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Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort?

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ABSTRACT

An interaction of drug with food, herbs, and dietary supplements is usually the consequence of a physical, chemical or physiologic relationship between a drug and a product consumed as food, nutritional supplement or over-the-counter medicinal plant. The current educational review aims at reminding to the prescribing physicians that the most clinically relevant drug-food interactions may not be strictly limited to those with grapefruit juice and with the Saint John's Wort herbal extract and may be responsible for changes in drug plasma concentrations, which in turn decrease efficacy or led to sometimes life-threatening toxicity. Common situations handled in clinical practice such as aging, concomitant medications, transplant recipients, patients with cancer, malnutrition, HIV infection and those receiving enteral or parenteral feeding may be at increased risk of drug-food or drug-herb interactions. Medications with narrow therapeutic index or potential life-threatening toxicity, e.g., the non-steroidal anti-inflammatory drugs, opioid analgesics, cardiovascular medications, warfarin, anticancer drugs and immunosuppressants may be at risk of significant drug-food interactions to occur. Despite the fact that considerable effort has been achieved to increase patient' and doctor's information and ability to anticipate their occurrence and consequences in clinical practice, a thorough and detailed health history and dietary recall are essential for identifying potential problems in order to optimize patient prescriptions and drug dosing on an individual basis as well as to increase the treatment risk/benefit ratio.

1. The clinical significance of drug–drug & drug-food interactions

Dietary substances can alter drug absorption, distribution, metabolism and/or elimination via physiologic and physicochemical mechanisms. For more than 15 years, the clinical relevance of drug–drug and drug-food interaction has been focused and limited to the modulation of drug metabolism and, to a lesser extent transport, within the cells of the liver and the proximal small intestine where the largest quantity of drug-metabolizing enzymes and transporters are located [1]. The clinical relevance of pharmacokinetic or pharmacodynamic drug–drug or drug-food interactions is questioned when enhanced toxicity and/or therapeutic failure might occur at clinically relevant dosing regimen [2]. While some drug–drug or drug-food interactions may be used to improve dosing regimen and clinical outcome (e.g., using ritonavir or grapefruit juice to increase human immunodeficiency virus (HIV) protease inhibitors bioavailability), most of them will have unpredicted and sometimes life-threatening consequences (e.g., erythromycin plus cisapride increases the risk of torsades de pointes). Age, malnutrition, malabsorption, chronic liver disease, kidney failure, polymedication, long-term drug dosing, and pharmacogenetics are well-known risk factors for drug–drug and drug-food interactions. In a study of 205 consecutive patients admitted to an emergency room, the prevalence of potential drug interactions was 13% with two drugs during long-term treatment and increased up to 82% with 7 or more [3].

There are three major categories of drug interactions: pharmacodynamics (associations of antihypertensive drugs, pain killers and anticoagulants), pharmaceutical (physicochemical incompatibility between two different drugs such as for instance the

Abbreviations: HIV, Human Immunodeficiency Virus; CYP, Cytochrome P450; TKI, tyrosine kinase inhibitor; P-gp, P-glycoprotein; OATP, Organic Anion Transporting Polypeptide; INR, International Normalized Ratio.

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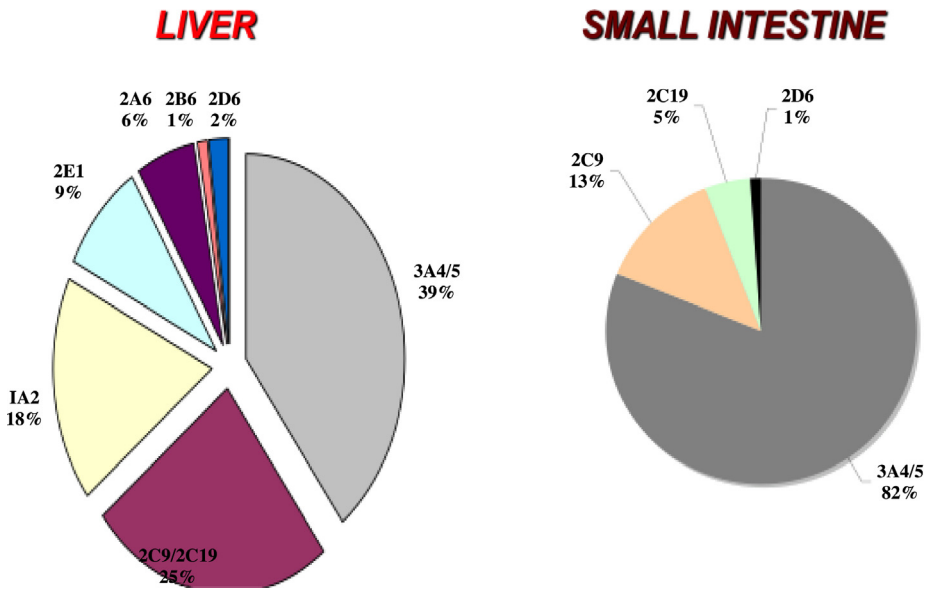

Fig. 1. Human liver and small intestinal CYP distribution [5,6].

administration of ciprofloxacin with calcium carbonate), and pharmacokinetics [4]. Drug interactions that affect a drug's absorption, distribution (or protein binding), metabolism or excretion are considered pharmacokinetic interactions. By understanding the mechanism by which drugs are normally metabolized, many pharmacokinetic drug interactions can be better understood, increasing the ability to predict and prevent potentially serious interactions.

Changes in drug systemic exposure and oral bioavailability may be related to the induction of metabolism and transport, a rapid source of elimination and underdosing or, conversely, to an inhibition leading to overdosing and toxicity. For drugs taken orally, the small intestine expresses high amounts of numerous active cytochrome P450 (CYP) isoforms and is the first step of the first-pass effect of drugs [5,6]. The expression of CYP is variable from one individual to another, explaining in part the differences in bioavailability of certain drugs. CYP3A4, the main metabolic pathway of over 60% of currently marketed drugs, represents 35% and 80% of CYPs expressed in the liver and the small intestine, respectively (Fig. 1) [5,6].

In the Western world, functional foods, health foods and food supplements deliver the necessary macro- and micronutrients to enhance health [7]. Hence, a growing number of patients are using over-the-counter products with bioactive ingredients together with prescribed medications, thus increasing the risk of serious adverse reactions due to interactions between prescribed medication and potentially bioactive compounds.

Drug-food interactions occur more often than thought. They are defined by any food, herbal medicines, or dietary supplements-induced changes in oral bioavailability leading to changes in drug concentrations that may affect efficacy and/or toxicity [8]. Despite, the critical importance of drug-food interaction clinical studies, including during the clinical phases of new drug candidate development, robust methodological guidelines for such clinical pharmacology studies are lacking in order to make definitive clinical & regulatory recommendations [9]. Indeed, examination of the effects of food consumption on the pharmacokinetics of drugs should not be limited to basic recommendations such as "take with or without food" since prescribing physicians are willing to understand the mechanisms by which food, dietary supplements and medicinal plants may alter systemic drug availability [9].

The current manuscript describes the most common drug-food interactions the prescribing physicians may encounter in primary care practice. As this review rather stands for an educational review rather than a systematic literature review and in order to better understand how food, beverages, dietary supplements or herbal medicines may interact with orally administered medications, we have tried to summarize the major mechanisms underlying these interactions.

2. Underlying mechanisms of food, herbs, micronutrients or dietary supplements effect on drug exposure & response

Underlying mechanisms by which food, herbs, micronutrients or dietary supplements exert interactions with drugs generally physiologic, physicochemical and/or biochemical processes [9]. Dietary substances can alter drug absorption, distribution, metabolism and/or excretion via physiologic and physicochemical mechanisms. Drug-food interactions have long been thought to be limited to the influence of the type or timing of meals on the absorption of a drug. Food does indeed delay gastric emptying, raise the pH of the proximal small intestine, increase hepatic blood flow and extend the time of gastrointestinal transit, in comparison with fasting [8,10]. A meal reduces by up to 70% the plasma concentrations of isoniazid, rifampicin, ethambutol, valsartan, furosemide and hydralazine, requiring fasting conditions and spacing between meals to maintain the effectiveness of these drugs [11,12]. The peak plasma concentration of quinidine was significantly decreased by concomitant salt intake, without altering the metabolic activity of 17 healthy volunteers [13]. High-fat meals decrease the intestinal absorption and plasma concentrations of alkylating agents (melphalan, chlorambucil, busulfant), antimetabolites agents (methotrexate, 5-fluorouracil, 6-mercaptopurine), vinorelbine, topotecan, rubitecan, and some tyrosine kinase inhibitors (TKIs), e.g., gefitinib and ionafamib [10]. Based on the recent recommendations published by Singh et al., the majority of cytotoxic agents must be taken with or immediately after meals, in order to optimize their intestinal absorption and reduce variability [10]. Likewise, the systemic exposure of daclatasvir, a direct acting antiviral agent recently marketed in the treatment of hepatitis C was decreased by almost 30% with a high-fat meal but this reduction was not considered clinically significant [14].

Conversely, a high-fat, high-calorie breakfast increased by 61% and up to 211% the systemic exposure of simeprevir and pari-

taprevir combined with ombitasvir, respectively, three direct acting antiviral agent recently marketed in the treatment of hepatitis C. In this regard, simeprevir and the paritaprevir/ombitasvir combination are best taken with food [14]. Sofosbuvir, another direct acting antiviral agent was not altered in the presence of high-fat meal and therefore can be taken with or without food.

