

Drug-Food Interactions with a Focus on Mediterranean Diet

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Abstract: There is a growing interest among people in western countries for adoption of healthier lifestyle habits and diet behaviors with one of the most known ones to be Mediterranean diet (Med-D). Med-D is linked with daily consumption of food products such as vegetables, fruits, whole grains, seafood, beans, nuts, olive oil, low-fat food derivatives and limited consumption of meat or full fat food products. Med-D is well-known to promote well-being and lower the risk of chronic conditions such as cardiovascular diseases, diabetes, and metabolic syndrome. On the other hand bioactive constituents in foods may interfere with drugs' pharmacological mechanisms, modulating the clinical outcome leading to drug-food interactions (DFIs). This review discusses current evidence for food products that are included within the Med-D and available scientific data suggest a potential contribution in DFIs with impact on therapeutic outcome. Most cases refer to potential modulation of drugs' absorption and metabolism such as foods' impact on drugs' carrier-mediated transport and enzymatic metabolism as well as potential synergistic or antagonistic effects that enhance or reduce the pharmacological effect for some drugs. Adherence to Med-D can improve disease management and overall well-being, but specific foods should be consumed with caution so as to not hinder therapy outcome. Proper patient education and consultation from healthcare providers is important to avoid any conflicts and side effects due to clinically significant DFIs.



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1. Introduction

Mediterranean diet (Med-D) represents one of the most famous and well received diet food habits, particularly in the western countries [1]. Med-D originates from the eating patterns that people around Mediterranean basin have been following since the ancient years, along with the adoption of food products that were cultivated later in the area (i.e., potatoes) [2,3]. Med-D promotes the consumption of all food types but focuses on vegetables, fruits, the nearly exclusive use of olive oil in food preparation, routine consumption of marine food, low fat white meat (chicken, turkey) along with cereals, grains, nuts, wine and lesser consumption of high-fat meat products [3]. UNESCO states regarding Med-D: “The Mediterranean diet is characterized by a nutritional model that has remained constant over time and space, consisting mainly of olive oil, cereals, fresh or dried fruit and vegetables, a moderate amount of fish, dairy and meat, and many condiments and spices, all accompanied by wine or infusions, always respecting beliefs of each community” [4]. Since the first observations in 1960s [5], Med-D has shown undisputable, longitudinal, and high-quality evidence to support its health benefits against specific diseases for people that remain adherent to Med-D dietary patterns [6–9]. A reduced risk of overall mortality related with metabolic syndrome, cardiovascular diseases, coronary heart disease, myocardial infarction, cancer incidence, diabetes, neurodegenerative diseases, kidney disease and arthritis are mostly identified regarding clinical data availability [10–21]. Moreover, for Med-D food products we can recognize specific active constituents (i.e., oleuropein, resveratrol, retinoids,

flavonoids, terpenes, catechins, ω -3-fatty acids etc.) with pharmacological effects (i.e., antioxidant and anti-inflammatory) that are related with the health benefits from adherence in Med-D [22–31]. In this respect, the question that arises is whether there could be cases in which pharmacologically active compounds that are present in Med-D foods could potentially interfere with the pharmacological action of drugs and lead in clinically significant DFIs.

Drug interactions are an important clinical issue for optimum healthcare provision. The proper drug administration and drug combinations ensures the minimization of risks for adverse drug reactions (ADRs) due to drug-drug interactions [32–34]. Moreover, drug interactions can emerge due to co-administration of several complementary and alternative medicine (CAM) products such as herbal medicinal products (HMPs) as well as dietary supplements (DS) and food products [35–38]. A DFI describes the physical, biochemical or physiological modulation of a pharmacological process that a drug is following due to the presence of one or more constituents within a food product or other nutraceuticals [39,40]. These bioactive constituents that are present in dietary products may interfere with drugs' biological pathways and alter drugs' pharmacological action or levels in the body. Especially for food products there are well-established clinical examples of drug-food interaction (DFI) such as foods containing tyramine and monoamine-oxidase inhibitors (MAOIs), alcoholic beverages or spirits with central nervous system (CNS) drugs as well as grapefruit and its impact in systemic concentration of several drugs [38,41–43]. Overall, DFIs can occur during the habitual use of certain foods whose components can modify pharmacological processes and pathways that take place in the body for drugs. These pathways can be related with the absorption, distribution, metabolism, and elimination processes (pharmacokinetic drug-food interactions, PK-DFIs) or with biological pathways related with the main—or secondary—pharmacological action of a drug (pharmacodynamic drug-food interactions, PD-DFIs) [44,45].

The aim of this review is to summarize available knowledge regarding DFIs focusing mostly on products that are included within Med-D diet. The analysis focuses on the most common and known food products considering cultural, ethnic, agricultural variations among the regions around Mediterranean area which account for alterations in Med-D dietary habits. The level of evidence is following the general principle of evidence pyramid characterized as: (i) “theoretical” if mechanisms can be proposed; (ii) “low” if in vitro data are available; (iii) “moderate” if in vivo data are available; (iv) “good” if the DFI is observed clinically and (v) “high” if the level of evidence is adequate with randomized clinical studies and other data sources available [46–49]. The review is structured to present initially general pharmacological mechanisms of potentially clinically significant DFIs with some characteristic examples. Subsequently available scientific data and the level of evidence regarding DFIs between Med-D foods and drugs are presented and discussed. The potential impact of heavy metal or other pollutants is not included.

2. Pharmacological Mechanisms of Drug-Food Interactions

Pharmacological mechanisms of DFIs include the influence of PK processes and/or the PD effect of drugs in organs and secondary tissues (Figure 1). For a DFI to have a clinically significant impact it must modulate the pharmacological profile of a drug out of its therapeutic window. For example, in cases of PK-DFIs, one or more constituents of a food product must increase or decrease drug's concentration out of the minimum or maximum effective concentration, respectively, and/or change the time of drugs action. (Figure 2). Therefore, clinically significant DFIs occur when one or more food constituents are (i) contained in fair and consistent amounts in the product; (ii) can reach systemic circulation and biological ways in adequate concentrations and (iii) modulate meaningfully the drug's pharmacological action [50,51].

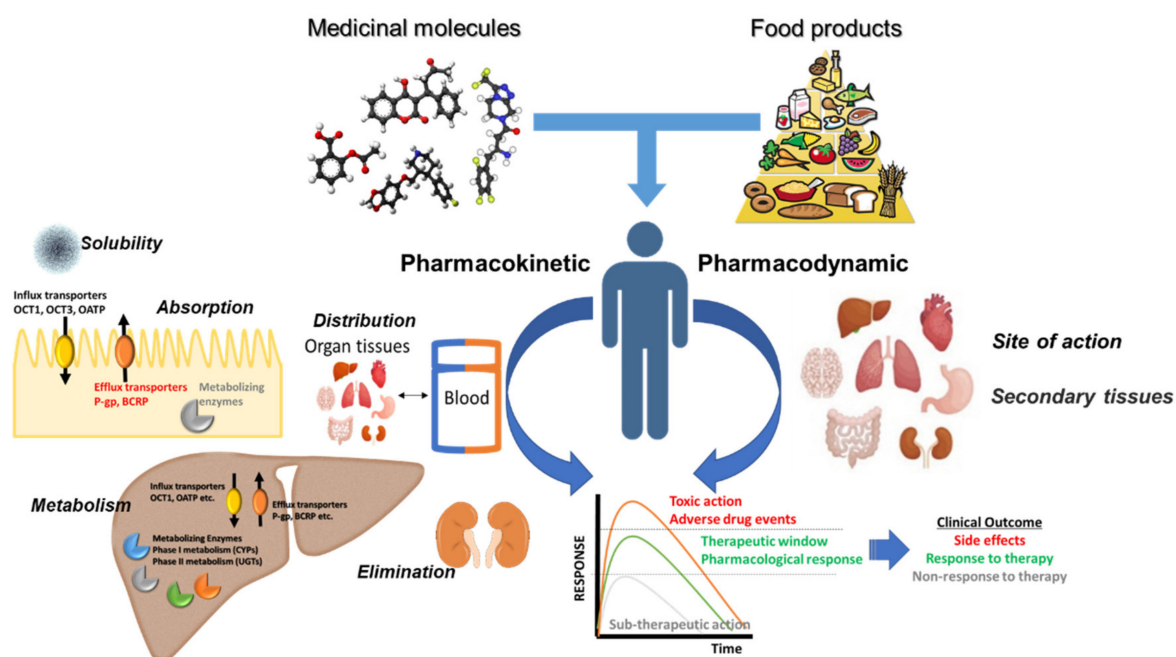


Figure 1. Representation of pharmacological mechanisms of DFIs and their impact on clinical outcome.

