A Review of the Clinical Significance of Fruit and Vegetable Natural Products on Cytochrome P450 Activity

Abstract

The primary goal of drug metabolism, sometimes referred to as pharmacokinetic process, is to change a medication's chemical structure to make it more readily excretable. Typically, phase I and phase II reactions involve this mechanism. Xenobiotics can stimulate or inhibit the activity of cytochrome P450 (CYP450) enzymes involved in phase I processes. The goal of this research is to clarify the clinical significance of CYP450 induction and inhibition by demonstrating how certain bioactive compounds found in foods or natural products derived from fruits and vegetables can alter CYP450 enzyme activity, impacting drug bioavailability and depuration in addition. The interaction between natural products and foods derived from fruits and vegetables and some pharmaceuticals that can result in toxicity or therapeutic failure will be explained with a few instances. This will make it possible to compile pertinent data regarding appropriate pharmaceutical management in a range of clinical contexts.

Keywords: Fruits, Vegetables, Cytochrome P450, Clinical

Introduction

Many health problems can be treated and resolved with the help of medicines. To ensure that they are secure and goal-oriented, they must be administered appropriately. Actually speaking, drugs should be incredibly specific in how they work, affect patients in the same way as expected, be unaffected by food or other medications taken at the same time, show direct potency, be completely non-toxic at all dosages, and only need to be taken once to effect a permanent cure [1]. Nevertheless, the perfect medication has not yet been found. Potent substances found in many medications interact with the body in various ways. Most of the time, dietary habits can have a big impact on drug use [2]. Drug interactions are situations when a substance alters the way that drugs work, either by intensifying or lowering their effects, or by producing an entirely new effect that is not intended by the original target. Drug interactions, or drug-drug interactions, naturally come to mind when this happens [3]. Nevertheless, there can be drug interactions between medications and foods (drug-food interactions) as well as between medications and herbs (drug-herb interactions) [4]. These may occur accidentally or as a result of not knowing what the substances' active ingredients are. Drug effects can inadvertently be increased or decreased by interactions between food and medications. Certain commonly used herbs, fruits, vegetables, and alcohol might cause therapeutic failure to the point where the patient's condition deteriorates. The majority of clinically significant drug-food interactions result from modifications in the drug's bioavailability brought on by food [5].

The majority of pharmacological side effects are typically related to dietary components, which include changes in absorption brought on by diets heavy in protein, fatty acids, and fiber [6]. Bioavailability is a crucial pharmacokinetic parameter that is linked to the majority of medicines' therapeutic effects. Moreover, food intake's influence on the drug's therapeutic effect must be quantified in order to assess the clinical significance of food-drug interactions [7].

The majority of interactions that have clinical significance are associated with a high probability of treatment failure because of a marked decrease in bioavailability in the fed state. Chelation with food's constituents frequently results in such reactions. Specifically, stomach acid secretion can either improve or decrease the bioavailability of certain medications in terms of the physiological response to food ingestion [8].

Drug interactions may result in changes to a drug's pharmacokinetics or pharmacodynamics. Pharmacodynamic interactions can have antagonistic, additive, or synergistic effects on a medicine. Drug interactions (DIs) are the most significant and frequently overlooked cause of pharmaceutical errors [9].The concurrent use of various medicines that have a large surface area upon which the drug can be bonded, absorbed, or chelate, change the pH of the stomach, alter gastrointestinal motility, or disrupt transport proteins like P-glycoprotein can all have an impact on the absorption of drugs in the gastrointestinal tract [10]. A decrease in a drug's rate of absorption alone is rarely clinically significant, but a decrease in the amount of absorption may be if it results in serum levels that are below therapeutic limits [11].

The kinetic behavior of an enzyme can be changed by variables such nonspecific binding, abnormal kinetics, low effector solubility, and different ratios of accessory proteins. These variations can therefore complicate the extrapolation of in vitro findings to the human condition [12].Because Coenzyme Q-10 (CoQ10) is widely recognized by the general population as a crucial vitamin in sustaining human health, people eat large amounts of CoQ10 as food supplements. Food-drug interactions occur as a result of its interference with the intestinal efflux transporter P-glycoprotein (P-gp) [13].