For over 15 years, certain foods may have shown to affect the pharmacokinetics of drugs taken orally by acting on their intestinal metabolism and/or transport [8]. Some food products or herbal medicines can result in lower plasma drug concentrations and a risk of treatment failure due to enzyme induction, or conversely, increased concentrations and an increased risk of sometimes life-threatening toxicity due to enzyme inhibition. Patients aged over 65 years (accounting for 13–15% of the general western countries population), those aged over 85 (accounting for more than 5% of the general population), transplant, cancer, HIV-positive patients, all of whom taking up to 31 concomitant medications, some of which being issued without prescription, and those on enteral nutrition are theoretically more exposed [8,15–17]. Several pathophysiologic mechanisms may led to clinically significant drug-food interaction with routinely prescribed medications, i.e., "*ex-vivo* bio-inactivation", alteration of the gastric pH, intestinal transit time, or of the dissolution of the drug, induction or inhibition of intestinal metabolism and/or transport particularly with citrus juices or herbal medicines, and pharmacodynamics interactions that occur once the drug has entered the systemic circulation [18–20]. Examples of the latter mechanism include interaction between repeated ingestion of vitamin K-rich food (e.g., cabbage, asparagus, lettuce, spinach, avocado, liver) and vitamin K antagonists (the former typically decreasing the pharmacological activity of the latter) and interaction between Glycyrrhizin ("liquorice") and digoxin (the former increasing the pro-arrhythmogenic potential of digoxin because of its hypokaliemic effect) [8,9,18,19]. Ledipasvir, a recently released direct-acting antiviral agent used in the treatment of hepatitis C exhibited pH-dependent solubility but clinical studies showed that the systemic exposure of ledipasvir and sofosbuvir were not significantly altered by meal so ledipasvir/sofosbuvir can be taken with or without food [14].

As typical examples of "*Ex-vivo* bio-inactivation", alendronate or etidronate, didanosine and tetracyclines should not be taken soon after or before meals, due to the risk of chelation and malabsorption [19]. Tetracyclines may be chelated by calcium-enriched food products [18,19]. Phenytoin binds to salts and proteins in enteral nutrition formulations, reducing its absorption and therapeutic efficacy. Conversely, a fatty meal maximizes the bioavailability of highly lipophilic drugs such as HIV protease inhibitors [9,18–20]. Ciprofloxacin, norfloxacin, avitriptan, indinavir, itraconazole, levodopa, melphalan, perindopril, and mercaptopurine are also exposed to the risk of "*ex-vivo* bio-inactivation" by food products [19]. The food-related increase in gastric acid secretion may decrease the oral bioavailability of ampicillin, azithromycin, erythromycin and isoniazid [19]. Conversely, albendazole, atovaquone, griseofulvin, isotretinoin, lovastatin, mefloquine saquinavir, tacrolimus oral bioavailability may be increased by increased gastric acid secretion [19].

Over a 15-year period, the Netherlands Pharmacovigilance Centre Lareb received 55 reports on suspected interactive effects of food supplements or herbal medicinal products with widely prescribed drugs, 26 of which being of as yet unknown mechanism [7]. These suspected interactive effects, leading to various adverse events in terms of severity, were reported by prescribing physicians, consumers and the pharmaceutical industry based on experienced adverse reactions to medicines and vaccines. As stated by the authors of this recent report, we hypothesize that the number of interactions occurring between these health enhancing products with medications is largely underestimated, due to the spontaneous nature of their Pharmacovigilance reporting system.

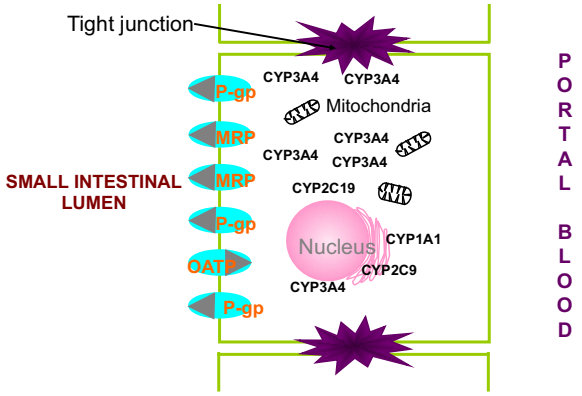

Fig. 2. Main transporters and drug metabolizing enzymes localized within the small intestinal enterocyte and involved in clinically relevant drug-food interactions (P-gp: P-glycoprotein; MRP: multidrug resistance protein; OATP: organic anion transporting peptide; CYP: cytochrome P450).

Finally, a recent analysis of 19 published human studies showed that ingestion of sulfotransferase 1A inhibitors such as coffee (including decaffeinated), tea, chocolate, bananas and citrus fruits can elicit catecholamine increases, blood pressure changes, migraine headaches, and/or atrial fibrillation in susceptible individuals [21].

3. Role of the intestinal first-pass extraction in the most clinically relevant drug-food interactions

The clinical significance of the small intestine as a barrier to drug absorption and as a site for drug–drug interactions is widely recognized [1,5,6,9]. The daily practicing physician must remain aware of the major mechanisms for drug-food interactions, among which the drug-metabolizing enzyme and transporter inhibitory or induction potential of some of the chemical compounds contained in food, herbal medicines and dietary supplements, leading to changes in the systemic exposure clearance of drugs, are paramount. Food such as citrus juices, some dietary supplements and herbal remedies or so-called "natural" products can modulate *in vitro* and *in vivo* the activity of some of the drug metabolizing enzymes and the influx and efflux transporters expressed along the brush border of enterocytes in the small intestine (Fig. 2) and may play a major role in what is currently considered so far as the most clinically relevant drug-food interactions [9].

The small intestine is a major step in the first-pass effect, and is a genuine barrier to the passage of drugs and xenobiotics into systemic circulation (Fig. 3) [9,22,23]. The majority of CYPs and phase II enzymes (uridyl-diphosphate-glucuronosyltransferase, sulfotransferase, glutathione *S*-transferase, N-acetyltransferase) are expressed at the level of the brush border of the small intestine, and are primarily responsible for the metabolism of many commonly used drugs including midazolam, verapamil, amiodarone, nifedipine, saquinavir, and ciclosporin [5,24]. Efflux (preventing the entry of xenobiotics in the body), influx (promoting the intestinal absorption of drugs) or bidirectional transporters are also expressed along the edge of the small intestine and colon, some of them being represented in Fig. 2 [9,23]. P-glycoprotein (P-gp), an energy-dependent efflux pump expressed along the small intestinal tract, provides a barrier to the absorption of many drugs and xenobiotics [25,26]. Most drugs metabolized by CYP3A4 being also substrates of P-gp, these colocalized enzymes provide an effective barrier against the intestinal absorption of drugs and xenobiotics,

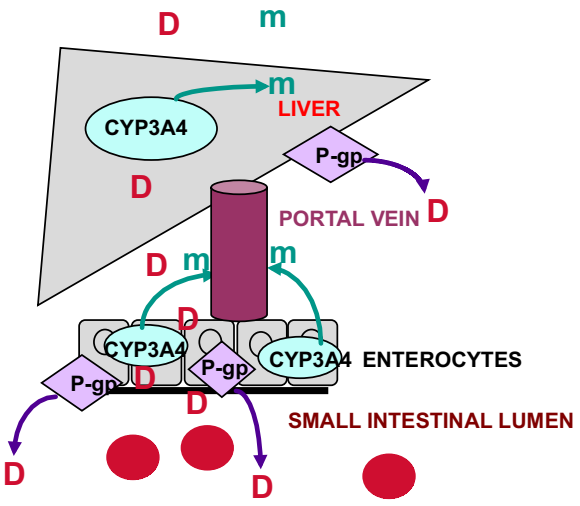

Fig. 3. Schematic representation of human combined liver & intestinal first-pass extraction of drugs [9,23] (CYP3A4: cytochrome P450 3A4; P-gp: P-glycoprotein; D: drug; m: metabolite).

upstream of the liver, which in turn allows optimal control of plasma concentrations (Fig. 3) [27–29].

The consumption of citrus juices as well as the use of so-called "natural" products (plant extracts, *Hypericum perforatum* (Saint John's Wort), and dietary supplements) for medicinal purposes is increasing worldwide and may be the source of numerous clinically relevant and sometimes life threatening drug-food interactions that are not anticipated in the routine clinical setting [30–32]. The role of several flavonoids (e.g., kaempferol, quercetin, galangin) and other chemical compounds present in fruits (e.g., grapefruit), some herbal extracts (e.g., Saint John's Wort), vegetables (onions) and drinks (tea and wine) were mentioned because of their ability to modulate intestinal CYP3A4 and/or P-gp [8].

Organic anion transporting polypeptide 1B1 (OATP1B1) is an important liver-specific uptake transporter; which mediates transport of numerous endogenous substances and drugs blood into hepatocytes [33]. Flavonoids including quercetin, rutin, chrysanthemum and mulberin, and triterpenoids including glycyrrhizic acid contained in several fruit juices and herbal medicines displayed strong inhibitory potencies of OATP1BI *in vitro*, with IC50 values comparable to blood concentrations recovered in clinical practice [33]. Whether or not these flavonoids and triterpenoids may be responsible of clinically relevant drug-food interactions in clinical practice through OATP1B1 inhibition is probably substrate specific and certainly requires further clinical investigations.