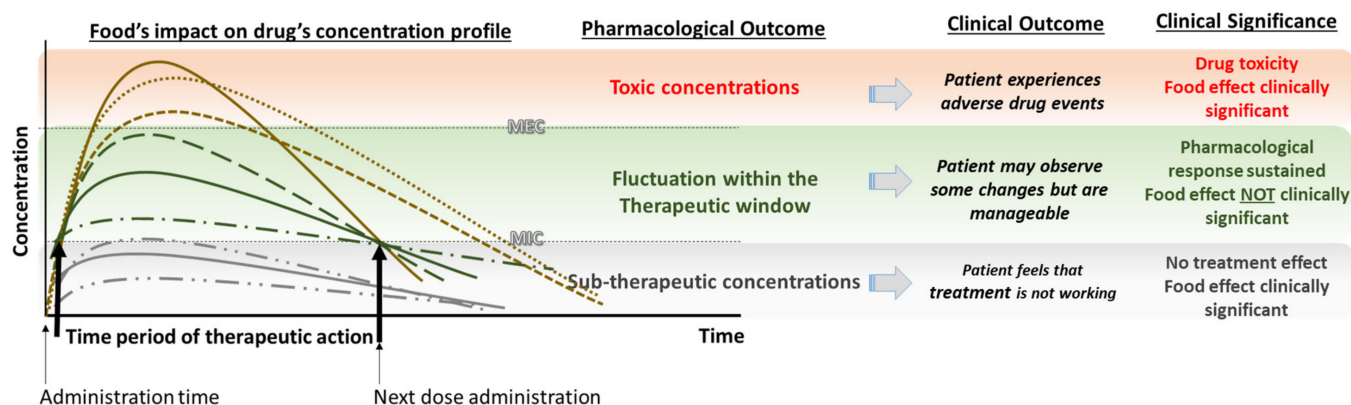


Figure 2. Graphical representation of food effect on the PK profile of a drug that leads in clinically significant DFIs (MEC maximum effective concentration, MIC: minimum effective concentration).

2.1. Pharmacokinetic Drug-Food Interactions (PK-DFIs)

2.1.1. Absorption

Drug's absorption—for orally administered drugs—is determined by its physicochemical properties, formulation, the capability of transportation (active or passive) across epithelial cells in the gastro-intestinal (GI) tract and the administration during fasted/fed state (Figure 3) [52]. Any modulation of intestinal transit time can change the drug's bioavailability—the fraction that reaches systemic circulation—and alter its systemic concentration. This is very important for drugs with reduced aqueous solubility but sufficient permeability [53,54]. Dietary compounds can modulate absorption either through biological activities or due to physicochemical mechanisms that change GI-environment, thus altering the biopharmaceutical properties of a drug formulation. For example, radish extract has been shown to stimulate GI motility in vitro through activation of muscarinic pathways [55]. Oat brans and fibers, although assisting in lowering cholesterol, also inhibit the intestinal absorption of statins, altering their PD properties, thus concurrent adminis-

tration and consumption is proposed to be avoided or limited [56,57]. High-fat diets may lead in raised bile salt secretion which may increase the solubilization and absorption of lipophilic drugs such as anticancer drugs pazopanib, vemurafenib and lapatinib [58,59]. Generally the impact of fasted/fed state seems to be an important factor for orally administered drugs and especially for drugs used in oncology [60,61]. Thus, it is important relative information to be placed on drug labels since certain foods can change the pH in the stomach, alter the solubility, delay gastric emptying, change the stimulation of bile and blood flow, create unabsorbed chelate ligands, or change the gut microflora [50,62].

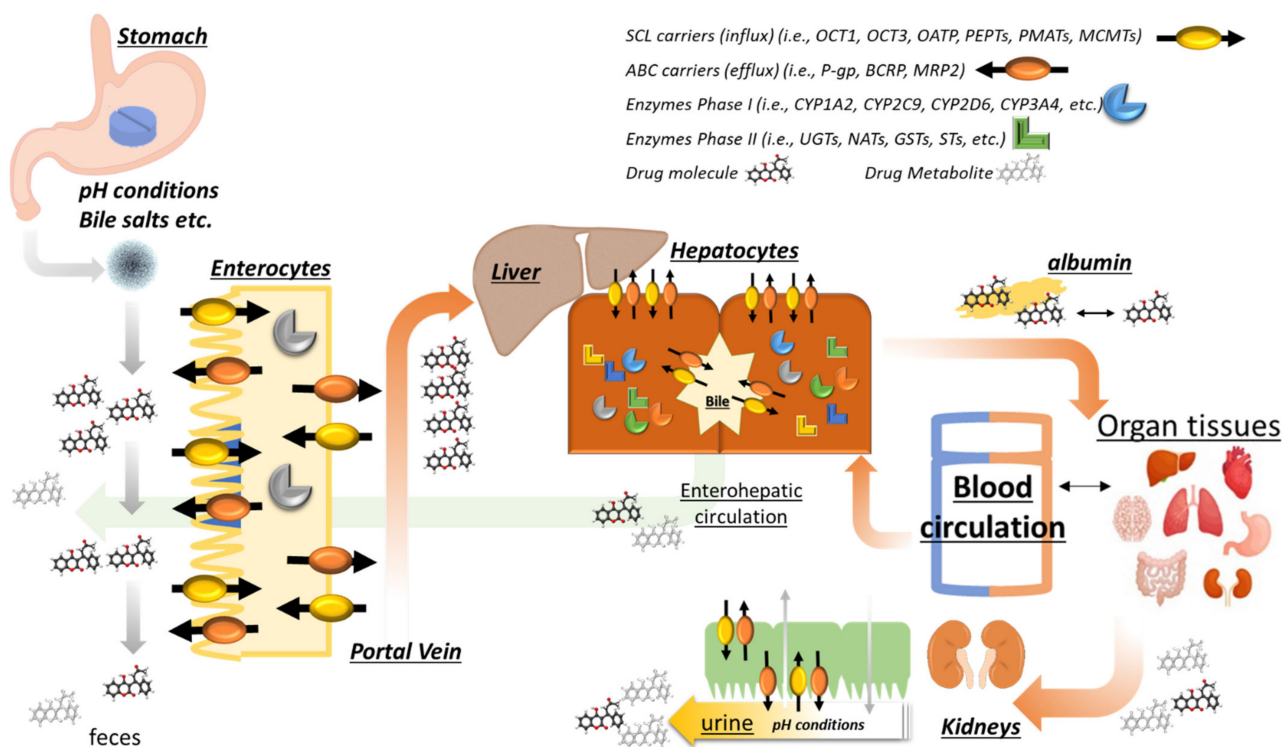


Figure 3. Pharmacokinetic processes for orally administered drugs and sites of potential PK-DFIs.

