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Fruit/Vegetable-Drug Interactions: Effects on Drug Metabolizing Enzymes and Drug Transporters

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1. Introduction

Dietary habits are an important modifiable environmental factor influencing human health and disease. Epidemiologic evidence suggests that regular consumption of fruits and vegetables may reduce risk of some diseases, including cancer [1]. These properties have been attributed to foods that are rich sources of numerous bioactive compounds such as phytochemicals [2]. Modifying the intake of specific foods and/or their bioactive components seems to be a prudent, noninvasive, and cost-effective strategy for preventing some diseases in people who appear to be “healthy” [3]. As will be discussed in this chapter, potential problems occur when patients taking medicines regularly also consume certain fruits or vegetables.

Thousands of drugs are commercially available and a great percentage of the population takes at least one pharmacologically active agent on a regular basis. Given this magnitude of use and variability in individual nutritional status, dietary habits and food composition, there is a high potential for drug-nutrient interactions. However, there is a relatively short list of documented fruit-drug or vegetable-drug interactions, necessitating further and extensive clinical evaluation. Healthcare providers, such as physicians, pharmacists, nurses, and dietitians, have to be aware of important food-drug interactions in order to optimize the therapeutic efficacy of prescribed and over-the-counter drugs. Here, we review some of the most widely consumed fruits and vegetables to inform healthcare providers of possible nutrient-drug interactions and their potential clinical significance.

There are numerous patients who encounter increased risks of adverse events associated with drug-nutrient interactions. These include elderly patients, patients with cancer and/ or

malnutrition, gastrointestinal tract dysfunctions, acquired immunodeficiency syndrome and chronic diseases that require the use of multiple drugs, as well as those receiving enteral nutrition or transplants. Therefore, the main reason for devoting a major review to nutrient-drug interactions is the enormous importance of fruits and vegetables used for their beneficial effects as nutrients and as components in folk medicine. There are currently few studies that combine a nutrient-based and detailed pharmacological approach [4], or studies that systematically explore the risk and benefits of fruit and vegetables [5-7].

2. Food-drug interactions

A drug-nutrient interaction is defined as the result of a physical, chemical, physiological, or pathophysiological relationship between a drug and a nutrient [8,9]. An interaction is considered significant from a clinical perspective if it alters the therapeutic response. Food-drug interactions can result in two main clinical effects: the decreased bioavailability of a drug, which predisposes to treatment failure, or an increased bioavailability, which increases the risk of adverse events and may even precipitate toxicities (See Figure 1) [4, 10,11].

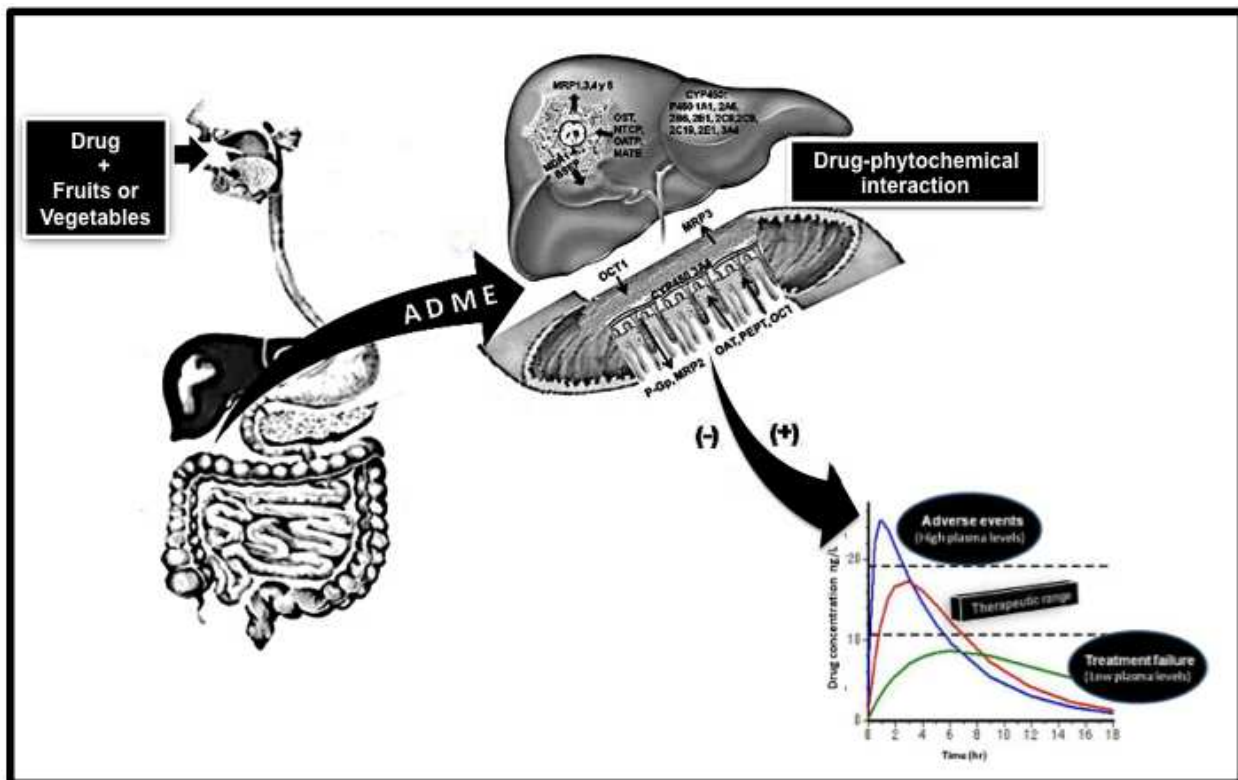


Figure 1. Drug-fruit/vegetable interaction and effects on bioavailability of drugs. During the consumption of drugs with fruits or vegetables the **ADME** properties of drug (**A**bsorption, **D**istribution, **M**etabolism and **E**xcretion) can be modified by drug-phytochemical interaction. As a result of this interaction can be increased or decreased plasma concentrations of a drug which can lead to the presence of adverse events or treatment failure.

Nutritional status and diet can affect drug action by altering metabolism and function. In addition, various dietary components can have pharmacological activity under certain circumstances [12]. For healthy-treatment intervention, it is necessary to understand how these drug-food interactions can induce a beneficial result or lead to detrimental therapeutic conditions (less therapeutic action or more toxicity). Drug-drug interactions are widely recognized and evaluated as part of the drug-approval process, whether pharmaceutical, pharmacokinetic, or pharmacodynamic in nature. Equal attention must be paid to food-drug interactions (Figure 2).