4. Interactions with fruits, vegetables, juices and other beverages

Fruits and vegetables are important food sources that are highly recommended because of their low caloric intake combined with substantial amounts of micronutrients and dietary fibre [8,15,19,32]. Furthermore, fruit juices, as well as teas, and alcoholic drinks (especially red wine) are increasingly consumed because of the pharmacologic (e.g., antioxidant) effects of specific constituents [9,34]. However, some fruits and vegetables being eaten whole or in concentrate form may cause clinically relevant drug-food interactions.

4.1. *Interactions with grapefruit* (Citrus paradise, citrus)

The interactions of some drugs with grapefruit (*Citrus paradisi, Citrus*), grapefruit juice, fruit-derived from grapefruit (Seville orange, lime, pomelo) but not orange juice were discovered more than 20 years ago [35–41]. Grapefruit juice is a complex mixture of several hundreds of ingredients including furanocoumarins (e.g., bergamottin and 6′7′ dihydroxybergamottin) and flavonoids (e.g., naringin, naringenin). Mechanisms of drug interactions involving grapefruit, grapefruit juice, Seville orange juice, and Pomelo have been extensively reviewed and published elsewhere [9,32,35–40].

More than 85 available drugs are known to or may interact with grapefruit, due to inhibition by the latter of their intestinal metabolism, consequently increasing their peak plasma concentrations and the risk of adverse events (of which more than half are serious); of these, torsades de pointes, rhabdomyolysis, bone marrow toxicity, respiratory depression, gastrointestinal bleeding, renal toxicity are widely published or reported (Table 1) [35–41]. Between 2008 and 2012, the number of drugs with which serious complications have been reported during concomitant intake of grapefruit has increased threefold [38]. A recent review of 236 articles on antihypertensive therapy has shown for instance that calcium channel blockers (nifedipine, amlodipine, nicardipine, felodipine, nisoldipine, barnidipine, isradipine, verapamil, diltiazem) may increase their oral bioavailability and risk of side effects (oedema, flush, hypotension) when taken concomitantly or shortly after grapefruit or grapefruit juice, due to CYP3A4 inhibition [12]. One case report of life-threatening interaction between amiodarone and grapefruit juice, leading to marked QT prolongation and ventricular arrhythmia has been recently published [9]. More recently, it has been suggested that grapefruit juice may increase the systemic exposure of most direct-acting antiviral agents used to treat hepatitis C (i.e., simeprevir, daclatasvir, paritaprevir, ombitasvir, dasabuvir) which are substrates of CYP3A4, although such assumption has never been confirmed by clinical studies [14]. Recent clinical studies, mostly conducted in healthy volunteers, were summarized by Won CS et al. in a recent review and showed that grapefruit juice significantly increased the systemic exposure of *S*-ketamine and tolvaptan by 185% and 73%, respectively, but not of colchicine or imatinib [9].

Oxycodone, a widely prescribed synthetic opioid receptor agonist, displays high oral bioavailability of approximately 60–87% and is mainly metabolized by CYP3A and CYP2D6 enzymes [42]. In a recent clinical study conducted in healthy volunteers, repeated ingestion of 200 ml grapefruit juice for 5 days increased the systemic exposure of oxycodone by 1.7-fold and its elimination half-life by only 1.2-fold, concomitantly decreasing the metabolic ratio by almost 50%, suggesting inhibition of CYP3A-mediated intestinal metabolism of oxycodone by grapefruit juice [42]. The extent of inhibition of CYP3A-mediated oxycodone metabolism by grapefruit juice was similar to that observed with the well-known CYP3A4 inhibitor clarithromycin in young and elderly healthy subjects, suggesting that such drug-food interaction may be relevant in clinical practice and dose reduction may be necessary in the most sensitive patients to avoid adverse effects of oxycodone [43].

Grapefruit also increases plasma concentrations and the risk of toxicity of amiodarone, quinidine, disopyramide and propafenone by inhibiting their intestinal metabolism [44]. In the case of long-term treatments, the consumption of grapefruit or its derivatives is not recommended for these patients.

All forms of grapefruit (i.e., the whole fruit, fresh fruit juice or frozen concentrate) may be responsible for drug-food interactions [35–41]. The interactions observed are not class effects but "drug-specific". As shown in Table 1, the drugs concerned are mostly taken orally and have low oral bioavailability (<50%) due to an extensive intestinal metabolism by CYP3A4. The lower the bioavailability, the higher the likelihood of the interaction to be potentially dangerous, due to the potentially significant increase in concentrations in the presence of grapefruit [35–41]. The drug production information in which the main pharmacokinetic properties are specified may

Table 1
Main drug-food interactions observed with grapefruit, Seville orange and pomelo [35–41].

Drug	Oral bioavailability (%)	Increased concentrations (%)	Clinical consequences
Calcium channel blockers	5–40	150–300	Severe hypotension, weakness, lower limb edema
Tyrosine kinase inhibitors, e.g., erlotinib, nilotinib, crisotinib, venurafenib	<30	150–250	Torsades de pointe, bone marrow suppression
Anti-infective agents (erythromycin, primaquine, halofantrine, maraviroc, rilpivirine, quinine)	30–60	>250	Torsades de pointe, bone marrow suppression
Triazolam, midazolam	30–40	150	Increased sedation
Cyclosporine, everolimus, sirolimus, tacrolimus	20	150–1000	Increased oral bioavailability[a], nephrotoxicity, bone marrow suppression
Amiodarone, apixaban, eplerenone, quinidine, rivaroxaban, ticagrelor, ivabradin	30–70	150–300	Torsades de pointe, gastrointestinal bleeding, cardiac arrythmia, hyperkalemia
Clopidogrel	<20	<20	Decreased efficacy[b]
Oxycodone, pimozide, quetiapin, alfentanil, fentanyl	30–60	>300	Increased sedation, Torsades de pointes
Buspirone, dextromethorphan, ketamine, lurasidone	<20	>500	Hallucination, dizziness, increased sedation, drowsiness
Domperidone	<30	>300	Torsades de pointes
Simvastatin, atorvastatin	5–20	600–1600	Rhabdomyolysis

[a] Grapefruit may also decrease cyclosporine inter- & intraindividual variability and eventually decrease daily dosing.
[b] Grapefruit decrease clopidogrel biotransformation into its active form and may therefore decreased its efficacy.

be helpful to the clinician to anticipate such drug-food interaction to occur. However, the amount of active CYP3A4 expressed in the intestine varies by a factor of 10 to 20 in humans and is not routinely determined [45]. It has been observed with calcium channel blockers that the higher the amount of active intestinal CYP3A4, the greater the risk of interaction [12,32].

Grapefruit, Seville orange, lime and pomelo contain furanocoumarins (bergamottin, 6′7′-dihydroxybergamottin) that strongly and irreversibly inhibit intestinal but not hepatic drug metabolism by forming a covalent bond with CYP3A4, until new active enzymes are synthesized (about 24 h), explaining why the main changes observed are a major increase in the peak plasma concentration of the drugs concerned, without alteration of the accumulation and elimination half-life, which mainly depend on hepatic metabolism, tissue distribution and renal elimination [32,39]. This risk is significant when the interval between the consumption of grapefruit and intake of the drug is less than 4 h. However, even an interval of 10 h still exhibits a risk of interaction of about 50%, while that for a 24-h interval exhibits a risk of 25% [39,46]. An interval of three days between the ingestion of grapefruit and drug intake completely offsets this risk, because this is the time required for the total renewal of intestinal CYP3A4 activity [46,47]. Finally, patients over 70 years of age, especially those concomitantly receiving multiple medications (including lipid lowering, sedative or cardiovascular treatment) and who consume grapefruit are most at risk of serious or fatal interaction [32].

4.2. *Interactions with cranberry juice (*Vaccinium macrocarpon*)*

Cranberry juice, which possesses urinary antiseptic properties, is widely consumed, especially in the United States [31,32,48,49]. Interactions involving cranberry juice appear to be related to the presence of flavonoids (quercetin, carotenoid, anthocyanin), phenolic and organic acid inhibiting intestinal CYP3A4 and CYP2C9 [32,49]. To the best of our knowledge, only 8 cases of food-drug interaction between cranberry and warfarin (increased International Normalized Ratio (INR) and occurrence of bleeding) and one case of food-drug interaction between cranberry and midazolam (drowsiness) have been published [32,49]. These case reports occurred after ingestion of up to 700 ml/day of cranberry juice over several days [49]. Drugs substrates of CYP2C9 and/or CYP3A4 displaying high potential for toxicity and side effects, such as, non steroidal anti-inflammatory (diclofenac, flurbiprofen), calcium channel blockers, calcineurin inhibitors (cyclosporine) may be at risk of interaction with cranberry juice, although clinical data are still lacking [32,49].

4.3. *Interaction with other drinks*

Apple, mango, guava, raspberry, garlic, broccoli, watercress, tomato (and tomato juice), carrot, avocado, celery also contain many flavonoids and other chemical compounds that were tested *in vitro* at clinically relevant concentrations, in order to modulate the activity of CYP and many transporters in humans. To date, only garlic is likely to significantly interact with vitamin K antagonists (increasing the risk of bleeding) and the HIV-protease inhibitor saquinavir (loss of efficacy), the latter being no longer used in clinical practice [32,50,51].