Following dispersion and dissolution in the GI track, a drug molecule is transported across epithelial GI-cells to the portal vein through active transport. Drug carriers can be classified into two major superfamilies, (i) ATP-binding cassette (ABC) transporters with efflux activity and (ii) solute carrier (SLC) transporters with influx activity [63–67]. P-glycoprotein (P-gp) is the most well-known efflux carrier regulating the absorption of drugs (i.e., anticancer, immunosuppressants, cardiovascular and lipid-modifying agents, antivirals, antibiotics, antiepileptics). Additional efflux transporters are: (i) the breast cancer resistance protein (BCRP) alleged to prevent absorption of toxic compounds and regulate the absorption of chemotherapeutics, and drugs such as prazosin, glyburide, cimetidine, sulfasalazine, rosuvastatin etc.; and (ii) the multidrug resistance-associated protein 2 (MRP2) that plays a role in the absorption of chemotherapeutic products [64,66,67]. Regarding influx transport, it is regulated by SLCs superfamily and includes a wide number of carriers such as organic anion transporters proteins (OATPs); organic cation transporters (OCTs); proton-dependent oligopeptide transporters (PEPTs); plasma membrane monoamine transporters (PMATs); and the monocarboxylate transporters (MCTs), all of which have been shown to play roles in drug transport across cell membranes [65,67].

Constituents of food products and DS can influence transporter's activity [68–71]. The efflux activity of P-gp has been shown in vitro to be inhibited from rosemary extracts, orange juices, strawberry and apricot extracts, dietary fatty acids, mint extracts, and spices constituents found in black pepper (piperine), chili peppers (capsaicin), and sesame oil (sesamin) [72]. Flavonoids such as quercetin, rutin, genistein, and silymarin, and terpenoids

such as glycyrrhethinic acid are typical examples inhibiting activity in P-gp and in some cases for BCRP [73–76]. Green tea beverages have been shown *in vivo* to inhibit hepatic OATP2 reducing hepatic drug uptake and increase plasma exposure to atorvastatin [77].

2.1.2. Distribution

Drug distribution describes the reversible transfer of a drug from the blood to organs through vascular permeability into interstitial-intracellular space, and from there inside the cells [78]. Drug's physicochemical properties, plasma and/or tissue protein binding, tissue composition and the presence of several barriers (i.e., blood-brain barrier) are factors that play roles in distribution [79]. Drug's distribution is often related with the volume of distribution (Vd). It is defined as the apparent volume in which the existing amount of drug in the body must be dissolved to give its measured plasma concentration. Low Vd values are for drugs that remain mainly in plasma while high values are for lipophilic molecules that are distributed in tissues with high body-fat (i.e., CNS drugs). Regarding drugs in plasma, they are either bound (fb) or unbound (fu) to plasma proteins (i.e., human serum albumin (HAS), α 1-acid-glycoprotein) depending on their affinity with them. This is important since only unbound drugs are distributed in the tissues and give the pharmacological action, as well as are eliminated. Protein binding is a site of potential drug interactions and alteration of protein binding can be significant in cases of $f_u < 0.05$, low Vd (high plasma concentration) and narrow therapeutic index (NTI) [80]. For example, if a drug with $f_u = 0.05$ changes it to $f_u = 0.1$ and no added elimination occurs, the drug will double its action which can potentially lead in ADRs. Phenolic derivatives (i.e., flavonoids, phenolic acids, anthocyanidins, gallic acid derivatives, stilbene derivatives etc.) can form reversible complexes with plasma proteins such as albumin [81,82]. Flavonoids such as baicalin, rutin and quercetin that are found in several DS have been suggested to alter the albumin binding of drugs such as theophylline, nifedipine, promethazine, and ticagrelor [82]. As far as displacement of warfarin, experimental results vary from no risk up to clinically significant DFIs. For DFIs in protein binding with warfarin, an allosteric alteration of different binding regions is proposed, but the interaction is a minor one due also to the fact that S-warfarin (the active enantiomer) has lower protein binding [83].

2.1.3. Metabolism

Metabolic transformation of drugs occurs through a series of pathways in the liver and is divided in two phases (phase I and phase II) (Figure 2). Phase I reactions encompass the formation, or the modification of a functional group through oxidation, reduction, or hydrolysis while phase II are conjugation reactions.

Cytochromes P450 (CYPs) are responsible for 80% of the total phase I oxidation reactions [84]. Of the total 18 CYP families described in humans, the first three participate the most in drug metabolism. Variations in CYP genes among individuals results in phenotypes of different metabolic activity and usually classifying them as ultra-rapid, extensive, intermediate, and poor metabolizers [85–87]. CYP2D6 is the most recognized example regarding inter-individual and inter-population variability regarding phenotypes [88]. Pharmacogenetic testing for CYP2D6 has become an important clinical aspect of personalized therapy, especially since it is responsible for the metabolism of 20–25% of drugs such as CNS and cardiovascular medications [87,88]. This unique characteristic of CYP2D6 often makes it a focus point for potential drug interactions, including DFIs. CYP3A subfamily is the most abundant isoenzyme that plays role in drugs pharmacokinetics. CYP3A isoenzymes (CYP3A4 and CYP3A5) are expressed in the small intestine and the liver, and their metabolic activity accounts for 70–75% of drug metabolism [86]. Over the previous years it has become evident that CYP3A4 and P-gp play complementary roles for absorption, disposition, and metabolism processes. Hence, in many cases, interaction mechanisms for drugs often include both biological pathways of transport and metabolism [89].

The roles of food products in drug metabolism have been extensively evaluated [51]. St John's Wort (SJW) is a well-known example of DS involved in drug interactions through CYP3A4 and P-g. SJW has been promoted as a well-documented natural antidepressant supplement after long term use [90]. SJW's constituents (mainly hyperforin) can initially inhibit and subsequently induce the expression of CYP3A in the liver as well as induce the expression of P-gp [91,92]. The overall effect is an initial increase in drug exposure but the later induction of P-gp and CYP3A leads in reduced and sub-therapeutic concentration of CYP3A and P-gp substrates. The impact of SJW on P-gp and CYP3A is correlated with the hyperforin content in the product [93]. As of today there are several drug categories reported to interact with SJW such as anticancer drugs (i.e., imatinib, irinotecan, docetaxel), HIV drugs (i.e., indinavir), immunosuppressants (cyclosporine, tacrolimus), anticoagulants (i.e., coumarin analogues), cardiovascular medications and lipid modifying agents (i.e., digoxin, statins etc.), antiepileptics (i.e., carbamazepine), and oral contraceptives (i.e., levonorgestrel etc.) [92]. Hence, SJW, although promoted as a good natural antidepressant, needs special precautions when it is used for patients under therapies with NTI drugs [94].

Other important CYP enzymes are the CYP1A1 and CYP1A2, CYP2C9 and CYP2C19 that also metabolize a wide number of drugs. Polycyclic aromatic hydrocarbons (PAHs) present in tobacco are bio-transformed by CYP1A1 and CYP1A2 to oxy-derivatives, which can bind to DNA and initiate carcinogenesis. Tobacco can also induce CYP1A1 and CYP1A2 expression and modulate the systemic concentration of drugs that are substrates for these enzymes [95]. Isothiocyanates and other natural occurring polyphenols that are present in several vegetables have been shown to reduce the CYP1A enzyme activity, thus limiting the effect of PAHs [96]. CYP2C9 participates in the metabolism of coumarin anticoagulants (i.e., warfarin and acenocoumarol), thus is a site of potential interactions for anticoagulation treatment. A known case is that of ginkgo biloba, where ginkgolic acid I and II can inhibit CYP2C9, however the interaction is negligible [97,98].

In Phase II, metabolism transferases such as UDP-glucuronosyltransferases, sulfo-transferases, N-acetyltransferases, glutathione S-transferases and methyltransferases insert hydrophilic groups to the initial drug or the formed metabolite prior to renal elimination. Dietary polyphenols found in fruits, vegetables, wine, olive oil, tea and cocoa products are potential substrates and/or inhibitors of Phase II enzymes due to the presence of hydroxylic groups (-OH) that gives them structural similarity with drugs' metabolites. Until now, studies (mostly in vitro) have shown natural polyphenols' potential inhibitory activities on UDP-glucuronosyltransferases. For example, molecules such as glycyrrhetic acid (licorice), chrysin (passiflora, mushrooms), silymarin (milk thistle), quercetin (onions, apples, grapes, berries, broccoli etc.), myricetin (tomatoes, oranges, berries, red wine etc.), naringenin (citrus fruits), luteolin (celery, parsley, broccoli, onion leaves), phloretin (apples), piceatannol (passion fruit and blueberries), resveratrol (grapes, wine, grape juice) etc. have been found to exhibit inhibitory activity against UGTs thus they can play role during Phase II metabolism of drugs and possibly contribute in DFIs [99–102].