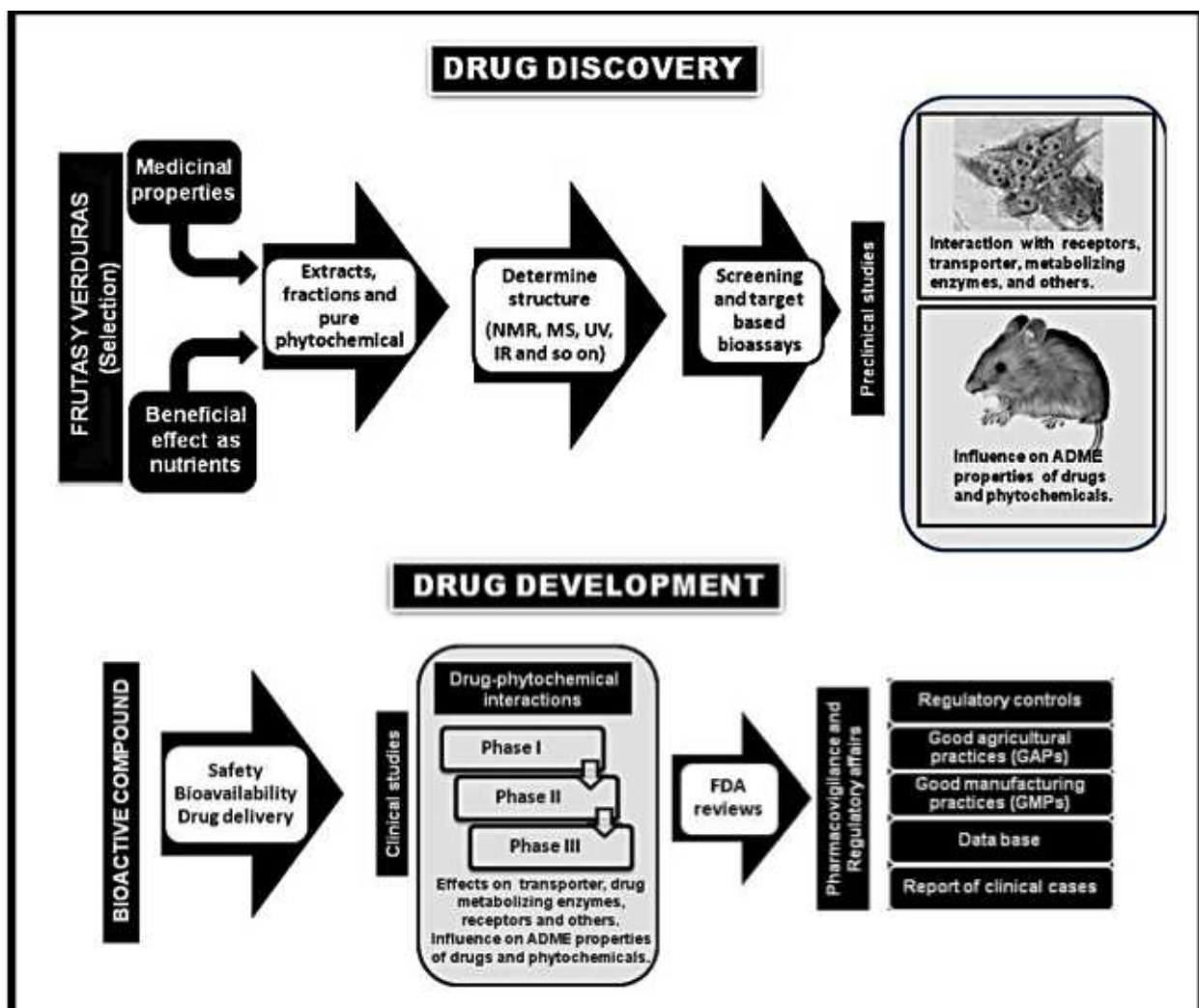


Figure 2. Bioassay models for studying drug-phytochemical interaction.

There are four types of accepted drug-food interactions based on their nature and mechanisms.

- Type I are *ex vivo* bioinactivations, which refer to interactions between the drug and the nutritional element or formulation through biochemical or physical reactions, such as hydrolysis, oxidation, neutralization, precipitation or complexation. These interactions usually occur in the delivery device.
- Type II interactions affect absorption. They cause either an increase or decrease in the oral bioavailability of a drug. The precipitant agent may modify the function of enzymes or transport mechanisms that are responsible for biotransformation.
- Type III interactions affect the systemic or physiologic disposition and occur after the drug or the nutritional element has been absorbed from the gastrointestinal tract and entered the systemic circulation. Changes in the cellular or tissue distribution, systemic transport, or penetration to specific organs or tissues can occur.
- Type IV interactions refer to the elimination or clearance of drugs or nutrients, which may involve the antagonism, impairment or modulation of renal and/or enterohepatic elimination [13].

Drug metabolizing enzymes and drug transporters play important roles in modulating drug absorption, distribution, metabolism, and elimination. Acting alone or in concert with each other, they can affect the pharmacokinetics and pharmacodynamics of a drug. The interplay between drug metabolizing enzymes and transporters is one of the confounding factors that have been recently shown to contribute to potential complex drug interactions [14].

3. Food and drug transporters

The oral administration of drugs to patients is convenient, practical, and preferred for many reasons. Oral administration of drugs, however, may lead to limited and variable oral bioavailability because of absorption across the intestinal barrier [15,16]. Drug absorption across the gastrointestinal tract is highly dependent on affinity for membrane transporters as well as lipophilicity [17]. On the other hand, the liver plays a key role in the clearance and excretion of many drugs. Hepatic transporters are membrane proteins that primarily facilitate nutrient and endogenous substrate transport into the cell via uptake transporters, or protect the cell by pumping out toxic chemicals via canalicular transporters [18]. Consequently, drug transporters in both the gut and the liver are important in determining oral drug disposition by controlling absorption and bioavailability [19].

The major uptake transporters responsible for nutrient and xenobiotic transport, both uptake and efflux transporters, belong to the two solute carrier (SLC and SLCO) superfamilies [20]. The SLC superfamily encompasses a variety of transporters, including the organic anion transporters (OAT, SLC22A), the organic cation transporters (OCT, SLC22A), the electroneutral organic cation transporters (OCTN, SLC22A), the equilibrative nucleoside trans-

porters (ENT, SLC29), the concentrative nucleoside transporters (CNT, SLC28), the apical Na⁺-dependent bile salt transporter (ASBT, SLC10), the monocarboxylate transporters (MCT, SLC16), and the peptide transporters (PEPT, SLC15) [21]. The SLCO family is made up of the organic anion transporting polypeptides (OATP) [22]. Efflux transporters expressed in the intestine and liver include P-glycoprotein (Pgp, ABCB1), bile salt export pump (BSEP, ABCB11), multidrug resistance proteins (MRP1-6, ABCC1-6), and breast cancer resistance protein (BCRP, ABCG2), all members of the ATP-Binding Cassette superfamily (ABC transporters) [23]. Members of this superfamily use ATP as an energy source, allowing them to pump substrates against a concentration gradient. In the liver, uptake transporters are mainly expressed in the sinusoid, and excretion transporters are mainly expressed on the lateral and canalicular membranes. There are transporters on the lateral membrane the primary function of which is pumping drugs back into the blood circulation from the hepatocytes. Nowadays, a large amount of work has identified and characterized intestinal and hepatic transporters in regards to tissue expression profiles, regulation, mechanisms of transport, substrate and inhibitor profiles, species differences, and genetic polymorphisms. Given the circumstances outlined above, there is no doubt of the overall relevance of drug transport for clinical pharmacokinetics.

Until recently, little regard was given to the possibility that food and food components could cause significant changes to the extent of drug absorption via effects on intestinal and liver transporters. It is now well known that drug-food interactions might affect the pharmacokinetics of prescribed drugs when co-administered with food [24]. Common foods, such as fruits and vegetables, contain a large variety of secondary metabolites known as phytochemicals (Table 1), many of which have been associated with health benefits [25]. However, we know little about the processes through which these phytochemicals (and/or their metabolites) are absorbed into the body, reach their biological target, and are eliminated. Recent studies show that some of these phytochemicals are substrates and modulators of specific members of the superfamily of ABC transporting proteins [26]. Indeed, *in vitro* and preclinical data in rats suggest that a variety of foodstuffs [27,28], including herbal teas [29,30] and vegetables and herbs [31,32] can modulate the activity of drug transporters. It is not yet known whether these effects are predictive of what will be observed clinically.

4. Foods and drug-metabolizing enzyme

It has been shown that, before reaching the systemic circulation, the metabolism of orally ingested drugs ('first-pass metabolism' or 'presystemic clearance') has clinically relevant influences on the potency and efficacy of drugs. Both the intestine and liver account for the presystemic metabolism in humans. Drug metabolism reactions are generally grouped into 2 phases. Phase I reactions involve changes such as oxidation, reduction, and hydrolysis and are primarily mediated by the cytochrome P450 (CYP) family of enzymes. Phase II reactions use an endogenous compound such as glucuronic acid, glutathione, or sulfate, to conjugate with the drug or its phase I-derived metabolite to produce a more polar end product that can be more readily excreted [33].