Recent *in vitro* studies have revealed that certain flavonoids (tangeretin, naringenin, quercetin, hesperidin) contained in grapefruit, apple and orange may also inhibit the activity of influx transporters expressed along the brush border of enterocytes and at the basolateral site of the hepatocyte [33,48]. Unlike interactions observed previously, the inhibition of such transporters, mainly OATP1A2, OATP1B1 & OATP2B1 causes a significant decrease in plasma concentrations of substrate drugs, e.g., the cardioselective beta-adrenergic receptor blocker celiprolol or the leukotriene receptor antagonist montelukast, with a risk of loss of efficacy (Fig. 2) [9,48]. The number of drugs involved is small, including fexofenadine (a 30–60% reduction in the event of concomitant consumption of orange or grapefruit juice), beta blockers (celiprolol, atenolol, and acebutolol), ciprofloxacin, levofloxacin, aliskiren and etoposide, the respective concentrations of which fell by 80%

during concomitant consumption of grapefruit juice [40,41,48]. However, most OATP substrates are unaffected by this type of interaction. Thus, oral antidiabetic medications (glyburide, glybenclamide, repaglinide), L-thyroxine and statins not metabolized by CYP3A4 (i.e., pravastatin, rosuvastatin, fluvastatin, pitavastatin) are unaffected by grapefruit, orange or apple juice. Moreover, these interactions are transient, as the effect of fruit juice on these carriers dissipates within a few hours, so that intake of the drug more than four hours after ingestion of the fruit juice reduces the risk of interaction by more than 60% [39–41]. In addition, large amounts of fruit juice (>300 ml/day) must be consumed daily for such interactions to be observed. Only orange juice may significantly interact with beta-blockers, fexofenadine, fluoroquinolones and the direct renin antagonist aliskiren through an inhibition of OATP1A2 and 2B1 [9]. Likewise, apple juice may decrease fexofenadine and atenolol plasma concentration and oral bioavailability by up to 70% [9].

Green tea, the most widely consumed beverage in the world second to water, contains large amounts of polyphenols (catechin in particular), which may double the trough concentration of some drugs such as tacrolimus [9]. Wine and beer are rich in flavonoids and polyphenols, known to modulate intestinal CYP activity. However, the magnitude of effect of red wine on the pharmacokinetics of CYP3A substrates may depend on both the amount and type of red wine consumed [9]. Two case reports of clinically relevant interactions characterized by a significant 50% decrease in the trough concentrations of chlorzoxazone and cyclosporine (and subsequent transplant rejection for the latter), due to concomitant consumption of red wine (which is rich in quercetin) have been reported so far, possibly because of the inducing effect of quercetin on intestinal P-gp [32,50]. Benign prostate hyperplasia is the most common disease in elderly men. A recent review aimed at assessing potential effects of consumed food, alcohol and fruit juices on the pharmacokinetics and pharmacodynamics of medications for benign prostate hyperplasia [52]. Pharmacokinetics of extended-release forms of alfusozin, tamsulosin and silodosin is well-known to be food-sensitive, especially due to their interaction with grapefruit juice and citrus juices, with an increased risk of severe adverse effects [52]. Alpha-1 adrenergic receptor antagonists are known to interact with alcohol, leading to orthostatic hypotension. Conversely, 5 alpha-reductase inhibitors (i.e., finasteride, dutasteride) may be taken regardless of meals. In this particular clinical setting, physicians should advise their patients not to drink alcohol and grapefruit citrus juices when treated with Alpha-1 adrenergic receptor antagonists [52].

Finally, although pomegranate (*Punica granatum* L.) and tomato juice were moderate CYP3A inhibitors *in vitro*, no clinically relevant drug interactions have been published with these beverages [9].

5. Drug interactions with herbal medicines, functional food including micronutrients

Herbal remedies, dietary supplements, nutrients or vitamins are freely available in supermarkets and pharmacies or from herbalists and are therefore increasingly used worldwide [53–59]. Over 30% of Americans use at least one dietary supplement, a third of which contain a medicinal plant [57]. A third of Americans who consume these herbal medicines and nutritional supplements also consume an oral treatment simultaneously [57–59]. It is a common conception that herbal preparations are devoid of side effects and safe to consume. However, several well documented herb-drug interaction clinical reports are available in literature, most of these being pharmacokinetics in nature occurring due to alteration in drug absorption and metabolism properties and are channeled through modulation of drug metabolizing enzymes (i.e., phase I and II enzymes) and/or efflux or uptake transporters [60].

Table 2
Clinically relevant drug interactions with herbal medicines and dietary supplements [53–59].

Herbal medicine & dietary supplement	Documented interaction
Ginkgo biloba	Increased bleeding risk with vitamin K antagonists, aspirin et non-steroidal anti-inflammatory drugs; decreased therapeutic efficacy of sodium valproate
Ginseng	Increased risk of hypoglycemia with oral antidiabetic agents
Saint John's Wort	Metabolizing enzyme and transporter induction with decreased efficacy of numerous medications, e.g., digoxin, ivabradin, nifedipine, talinolol, verapamil indinavir, nevirapine, theophyllin, ciclosporine, tacrolimus, oral contraceptive agents, oral anticoagulants, benzodiazepines, amytriptilin, buspirone, methadone, sertraline, phenytoin, simvastatin, atorvastatin, imatinib, irinotecan, cimetidin, omeprazole)
Aloe, Ma-huang*	Increased risk of cardiac arrhythmia with rhythm control medications due to laxative effect, *Increased risk of hypertension with monoamine oxidase inhibitors,
Salvia	Increased bleeding risk with vitamin K antagonists

5.1. Interactions with herbal medicines with special emphasis on gingko biloba, Saint John's Wort herbal extract and isoflavones

Gingko biloba extracts, rich in flavonoids ("ginkgolides") and recommended in the treatment of Alzheimer's disease, Menière's disease or peripheral arterial disease, are mainly consumed by elderly patients with multiple chronic conditions and concomitant medications [53]. Production and quality of these nutrients and herbal supplements are not necessarily controlled by any world regulatory agency [56,57]. Furthermore, doctors and patients are unaware of the potential consequences of consuming these food supplements. Information such as the actual consumption or dosage (which can at times be excessive or toxic), dosing schedule, particularly with respect to the dosing schedule of the drug, is usually unavailable during routine clinical practice [56]. Of the 55 drug-food interactions spontaneously reported to the Netherlands Pharmacovigilance Centre Lareb, Ginkgo biloba intake resulted in 6 reports of adverse drug reactions, mostly (4 out of 6) with vitamin K antagonists, through inhibition of CYP2C9 thus increasing the risk of bleeding [7].

Non-steroidal anti-inflammatory drugs, in particular aspirin, interact easily with herbal nutritional supplements possessing a platelet anti-aggregating activity (ginkgo, garlic, ginger, ginseng, bilberry, chamomile, turmeric, willow, meadowsweet) or containing coumarin (chamomile, fenugreek, red clover) due to an increased risk of bleeding. High dose (10–100 mg/kg/day) of Ginkgo biloba extracts may inhibit platelet aggregation and increase bleeding risk with aspirin and non-steroidal anti-inflammatory drugs (Table 2) [53,58,59]. Acetaminophen may also interact with ginkgo, and all the abovementioned plants by increasing the risk of bleeding [54]. Furthermore, acetaminophen hepatotoxicity and nephrotoxicity may be potentially increased in the presence of echinacea, kava or willow.

Saint John's Wort herbal extract (*Hypericum perforatum*) is a plant extract of the family Guttiferae found mainly in Central Europe and Asia, which has been used for centuries to treat insomnia and depression [59,61]. Many preclinical and clinical data indicate that hyperforin, contained in the Wort and possessing antidepressant properties, is also a powerful enzyme inducer for CYP1A2, CYP2C9, CYP2C19, CYP3A4, CYP2E1 and P-gp in the liver

and small intestine [59,61]. Many clinically relevant interactions have been reported between Saint John's Wort and commonly prescribed drugs and are summarized in Table 2 [55,59,61]. In all cases, the interaction is linked to an induction of the metabolism and accelerated elimination of the drug taken simultaneously, or in the days following the ingestion of herbal infusions containing Saint John's Wort, with a major risk of treatment inefficacy and failure [55,59,61]. This enzyme induction is dose-dependent, so that the severity of interaction observed increases with the dose. Of the 55 drug-food interactions reported to the Netherlands Pharmacovigilance Centre Lareb, 13 reports described the concomitant use of Saint John's Wort mostly with oral contraceptive, making the contraceptive less reliable, and with antidepressants increasing the risk of treatment failure or serotoninergic syndrome [7].

The success of organ transplantation is based on the administration of the optimal dose of immunosuppressive agents, such as calcineurin inhibitors (cyclosporine tacrolimus [FK506], sirolimus [rapamycin], and everolimus), which have a narrow therapeutic index [61,62]. Once issues of compliance and of the impact of genetic polymorphisms of the metabolic enzymes and transporters are eliminated, treatment failure or toxicity is usually due to drug or drug-food interactions, as all calcineurin inhibitors are mainly metabolized by the liver and small intestinal CYP3A4, and are substrates of P-gp and OATP1B1, responsible for low and variable bioavailability [61,62]. While consumption of grapefruit or its derivatives is contraindicated with these molecules, due to the risk of an increase in their plasma concentration and renal toxicity (Table 1), concomitant use of Saint John's Wort exposes patients to the risk of graft rejection risk, due to induction of their first-pass effect (Table 2, Fig. 3) [61]. Likewise, Saint John's Wort significantly decreased plasma concentrations and the efficacy of antiarrhythmic drugs by enzyme induction [44].