2.1.4. Elimination

Drug's removal from the body is occurring through excretion processes for an unmetabolized drug or its metabolite. Kidneys are the main organ of drug elimination and drugs (or their metabolites) are filtered through them into the urine and excreted. A secondary pathway is through the bile where the bio-transformed drugs in the liver are excreted in the bile and eliminated through enterohepatic circulation in the feces (Figure 3). Renal elimination of drugs involves the processes of glomerular filtration (drug passive diffusion from blood stream into the urine), proximal tubular secretion, and distal tubular reabsorption from passive diffusion or active transport. For renal elimination, two factors are playing roles for potential DFIs. The first is the urinary pH since drug's ionization—depending on the alkaline or acidic environment—plays a role in its capability to passively diffuse through membranes, trapped in ionized form and excreted, whereas the non-ionized form is re-absorbed. The second factor is the transporter-mediated interactions which can impact

drugs' elimination profile or accumulation in renal tubular cells, leading to drug-induced nephrotoxicity. Diet habits play a key role in the acidity or alkalinity of urine pH. Vegetables and fresh fruits are mostly related with alkaline diets, whereas high protein content diets usually acidify the urine [103]. An alkaline urine pH can reduce the excretion rate of weakly basic drugs and an acidic urine pH from diet may decrease the excretion amount for weakly acidic drugs. Memantine and flecainide are two characteristic examples where their elimination profile is changing based on the urine pH conditions [104,105].

2.2. Pharmacodynamic Drug-Food Interactions (PD-DFIs)

Pharmacodynamic interactions refer to modulation of the pharmacological action of a drug in the site of action or in secondary tissues that can induce ADRs and side effects. PD-DFIs are usually related with additive, synergistic, or antagonistic effects from food compounds on the pharmacological pathways of a drug. One of the most well-known DFIs is for foods containing tyramine (i.e., wine and cheese). These foods are to be avoided from patients treated with monoamine oxidase inhibitors (MAOIs) [42]. Another typical example is the potential modulation of anticoagulating action of coumarin analogues (warfarin, acenocoumarol, phenprocoumon) from vitamin K (Vit-K) [106]. Vit-K1 (dihydroquinone, KH₂) is the necessary cofactor for activation of the clotting factors, thus coumarin analogues and Vit-K are antagonizing each other. Foods rich in Vit-K such as kale, collard greens, broccoli, spinach, cabbage, and lettuce should be consumed from patients under anticoagulation treatment keeping in mind potential alterations in international normalized ration (INR). The general guidance is that patients need to sustain a stable diet, so the daily intake of Vit-K must remain constant throughout their treatment [107,108]. Similarly to Vit-K, special precautions should be taken for diets rich in minerals such as Potassium (K⁺) in cases of cardiovascular diseases treated with K⁺ sparing diuretics (spironolactone, amiloride, triamterene etc.) or agents acting on the renin–angiotensin system (i.e., angiotensin-converting enzyme inhibitors, ACEs, angiotensin receptor blockers, ARBs, etc.). In this respect, fruits such as bananas, oranges, and apricots, and vegetables such as spinach, potatoes, mushrooms, and peas should be consumed keeping in mind that high intake may lead to hyperkalemia resulting in cardiac side effects and arrhythmias [109,110].

3. Mediterranean Food Products and Potential DFIs

3.1. Med-D Food Products

Med-D allows the intake of all types of foods following a general food guidance pyramid (Figure 4) [2,3]. In its base (level 1) are vegetables, fruits, nuts, and cereals that should be consumed in greater amounts and at daily frequency. Above them (level-2), sea food proteins and omega-3-fatty acids (n-3 FAs) are suggested to be consumed biweekly. Animal food products (level3) such as dairy, cheese, and eggs can be consumed in moderate portions during the week. Red meat (level 4) should be consumed in less proportions during the week along with saturated fat products and sweets. Regarding alcohol, a moderate consumption of wine and other fermented beverages is recommended (one to two glasses with meals). The pyramid is complete considering daily activities and physical exercise. Tables 1–3 summarize available data regarding potential DFIs for food products of level1 in the Med-D pyramid.

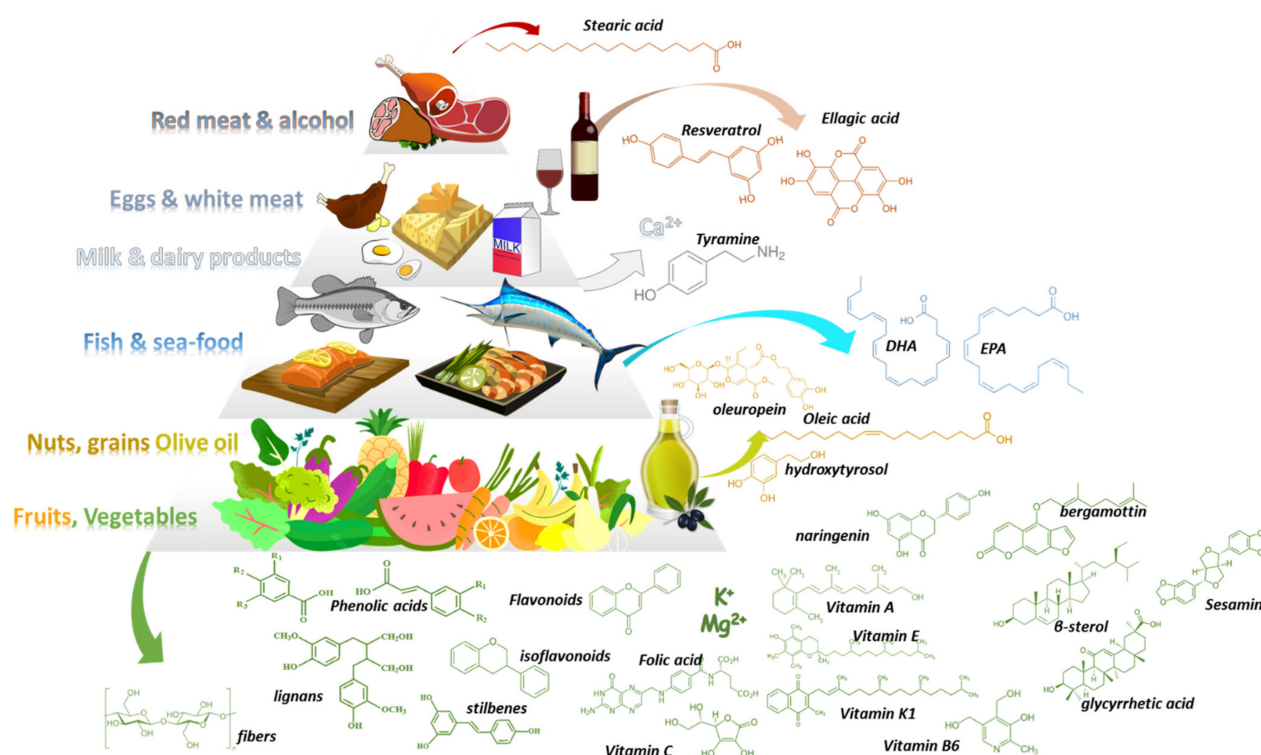


Figure 4. The Mediterranean diet pyramid along with examples of characteristic constituents that can be found in Med-D's food products.

Table 1. DFIs, pharmacological mechanism, significance, and level of evidence for vegetables and herbs that are contained in the base of Med-D pyramid (PK: pharmacokinetic, PD: Pharmacodynamic, DFI: drug-food interaction).