One hidden issue that frequently arises in clinical practice is the interaction between medications and natural products. The same pharmacokinetic and pharmacodynamic principles that govern interactions between medicines and natural products also govern interactions between pharmaceuticals and natural products. Agents that influence the enzymes responsible for metabolizing drugs have been found in a number of fruits and berries [14].The most well-known example is grapefruit, but other fruits that inhibit cytochrome P450 3A4 (CYP3A4), the most significant enzyme in drug metabolism, include sevillian orange, pomelo, and star fruit [15].

It is anticipated that research on genetic variables influencing pharmacokinetics and pharmacodynamics as well as drug-drug, food-drug, and herb-drug interactions will enhance drug safety and facilitate customized medication therapy. Only when prescribed in the right dosage, in the right combination with the right meals, and at the right time can medications demonstrate their effectiveness [16].

Information regarding food-drug interactions is not always easily accessible, in contrast to information about drug-drug interactions. Accurately determining the effects of diet and nutrition

on a certain medicine is a challenging and complex subject. The purpose of this page is to increase the awareness of patients and healthcare professionals, particularly doctors, pharmacists, and other medical professionals, about drug and food interactions.

Conversely, the most prominent phase I drug-metabolizing enzyme system, cytochrome P450 (CYP), is in charge of the metabolism of numerous xenobiotics, including medicinal medications and some significant endogenous compounds like steroids [17]. Human hepatic CYPs are represented by the following relative abundances: CYP1A2 (13%), 2A6 (4%), 2B6 (<1%), 2C (20%), 2D6 (2%), 2E1 (7%), and 3A4 (30%) [18].

Every CYP enzyme has a different role in human drug metabolism; for example, CYP2D, CYP3A, and CYP2C are all responsible for 20%, 25%, and 50% of the medications that are currently on the market [17].

There is often inter-individual heterogeneity in CYP expression, which can be influenced by both environmental (such as inducers and inhibitors) and genetic (such as genetic mutation) variables [19].

Polymorphisms in CYP1A2, CYP2A6, CYP2D6, CYP2C9, CYP2C19, and CYP3A have been suggested by some evidence [20].

When two medications are taken together, it is common for drug interactions to occur when one medication affects the other's metabolic clearance by inhibiting or inducing a particular CYP enzyme. These interactions can have catastrophic consequences. It is likely that components in herbal preparations may be substrates, inhibitors, or inducers of CYPs and have an impact on the pharmacokinetics of any co-administered drugs metabolized by this system given the rising use of medicinal herbs, particularly in the West where they are frequently administered in combination with conventional therapeutic drugs [22]. This review focuses on known or suspected interactions between herbs and CYP, discusses how to predict interactions between herbs and drug metabolism, and goes into additional detail on the clinical and toxicological ramifications of these interactions.

When a patient is receiving pharmaceutical treatment and, eventually, a pharmacological reaction that deviates from expectations is seen. This could have happened due of a pharmaceutical interaction. This occurs when a medication is administered or ingested in conjunction with other medications, foods, or botanical remedies [23]. In this instance, the patient's response to the medication may shift in a favorable or negative way. Examining the detrimental alterations in pharmacological reactions, such as intoxication or treatment failure, is very important.

In this review, we primarily discuss how medications and diets derived from fruits and vegetables interact to affect cytochrome P450 function. Natural compounds have the potential to alter medication plasmatic concentrations through enzymatic activation or inhibition [24].

Understanding this subject is crucial for clinical practice because it helps a clinician determine which foods with a vegetable origin should be avoided when a patient is receiving pharmaceutical treatment. It also helps patients avoid experiencing a change in their response to prescription medications, which could potentially be fatal.

Aspect of pharmacokinetics in general

We will begin with a brief overview of pharmacokinetics in order to comprehend the impact of chemical compounds found in some medicinal plants and foods derived from vegetables on the activity of cytochrome P450 (CYP450), as this enzyme is involved in the phase I reactions of drug metabolism.

The area of pharmacology known as pharmacokinetics is in charge of examining and elucidating the mechanisms via which medications are taken up, distributed, metabolized, and excreted from the body [25]. Understanding these pharmacokinetic processes and how they affect a drug's bioavailability is crucial [26]. The amount of a medicine that is in the bloodstream and able to have a pharmacological impact is referred to as its bioavailability [27]. Nonetheless, a drug's pharmacological response will change if its plasma amount changes [28]. The medications' bioavailability is influenced by the four pharmacokinetic processes. As seen in Figure 1, the medicines' plasma concentrations during metabolism can be altered by either inducing or inhibiting distinct CYP isoenzymes.