In a recent randomized placebo-controlled crossover study with two phases at intervals of 4 weeks and conducted in healthy volunteers, repeated ingestion of Saint John's Wort for 15 days significantly decreased oxycodone systemic exposure by 50% as well as elimination half-life by 30% together with a significant decrease in the self-reported analgesic effect of oxycodone, suggesting significant induction of liver and intestinal CYP3A-mediated N-demethylation of oxycodone by Saint-John's Wort [63]. Dose adjustments may be needed to maintain pain relief by oxycodone during Saint John's Wort use and dose reduction may be necessary when Saint John's Wort administration is finished.

Most direct-acting antiviral agents used to treat hepatitis C (i.e., simeprevir, daclatasvir, paritaprevir, ombitasvir, dasabuvir) are substrates of CYP3A4 and intestinal P-gp and may therefore be at risk of clinically significant drug-food interactions with Saint John's Wort, although such assumption has never been confirmed by clinical studies [14].

Other herbal medicines, including Aloe, Ma-huang and Salvia may increase the risk of cardiac arrhythmia when taken concomitantly with rhythm control medications and the bleeding risk when taken with vitamin K antagonists, respectively (Table 2).

Isoflavones, including genistein, daidzein and glycetein, are polyphenolic compounds found exclusively in plants, particularly Leguminosae [64]. Soybean for instance contains on average 26–120 mg genistein and 85 mg daidzein per 100 g dry weight. Isoflavones is widely found in food and dietary products, but also increasingly used as herbal preparations for therapeutic as well as preventive medicine. The metabolic pathways involved in the disposition of isoflavones is shared by many drugs commonly used in clinical practice [60]. Thus, when taken concomitantly for a long period of time with therapeutic drugs either as a component of daily diet or as herbal supplements, there is a probability that these isoflavones may alter the pharmacokinetics of coadministered medications. There is strong *in vitro* evidence that isoflavones are potent inhibitors of various CYP enzymes with IC50 for most isoflavones lying above 1 μM while the blood concentrations of free isoflavones may reach up to 0.5 μM [64]. Likewise, genistein, daidzein, biochanin A and peurarin have been shown to moderately inhibit P-gp, Multidrug Resistance Protein (MRP), Breast Cancer Related Peptide (BCRP) and the uptake Organic Anion Transporting Polypeptide (OATP) 1B1 in various *in vitro* cell culture systems [64]. Although the effects of isoflavones on drug metabolizing enzymes and transporters have been researched widely, only two clinical studies conducted in healthy volunteers have been reported determining the effects of isoflavones in humans [65,66]. Peng WX, et al. demonstrated that 200 mg bid of Daidzein for 10 days inhibited CYP1A2-mediated theophylline metabolism and in 2006, Nakajima et al. observed that abstinence of soy food considerably increased the activity of CYP2A6 and altered nicotine metabolism [65,66]. Further clinical evidence of isoflavones-drug interaction in clinical practice is warranted, as the clinical outcome of such drug-herb interaction cannot be predicted from experimental data alone.

5.2. Drug-food interactions with functional food including micronutrients

Micronutrient is a term generally used to define all essential vitamins and minerals taken from food sources and which are necessary for vital functions [67]. Micronutrients deficiencies are a very common condition affecting about 2 billion people in the world, iron, vitamin A, folate, iodine and zinc being the most frequent deficiencies. As with medicinal plants, many supplements of varied formulation are sold without prescription. The risk of interactions involving these supplements is difficult to anticipate, due to a lack of adequate quality control and prescribers' lack of awareness of the dosage consumed by patients. Currently, legislation does not fit the landscape of health enhancing products, as the wide variety of bioactive compounds is being regulated by many different rules and regulations worldwide. In Latin American scientific and regulatory communities for instance, the concept of health enhancing products has been associated with foods having health benefits beyond those of basic nutrition but is not defined officially in the emerging regulatory codes. Regulation existing in some countries, including the European Union and the United States of America is focused on safety and efficacy; both functional and health claims are allowed in terms of risk reduction provided they have scientific validation. This allowed introduction on the market of several products with health claims, some of them submitted to post-marketing surveillance. However, the risk of drug interactions with functional foods, especially in patients taking polypharmacy is not enough documented the current legislation of these bioactive products [67]. Over 300 remedies are capable of interacting with nutrient or food components, through micronutrient antagonism, induction or inhibition of micronutrient metabolism, impairment of gastrointestinal motility, damage to oral mucosa leading to impaired drug or micronutrient intestinal absorption, or increased intestinal transport. Factors that may enhance the type and intensity of drug-micronutrient interactions include patient-related variables as age, gender, comorbidities, nutritional status, and also drug- and nutrient-associated factors as route of administration, nutrient status, and pharmacological/toxicological profile of the drug. Of the 55 drug-food interactions reported to the Netherlands Pharmacovigilance Centre Lareb, interactions following multivitamin supplements consumed with drugs were reported in 6 cases, involving vitamin K antagonists (2 cases), antidepressants (2 cases), antiseizure drug (one case) and oral contraceptive (one case) [7]. Although the mechanism suspected to explain the multivitamin-vitamin K antagonist interaction is the presence of vitamin K in the multivitamin preparation, the other interactions reported remained unexplained. Finally, examples of drug interac-

Table 3
Drug-micronutrient interactions leading to changes in drug efficacy and/or toxicity [19,68].

Dietary supplements	Drug	Consequences	Recommendation
Vitamin A	Paclitaxel	Bone marrow suppression	Decrease paclitaxel dosing regimen
Vitamin B9	Phenytoin	Seizures	Avoid combination
Vitamin C	Acetazolamide	Kidney stones	Contra-indication
Vitamin D	Calcium-vitamin D	Hypercalcemia	Use with caution
Vitamin E	Warfarin	Increased bleeding risk	Avoid combination
Calcium	Digoxin	Digitalic toxicity	Avoid combination
Calcium, iron, magnesium, aluminium, zinc	D-penicillamin, tetracyclines, fluoroquinolones, risedronate, alendronate	Decreased drug plasma concentrations due to decreased intestinal absorption	Drug and dietary supplement intake should be separated by at least two hours
L-tryptophan	Fluvoxamine, paroxetine	Serotoninergic syndrome	Avoid combination
Tyramin	Isoniazid	Hypertension	Avoid combination

tion with multivitamin complex affecting the pharmacodynamic stage include the decreased effectiveness of oral contraceptives when combined with vitamin B6 or the increased efficacy of acetylsalicylic acid when taken together with vitamin E [7].

Table 3 summarizes the main clinically relevant drug interactions that may occur between some widely used oral medications and the most frequently & increasingly used food supplements including vitamins, trace elements and essential amino acids [55,56,68]. For most of these drug-micronutrient interactions, the mechanism is still unclear and controversial. Several minerals (iron, zinc, ions, calcium) contained in enteral nutrition generate a complexing phenomenon with certain drugs (tetracyclines, fluoroquinolones, antacids, levodopa), thus reducing their intestinal absorption (Table 3) [19,55,56,68]. Conversely, drug-micronutrient interactions may also led to nutrient depletion, as shown in Table 4 [67]. Whatever the mechanism involved, physicians should coordinate with nutritionists, nurses, and pharmacists in order to minimize drug-micronutrient interactions and adverse outcomes [67]. Awareness of drug interactions with common dietary agents, defined drug administration schedules, periodic review of current drug therapy and dietary habits, proper education of healthcare providers and computerizes drug interaction screening and warning software combined with patient counseling are crucial steps of such comprehensive strategy.

Of the 55 drug-food interactions reported to the Netherlands Pharmacovigilance Centre Lareb, 8 reports concerning interactions with glucosamine supplements (containing at least 1500 mg) were received, including 4 interactions with vitamin K antagonists, two with oral antidiabetic drugs and two with antiepileptic drugs [7]. The exact mechanism of such interactions is currently unknown.

6. Are enteral or parenteral nutrition at risk of clinically relevant drug interactions?

The increasing use of enteral and parenteral nutrition raises the issue of the impact of these nutritional "interventions" on the pharmacokinetics of drugs taken simultaneously [19]. The effects and clinical significance of enteral nutrition on the intestinal absorption of certain drugs are variable, mainly depending on the therapeutic index of the drug concerned, its dose-response curve, gastric emptying and the delay between enteral feeding and drug intake [19,69]. Based on the profiles and kinetics of emptying of liquid nutrients and homogenized solids, a window of 3 h between administration of the enteral feeding and any medication with particle

Table 4
Drug-micronutrient interactions involving widely used drug with possible drug-induced pathways leading to nutrient depletion [67].