Food	Type of DFIs	Suggested Mechanism	Clinical Significance	Level of Evidence
Artichoke	PK	CYP mediated drug metabolism	Moderate	Moderate
Arugula	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Asparagus	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Beetroots	-	-	-	-
Bell pepper	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Broccoli	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Brussel Sprouts	PK	CYP mediated drug metabolism	Moderate	Moderate
Cabbage	PK	CYP mediated drug metabolism	Moderate	Good
Carrots	PK	CYP mediated drug metabolism	Minor	Low
Cauliflower	PK	CYP mediated drug metabolism	Minor	Moderate
Celery	PD	Synergism sedatives	Minor	Good
Collard greens	PD	Synergism antidiabetic medications	Minor	Low
Cucumbers	-	-	-	-
Dandelion greens	PD	Lithium	Moderate	Low
Eggplant	-	-	-	-
Fennel	-	-	-	-
Fava beans	PD	synergism with anti-parkinson drugs (L-dopa content)	Moderate	Low

Table 1. Cont.

Food	Type of DFIs	Suggested Mechanism	Clinical Significance	Level of Evidence
Garlic	PK		Moderate	Good
Green beans	-	-	-	-
Kale	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Leeks	PD	Anticoagulants—Vitamin K	Minor	Theoretical
Mushrooms	-	-	-	-
Onions	PD	Anticoagulants—Vitamin K	Minor	Theoretical
Potatoes	-	-	-	-
Radish	PK	stimulate GI motility & transit time	Minor	Moderate
Scallions	PD	Anticoagulants—Vitamin K	Minor	Theoretical
Shallots	PD	Anticoagulants—Vitamin K	Minor	Theoretical
Spinach	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Squash	PD	stimulant laxative may alter K+	Minor	Theoretical
Sweet potatoes	-	-	-	-
Swiss chard	PD	Anticoagulants—Vitamin K	Minor	Theoretical
Tomatoes	PK	CYP mediated drug metabolism	Minor	Moderate
Turnips	PD	Synergism antidiabetic medications	Minor	Moderate
Yams	PD	Synergism with estrogens	Moderate	Good
Zucchini	-	-	-	-
Anise	PK	CYP mediated metabolism	Moderate	Good
Basil	PD	Anticoagulants, n-3 FAs	Moderate	Low
Bayleaf	PD	Synergism with antidiabetics & sedatives	Minor	Low
Cinnamon	PD	Synergism antidiabetic & hepatotoxicity	Minor	Low
Cloves	PD	potentiate the effects of drugs that affect hemostasis	Moderate	Moderate
Cumin	PD	Synergism antidiabetic medications	Moderate	Moderate
Fennel	-	-	-	-
Lavender	PD	Synergism with sedatives	Moderate	Low
Marjoram	PD	Potentiate effects of drugs for hemostasis	Moderate	Low
Mint	-	-	-	-
Oregano	PD	Potentiate effects of drugs for hemostasis	Moderate	Low
Parsley	-	-	-	-
Pepper	PK	CYP mediated drug metabolism	Minor	Moderate
Rosemary	-	-	-	-
Sage	PD	Synergism with sedatives	Moderate	Low
Savory	PD	Anticoagulants, n-3 FAs	Moderate	Low
Sumac	PD	Induce nephrotoxicity of drugs	Minor	Low
Tarragon	PD	Anticoagulants, n-3 FAs	Moderate	Low
Thyme	PD	Anticoagulants, n-3 FAs	Moderate	Low

Level of evidence: (i) Theoretical (ii) low: in vitro data (iii) moderate (in vitro/in vivo) Good (in vitro/in vivo/clinical); (iv) High (in vitro/in vivo/clinical observations/clinical trials).

Table 2. DFIs, pharmacological mechanism, significance, and level of evidence for fruits that are contained in the base of Med-D pyramid (PK: pharmacokinetic, PD: Pharmacodynamic, DFI: drug–food interaction).

Fruit	Type of DFIs	Suggested Mechanism	Clinical Significance	Level of Evidence
Apples	PK	OAT transporter inhibition	Moderate	Good
Apricots	-	-	-	-
Avocados	PD	Anticoagulants—Vitamin K	Moderate	Theoretical
Bananas	PD	Hyperkalemia, high K ⁺	Moderate	Theoretical
Cherries	-	-	-	-
Clementines	PK	CYP mediated drug metabolism	Moderate	Moderate
Grapefruit	PK	P-gp transport & CYP mediated drug metabolism	Serious-avoid	High
Grapes	PK	UGT mediated drug metabolism	Moderate	Good
Lime	PK			
Melons	PD	Synergism antidiabetic medications	Low	Theoretical
Oranges	PK	OAT transporter inhibition	Moderate	Good
Peaches	PD	Hyperkalemia, high K ⁺	Moderate	Theoretical
Pears	-	-	-	-
Pomegranates	PK	CYP mediated drug metabolism	None	High
Pomelo	PK	P-gp transport & CYP mediated drug metabolism	Use with caution	Good
Strawberries	PK/PD	Metabolism & anticoagulation	Low	Theoretical
Tangerines	PK	CYP mediated drug metabolism	Moderate	Moderate

Level of evidence: (i) Theoretical (ii) low: in vitro data (iii) moderate (in vitro/in vivo) Good (in vitro/in vivo/clinical); (iv) High (in vitro/in vivo/clinical observations/clinical trials).

Table 3. DFIs, pharmacological mechanism, significance, and level of evidence for nuts, and cereals that are contained in the base of Med-D pyramid.

Food	Type of DFIs	Suggested Mechanism	Clinical Significance	Level of Evidence
Barley	PK	Modulation GI absorption	Moderate	Low
Buckwheat	-	-	-	-
Bulgur	-	-	-	-
Farro-flax seed	PD	Anticoagulants, n-3 FAs	Moderate	Low
Millet	-	-	-	-
Oats & fibers	PK	Modulation GI absorption	Moderate	Good
Polenta	-	-	-	-
Rice	-	-	-	-
Wheat Berries	PK	Modulation GI absorption	Moderate	Low
Breads	-	-	-	-
Couscous	-	-	-	-
Almonds	-	-	-	-
Cashews	PD	Synergism antidiabetic medications	Minor	Low
Chickpeas				
Fava beans	PD	Synergism with anti-Parkinson drugs (high L-dopa content)	Moderate	Low
Green peas	-	-	-	-
Hazelnuts				
Kidney beans	PK	Modulation GI absorption	Minor	Low
Lentils	PD	Hyperkalemia, high K ⁺	Minor	Low
Peanuts	PD	Tyramine pressure effect (MAOIs)	Use with caution	Low
Pistachios	-	-	-	-
Sesame seeds (tachini)	PK	CYP mediated metabolism	None	Moderate
Split peas	PK	Modulation GI absorption	Minor	Theoretical
Walnuts	PK	Modulation GI absorption	Moderate	Theoretical

Level of evidence: (i) Theoretical (ii) low: in vitro data (iii) moderate (in vitro/in vivo) Good (in vitro/in vivo/clinical); (iv) High (in vitro/in vivo/clinical observations/clinical trials).