The significance of sticking to a treatment plan in order to prevent variations in plasmatic concentration is better illustrated by the example that follows. When patients are receiving pharmaceutical treatment, following the dosage schedule is crucial. For instance, this patient should take precisely three 500 mg acetaminophen tablets daily if the prescription calls for 500 mg to be taken every eight hours.

The dosage and timing of each shot must be followed in order for the patient to receive an appropriate acetaminophen pharmacological response and to reduce the likelihood of side effects or therapeutic failure. The drug's plasma concentration and, thus, its reaction, are subject to alter if the patient modifies any of these two factors [29].

Following the oral administration of a single dose, the drug's plasma concentrations increase over time until they reach their maximum level. Maximum plasma concentration (Cmax) is the name given to this maximum point, which is attained in a predetermined maximum time (tmax). Every medication has different parameters [30]. A drug's Cmax falls inside its therapeutic range [31].

Conversely, following many medication administrations, the residual amount of the prior dose causes the final concentration to rise until it reaches a steady state known as the equilibrium state [31]. Usually, four to five half-lives are needed to reach a steady state [30]. The amount of time needed for a medicine to reduce its starting concentration by half is known as its half-life (t1/2) [30].

The range of therapeutic impact is occupied by the drug plasmatic concentrations in the equilibrium state. Therapeutic failure results from plasma levels falling to concentrations below

the therapeutic level when a patient stops taking their medication. A medication is usually eliminated after four to five half-lives [31].

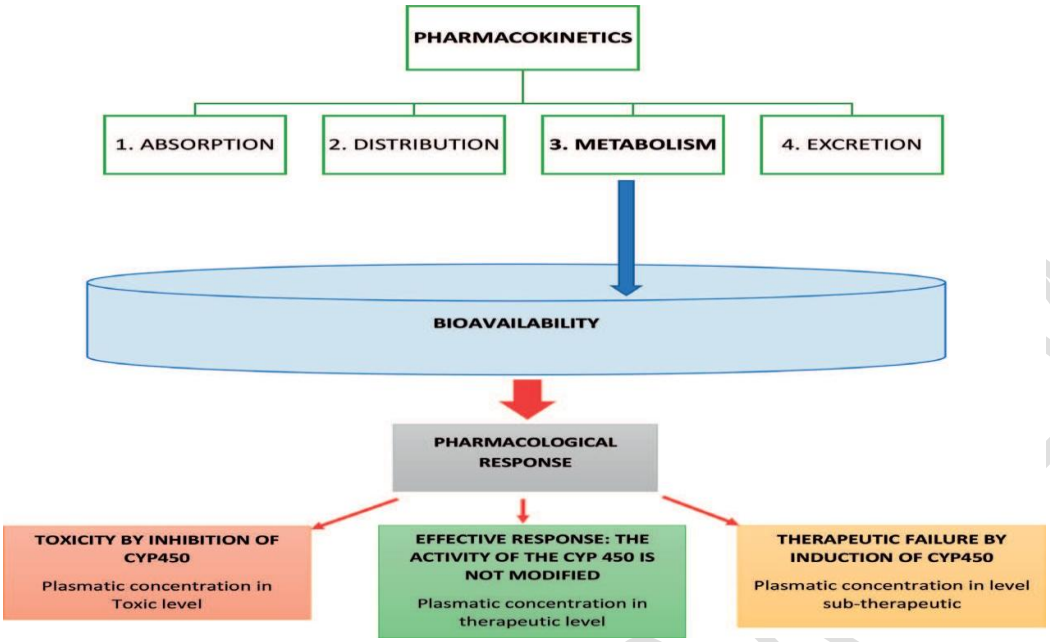

Figure 1. Impact of medication metabolism on the pharmacological reaction.

Drug metabolism through the pharmacokinetic process

Chemically, the medications are classified as acids or weak bases. During the absorption process, the substance that passes biological membranes is known as the nonionized fraction because of its lipid solubility. The drug will continue to remain in the body through processes of reabsorption at the renal level or the enterohepatic circuit and redistribution from drug deposits in adipose tissue as long as the condition of lipid solubility is not lost [32].