Widely used drug	Proposed mechanism	Micronutrient depleted
Proton pump inhibitors & H_2 antagonists	Decreased absorption	Calcium, iron, zinc, folic acid, vitamin D, vitamin B_{12}, magnesium
Antibiotics	Decreased absorption Complex formation Chelation Enzyme induction Mucosal damage	Folic acid, vitamin A, D, K & B_1, B_2, B_3, B_6, B_{12}, iron, calcium magnesium
Anti-hypertensives	Decreased cell availability Increased renal clearance	Zinc, vitamin B_1, B_6, folic acid, coenzyme Q_{10}
Anti-convulsants	Decreased absorption, enzyme induction, chelation	Calcium, folic acid, vitamin B_1, B_2, D & K, L-carnitine
Psychotropic drugs	Enzyme induction	Folic acid, melatonin, calcium, coenzyme Q_{10}, vitamin B_2
Statins	Decreased cell availability	Coenzyme Q_{10}, vitamin D
Digoxin	Increased renal clearance	Magnesium, potassium, calcium, phosphorus, vitamin B_1
Metformin	Decreased absorption	Vitamin B_{12}
Oral Contraceptives	Decreased absorption, enzyme induction	Vitamin B_6, folic acid, magnesium
Estrogens	Decreased absorption, increased metabolism and excretion	Vitamin B_6, folic acid, magnesium
Analgesics & anti-inflammatory drugs	Decreased absorption & cell availability	Iron, folic acid, vitamin C, sodium, potassium

Table 5
Drug-food interactions involving warfarin, with respect to the respective level of evidence [58,71].

Level of evidence	Potentiation	Inhibition	No expected effect
I (high probability)	Alcohol (with no liver disease), fennel, fish oil, mango, quillingao	Enteral/parenteral feeding, sprouts, asparagus, lettuce, spinach, avocado, liver	Alcohol (with no liver disease), vitamin E
II (intermediate probability)	Danshen, Dong quai, grapefruit juice, bergamottin, eucalyptus, garlic, *Lycium barbarum*	Dietary supplements, Soya milk, Ginseng, Saint John's Wort	Ginkgo
III (low probability)	Acarbose, cranberry juice	Seaweed-based sushi	–

size <1 mm would be expected to allow a median of 80% of such medication to empty of the stomach and, hence, avoid potential drug-food interaction [69].

Intestinal absorption of phenytoin may be delayed or decreased, reducing the efficacy of this anti-seizure drug. For example, enteral nutrition formulas are incompatible with phenytoin, which can bind to proteins and salts in enteral formulations, resulting in reduced phenytoin absorption and potentially inadequate seizure control [9]. Conversely, the intestinal absorption of hydrochlorothiazide, diazepam, propranolol, griseofulvin may be increased, when simultaneously taken with enteral feeding, which in turn may increase their respective toxicity [19]. Drug interactions involving enteral nutrition also vary from one patient to another, or within the same patient, depending on age (infants, children and the elderly displaying the highest risk), position of the feeding tube in the gastrointestinal tract (due to potential gastrointestinal pH variations), composition of enteral nutrition. Enteral nutrition rich in dietary fibre (pectin, guar gum) decreases by at least 50% the intestinal absorption and efficacy of acetaminophen, glibenclamide, metformin, amoxicillin, tricyclic antidepressants, carbamazepine, cimetidine and lovastatin due to increased adsorption [19,68,70]. The concomitant ingestion of lithium and ispagula husk reduced serum lithium levels by 48% [68,70]. Conversely, taking levodopa in conjunction with an insoluble fibre-rich diet increases its plasma levels [70]. The concomitant intake of Guar gum and gemfibrozil increases its lipid-lowering effect by 95% [70]. Intestinal absorption of isoniazid, ketoconazole, sucralfate, and vitamins B1 and B12 is increased when gastroduodenal pH decreased with enteral nutrition. Conversely, increasing the pH may enhance the intestinal absorption of omeprazole, didanosine or ciprofloxacin [19]. The bioavailability of theophylline is decreased when taken with high-protein enteral feeding, and increased if taken with a diet high in lipids [19]. In case of concomitant intake of vitamin K antagonist, it is recommended to avoid enteral feeding containing more than 75 mg of vitamin K/1000 kcal, in order to prevent the risk of inefficacy [19].

In clinical practice, for any patient requiring enteral feeding and taking oral medications in the long term, it is highly recommended to stop tube feeding 2 h before and 2 h after taking medication, conduct regular monitoring of plasma concentrations especially in case of drug displaying proven dose-response or dose-toxicity relationship, to monitor any clinical event suggestive of unexpected loss of therapeutic efficacy or toxicity and to work with pharmacists to adapt the dosage form of the drug in order to make it compatible with enteral feeding [19].

Parenteral nutrition is a complex mixture of dextrose, amino acids, fat emulsion, electrolytes, vitamins and trace elements associated with many additives, each with their own physical and chemical characteristics [70]. Compatibility between parenteral nutrition and treatments administered intravenously has been demonstrated for several widely used medications including anti-ulcer drugs, cyclosporine, insulin, heparin, aminophylline, hydromorphone, vitamins A and B1, and iron dextran [70]. Conversely, parenteral feeding including a lipid emulsion may decrease the therapeutic efficacy of ampicillin, midazolam, barbiturates, dopamine, gentamicin, doxorubicin, 5-fluorouracil, acyclovir, ganciclovir, and phenytoin [70].

7. The evolving challenge of food-drug interactions with oral anticoagulants

Vitamin K antagonists continue to be the reference treatment for deep venous thrombosis, pulmonary embolism and for the prevention of arterial thromboembolic events during atrial fibrillation, provided they are taken at the dosage required to achieve the target INR sustainably [58,59,71]. They are primarily metabolized in the liver by CYP2C9, which is genetically determined, and a recent literature review of more than 180 citations identified 120 drug or drug-food interactions involving warfarin, as summarized in Table 5 with respect to their level of clinical evidence and consequences [58,71]. The frequency of drug interactions with warfarin is significantly higher than that of interactions with food, but these are rarely detected in clinical practice, which could partly explain this difference. A recent study noted that many foods, herbs and supplements are rich in vitamin K and/or derivatives of warfarin (arnica, chamomile, black radish, celery salt, fennel, wild lettuce, wild carrot) and should be consumed cautiously due to the increased risk of clot formation or bleeding, respectively [9,58]. A recent literature search identified 58 different plant species that may interact with warfarin in a clinically relevant manner, including mostly garlic (*Allium sativatum*), ginkgo (*Ginkgo biloba*), Saint John's Wort and ginseng (*Panax ginseng*), mostly described in case reports [72]. Mechanistic hypotheses were only theoretical concerning the effects of the herbal product on the coagulation processes such as platelet function (29 case reports), coagulation cascade and fibrinolysis (2 case reports) or on the pharmacokinetics of warfarin (12 case reports). Among these citations, 84% describe the potentiation of warfarin and 16% relate the inhibition of warfarin. Thus, the greatest risk that can occur due to inadequate or unsupervised use of herbs by anticoagulated patients is bleeding, which increases the morbidity, mortality, and resource use [72]. Pomegranate for instance inhibits the CYP and then warfarin metabolism and so do ginkgo, horse chestnut (*Aesculus hippocastanum*) and danshen (*Salvia miltiorrhiza*), thus increasing the bleeding risk with warfarin. Conversely, Aloe (*Aloe vera* L.), Lucerne (*Medicago sativa* L.) and Psillium (*Plantago ovata* Forssk.) decrease warfarin intestinal absorption and/or increase warfarin renal clearance, thus leading to loss of efficacy. Finally, five plants with high vitamin K contents have been identified, including green tea (*Camellia sinensis*), juniper (*Juniperus sargentii*), passion flower (*Passiflora edulis*), soybean (*Glycine max*) and vervain (*Verbena officinalis*). These plants may therefore decrease the anticoagulant effect of warfarin. In summary, warfarin pharmacotherapy can be affected in many ways by the concomitant use of herbs and can cause unpredictable changes in the degree of anticoagulation experienced by the patients [72].

For 5 years, several direct oral anticoagulants have been released in the market, including dabigatran, rivaroxaban, apixaban and more recently edoxaban [58,73,74]. Rivaroxaban, apixaban and edoxaban are primarily metabolized by intestinal and hepatic

CYP3A4 and all of these, including dabigatran, are substrates of P-gp [58,73,74]. Few drug-food interactions have been described to date, but their metabolic profile unquestionably exposes them to such a risk, especially in conjunction with grapefruit, which is likely to increase the risk of bleeding in these patients. Conversely, Saint John's Wort may decrease the effectiveness of these direct oral anticoagulants, as has been suspected with dabigatran, and the consumption of Saint John's Wort with these molecules has been strongly discouraged [58,73,74]. A fat meal has not been shown to alter new anticoagulants' oral bioavailability. However, the very recent nature of their entry into the market, the increasing use of these medications by internists, cardiologists, and anaesthesiologists and the large number of interactions observed with vitamin K antagonists over 30 years, means that caution is warranted and also the reporting of any suspicion of food interactions involving these molecules, about which much remains unknown (in particular, the influence of gastric pH changes or intestinal motility on their pharmacokinetics, all of which are parameters altered by feeding) [58]. To date, most of the studies have been organized by pharmaceutical companies. Independent research and registries will provide more information about drug-food interactions involving the new direct oral anticoagulants and may confirm that P-gp and CYP3A4 will be the main pathways where the most drug-food interactions with these medications may occur [74].