3.2. Drug-Med Diet Interactions

3.2.1. Vegetables, Herbals, Olive Oil, Cereals, and Nuts

The Med-D has its basis in foods of plant-origin with a wide variety of vegetables along with other herbals. It contains an extensive list of domestic and imported vegetables that reached the area through historical trading routes. The most common vegetables include artichokes, arugula, asparagus, beetroots, broccoli, brussel sprouts, cabbage, carrots, celery, collard greens, cucumbers, dandelion greens, eggplant, fennel, garlic leeks, lettuce, mushrooms, mustard greens, onions (all types), peas, peppers, potatoes, pumpkin, radishes, spinach, turnips, zucchini. Case reports and clinical data suggest that potential PK-DFIs can result from consumption of artichoke, broccoli, brussel sprouts, cabbage, cauliflower, and tomatoes [111–113]. A pharmacological mechanism can be attributed to the isothiocyanate content (i.e., broccoli, cauliflower etc.) and their capability to modulate drugs' CYP-mediated metabolism or transport (ABC-transporters) [112]. Especially for CYP1A2, it has been shown through clinical trial that brassica vegetables can induce CYP1A2 metabolic activity modulating caffeine's pharmacokinetics [114]. In addition, celery and other apiaceous vegetables (i.e., carrot, celery, dill, cilantro, parsnip, parsley etc.) can decrease cytochrome CYP1A2 activity as has been shown through several studies [112,114]. Garlic components have shown inhibitory action for CYPs 2C, 2D, and 3A-mediated metabolism in vitro but in a later clinical pharmacokinetic study, long-term use of garlic caplets led to a significant decline in the plasma concentrations of saquinavir which is metabolized from CYP3A4 [115,116]. Tomato juice was shown in vitro to contain mechanism-based and competitive inhibitor(s) of CYP3A4 [117,118]. Cabbage and onion juices have also shown potential inhibiting activities on CYP3A4 in vitro [119]. Basil demonstrated in vitro potential reversible and time-dependent inhibition of CYP2B6 and CYP3A4 as well as esterase-mediated metabolism of rifampicin, but the concentrations were higher than the ones used in daily food consumption [120]. The significance of these potential PK-DFIs is currently unresolved and the level of evidence for most of the cases is low. The frequent consumption of these foods may contribute in an observed inter-individual variability within the treatment goals. A recent systematic review and meta-analysis of twenty-three dietary intervention trials in humans analyzed the effect of cruciferous vegetable-enriched diets on drug metabolism. The meta-analyses showed a significant effect on CYP1A2 and glutathione S-transferase-alpha (GSTa) [113]. Thus, healthcare advice is needed in case patients habitually consume excessive amounts of vegetables such as broccoli, brussel sprouts, cabbage, cauliflower, radish, and watercress and are under treatment with CYP1A2 substrates (i.e., clozapine, olanzapine, fluvoxamine, haloperidol, melatonin, ramelteon, tizanidine, and theophylline).

Regarding PD-DFIs, arugula, asparagus, bell peppers, broccoli, celery, collard greens, kale, onions and leeks, spinach, and chard due to their content of vitamin-K could modulate the INR for people treated with coumadin analogues such as warfarin or acenocoumarol. However, despite this, DFI represents a clinically significant case; it is estimated to be of moderate importance and has a low level of evidence with studies suggesting that a balanced consumption of vegetables does not interfere with INR in a clinically significant way [107,108]. Concerning other potential PD-DFIs, anise and aniseed's essential oil (used to enhance the flavor of Greek Ouzo and mastic) in vivo enhanced the effects of CNS drugs (codeine, diazepam, midazolam, pentobarbital, imipramine and fluoxetine) in mice suggesting potential synergism and a clinically significant PD-DFI if it is used in extensive doses [121]. Garlic has shown promising data as an antidiabetic agent; thus it may enhance the pharmacologic effect of antidiabetic medicines [122]. Turnips have demonstrated synergism with antidiabetic drugs towards hypoglycemia while yams have a good quality of evidence for synergy with estrogens and thus special precautions should be made for patients under estrogen therapy [123,124]. Naturally occurring levodopa and carbidopa have been quantified in fava beans in fair amounts, thus patients with Parkinson's under treatment should be aware of possible synergism with co-administered medications [125].

Concerning olive oil, its protective role against inflammation-related chronic non-communicable diseases (cardiovascular, diabetes, cancer etc.) have been described thoroughly [126]. Proposed mechanisms involve the action of bioactive constituents of olive oil on interleukin-6 (IL-6) and platelet activating factor (PAF) inflammation pathways. In particular, PAF, which is a class of lipid chemical mediators with messenger functions, has gained research attention as a potential drug target due to its involvement in inflammatory diseases such as allergies, asthma, atherosclerosis, diabetes etc. [127]. Moreover, it is a point of focus as a contributing biological mechanism for anti-inflammatory action of several food products with protective roles against inflammation [31]. Several bioactive phytochemical compounds such as terpenes and constituents in olive oil with PAF action have been related to protective mechanisms against atherosclerosis [128,129]. In addition, as of today there is no contribution of olive oil or its constituents in potential DFIs. On the other hand, for some terpenes with PAF action, i.e., cedrol, inhibiting properties against human P450 have been described in vitro and further studies are needed to clarify potential DFIs [130]. Regarding potential PD-DFIs of PAF modulators with anti-platelet medications, there are not any reports suggesting potential contribution in DFIs.

3.2.2. Fruits and Fruit Juices

The Mediterranean fruits are among the most famous and widely consumed food products globally. Apples, apricots, avocados, cherries, clementines, figs, grapefruits, grapes, melons, nectarines, oranges, peaches, pears, pomegranates, strawberries, tangerines are the most common ones that are consumed by people following the Med-D style. Regarding fruit juices, the fermentable but unfermented product obtained from the edible part of the fruit and preserved fresh, they sometimes contain (due to the extraction process) different constituents or quantities from the original fruit.

The most notorious DFI regarding fruits and/or fruit juice with medications is that of grapefruit and its juice (GFJ) [41,131–133]. GFJ constituents (i.e., furanocoumarins etc.) can inhibit CYP activity (mainly CYP3A) through mechanism-based inhibition as well as transporter proteins in the intestine and liver (i.e., P-gp) [131,133–136]. This can elevate drugs' bioavailability which, along with reduction in drugs' intrinsic clearance, can result in increased concentrations and potential side effects. Typical examples are the concomitant use of GFJ with: (i) Ca^{2+} channel antagonists that result in low blood pressure; (ii) HMG-CoA reductase inhibitors that may lead to rhabdomyolysis and renal impairment; and (iii) adverse pulmonary effects caused by amiodarone co-administration [41,70,131,137].

Grapefruit as a plant belongs to the plant family of Rutaceae within the genus of Citrus fruits such as lemons, oranges, limes, tangerines fruits that are widely consumed. As a result, the frequent consumption of these products alerted the previous years the scientific community to the need to examine if DFIs could be further observed [138–140]. Until today, the most often described mechanism for potential DFIs are related with modulation of the activity of OATP transporters and CYPs metabolic activities [141–143]. Citrus fruits such as orange, lemon, pomelo, and lime have been assessed for potential DFIs and compared with GFJ. Pomelo juice increased the bioavailability of cyclosporine in an open-label crossover PK study probably due to inhibition of CYP3A4 and P-gp [144]. Orange juice reduced the bioavailability of alendronate and aliskiren [145,146], whereas Seville orange juice interacts with felodipine in a similar way to GFJ [147]. Lime juice has been shown in vivo to increase (similarly to GFJ) the bioavailability and systemic concentrations of carbamazepine with a clinically significant risk for liver and kidney toxicity [148]. Although tangerine (fruit and juice) showed some effect in vitro on CYP3A4-mediated metabolism of midazolam, this was of no clinical significance [149]. Narirutin found in Citrus fruits has also been observed in vivo to inhibit OATP1A2 and OATP2B1 [150].

Regarding apple juice, there is evidence from in vitro, in vivo and clinical studies of inhibiting activity on OATPs and modulation of the PK profile of drugs such as fexofenadine, montelukast and aliskiren [142,143,146,151]. It also contributed to a DFI with atenolol in a dose-response relationship but with limited effect on the PD-profile of the drug [152].

Cranberry juice and its constituent avicularin inhibited uptake transporters OATP1A2 and AOATP2B1 in vitro [153]. In addition, in vitro data indicated inhibition of CYP-mediated metabolism (CYP2C9 and CYP3A4) similar to ketoconazole and fluconazole. The effect is mainly attributed to anthocyanins content but these compounds show poor bioavailability, thus in vitro data were not repeated in vivo or through clinical studies [154–156]. Pomegranate juice has demonstrated in vitro/in vivo inhibiting action against CYP2C9 and CYP3A4 but with no clinical impact based on the available clinical data [157].