The CYP enzymes involved in drug metabolism in humans are expressed predominantly in the liver. However, they are also present in the large and small intestine, lungs and brain [34]. CYP proteins are categorized into families and subfamilies and can metabolize almost any organic xenobiotic [35]. CYP enzymes combined with drug transport proteins constitute the first-pass effect of orally administered drugs [33]. On the other hand, the Phase II drug metabolizing or conjugating enzymes consist of many enzyme superfamilies, including sulfotransferases (SULT), UDP-glucuronosyltransferases (UGT), DT-dia-phorase or NAD(P)H:quinone oxidoreductase (NQO) or NAD(P)H: menadione reductase (NMO), epoxide hydrolases (EPH), glutathione S-transferases (GST) and *N*-acetyltransferases (NAT). The conjugation reactions by Phase II drug-metabolizing enzymes increase hydrophilicity and thereby enhance excretion in the bile and/or the urine and consequently affect detoxification [36].

The metabolism of a drug can be altered by foreign chemicals and such interactions can often be clinically significant [37]. The most common form of drug interactions entail a foreign chemical acting either as an inhibitor or an inducer of the CYP enzyme isoform responsible for metabolizing an administered medicinal drug, subsequently leading to an unusually slow or fast clearance of said drug [38,39]. Inhibition of drug metabolism will result in a concentration elevation in tissues, leading to various adverse reactions, particularly for drugs with a low therapeutic index.

Often, influence on drug metabolism by compounds that occur in the environment, most remarkably foodstuffs, is bypassed. Dietary changes can alter the expression and activity of hepatic drug metabolizing enzymes. Although this can lead to alterations in the systemic elimination kinetics of drugs metabolized by these enzymes, the magnitude of the change is generally small [8, 40]. Metabolic food-drug interactions occur when a certain food alters the activity of a drug-metabolizing enzyme, leading to a modulation of the pharmacokinetics of drugs metabolized by the enzyme [12]. Foods, such as fruits, vegetables, alcoholic beverages, teas, and herbs, which consist of complex chemical mixtures, can inhibit or induce the activity of drug-metabolizing enzymes [41].

The observed induction and inhibition of CYP enzymes by natural products in the presence of a prescribed drug has (among other reasons) led to the general acceptance that natural therapies can have adverse effects, contrary to popular beliefs in countries with active ethno-medicinal practices. Herbal medicines such as St. John's wort, garlic, piperine, ginseng, and ginkgo, which are freely available over the counter, have given rise to serious clinical interactions when co-administered with prescription medicines [42]. Such adversities have spurred various pre-clinical and *in vitro* investigations on a series of other herbal remedies, with their clinical relevance yet to be established. The CYP3A4-related interaction based on food component is the best known; it might be related to the high level of expression of CYP3A4 in the small intestine, as well as its broad substrate specificity. If we consider that CYP3A4 is responsible for the metabolism of more than 50% of clinical pharmaceuticals, all nutrient-drug interactions should be considered clinically relevant, in which case all clinical studies of drugs should include a food-drug interaction screening [43].

5. Nutrient-drug interactions: examples with clinical relevance

Fruits and vegetables are known to be important components in a healthy diet, since they have low energy density and are sources of micronutrients, fiber, and other components with functional properties, called phytochemicals (See Figure 2). Increased fruit and vegetable consumption can also help displace food high in saturated fats, sugar or salt. Low fruit and vegetable intake is among the top 10 risk factors contributing to mortality. According to the World Health Organization (WHO), increased daily fruit and vegetable intake could help prevent major chronic non-communicable diseases [44]. Evidence is emerging that specific combinations of phytochemicals may be far more effective in protecting against some diseases than isolated compounds (Table 1 and 2). Observed drug-phytochemical interactions, in addition to interactions among dietary micronutrients, indicate possibilities for improved therapeutic strategies. However, several reports have examined the effects of plant foods and herbal medicines on drug bioavailability. As shown in Tables 3 and 4 and as discussed below, we have surveyed the literature to identify reports suggesting important food and phytochemical modulation of drug-metabolizing enzymes and drug transporters leading to potential important nutrient-drug interactions.

| Fruit | Phytochemicals | Traditional Uses |
|---|---|---|
| Grapefruit <i>Citrus paradisi</i> , <i>Citrus reticulata</i> | Bergamottin, flavonoids (nobiletin, tangeretin, quercetin, diosmin, naringenin, naringin and kaempferol), and furanocoumarins. | Insomnia, and anxiety or nervousness |
| Orange <i>Citrus sinensis</i> , <i>Citrus aurantium</i> | Flavonoids as tangeretin, nobiletin, diosmin and hesperetin. | Inflammatory ailments in respiratory tract, Arthritis, gastrointestinal tract ailments and others |
| Tangerine <i>Citrus reticulata</i> , <i>Citrus deliciosa</i> | Flavonoids as diosmin, tangeretin, nobiletin and quercetin. | Inflammatory ailments in respiratory tract, arthritis, gastrointestinal tract ailments and others |
| Grapes <i>Vitis vinifera</i> | Stilbens (resverestrol, viniferin), and flavonoids, | Antianemic, Inflammatory ailments in respiratory tract and others |
| Cranberry <i>Vaccinium macrocarpon</i> <i>Vaccinium myrtillus</i> | Flavonoids as anthocyanidin (cyaniding and poenidin) and flavonols (quercetin); and carotenoids. | Genitourinary ailments, nephrolithiasis, wound healing and others |
| Pomegranate <i>Punica granatum</i> | Phenolic acids (punicalagin and tannins), flavonoids (anthocyanins) and pectin. | Inflammatory ailments in respiratory tract and others Gastrointestinal tract ailments and others |
| Apple <i>Malus domestica</i> | Phenolic acids (tannins), flavonoids (including quercetin), glycosylated xanthones (mangiferin) and Saponins. | Diuretic, genitourinary ailments, inflammatory ailments in respiratory tract and others |
| Mango <i>Mangifera indica</i> | Phenolic acids (tannins), flavonoids (anthocyanins), carotenoids, essential oils, fatty acids, lectins, phenols, saponins, alkaloids, and triterpenes. | Recommended to combat heart disease. It is also a laxative, and diuretic |
| Black raspberry <i>Rubus coreanus</i> , <i>Rubus idaeus</i> , <i>Rubus fruticosus</i> | Phenolic acids (ellagic acid, gallic acid), flavonoids (quercetin, anthocyanins, pelargonidins, Kaempferol and cyanidins), catechins and salicylic acid. | Antianemic, anti-infectious, inflammatory ailments in respiratory tract, gastrointestinal tract ailments and others |
| Black mulberry <i>Morus nigra</i> | 2-arylbenzofuran derivative, flavones (mornigrol D, mornigrol G, mornigrol H, and norartocarpetin), flavonol (dihydrokaempferol), albanin A, albanin E, stilbenes (moracin M), and albufuran. | Genitourinary ailments, Inflammatory ailments in respiratory tract, gastrointestinal tract ailments and others |
| Guava <i>Psidium guajava</i> | Flavonoid as quercetin and phloretin. | Genitourinary ailments, hypertension |
| Papaya (<i>Carican papaya L.</i>) | beta-cryptoxanthin and benzyl isothiocyanates. | Abdominal discomfort, pain, malaria, diabetes, obesity, infections and oral drug poisonings |

Data from: [26,52,53,55, 82, 111, 112]

