013; 16(2): 289-303.
60. Shader RI, Foods Genetics, and Drug Interactions. *Journal of Clinical Psychopharmacology*, 2003; 23(3): 221-222.
61. Borrelli F, Capasso R, Izzo A, A Garlic (*Allium sativum* L): Adverse effects and drug interactions in humans. *Molecular Nutrition & Food Research*, 2007; 51(11): 1386-1397.
62. Abebe W, Herbal medication: potential for adverse interactions with analgesic drugs. *Journal of Clinical Pharmacy and Therapeutics*, 2002; 27(6): 391-401.
63. Boullata J, Natural Health Product Interactions with Medication. *Nutrition in Clinical Practice*, 2005; 20(1): 33-51.
64. Rogovik AL, Vohra S, Goldman RD, Safety Considerations and Potential Interactions of Vitamins: Should Vitamins Be Considered Drugs? *Annals of Pharmacotherapy*, 2009; 44(2): 311-324.
65. Hussain MS, Patient counseling about herbal-drug interactions. *Afr J Tradit Complement Altern Med.*, 2011; 8(5 Suppl): 152-163.
66. Ioniță AC, Ghica M, Moroșan E, Nicolescu F, Mititelu M, *In vitro* effects of some synthesized aminoacetanilide n'-substituted on human leukocytes separated from peripheral blood, *Farmacia*, 2019; 67(4): 684-690.
67. Mititelu M, Ghica M, Ionita AC, Moroşan E, The influence of heavy metals contamination in soil on the composition of some wild edible mushrooms. *Farmacia*, 2019; 67(3): 398-404.
68. Nowack R, Review Article: Cytochrome P450 enzyme, and transport protein mediated herb-drug interactions in renal transplant patients: Grapefruit juice, St John's Wort - and beyond! *Nephrology*, 2008; 13(4): 337-347.
69. Jauregui-Garrido B, Jauregui-Lobera I, Interactions between antiarythmic drugs and food. *Nutr Hosp.*, 2012; 27: 1399-1407.
70. Darbar D, Dell'Orto S, Mörike K, Wilkinson GR, Roden DM, Dietary salt increases first-pass elimination of oral quinidine. *Clin Pharmacol Ther.*, 1997; 61(3): 292-300.
71. Jauregui-Garrido B, Jauregui-Lobera I, Interactions between antihypertensive drugs and food. *Nutr Hosp.*, 2012; 27(6): 1866-1875.
72. Singh BN, Malhotra BK, Effects of Food on the Clinical Pharmacokinetics of Anticancer Agents. *Clinical Pharmacokinetics*, 2004; 43(15): 1127-1156.
73. Teweri T, Vinod T, Rajan S, Shashindran C, Adithan C, Effect of honey on CYP3A4, CYP2D6 and CYP2C19 enzyme activity in healthy human volunteers. *Bas Clin Pharmacol Toxicol.*, 2007; 100: 269-272.
74. Ho PC, Saville DJ, Wanwimolruk S, Inhibition of human CYP3A4 activity by grapefruit flavonoids, furanocoumarins and related compounds. *J Pharm Pharm Sci.*, 2001; 4: 217-227.
75. Koumaravelou K, Adithan C, Shashindran CH, Asad M, Abraham BK, Effect of honey on carbamazepine kinetics in rabbits. *Indian J Exp Biol.*, 2002; 40: 560-563.
76. Sukriti J, Garg SK, Influence of honey on the pharmacokinetics of phenytoin in healthy rabbits. *Methods Find Exp Clin Pharmacol.*, 2003; 25: 367-370.
77. Koumaravelou K, Adithan C, Shashindran CH, Asad M, Abraham BK, Influence of honey on orally and intravenously administered diltiazem kinetics in rabbits. *Indian J Exp Biol.*, 2002; 40: 1164-1168.
78. Muthiah YD, Ong CE, Sulaiman SA, Tan SC, Ismail R, *In-vitro* inhibitory effect of Tualang honey on cytochrome P450 2C8 activity. *J Pharm Pharmacol.*, 2012; 64(12): 1761-1769.
79. Backman JT, Filppula AM, Niemi M, Neuvonen PJ, Role of Cytochrome P450 2C8 in Drug Metabolism and Interactions. *Pharmacol Rev.*, 2016; 68(1): 168-241.
80. Meo SA, Ansari MJ, Sattar K, Chaudhary HU, Hajjar W, Alasiri S, Honey and diabetes mellitus: Obstacles and challenges - Road to be repaired. *Saudi J Biol Sci.*, 2017; 24(5): 1030-1033.
81. Mititelu M, Udeanu DI, Nedelescu M, Neacsu SM, Nicoara AC, Oprea E, Ghica M, Quality Control of Different Types of Honey and Propolis Collected from Romanian Accredited Bee-keepers and Consumer's Risk Assessment. *Crystals*, 2022; 12: 87: 1-18.
82. Erejuwa OO, Sulaiman SA, Ab Wahab MS, Sirajudeen KNS, Md Salleh S, Gurtu S, Glibenclamide or Metformin Combined with Honey Improves GlycemicM Control in Streptozotocin-Induced Diabetic Rats. *IntJBiolSci.*, 2011; 7(2): 244-252.
83. Fleisher D, Li C, Zhou Y, Pao L, Karim A, Drug, Meal and Formulation Interactions Influencing Drug Absorption After Oral Administration. *Clinical Pharmacokinetics*, 1999; 36(3): 233-254.
84. Lemmer B, Bruguerolle B, Chronopharmacokinetics. *Clinical Pharmacokinetics*, 1994; 26(6): 419-427.
85. Singh BN, Effects of Food on Clinical Pharmacokinetics. *Clinical Pharmacokinetics*, 1999; 37(3): 213-255.
86. Ioniță-Mîndrican C-B, Ziani K, Mititelu M, Oprea E, Neacșu SM, Moroșan E, Dumitrescu D-E, Roșca AC, Drăgănescu D, Negrei C, Therapeutic Benefits and Dietary Restrictions of Fiber Intake: A State of the Art Review. *Nutrients*, 2022; 14: 2641: 1-29.