8. Conclusion and remaining challenges in establishing the clinical significance of food-drug interactions

The number of adverse events observed in patients with multiple therapy increases with the number of drugs taken simultaneously (from 50% with 5 drugs, to more than 80% with 7 or more drugs), the percentage of inappropriate treatments prescribed, the increasing use of alternative medicines, and account for more than 30% of hospitalizations after the age of 65 [15–17]. Despite that drug-food interactions are increasingly reported or suspected, especially in the elderly (partly due to physiological changes such as decreased renal function, hepatic blood flow, liver function and lean body mass or increased body fat mass and volume of distribution) and those treated concomitantly with multiple medications, yet it is barely anticipated in the routine clinical setting. Besides, their epidemiology and actual consequences is certainly underestimated and still deserve further studies. To the best of our knowledge, and based on this non exhaustive literature review, for most dietary or herbal products other than grapefruit juice, Seville orange juice or Saint John's Wort, clinical evidence remains scarce. The current review have focused on these most clinically relevant drug-food interactions being due to a significant modulation of intestinal first-pass extraction. However, a few other examples of drug-food interactions, not due to modulation of CYP3A4/P-gp activity, may still be clinically relevant and in this regard, they should be known from prescribers. Furthermore, development of more systematic methods and guidelines is needed to address the fundamental deficiency of information on examining drug-dietary substance interactions prospectively. Because many clinical studies are incomplete, flawed, and methodologically weak, a checklist of recommended questions to consider when evaluating submitted research articles or already published literature has been recently proposed [9]. Among these recommendations, the importance of designing clinical studies that reflect typical eating/drinking habits as well as the accuracy of pharmacokinetic-pharmacodynamic modeling is paramount.

Generally speaking underreporting is a reality for spontaneous reporting systems and probably the level of underreporting is even higher for herbal and food supplements because the use of these products is often unknown from prescribers or considered completely safe and unable to interact with any kind of oral medication [7]. These efforts require a better understanding of the molecular mechanisms involved in interactions between food, vitamins, herbs, micronutrients and drugs taken orally, through the use of clinical studies in humans taking individual differences and genetic background into account.

On a clinician's point of view, a thorough and detailed health history and dietary recall are essential for identifying potential problems in order to optimize patient prescriptions and drug dosing on an individual basis as well as to increase the treatment risk/benefit ratio. Besides, should a drug-food interaction being identified by primary care physicians, it should be self-reported by them to the pharmacovigilance database in order to fuel our knowledge of such underestimated drug interaction adverse event and raise the appropriate warnings for clinical decision support to improve patient care based on clinically relevant content, thus reducing alert fatigue and improving patient safety [75].

Anticipating the risk of drug interaction with food must also extend to medicinal plants, in particular through a better knowledge of the content of preparations containing commonly used plants (such as their purity and manufacturing process). The main objective should be the development of manufacturing standards and sanitary checks that ensure the safety and quality of preparations in order to render those compatible with concomitant medications [51]. Minimizing prescriptions in elderly patients whenever possible in clinical practice, as well as early identification during use or clinical development of drugs at risk of interactions with food is essential to better disseminate information to clinicians and optimize patient care.

Conflict of interest statement

Pr Stéphane Mouly has received honorarium and consulting fees from Abbott Products SAS, Alimera Sciences France, Bristol Myers Squibb, GlaxoSmithKline, Sanofi-Aventis France & Gilead Sciences. The remaining authors have no conflict of interest to declare with respect to the main topic of the current article.

References

[1] G.K. Dresser, D.G. Bailey, A basic conceptual and practical overview of interactions with highly prescribed drugs, Can. J. Clin. Pharmacol. 9 (2002) 191–198.
[2] J.H. Lin, A.Y. Lu, Inhibition and induction of cytochrome P450 and the clinical implications, Clin. Pharmacokinet. 35 (1998) 361–390.
[3] R.M. Goldberg, J. Mabee, L. Chan, S. Wong, Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population, Am. J. Emerg. Med. 14 (1996) 447–450.
[4] M. Shou, Prediction of pharmacokinetics and drug–drug interactions from *in vitro* metabolism data, Curr. Opin. Drug Discov. Dev. 8 (2005) 66–77.
[5] P.B. Watkins, Drug metabolism by cytochromes P450 in liver and small bowel, Gastrointest. Pharmacol. 21 (1992) 511–525.
[6] M.F. Paine, H.L. Hart, S.S. Ludington, R.L. Haining, A.E. Rettie, D.C. Zeldin, The human intestinal cytochrome P450 pie, Drug Metab. Dispos. 34 (2006) 880–886.
[7] A. De Boer, F. van Hunsel, A. Bast, Adverse food-drug interactions, Regul. Toxicol. Pharmacol. 73 (2015) 859–865.
[8] D. Genser, Food and drug interaction: consequences for the nutrition/health status, Ann. Nutr. Metab. 52 (Suppl. 1) (2008) 29–32.
[9] C.S. Won, N.H. Oberlies, M.F. Paine, Mechanisms underlying food-drug interactions: inhibition of intestinal metabolism and transport, Pharmacol. Ther. 136 (2012) 186–201.
[10] B.N. Singh, B.K. Malhotra, Effects of food on the clinical pharmacokinetics of anticancer agents, Clin. Pharmacokinet. 43 (2004) 1127–1156.
[11] M.Y. Lin, S.J. Lin, S.C. Chan, Y.C. Lu, Impact of food and antiacids on the pharmacokinetics of anti-tuberculosis drugs: systematic review and meta-analysis, Int. J. Tuberc. Lung Dis. 14 (2010) 806–818.
[12] B. Jauregui-Garrido, I. Jauregui-Lobera, Interactions between antihypertensive drugs and food, Nutr. Hosp. 27 (2012) 1866–1875.
[13] D. Darbar, S. Dell'Orto, K. Mörike, G.R. Wilkinson, D.M. Roden, Dietary salt increases first-pass elimination of oral quinidine, Clin. Pharmacol. Ther. 61 (1997) 292–300.
[14] S. Talavera Pons, A. Boyer, G. Lamblin, P. Chennell, F.T. Chatenet, C. Nicolas, et al., Managing drug–drug interactions with new direct-acting antiviral