Table 1. Commonly Consumed Fruits

| Vegetable | Phytochemicals | Traditional Uses |
|--|---|--|
| Broccoli <i>Brassica oleracea var. italica</i> | Isothiocyanate sulforaphane, glucosinolate glucoraphanin, glucosinolates, phenolic acid, indol and dithiothiones. | Antioxidant, Anti-cancer, Antiseptic, anti-ulcerous, hypoglycemic, anti-anemic, Gastrointestinal tract ailments and others |
| Cauliflower <i>Brassica oleracea var. botrytis</i> | Isothiocyanate, glucosinolate, indole-3-Carbinol, sulforaphane, indol, | Antioxidant |
| Spinach <i>Spinacia oleracea</i> | Flavonoids and <i>p</i> -coumaric acid derivatives, α -lipoic acid, polyphenols, lutein, zeaxanthin, betaine | Diuretic, inflammatory ailments, gastrointestinal tract ailments, Inflammatory ailments in respiratory tract and others. |
| Watercress <i>Nasturtium officinale</i> | phenylethyl isothiocyanate (PEITC) and methylsulphonylalkyl isothiocyanates (MEITCs), flavonoids such as quercetin, hydroxycinnamic acids, and carotenoids such as β -carotene and lutein | Antioxidants, diuretic, gastrointestinal tract ailments, Inflammatory ailments in respiratory tract and others. |
| Tomato <i>Lycopersicon esculentum</i> | Carotenoids phytofluene, phytoene, neurosporene, γ -carotene, and ζ -carotene lycopene, phytoene, phytofluene, quercetin, polyphenols, kaempferol | Antioxidant, hydratant, hypocholesterolemic |
| Carrot <i>Dactus carota</i> | Polyphenols, α and β -carotene, quercetin, myrecetin and panaxynol | Constipation |
| Avocado <i>Persea americana</i> | Persin, carotenoids (zeaxanthin, α -carotene, and β -carotene), lutein, β -sitosterol, glutathione | Genitourinary ailments, inflammatory ailments in respiratory tract, gastrointestinal tract ailments and others |
| Red pepper (<i>Capsicum annuum L.</i>) | Capsaisin, lycopene, anthocyanins | Scarlatina, putrid sore throat, hoarseness, dyspepsia, yellow fever, peals and snakebite |

Data from: [26,105,114,126, 151]

Table 2. Commonly Consumed Vegetables

| Fruit | Molecular Target | Drug Interactions in Humans and Others |
|------------------------|--|--|
| Grapefruit | Inhibits CYP3A4, CYP1A2, MRP2, OATP-B and P-glycoprotein, [29, 45, 50, 53, 54, 65] | In humans: reports of more than 40 drug interactions: calcium channel antagonists [57], central nervous system modulators [58], HMG-CoA reductase [59], immunosuppressants [60], anti-virals [61], phosphodiesterases-5 inhibitor [62], antihistamines [63], antiarrhythmics [62], and antibiotics [64]. |
| Sevilla orange | Inhibits CYP3A4, P-glycoprotein, OATP-A, OATP-B [11, 29, 5469, 117] | <i>In vitro</i> system: vinblastine [55], fexofenadine [29], glibenclamida [53] In humans: atenolol, ciprofloxacin, ciclosporine, celiprolol, levofloxacin and pravastatin [54, 72] |
| Tangerine | Stimulates CYP3A4 activity and inhibits P-glycoprotein [52] | <i>In vitro</i> system: nifedipine [74], digoxina [52] |
| Grapes | Inhibits CYP3A4 and CYP2E1 [13] | In humans: cyclosporine [78]. |
| Cranberry | Inhibits CYP3A and CYP2C9 [31, 81, 83] | In humans: Warfarin [81, 82] <i>In vitro</i> system: Diclofenac [83] |
| Pomegranate | Inhibits CYP3A and phenol sulfotransferase activity [56,89] | Animals: carbamacepine [56] |
| Mango | Inhibits CYP1A1, CYP1A2, CYP 3A1, CYP2C6, CYP2E1, P-glycoprotein (ABCB1) [97] | <i>In vitro</i> system: midazolam, diclofenac, chlorzoxazone [95, 96]; Verapamil [97]. |
| Guava | Inhibits P- glycoprotein [23] | Not documented |
| Black raspberry | Inhibits CYP3A [49] | <i>In vitro</i> system: midazolam |
| Black mulberry | Inhibits CYP3A and OATP-B [49] | <i>In vitro</i> system: midazolam; glibenclamida [53] |
| Apple | Inhibits CYP1A1, OATP family (Oatp-1, Oatp-3 and NTCP) [63, 110] | <i>In vitro</i> system: fexofenadine [63] |
| Papaya | Inhibits CYP3A4 [114] | No documented |

Table 3. Fruit-Drug Interactions

| Vegetable | Molecular target | Drug Interactions in Humans and Others. |
|--------------------|---|---|
| Broccoli | Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucosyltransferases, Sulfotransferases, Quinone reductases phenolsulfotransferases [26, 120,121] Induces: UDPglucuronosyltransferases, (UGTs), sulfotransferases, (SULTs) and quinone reductases (QRs) [26] | Not documented |
| Cauliflower | Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, Glucosyltransferases, Sulfotransferases, Quinone reductases phenolsulfotransferases [26,120, 121] Induces: UDPglucuronosyltransferases, (UGTs), sulfotransferases, (SULTs) and quinone reductases (QRs) [26] | Not documented |
| Watercress | Inhibits: CYP2E1, P-glycoprotein, MRP1, MRP2 and BCRP [26, 126] | In humans: Chlorzoxazone |
| Spinach | Possible inhibition of CYP1A2 [1132] | <i>In vitro</i> system: heterocyclic aromatic amines |
| Tomato | Inhibits: CYP1A1, CYP1B1, UGP, [138] Increases: UGT and CYP2E1, [139] | <i>In vitro</i> system: diethylnitrosamine, N-methyl-N-nitrosourea, and 1,2-dimethylhydrazine |
| Carrot | Induces: phenolsulfotransferases and ethoxycoumarin O-deethylase ECD [123, 143] Inhibits: CPY2E1 [122] | Not documented |
| Avocado | Unknown | Humans: Warfarin |
| Red pepper | Inhibits CYP 1A2, 2A2, 3A1, 2C11, 2B1, 2B2 and 2C6 [154,155] | <i>In vitro</i> and <i>in vivo</i> |

Table 4. Vegetable-Drug Intractions

5.1. Grapefruit (*Citrus paradisi*)

The interaction of grapefruit with certain drugs was unintentionally discovered two decades ago [45]. Since then, there have been numerous reports on the effects of grapefruit and its components on CYP450 drug oxidation and transportation [46,47]. Several findings showed that grapefruit juice had a major effect on the intestinal CYP system with a minor effect at the hepatic level [48]. The predominant mechanism for this interaction is the inhibition of cytochrome *P*-450 3A4 in the small intestine, which results in a significant reduction of drug presystemic metabolism. Grapefruit juice intake has been found to decrease CYP3A4 mRNA activity through a post transcriptional activity, possibly by facilitating degradation of the enzyme [49]. An additional mechanism may be the inhibition of P-glycoprotein and MRP2-mediated drug efflux, transporters that carry drugs from enterocytes back to the gut lumen, all of which results in a further increase in the fraction of drug absorbed and increased systemic drug bioavailability [50-52]. It has also been reported that the major constituents of grapefruit significantly inhibit the OATP-B function *in vitro* [53,54].

The interaction between grapefruit juice and drugs has been potentially ascribed to a number of constituents [27]. It has been suggested that flavonoids such as naringin, naringenin, quercetin, and kaempferol, major components in grapefruit, are responsible for drug interaction. Some of these chemicals are also found in other fruit juices. Pomegranate, for example, shares certain properties with grapefruit, suggesting that both could modify the bioavailability of drugs [55,56]. Another group of compounds that has been detected in grapefruit juice are the furanocoumarins (psoralens), which are known to be mechanism-

based inactivators of CYP450. The major furanocoumarin present in grapefruit is bergamottin, which demonstrated a time- and concentration-dependent inactivation of CYP enzymes *in vitro* [49]. One interesting characteristic of this interaction is that grapefruit juice does not need to be taken simultaneously with the medication in order to produce the interaction. The bioavailability of drugs has been reported to be doubled by grapefruit juice, even when taken 12 h after ingestion. Colored grapefruit juice and white grapefruit juice are equally effective in producing drug interactions.