Drug interactions with fruits, fruit juices or pulps can also be related with PD-DFIs, and especially for fruits that contain considerable amounts of potassium (K^+). Bananas, apricots, and oranges are some typical examples of high- K^+ fruits and in theory their over consumption can be implicated in potential PD-DFIs with ARBs and diuretics [109,110]. Although this effect is based in theoretical statements, an in vivo study with palm fruits and lisinopril demonstrated elevated serum K^+ levels [158]. The risk of potential hyperkalemia is clinically significant, especially in cases of kidney diseases. Although observational studies suggest that adherence to Med-D improves survival for CKD patients, there is a lack of conclusive clinical data regarding DFIs and hyperkalemia, hence vigilance should be advised from healthcare providers [159,160].

3.2.3. Fish and Sea Food

Fish and sea food (clams, cockles, crabs, groupers, lobsters, mackerel, mussels, octopuses, oysters, salmon, sardines, sea basses, shrimps, squids, sea breams, tunas, etc.) are the main sources of protein and fat within the Med-D diet. They contain high amounts of essential amino acids along with n-3 fatty acids (FA) (i.e., eicosapentaenoic acid and docosahexaenoic acid) especially the pelagic fishes (sardines, anchovies, mackerels etc.) [161]. Apart of the nutritional value in Med-D, marine n-3 FAs are known to have positive effects on human health such as a protecting role in cardiovascular diseases, inflammation, diabetes, neurocognitive disorders etc. [162]. Regarding DFIs, omega-3 FAs seem to reduce coagulation factors (i.e., fibrinogen and prothrombin), thus in theory can potentiate the effects of anticoagulants [163]. As of today there have been some case reports of interactions between warfarin co-administration with fish-oil supplements, but the results were not repeated in a retrospective study of a larger cohort of patients with atrial fibrillation and deep vein thrombosis [164–166]. Considering also that DS usually have a higher content of n-3 FAs than the consumed food, the potential DFI is of minor importance and negligible for patients that remain adherent in their treatment plan.

3.2.4. Milk Dairy Products, White and Red Meat

Milk and dairy products (yoghurt, cheese) are part of the traditional domestic livestock practices around the Mediterranean basin and are part of the historical heritage of the dietary habits for the region. In medicine, milk and dairy products are an old case of potential DFIs due to their content in Ca^{2+} and tyramine. The presence of Ca^{2+} in milk and dairy products can create unabsorbed chelate ligands with antibiotic classes of tetracyclines and quinolones resulting in reduced bioavailability (PK-DFIs) [62]. Tyramine is a precursor of catecholamines and the inhibition of their metabolism from MAOIs can lead to increased catecholamine levels which can cause hypertension. Tyramine is known to interact with mono-amino oxidase inhibitors (MAOIs) resulting in an effect known as tyramine pressor response with high blood pressure and risk of cerebral hemorrhage which can be fatal [42,167]. Finally, another important PK-DFI is the reduced bioavailability of ferrous from cow milk. Caseins in cow milk bind Fe^{2+} by clusters of phosphoserines, keeping it soluble in GI's alkaline pH, preventing its free form from being available for absorption, thus decreasing its bioavailability in cases of ferrous supplement co-administration [168]. In addition, co-administration of mercaptopurine and cow milk in patients with chronic myelogenous leukemias reduces the bioavailability of the drug due to milk's high content of xanthine oxidase, thus this co-administration should be avoided [169,170].

Meat products within Med-D, although consumed to a limited extent, are a valuable source of nutrients for a healthy and balanced diet. Their dietary value lies in their high protein content with essential amino acids, ferrous from red meat, vitamin B12 and other vitamins of B-complex, zinc, selenium, and phosphorus. Fat content is dependent on meat species, feeding system, as well as the meat part that is used in food [171]. As stated earlier, high-fat content may lead to raised salt and increase the solubilization of lipophilic drugs [38].

3.2.5. Wine and Other Beverages

Wines, except for their alcohol content (~11% for whites and 15% for reds), have a rich composition of bioactive compounds such as polyphenols. Resveratrol, anthocyanins, catechins, and tannins (proanthocyanins and ellagitannins) are some of the most often found polyphenols with a higher content in red wines which also explicate the beneficial effect of from wine consumption [172,173]. One of the most known examples is the French paradox, the epidemiological observation of low coronary heart disease death rates despite high intake of dietary cholesterol and saturated fat in southern France which is attributed in red wine consumption in those populations [174]. Regarding DFIs, polyphenols can modulate the phase I and II metabolism as stated earlier but for wine this effect can be considered minimal compared to the effects of alcohol in the case of regular or heavy drinking.

Alcohol can enhance the effects of medications, especially in cases of chronic conditions. PK-DFIs of alcohol are related mostly with induction of CYP2E1 and to a lesser extent CYP3A3 and CYP2A1. Heavy alcohol drinking can lead to PD-DFIs of alcohol such as sedation when combined with CNS acting drugs (sedatives, antihistamines, antidepressants, antipsychotics etc.), induce gastric bleeding when combined with aspirin and relative painkillers or anticoagulants, and hypoglycemia with antidiabetic drugs [43,175]. Regarding the vexed issue, the widespread opinion that concomitant drink of alcohol with antibiotics or other antimicrobials will cause toxicity or treatment failure, a recent review of the available evidence suggested that the data are poor and sometimes controversial [176]. The reduced efficacy refers mostly to erythromycin and doxycycline. Disulfiram-like reaction (distress, pain, flushes, irregular heartbeat) can occurs in co-administration of metronidazole, ketoconazole, griseofulvin and cephalosporines (i.e., cefuroxime, cefotetan, ceftriaxone, cefoperazone, ceftriazone). Ambiguous data for ADRs exist for trimethoprim sulfamethoxazole. On the other hand, penicillins, fluoroquinolones, azithromycin, tetracyclines, nitrofurantoin, secnidazole, tinidazole, and fluconazole have not been causally related to ADRs [176]. Another mechanism involved is the reduction in the immune response and epidemiological studies have shown alcohol abuse to be associated with an increased incidence of infectious diseases. But this is related mostly to cases of alcohol abuse, consumption of high content alcoholic drinks and overall, a poor quality of life regarding well-being and disease prevention. Thus, it is a good idea from the healthcare perspective, especially for heavy-drinking patients under treatment, to advise towards drinking cessation [177,178]. On the other hand, the moderate consumption of red wine seems to be beneficial in cases of immune protection due to its polyphenol content [177]. Thus, although the quality and quantity of data are vague, the avoidance of or reduction in consuming alcohol in low or moderate amounts (e.g., a social occasion with one glass of wine or beer) as is suggested through Med-D can be enjoyed.

4. Discussion

It is of no debate that a healthy diet and nutrition is essential for good health and shields from several chronic non-communicable diseases, such as cardiovascular heart disease, diabetes, CNS disorders, autoimmune disease and cancer [11,17,22,26,31,163,179,180]. Thus, in the context of optimum healthcare provision is important to support patients as well as the general population to embrace a healthier balanced diet and remain adherent and compliant to it along with their medication [181]. Healthcare providers should be

able to educate patients and in the context of precision medicine era, to individualize their consultation so as to empower patients to improve their health and well-being [182–184].

Med-D remains one of the most valuable and widely studied dietary habits for promoting well-being. The clinical evidence supports that long-term adherence to Med-D is valuable against metabolic disorders and cardiovascular diseases. Numerous studies demonstrate the anti-inflammatory and anti-oxidative properties of constituents found within the Med-D foods against risk factors and pathophysiological mechanisms lowering the risk for developing most of the major non-communicable disorders [2,6,8,23,28,185,186]. All those food products and nutraceuticals that promote well-being have been the focus of research the recent years for the identification of bioactive compounds that can be related with molecular mechanisms by which dietary components promote health and prevent diseases [187–189]. On the other hand, these bioactive dietary compounds can share same biological mechanisms with drug molecules and interfere with pharmacological mechanisms modulating the clinical outcome due to DFI [45].