agents in chronic hepatitis C, Br. J. Clin. Pharmacol. (2016), http://dx.doi.org/10.1111/bcp.13095 (Epub ahead of print).
[15] N. Ohnishi, T. Yokoyama, Interactions between medicines and functional foods or dietary supplements, Keio J. Med. 53 (2004) 137–150.
[16] R. Heuberger, Polypharmacy and food-drug interactions among older persons: a review, J. Nutr. Gerontol. Geriatr. 31 (2012) 325–403.
[17] B.J. McCabe, Prevention of food-drug interactions with special emphasis on older adults, Curr. Opin. Clin. Nutr. Metab. Care 7 (2004) 21–26.
[18] R.J. Weaver, Assessment of drug–drug interactions: concept and approaches, Xenobiotica 31 (2001) 499–508.
[19] L.E. Schmidt, K. Dalhoff, Food-drug interactions, Drugs 62 (2002) 1481–1502.
[20] L.-N. Chan, Drug-nutrient interaction in clinical nutrition, Curr. Opin. Clin. Nutr. Metab. Care 5 (2002) 327–332.
[21] K. Eagle, Toxicological effects of red wine, orange juice, and other dietary SULT1A inhibitors via excess catecholamines, Food Chem. Toxicol. 50 (2012) 2243–2249.
[22] K.E. Thummel, K.L. Kunze, D.D. Shen, Enzyme-catalyzed processes of first-pass hepatic and intestinal drug extraction, Adv. Drug Deliv. Rev. 27 (1997) 99–127.
[23] S.D. Hall, K.E. Thummel, P.B. Watkins, K.S. Lown, L.Z. Benet, M.F. Paine, et al., Molecular and physical mechanisms of first-pass extraction, Drug Metab. Dispos. 27 (1999) 161–166.
[24] D.R. Krishna, U. Klotz, Extrahepatic metabolism of drugs in humans, Clin. Pharmacokinet. 26 (1994) 144–160.
[25] S. Mouly, M.F. Paine, P-glycoprotein increases from proximal to distal regions of human small intestine, Pharm. Res. 20 (2003) 1595–1599.
[26] F. Thiebaut, T. Tsuruo, H. Hamada, M.M. Gottesman, I. Pastan, M.C. Willingham, Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues, Proc. Natl. Acad. Sci. U. S. A. 84 (1987) 7735–7738.
[27] Y. Zhang, L.Z. Benet, The gut as a barrier to drug absorption: combined role of cytochrome P450 3A and P-glycoprotein, Clin. Pharmacokinet. 40 (2001) 159–168.
[28] P.B. Watkins, Barrier function of CYP3A4 and P-glycoprotein in the small bowel, Adv. Drug Deliv. Rev. 27 (1997) 161–170.
[29] V.J. Wacher, C.Y. Wu, L.Z. Benet, Overlapping substrate specificities and tissue distribution of cytochrome P450 3A and P-glycoprotein: implications for drug delivery and activity in cancer chemotherapy, Mol. Carcinog. 13 (1995) 129–134.
[30] V. Butterweck, H. Derendorf, W. Gaus, A. Nahrstedt, A. Schulz, M. Unger, Pharmacokinetic herb-drug interactions: are preventive screenings necessary and appropriate, Planta Med. 70 (2004) 784–791.
[31] A. Aszalos, Role of ATP-binding cassette (ABC) transporters in interactions between natural products and drugs, Curr. Drug Metab. 9 (2008) 1010–1018.
[32] L. Rodriguez-Fragoso, J.L. Martinez-Arismendi, D. Orozco-Bustos, J. Reyez-Esparza, E. Torres, S.W. Burchiel, Potential risks resulting from fruit/vegetable-drug interactions: effects on drug-metabolizing enzymes and drug transporters, J. Food Sci. 76 (2011) R112–R124.
[33] M.Z. Shi, Y. Liu, J.L. Bian, M. Jin, C.S. Gui, The interaction between natural products and OATP1B1, Yao Xue Xue Bao 50 (2015) 848–853.
[34] J. Gruenwald, Novel botanical ingredients for beverages, Clin. Dermatol. 27 (2009) 210–216.
[35] D.G. Bailey, M.O. Arnold, J.D. Spence, Grapefruit juice-drug interactions, Br. J. Clin. Pharmacol. 46 (1998) 101–110.
[36] G.C. Kane, J.J. Lipsky, Drug-Grapefruit juice interactions, Mayo Clin. Proc. 75 (2000) 933–942.
[37] F. Lohezic-Le Devehat, K. Marigny, M. Doucet, L. Javaudin, Jus de pamplemousse et medicaments: une association à surveiller? Thérapie 57 (2002) 432–445.
[38] D.G. Bailey, G. Dresser, M.O. Arnold, Grapefruit-medication interactions: forbidden fruit or avoidable consequences, CMAJ 185 (2013) 309–316.
[39] G.K. Dresser, D.G. Bailey, The effects of fruit juices on drug disposition: a new model for drug interactions, Eur. J. Clin. Invest. 33 (2003) 10–16.
[40] M.J. Hanley, P. Cancalon, W.W. Widmer, D.J. Greenblatt, The effect of grapefruit juice on drug disposition, Expert Opin. Drug Metab. Toxicol. 7 (2011) 267–286.
[41] K. Seden, L. Dickinson, S. Khoo, D. Back, Grapefruit-drug interactions, Drugs 70 (2010) 2373–2407.
[42] T.H. Nieminen, N.M. Hagelberg, T.I. Saari, M. Neuvonen, P.J. Neuvonen, K. Laine, et al., Grapefruit juice enhances the exposure to oral oxycodone, Basic Clin. Pharmacol. Toxicol. 107 (2010) 782–788.
[43] A. Liukas, N.M. Hagelberg, K. Kuusniemi, P.J. Neuvonen, K.T. Olkkola, Inhibition of cytochrome P450 3A by clarithromycin uniformly affects the pharmacokinetics and pharmacodynamics of oxycodone in young and elderly volunteers, J. Clin. Psychopharmacol. 31 (2011) 302–308.
[44] B. Jauregui-Garrido, I. Jauregui-Lobera, Interactions between antiarythmic drugs and food, Nutr. Hosp. 27 (2012) 1399–1407.
[45] M.F. Paine, M. Khalighi, J.M. Fisher, D.D. Shen, K.L. Kunze, C.L. Marsh, et al., Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism, J. Pharmacol. Exp. Ther. 283 (1997) 1552–1562.
[46] D.J. Greenblatt, L.L. von Moltke, J.S. Harmatz, G. Chen, J.L. Weemhoff, C.J. Kelley, et al., Time course of recovery of cytochrome P450 3A function after single dose of grapefruit juice, Clin. Pharmacol. Ther. 74 (2003) 121–129.
[47] J.J. Lilja, K.T. Kivisto, P.J. Neuvonen, Duration of effect of grapefruit juice on the pharmacokinetics of the CYP3A4 substrate simvastatin, Clin. Pharmacol. Ther. 68 (2000) 384–390.
[48] M.J. Dolton, B.D. Roufogalis, A.J. McLachlan, Fruit juices as perpetrators of drug interactions: the role of organic anion-transporting polypeptides, Clin. Pharmacol. Ther. 92 (2012) 622–630.
[49] N.R. Srinivas, Cranberry juice ingestion and clinical drug–drug interaction potentials; review of case studies and perspectives, J. Pharm. Pharm. Sci. 16 (2013) 289–303.
[50] Shader R.I. Foods, genetics, and drug interactions, J. Clin. Psychopharmacol. 23 (2003) 221–222.
[51] F. Borrelli, R. Capasso, A.A. Izzo, Garlic (Allium savitum L.): adverse effects and drug interactions in humans, Mol. Nutr. Food Res. 51 (2007) 1386–1397.
[52] P. Pasko, T. Rodacki, R. Domagala-Rodacka, D. Owczarek, Interactions between medications employed in treating benign prostatic hyperplasia and food—a short review, Biomed. Pharmacother. 83 (2016) 1141–1145.
[53] M. Unger, Pharmacokinetic drug interactions involving *Ginkgo biloba*, Drug Metab. Rev. 56 (2013) 353–385.
[54] W. Abebe, Herbal medication: potential for adverse interactions with analgesics drugs, J. Clin. Pharm. Ther. 27 (2002) 391–401.
[55] J. Boullata, Natural health product interactions with medication, Nutr. Clin. Pract. 20 (2005) 33–51.
[56] A.L. Rogovik, S. Vohra, R.D. Goldman, Safety considerations and potential interactions of vitamins: should vitamins be considered drugs, Ann. Pharmacother. 44 (2010) 311–324.
[57] S. Hussain, Patient counseling about herbal-drug interactions, Hussain Afr. J. Tradit. Complement. Altern. Med. 8 (2011) 152–163.
[58] E. Nutescu, I. Chuatrisorn, E. Hellenbart, Drug and dietary interactions of warfarin and novel oral anticoagulants: an update, J. Thromb. Thrombolysis 31 (2011) 326–343.
[59] S.M. Vieira MdL.T. Huang, Botanical-drug interactions: a scientific perspective, Planta Med. 78 (2012) 1400–1415.
[60] A. Fugh-Berman, Herb-drug interactions, Lancet 355 (2000) 134–138.
[61] R. Nowack, 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 13 (2008) 337–347.
[62] R. Nowack, J. Andrassy, M. Fischereder, M. Unger, Effects of dietary factors on drug transport and metabolism: the impact on dosage guidelines in transplant patients, Clin. Pharmacol. Ther. 85 (2009) 439–443.
[63] T.H. Nieminen, N.M. Hagelberg, T.I. Saari, M. Neuvonen, K. Laine, P.J. Neuvonen, et al., St John's wort greatly reduces the concentrations of oral oxycodone, Eur. J. Pain 14 (2010) 854–859.
[64] I. Taneja, K.S. Rama Raju, M. Wahajuddin, Dietary isoflavones as modulators of drug metabolizing enzymes and transporters: effect on prescription medicines, Crit. Rev. Food Sci. Nutr. 56 (2016) S95–S109.
[65] W.X. Peng, H.D. Li, H.H. Zhou, Effect of daidzein on CYP1A2 activity and pharmacokinetics of theophylline in healthy volunteers, Eur. J. Clin. Pharmacol. 59 (2003) 237–241.
[66] M. Nakajima, M. Itoh, H. Yamanaka, T. Fukami, S. Tokudome, Y. Yamamoto, et al., Isoflavones inhibit nicotine C-oxidation catalyzed by human CYP2A6, J. Clin. Pharmacol. 46 (2006) 337–344.
[67] V. Karadima, C. Kraniotou, G. Bellos, G.T. Tsangaris, Drug-micronutrient interactions: food for thought and thought for action, EPMA J. 7 (2016) 1–5.
[68] J.M. Mirtallo, Complications associated with drug and nutrient interactions, J. Infus. Nurs. 27 (2004) 19–24.
[69] M. Camilleri, Drug-resin drug interactions in patients with delayed gastric emptying: what is the optimal time window for drug administration, Neurogastroenterol. Motil. 28 (2016) 1268–1271.
[70] A. Gonzales Canga, N. Fernandez Martinez, A.M. Sahagun Prieto, J.J. Garcia Vieitez, M.J. Diez Liebana, R. Diez Laiz, et al., Dietary fibers and its interaction with drugs, Nutr. Hosp. 25 (2010) 535–539.
[71] A.M. Holbrook, J.A. Pereira, R. Labiris, H. McDonald, J.D. Douketis, M. Crowther, et al., Systematic overview of warfarin and its drug and food interactions, Arch. Intern. Med. 165 (2005) 1095–1106.
[72] P.M. Leite, M.A.P. Martins, R.O. Castilho, Review on mechanisms and interactions in concomitant use of herbs and warfarin therapy, Biomed. Pharmacother. 83 (2016) 14–21.
[73] J.M. Walenga, C. Adiguzel, Drug and diatery interactions of the new and emerging oral anticoagulants, Int. J. Clin. Pract. 64 (2010) 956–967.
[74] C. Voukalis, G.Y. Lip, E. Shantsila, Drug-drug interactions of non-vitamin K oral anticoagulants, Expert Opin. Drug Metab. 18 (August) (2016) (Epub ahead of print).
[75] H. Tilson, L.E. Hines, G. McEvoy, D.M. Weinstein, P.D. Hansten, K. Matuszewski, et al., Recommendations for selecting drug–drug interactions for clinical decision support, Am. J. Health. Syst. Pharm. 73 (2016) 576–585.