This inhibitory interaction should be kept in mind when prescribing drugs metabolized by CYP3A4. Examples of drugs affected by grapefruit or its components include: calcium channel antagonists such as felodipine, nisoldipine, amlodipines, verapamil, and diltiazem [57]; central nervous system modulators, including diazepam, triazolam, midazolam, alprazolam, carbamazepine, buspirone and sertraline [58]; HMG-CoA reductase inhibitors, such as simvastatin, lovastatin, atorvastatin, and pravastatin [59]; immunosuppressants such as cyclosporine [60]; anti-virals such as saquinavir [61]; a phosphodiesterases-5 inhibitor such as sildenafil [62]; antihistamines, including as terfenadine and fexofenadine [63]; antiarrhythmics such as amiodarone [62]; and antibiotics such as erythromycin [64].

Epidemiologic studies reveal that approximately 2% of the population in the United States consumes at least one glass of regular strength grapefruit juice per day. This becomes pertinent if we consider that many people suffer from chronic metabolic diseases (including hypertension, hyperlipidemia, and cardiovascular diseases) and receive calcium channel antagonis therapy and HMG-CoA reductase inhibitors. Patients with mental disorders also chronically receive central nervous system modulators. In the case of many drugs, an increase in serum drug concentration has been associated with increased frequency of dose-dependent adverse effects [65-67]. In light of the wide ranging effects of grapefruit juice on the pharmacokinetics of various drugs, physicians need to be aware of these interactions and should make an attempt to warn and educate patients regarding the potential consequences of concomitant ingestion of these agents.

5.2. Orange (*Citrus sinensis*)

Consumption of most types of orange juice does not appear to alter CYP3A4 activity *in vivo* [55]. However, orange juice made from Seville oranges appears to be somewhat similar to grapefruit juice and can affect the pharmacokinetics of CYP3A4 substrates [68]. It has been previously shown that consumption of a single 240 mL serving of Sevilla orange juice resulted in a 76% increase in felodipine exposure, comparable to what is observed after grapefruit juice consumption [11]. Presumably, the mechanism of this effect is similar to that of grapefruit juice-mediated interactions, because Sevilla orange contains significant concentrations of flavonoids, mainly bergamottin and 6',7'-dihydroxybergamottin [69]. Orange juice has also been shown to exert inhibitory effects on P-glycoprotein (P-gp)-mediated drug efflux. Takanaga and others showed that 3,3',4',5,6,7,8-heptamethoxyflavon and tangeretin were the major P-gp inhibitors present in orange juice and showed that another component, nobiletin, was also a P-gp inhibitor [55]. Therefore, the intake of orange juice might inhibit the efflux

transporters by P-gp, which could enhance the bioavailability of drugs and thus lead to an increase in the risk of adverse events [52].

It has also been observed that components of orange juice -naringin in particular- are *in vitro* inhibitors of OATP transport activity [70]. Dresser et al., have previously reported that orange juice inhibits the function of human OATP-A (OATP1A2, gene symbol *SLC21A3/SLCO1A2*) *in vitro* [29]. OATP-A, however, is predominantly expressed in the brain, but not in the intestine. On the other hand, Satoh et al. reported that OATP-B-mediated uptake of glibenclamide as well as estrone-3-sulfate was significantly inhibited by 5% orange juice [53]. Orange juice might reduce the intestinal absorption of substrates of OATP-B (e.g., digoxin, benzylpenicillin, and hormone conjugates), resulting in a decrease in concentration in the blood.

Previous studies in humans using fexofenadine as a probe showed that oral coadministration with orange juice decreased the oral bioavailability of fexofenadine [63]. Orange juice and its constituents were shown to interact with members of the OATP transporter family by reducing their activities. The functional consequences of such an interaction are reflected in a significant reduction in the oral bioavailability of fexofenadine, possibly by preferential direct inhibition of intestinal OATP activity. Other reports indicate that orange juice slightly reduced the absorption of ciprofloxacin, levofloxacin and celiprolol [65]. A study of an interaction between orange juice and pravastatin showed an increase in AUC [54]. Orange juice also moderately reduces the bioavailability of atenolol, which may necessitate a dose adjustment [71,72].

5.3. Tangerine (*Citrus reticulata*)

Early studies demonstrated the influence of tangeretin, a flavonoid found in high levels in tangerine juice, on drug metabolizing liver enzymes. It was demonstrated that tangeretin inhibits P450 1A2 and P450 3A4 activity in human liver microsomes [73]. Tangeretin is a potent regioselective stimulator of midazolam 1'-hydroxylation by human liver microsomes CYP3A4. Although, clinical studies have shown no influence on midazolam pharmacokinetics *in vivo*, further studies are needed to evaluate its effects on other drugs [74]. Diosmin is one of the main components of citrus fruits, such as tangerine. Diosmin may increase the absorption or bioavailability of co-administered drugs able to serve as P-gp substrates. As a result, some caution may be required with its clinical use [52].

5.4. Grapes (*Vitis vinifera*)

Grapes are one of the most valued conventional fruits worldwide. The grape is considered a source of unique and potentially useful medicinal natural products; they are also used in the manufacturing of various industrial products [75,76](Yadav and others 2009; Vislocky and Fernandez 2010). The main biologically active and well-characterized constituent from the grape is resveratrol, which is known for various medicinal properties in treating human diseases [75](Yadav and others 2009). Resveratrol was shown to be an irreversible (mechanism-based) inhibitor of CYP3A4 and a non-competitive reversible inhibitor for CYP2E1 in

microsomes from rat liver and human liver cells containing cDNA-expressed CYPs [77,78] (Chan and Delucchi 2000; Piver and others 2001). Resveratrol is an electron-rich molecule with two aromatic benzene rings linked by an ethylene bridge. CYP3A-mediated aromatic hydroxylation and epoxidation of resveratrol are possible, resulting in a reactive p-benzoquinone methide metabolite which is capable of binding covalently to CYP3A4, leading to inactivation and potential drug interactions.

5.5. Cranberry (*Vaccinium macrocarpon*)

American cranberry is a fruit used as a prophylactic agent against urinary tract infections [79]. Drug interactions with cranberry juice might be related to the fact that the juice is rich in flavonol glycosides, anthocyanins, proanthocyanidins, and organic and phenolic acids [80]. Izzo [81] described a total of eight cases of interaction between cranberry juice and warfarin, leading to changes in international normalized ratio (INR) values and bleeding. The mechanism behind this interaction might be the inhibition by cranberry flavonoids of CYP3A4 and/or CYP2C9 enzymes, which are responsible for warfarin metabolism [31,82].

It has also been shown that cranberry juice inhibits diclofenac metabolism in human liver microsomes, but this has not been demonstrated clinically in human subjects [83]. Cranberry juice may increase the bioavailability of CYP3A4 substrates (e.g., calcium antagonists or calcineurin inhibitors) as was discussed [61]. Uesawa and Mohri have demonstrated that nifedipine metabolism in rat intestinal and human hepatic microsomes are inhibited by preincubation with cranberry juice. Furthermore, cranberry juice increased the nifedipine concentration in rat plasma. These findings suggest that cranberry juice might affect the plasma concentration of nifedipine in humans as well [84].

5.6. Pomegranate (*Punica granatum*)

Pomegranate is commonly eaten around the world and has been used in folk medicine for a wide variety of therapeutic purposes [85-86]. Pomegranate is a rich source of several chemicals such as pectin, tannins, flavonoids, and anthocyanins. It has been reported that pomegranate juice influenced the pharmacokinetics of carbamazepine in rats by inhibiting enteric CYP3A activity. Such inhibition of the enteric CYP3A activity by a single exposure to pomegranate juice appears to last for approximately 3 days [56]. Nagata and others [88] found that pomegranate juice inhibited human CYP2C9 activity and increased tolbutamide bioavailability in rats. Recently, pomegranate juice was shown to potently inhibit the sulfoconjugation of 1-naphthol in Caco-2 cells. It has been suggested that some constituents of pomegranate juice, most probably punicalagin, may impair the metabolic functions of the intestine (specifically sulfoconjugation) and therefore might have effects upon the bioavailability of drugs [89].