The DFIs, although seeming to be summarized in a simple clinical question “shall I take this drug with this food?” are more than that. DFIs depend on the type and amount of food consumed on daily basis, patient’s health status, comorbidities, drug categories that are prescribed, time of drug administration and meal intake, the clinical significance of the DFI and whether it is beneficial or not [50,52]. Briguglio et al. in their work [45] described that DFIs can be categorized in three groups: (i) pharmaceutical, (ii) pharmacokinetic and (iii) pharmacodynamic based on the mechanism involved. Alternatively, four types can be considered based on the process prior to systemic concentration. Hence, pre-systemic interactions are referred to as type I ex-vivo interactions or type II modulation of enzyme (subtype a) or carriers (subtype b) and/or other deactivations in GI-track (subtype c). Post-systemic interactions are described as type III for modulation of distribution and metabolism in the body and type IV as modulation of drug’s renal or enterohepatic clearance. The latter description omits the PD-DFIs which could be considered as a type V post-systemic phase interaction.

This work aimed to provide a literature review regarding DFIs focusing on examples of foods that are included in the Med-D and discuss cases in which they can be related with significant DFIs. DFIs for Med-D food products are associated with modulation of PK processes and primarily with drugs’ first pass effect from the GI-track to reach the systemic circulation. The majority the cases discussed refer to type II and III (subtypes a and b) with the addition of PD-effects that can occur for some products (Figure 5). Absorption and metabolism are the two main processes that should be considered when the question comes to food effects for a drug and the main pathways involved are the carrier-mediated transport across membranes and/or the mediated metabolism from Phase I and Phase II enzymes [39,112]. As shown in Tables 1–3, there is a good quality of evidence that cruciferous vegetables may impact drug metabolism, and fruits (or juices) such as grapefruit, apples, pomelo, pomegranates, and Seville orange juice can modulate the PK profile of some drugs which can be clinically significant in cases of drugs with narrow therapeutic index [57,113,131,139,142]. In addition, oat brans and fibers can modulate the absorption of statins whereas the high-fat content foods can modulate the bioavailability of some orally administered cancer medications [56–59]. Regarding PD-effects, the high content in Vit-K and K^+ in some vegetables and fruits can modulate the pharmacological action for coumadin analogue anticoagulants (Vit-K) and contribute to hyperkalemia with ACEs, ARBs, and diuretics [106,109]. Although there are case reports and general literature discussion, the currently accepted scientific point of view is that patients who remain adherent and compliant to a balanced diet prior to and during any therapy initiation can keep on consuming these food products in a similar way to before [45]. The key issue here is the communication of patient with healthcare provider in case any adverse event occurs and the healthcare provider’s awareness to report it and examine whether a DFI is related with it.

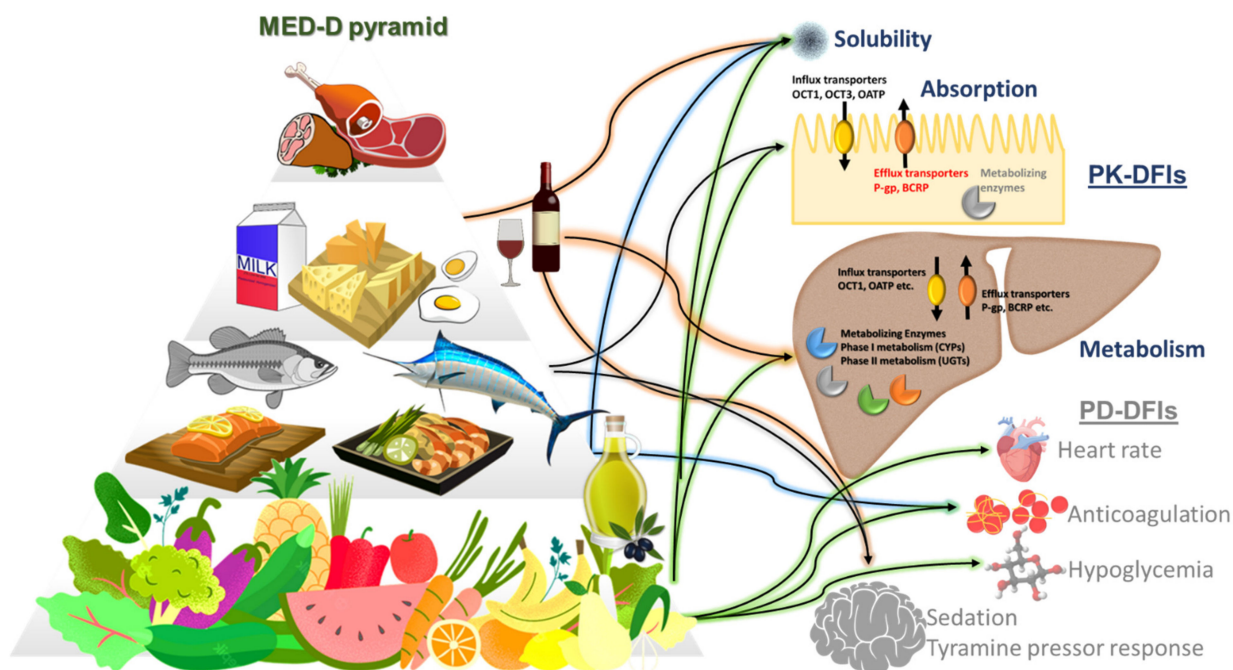


Figure 5. DFIs of Med-D food products regarding relation with type II and type III (subtypes a and b) interactions.

In addition, for cases where the food effect is negligible, or the pharmacological effect is sustained (Figure 2), it should be noted that Med-D diet can be considered as a collaborating partner with drugs [7,10,19,180,190]. For example, it may empower patients to better manage their health status and improve biochemical disease markers (i.e., blood glucose, cholesterol etc.) thus avoiding complicated therapeutic regimens with multiple medications that also raise the risk for adverse drug events from drug-drug interactions [32,191].

Apart from the well-documented cases (Tables 1–3) there are a lot of additional examples where data are scarce, theoretical, or poor. Hence, future studies are needed to further advance our knowledge in the field of DFIs. As the research is progressing on how dietary constituents engage in body homeostasis and health status, new knowledge is emerging towards prediction of food effects on drug's action. Increasing our understanding on PK and PD interaction mechanisms and utilization of novel experimental procedures will allow the gap on the available evidence regarding food effects on drugs to decrease. The incorporation of biomedical methods will allow the better prediction of potential interactions even through in silico methods during drug development or through big-data analysis [192–194]. From the citizen's perspective, the harnessing of digital evolution in relation to health promotion also cannot go unnoticed. Patient's oriented eHealth tools and apps are constantly emerging as means for patient empowerment to better manage their health status and well-being [195–200]. Even for Med-D, smartphone apps are available to assist people to remain adherent with the Med-D principles [201]. Moreover, a recent analysis of Android Google Play and Apple App Store Apps suggested that currently available apps can deliver information on the Med-D, but the integration of more behavioral change techniques within them is needed to expand the potential for improved adherence to Med-D [202]. Finally, eHealth evolution for patient empowerment can also assist in the dissemination of knowledge regarding DFIs, assisting patients to avoid potential interactions with DS and improve their communication with their healthcare providers [35,37,203,204].

5. Conclusions

The prediction, prevention, and management of DFIs is an essential element of optimum healthcare provision. Even for Med-D, one of the most effective diets, there can

be cases where food habits may have negative impact on therapeutic outcome. Proper patient consultation is important, so they are aware to avoid any potential conflicts between administered treatment and dietary habits. Adherence to a diet program similar to the one that is proposed through Med-D and individualized patient consultation and education from healthcare providers for potential DFIs will help patients to manage their disease and their overall well-being.

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