5.7. Mango (*Mangifera indica*)

The beneficial effects of mango include anti-inflammatory and antimicrobial activities [90,91] Preliminary phytochemical screening revealed the presence of flavonoids, including

quercetin and glycosylated xanthenes such as mangiferin [92,93] Quercetin has been shown to possess antioxidant, antimicrobial, antitumor, antihypertensive, antiatherosclerosis, and anti-inflammatory properties [94]. In a series of studies, Rodeiro and others have shown the effects of mango on drug metabolizing enzymes and drug transporters [95, 96] They found that exposure of hepatocytes to mango extract produced a significant reduction (60%) in 7-methoxyresorufin-O-demethylase (MROD; CYP1A2) activity and an increase (50%) in 7-penthoxyresorufin-O-depentylase (PROD; CYP2B1) activity. This group also studied the effect of mangiferin on CYP enzymes and found that mangiferin reduced the activities of five P450s: POD (CYP1A2), midazolam 1'-hydroxylation (M1OH; CYP3A1), diclofenac 4'-hydroxylation (D4OH; CYP2C6), S-mephenytoin 4'-hydroxylation (SM4OH), and chlorzoxazone 6-hydroxyaltion (C6OH; CYP2E1). Recently, mango and mango-derived polyphenols have been shown to potentially affect the activity of the multidrug transporter P-gp ABCB1 [97]. These findings suggest that mango and its components inhibit the major human P450 enzymes involved in drug metabolism and some transporters. The potential for drug interactions with mango fruit should therefore be considered.

5.8. Guava (*Psidium guajava* L)

Guava is an important food crop and medicinal plant in tropical and subtropical countries; it is widely used as food and in folk medicine around the world [98, 99]. A number of metabolites such as phenolics, flavonoid, carotenoid, terpenoid and triterpene have been found in this fruit. Extracts and metabolites of this plant, particularly those from the leaves and fruit, possess useful pharmacological activities [100]. There is only one report about the effect of guava extracts on drug transport: guava extract showed a potent inhibitory effect on P-gp mediated efflux in Caco-2 cells. It was also found to inhibit efflux transport from serosal to mucosal surfaces in the rat ileum [101]. This means that guava could interact with P-gp substrates such as digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, and paclitaxel in the small intestine. For this reason, this fruit should be consumed with caution by patients taking medicines.

5.9. Raspberry (*Rubus* spp.)

Berries have been shown to have a positive impact on several chronic conditions including obesity, cancer, and cardiovascular and neurodegenerative diseases [102-104]. Like other fruits, raspberries contain micro- and macronutrients such as vitamins, minerals, and fiber. Their biological properties, however, have been largely attributed to high levels of various phenolic compounds, as well as the interactive synergies among their natural phytochemical components (e.g., ellagic acid, quercetin, gallic acid, anthocyanins, cyanidins, pelargonidins, catechins, kaempferol and salicylic acid). Raspberry or raspberry constituents have antioxidant and anti-inflammatory properties, and inhibit cancer cell growth [105-107]. Black raspberries (*Rubus coreanus*) have been called the "king of berries" for their superior health benefits, whereas black mulberry (*Morus nigra*) is most commonly used for its antioxidants properties and for its high bioactive content of phenolics, anthocyanins, and gallic acid. It has been shown that black raspberry and black mulberry are able to inhibit the human

CYP3A-catalyzed midazolam 1-hydroxylation activity in liver microsomes, and the inhibitory effects are somewhat greater than those of pomegranate [49, 56]. It has also been reported that black mulberry extract potently inhibits OATP-B function at concentrations that seem to be physiologically relevant *in vitro* [53]. These results suggest that black raspberry and black mulberry may decrease the plasma concentrations of concomitantly ingested OATP-B substrate drugs or increase the plasma concentration levels of concomitantly ingested CYP3A-substrate drugs. *In vivo* studies on the interaction between black mulberry and black raspberry and CYP3A substrates are needed to determine whether inhibition of CYP3A activity by fruit juices is clinically relevant.

5.10. Apple (*Malus domestica*)

Apple and its products contain high amounts of polyphenols, which show diverse biological activities and may contribute to beneficial health effects such as protecting the intestine against inflammation due to chronic inflammatory bowel diseases [108, 109]. It has been found that apple juice extract inhibits CYP1A1 at levels of CYP1A1 mRNA, protein, and enzymatic activity [110]. On the other hand, it has also been reported that apple juice and its constituents can interact with members of the OATP transporter family (OATP-1, OATP-3 and NTCP) by reducing their activities *in vitro*. The functional consequence of such an interaction was a significant reduction in the oral bioavailability of fexofenadine in human plasma levels, possibly by preferential direct inhibition of intestinal OATP activity [29]. These findings suggest that apple might interact with OATP substrates (e.g., estrone-3-sulfate, deltorphin II, fexofenadine, vasopressin, and rosuvastatin).

5.11. Papaya (*Carican papaya* L.)

Papaya is prized worldwide for its flavor and nutritional properties. An ethno-botanical survey showed that papaya is commonly used in traditional medicine for the treatment of various human diseases, including abdominal discomfort, pain, malaria, diabetes, obesity, infections, and oral drug poisoning [111,112]. Papaya leaves and seeds are known to contain proteolytic enzymes (papain, chymopapain), alkaloids (carpain, carpasemine), sulfurous compounds (benzyl iso- thiocyanate), flavonoids, tannins, triterpenes, anthocyanins, organic acids and oils. Papaya fruit is a good source of nutrients and some phytochemicals such as beta-cryptoxanthin and benzyl isothiocyanates [113]. Hidaka et al. found that *papaya* produced an inhibition of CYP3A activity in human microsomes [114]. So far, there has been no clinical report suggesting adverse food-drug interaction caused by the intake of papaya. Accordingly, the inhibition of CYP3A by papaya may not be observed *in vivo*. However, the results obtained by others raised the hypothesis that papaya extracts were capable of altering the pharmacokinetics of therapeutic drugs coadministered via CYP3A inhibition, as in the case of grapefruit. Thus, the possibility of adverse food-drug interaction involving papaya and medicine acting via CYP3A metabolism should be examined *in vivo*. The empirical evidence regarding the wide use of fermented papaya preparation (FPP), especially by elderly people, has indicated an unknown collateral effect, i.e., drops in blood sugar levels, especially in the afternoon. Those findings have been corroborated by a clinical study that

shows that FPP use can induce a significant decrease in plasma sugar levels in both healthy subjects and type 2 diabetic patients [115]. Therefore, patients consuming papaya and taking antidiabetic therapy could suffer from potential drug-food interaction.

5.12. Leafy vegetables

Broccoli (*Brassica oleracea var. italica*) and cauliflower (*Brassica oleracea var. botrytis*) are unique among the common cruciferous vegetables that contain high levels of the aliphatics glucosinolate and glucoraphanin [116]. Upon hydrolysis, glucoraphanin produces several products that include the bioactive isothiocyanate sulforaphane. The percentage of isothiocyanate sulforaphane present in these vegetables may vary depending on conditions of hydrolysis, food handling, and preparation procedures [117, 118]. In animal studies, dietary freeze-dried broccoli was found to offer protection against several cancers [119]. However, broccoli, cauliflower and their glucosinolate hydrolysis products have been shown to induce phase I and phase II drug-metabolizing enzymes in intact liver cells from both rats and humans. The isothiocyanate sulforaphane decreased the enzyme activities hepatocytes associated with CYP1A1 and 2B1/2, namely ethoxyresorufin-O-deethylase and pentoxyresorufin-O-dealkylase, respectively, in a dose-dependent manner [120]. An increase in hGSTA1/2 mRNA has been observed in isothiocyanate sulforaphane-treated human hepatocytes, whereas the expression of CYP3A4, the major CYP in the human liver, markedly decreased at both mRNA and activity levels [121]. Conversely, it was recently shown that sulforaphane induces mRNA levels of MRP1 and MRP2 in primary hepatocytes and Caco-2 cells [122]. It has been additionally reported that broccoli is able to induce the activity of phenolsulfo-transferases [123]. These results suggest that other vegetables with a high content of isothiocyanates, such as those of the family *Cruciferae* (e.g., cabbage, cauliflower, Brussels sprouts, watercress, broccoli, and kale) and the genus *Raphanus* (radishes and daikons) may have pharmacological and toxicological implications in humans.

Watercress is another important member of the cruciferous vegetables, an excellent source for glucosinolates and other bioactive phytochemicals [124]. Watercress (*Nasturtium officinale*) is an exceptionally rich dietary source of beta-phenylethyl isothiocyanate (PEITC) [125]. Previous studies have shown that a single ingestion of watercress inhibits the hydroxylation of chlorzoxazone, an *in vivo* probe for CYP2E1, in healthy volunteers [126]. It has also been shown that watercress is a bifunctional agent with the ability to induce both phase I (CYP450) and II enzymes. Adding watercress juice to human liver cells induced the activity of CYP4501A and ethoxyresorufin-O-deethylase and NAD(P)H-quinone reductase [127]. According to reports, PEITC also has several anti-carcinogenic effects given that it can inhibit phase I enzymes and/or activate phase II enzymes. Watercress juice can increase the enzymes SOD and GPX in blood cells *in vitro* and *in vivo* [128]. Isothiocyanates also interact with ATP-binding cassette (ABC) efflux transporters such as P-glycoprotein, MRP1, MRP2 and BCRP, and may influence the pharmacokinetics of substrates of these transporters [26]. According to current data, watercress and isothiocyanate may have clinical repercussions by inducing changes in the bioavailability of some drugs.

Spinach (*Spinacia oleracea*) is an important antioxidant vegetable usually consumed after boiling the fresh or frozen leaves [129]. Freshly cut spinach leaves contain approximately 1,000 mg of total flavonoids per kilogram, and the occurrence of at least 10 flavonoid glycosides has been reported [130]. These are glucuronides and acylated di- and triglycosides of methylated and methylene dioxide derivatives of 6-oxygenated flavonols [131]. While epidemiological and preclinical data support the nutritional benefits of spinach and the safety of its consumption there are no publications about its effects on drug metabolizing enzymes and drug transporters. Little is currently known about the *in vivo* effects these compounds have on the bioavailability of xenobiotics the clearance and/or tissue distribution of which is determined by active transport and biotransformation. Platt and others [132] reported the protective effect of spinach against the genotoxic effects of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) by interaction with CYP1A2 as a mechanism of anti-genotoxicity. Its high isothiocyanate and flavonoid content demands additional research to evaluate possible nutrient-drug interactions.

5.13. Vegetable fruits

Tomatoes (*Lycopersicon esculentum*) and tomato-based products are a source of important nutrients and contain numerous phytochemicals, such as carotenoids, that may influence health (carotenoids such as phytofluene, phytoene, neurosporene, γ -carotene, and ζ -carotene) [133,134]. Tomatoes are also a source of a vast array of flavonols (e.g., quercetin and kaempferol), phytosterols, and phenylpropanoids [135]. Lycopene is the most important carotenoid present in tomatoes and tomato products, and their dietary intake has been linked to a decreased risk of chronic illnesses such as cancer and cardiovascular disease [136,137]. Studies performed on human recombinant CYP1 showed that lycopene inhibits CYP1A1 and CYP1B1. Lycopene has also been shown to slightly reduce the induction of ethoxyresorufin-O-deethylase activity by 20% by DMBA in MCF-7 cells [138]. It appears to inhibit bioactivation enzymes and induce detoxifying enzymes. It has been suggested that lycopene might have a potential advantage over other phytochemicals by facilitating the elimination of genotoxic chemicals and their metabolites [138]. Recent *in vitro* evidence suggests that high dose lycopene supplementation increases hepatic cytochrome P450E1 protein and inflammation in alcohol-fed rats [139].

Carrots (*Daucus carota*) are widely consumed as food. The active components of carrots, which include beta-carotene and panaxynol have been studied by many researchers [140-142]. Carrots induce phenolsulfotransferase activity [123] and decrease CYP1A2 activity [122]. It has been reported that a carrot diet increased the activity of ethoxycoumarin O-deethylase ECD activity in a mouse model [143].

Avocado (*Persea americana*) is a good source of bioactive compounds such as monounsaturated fatty acids and sterols [144]. Growing evidence on the health benefits of avocados have led to increased consumption and research on potential health benefits [145, 146]. Phytochemicals extracted from avocado can selectively induce several biological functions [147,148]. Two papers published in the 1990's reported avocados interact with warfarin, stat-

ing that the fruit inhibited the effect of warfarin. They, however, did not establish the cause of such inhibition [149, 150].

Red pepper (*Capsicum annuum* L.) is used as a spice that enhances the palatability of food and drugs such as the counterirritant present in stomach medicines across many countries [151]. The pungency of red pepper is derived from a group of compounds called capsaicinoids, which possess an array of biological properties and give it its spicy flavor. Two major capsaicinoids, dihydrocapsaicin (DHC) and capsaicin (CAP) are responsible for up to 90% of the total pungency of pepper fruits. Red pepper has several uses as a fruit stimulant and rubefacient in traditional medicine; it is also used in the treatment of some diseases such as scarlatina, putrid sore throat, hoarseness, dyspepsia, yellow fever, piles and snakebite [152]. Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a fundamental component of *Capsicum* fruits. Capsaicin is known to have antioxidant properties and has therefore been associated with potent antimutagenic and anticarcinogenic activities [153]. Early studies have reported that capsaicin strongly inhibited the constitutive enzymes CYP 2A2, 3A1, 2C11, 2B1, 2B2 and 2C6 [154]. There is also a report indicating that capsaicin is a substrate of CYP1A2 [155]. Pharmacokinetic studies in animals have shown that a single dose of *Capsicum* fruit could affect the pharmacokinetic parameters of theophylline, while a repeated dose affected the metabolic pathway of xanthine oxidase [156]. Therefore, a potential interaction may occur when it is taken along with some medicines that are CYP450 substrates. Recently, it has been evidenced that red pepper induces alterations in intestinal brush border fluidity and passive permeability properties associated with the induction of increased microvilli length and perimeter, resulting in an increased absorptive surface for the small intestine and an increased bioavailability not only of micronutrients but also of drugs [157]. Cruz et al. have shown that pepper ingestion reduces oral salicylate bioavailability, a likely result of the gastrointestinal effects of capsaicin [158]. On the other hand, Imaizumi et al. have reported capsaicinoid-induced changes of glucose in rats. Therefore, there is a possible interaction risk between red pepper and hypoglycemic drugs in diabetic patients [159]. Patients consuming red pepper and taking antidiabetic therapy could suffer potential drug-food interaction.

5.14. Other vegetables

Yeh and Yen have reported that asparagus, cauliflower, celery and eggplant induced significant phenol sulfotransferase -P (PST-P) activity, whereas asparagus, eggplant and potato induced PST-M activity [123]. It has been also reported that a diet supplemented with apiaceous vegetables (dill weed, celery, parsley, parsnip) resulted in a 13-15% decrease in CYP1A2 activity [122]. The authors speculate that furanocoumarins present in the apiaceous vegetables were responsible for the inhibitory effects on CYP1A2 [117,160].

Vegetables such as cabbage, celery, onion and parsley are known to have a high content of polyphenols. It has been reported that polyphenols can potentially affect phase I metabolism either by direct inhibition of phase I enzymes or by regulating the expression of enzyme levels *via* their interactions with regulatory cascades. Several studies have directly and indirectly shown that dietary polyphenols can modulate phase II metabolism [161]. In addition,

polyphenols have been shown to interact with ABC drug transporters involved in drug resistance and drug absorption, distribution and excretion [32].

6. Drug-food interaction in specific diets with high content of fruits and vegetables

Weight-reduction diets, vegetarian diets, hospitalization, or post-operative regimes all lead to dietary modifications. These diets are often maintained for long periods of time and are likely to result in metabolic changes due to subsequently administered drugs or exposure to environmental chemicals. Several epidemiologic, clinical, and experimental studies have established that certain types of diet may have beneficial effects on health. For example, the traditional Mediterranean diet has been shown to reduce overall mortality and coronary heart disease events [162]. This diet, however, varies across at least 16 countries bordering the Mediterranean Sea. Cultural, ethnic, religious, economic and agricultural differences in these regions account for variations in dietary patterns, which are widely characterized by the following: daily consumption of fruits, vegetables, whole grain breads, non-refined cereals, olive oil, and dairy products; moderate weekly consumption of fish, poultry, nuts, potatoes, and eggs; low monthly consumption of red meat, and daily moderate wine consumption [163]. Increasing evidence suggests that a Mediterranean-style diet rich in fruits, vegetables, nuts, fish and oils with monounsaturated fat and low in meat promotes cardiovascular health and aids cancer prevention because of its positive effects on lipid profile, endothelial function, vascular inflammation, insulin resistance, and its antioxidant properties [164,165].

Vegetarians, on the other hand, exhibit a wide diversity of dietary practices often described by what is omitted from their diet. When a vegetarian diet is appropriately planned and includes fortified foods, it can be nutritionally suitable for adults and children and can promote health and lower the risk of major chronic diseases [166]. A vegetarian diet usually provides a low intake of saturated fat and cholesterol and a high intake of dietary fiber and many health-promoting phytochemicals. This is achieved by an increased consumption of fruits, vegetables, whole-grains, legumes, nuts, and various soy products. As a result of these factors, vegetarians typically have a lower body mass index, low-density lipoprotein cholesterol levels, and lower blood pressure; a reduced ischemic heart disease death rate; and decreased incidence of hypertension, stroke, type 2 diabetes, and certain cancers that are more common among non-vegetarians [167]. The vegan dietary category may be more comparable across countries and cultures because avoiding all animal products leaves little choice but to include large quantities of vegetables, fruit, nuts, and grains for nutritional adequacy. Admittedly, vegetable and fruit variety may also vary widely according to location [168].

Due to their high content of fruits and vegetables, all these diets contain a large proportion of antioxidant vitamins, flavonoids, and polyphenols [169]. Phenolic compounds may help protect the gastrointestinal tract against damage by reactive species present in foods or generated within the stomach and intestines. However, they may be beneficial in the

gut in correct amounts. The overall health benefits of polyphenols are uncertain, and consumption of large quantities of them in fortified foods or supplements should not yet be encouraged [170].

Flavonoids have been known as plant pigments for over a century and belong to a vast group of phenolic compounds that are widely distributed in all foods of plant origin. Unfortunately, the potentially toxic effects of excessive flavonoid intake are largely ignored. At higher doses, flavonoids may act as mutagens, pro-oxidants that generate free radicals, and as inhibitors of key enzymes involved in hormone metabolism [171]. It has been shown that phenol ring-containing flavonoids yield cytotoxic phenoxyl radicals upon oxidation by peroxidases; co-oxidize unsaturated lipids, GSH, NADH, ascorbate, and nucleic acids; and cause ROS formation and mitochondrial toxicity [172]. In high doses, the adverse effects of flavonoids may outweigh their beneficial ones, and caution should be exercised when ingesting them at levels above those which would be obtained from a typical vegetarian diet [173]. Moreover, it is possible that people ingesting a vegetarian or Mediterranean diet may be taking medication and thus have drug-food interaction.

Inhibition of CYP enzymes, which are necessary for carcinogen activation, is a beneficial chemopreventive property of various flavonoids but may be a potential toxic property in flavonoid-drug interactions. Inhibition of CYP activities by flavonoids has been extensively studied because of their potential use as blocking agents during the initial stage of carcinogenesis [174]. The general conclusion after an analysis of available data on CYP-flavonoid interactions is that flavonoids possessing hydroxyl groups inhibit CYP activity, whereas those lacking hydroxyl groups may induce the metabolizing enzyme [175]. Flavonoids can either inhibit or induce human CYP enzymes depending on their structure, concentration, or experimental conditions [176]. The interaction of flavonoids with CYP3A4, the predominant human hepatic and intestinal CYP responsible for metabolizing 50% of therapeutic agents as well as the activation of some carcinogens, is of particular interest [177].

The simultaneous administration of flavonoids present in fruits or vegetables and clinically used drugs may cause flavonoid-drug interactions by modulating the pharmacokinetics of certain drugs, which results in an increase in their toxicity or a decline in their therapeutic effect, depending on the flavonoid structure [178]. Additional reasons for concern regarding mega flavonoid supplements include potential flavonoid-drug interactions, since flavonoids have been shown to both induce and inhibit drug-metabolizing enzymes [38, 39]. Further research regarding the potential toxicities associated with flavonoids and other dietary phenolics is required if these plant-derived products are to be used as therapy.

It is a fact that diets based on fruits and vegetables may have a variety of phytochemicals, as was mentioned earlier, so the possibility of developing a drug-food interaction is high. While dietary polyphenols may be beneficial in the correct amount, but too much may not be good and combining them with medication should be avoided.

7. Conclusion

WHO and the Food and Agriculture Organization of the United Nations (FAO) recommend a daily intake of at least 400 grams or five servings of fruits and vegetables to aid in the prevention of chronic illnesses such as heart disease, cancer, diabetes, and obesity. As a consequence, there is an increased global consumer demand for fruits and vegetables, and some consumers purchase organic foods with the understanding that they are healthy. The use of natural products for improving human health has evolved independently in different regions of the world and production, use, attitudes, and regulatory aspects vary globally. Although modern medicine may be available in most countries for the treatment of many chronic degenerative diseases, folk medicine (phytochemistry) has remained popular for historical and cultural reasons. Although the significance of interactions between drugs is widely appreciated, little attention has been given to interactions between drugs and nutrients. Most of the documented information about the effects of fruit and vegetables on metabolizing enzymes and drug transporters comes from preclinical studies. However, the possibility that these effects could occur in humans should not be ignored. Several clinical studies on the interactions of grapefruit juice and drugs have been conducted with impressive results. Most of the fruits and vegetables examined in this review contain a similar phytochemical mix to that of grapefruit juice. *In vitro* models and animal models have shown that many of these agents influence drug metabolizing enzymes and drug transporters. It is possible that other fruits and vegetables could have the same potential for fruit and drug interactions, and this should be taken into account. This review shows evidence of the influence of fruit, vegetables or their components (phytochemicals) on the CYP3A4 enzyme, which metabolizes most drugs used by the human population. A more consistent approach to the evaluation of nutrient-drug interactions in human beings is therefore needed. Said approach must be systematic in order to a) assess the influence of nutritional status, foodstuffs, or specific nutrients on a drug's pharmacokinetics and pharmacodynamics, and b) evaluate the influence of a drug on overall nutritional status or the status of a specific nutrient. In addition to all this, we must account for the fact that we live in an era of very varied lifestyles. Some people are vegetarians, others take high doses of flavonoids or antioxidants as supplements, some ingest large amounts of bottled water from plastic bottles, or use chlorinated disinfectants. In industrialized countries, fruits and vegetables tend to have been subjected to some sort of processing (e.g., refrigeration, acidification, fermentation, and thermal, high pressure, chemical, or physical processing) that might have an effect on the bioactive compound. All of these factors could have an impact on the metabolism or transport of drugs in an individual, potentially altering pharmacological responses. Our knowledge regarding the potential risk of nutrient-drug interactions is still limited. Therefore, efforts to elucidate potential risk of food-drug interactions should be intensified in order to prevent undesired and harmful clinical consequences.

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