The medication cannot be removed if this lipid solubility requirement is not met [33]. Thankfully, the metabolism's pharmacokinetic process aids in changing a drug's molecular structure to one that is more polar, facilitating easier excretion [34].

The liver is the primary organ involved in the metabolism of medications and other xenobiotics. But other tissues, such the brain, lungs, skin, kidneys, and gastrointestinal system, are also capable of metabolism [25].

The hepatocyte, which serves as this organ's functional unit, is made up of several enzymes found in the cytosol, smooth and rough reticulum membranes, mitochondria, and other structures [35]. In the course of this medication metabolism, the following could happen:

1. change into a molecule that is more active
2. transform toprovide biological activity (pro-drug).

3. change into a molecular inert state
4. change into a poisonous compound

It is noteworthy to emphasize that certain medications do not undergo transformation. They are removed without changing their chemical structure [36].

Impact of the first step'smetabolism

When medications are taken orally, they experience a phenomena known as elimination before the actual metabolism occurs. First-pass metabolism is the term for this phenomenon, which mostly affects the small intestine's epithelial cells in the gastrointestinal tract [37]. The substance that was not biotransformed then travels to the liver via the portal circulation, where the hepatocytes perform the actual metabolic process [37]. After liver extraction, there is enough bioavailable medication left to provide a sufficient pharmacological response. Because the effective dosages of the drugs used in the clinical ready are thought to be the result of the first step's metabolism, it is crucial to avoid changing its bioavailability. Above all, drugs like barbiturates, which have a limited safety margin, should be used with extreme caution [38].

Factors influencing how drugs' metabolism

Physiological factors: pregnancy and advanced age

Compared to the metabolic rate of a young adult, the metabolic rate is lower in children and elderly adults [39]. The child's microsomal enzymes are not fully activated at this time [40]. Hepatocyte counts and blood flow to this organ are decreased in the aged [41]. As a result, there are less cytochrome P450 enzymes available to break down medications. The metabolic rate rises during pregnancy due to increased hepatic perfusion and cytochrome P450 activity [42].

Pathological variables: liver disease

Both the metabolic rate and the quantity of hepatocytes decline. The half-lives and plasmatic concentrations of medications are also rising. As a result, to avoid toxicity, the dosage must be changed [43].

Medicinal plants, foods, and drugs

Certain drugs and phytochemicals found in foods and medicinal plants of plant origin have the ability to either stimulate or inhibit cytochrome P450 activity [44].

Drug metabolism phases

Phase I, or functionalization, and phase II, or conjugation, reactions are the two categories into which drug biotransformation events are separated [45].

Phase I chemical reactions enable the addition of functional groups such –OH, -NH2, -COOH, -SH, or -O–. Alkylation, dealkylation, hydrolysis, oxidation, and reduction are examples of very basic chemical reactions that fall under phase I [45]. The oxidation processes carried out by the cytochrome P450 enzymes (CYP450) are the most significant and often occurring chemical

reactions among these reactions in the metabolism of pharmaceuticals. The smooth endoplasmic reticulum is home to these enzymes primarily [45].

Phase II reactions are the next step in the drug's modification process when the addition of functional groups (-OH, -COOH, -SH, -O–, -NH2) is insufficient to change it into a more polar molecule [45]. Conjugation reactions are another name for phase II reactions. The drug or metabolite molecule that was previously generated in phase I reactions is conjugated with a large polar (hydrophilic) molecule in these reactions, such as acetyl Co-A, acid glucuronide, glycine, glutathione, phosphoadenosylphosphosulfate, and S-adenosylmethionine [46]. Transferases are specialized enzymes that facilitate these reactions; they are often found in the cytosol and microsomes [46].

Cytochrome P450 (CYP450) and its function in drug metabolism

Hemoproteins, or cytochrome P450 (CYP450) superfamily of enzymes, are defined as having a heme group [47]. When carbon monoxide and iron in the heme group combine, light with a wavelength of 450 nm is absorbed [48]. They have discovered that eukaryotic and prokaryotic cells contain around 8700 genes that code for their proteins [49]. They are in charge of biotransforming or metabolizing various xenobiotics, including medications, as well as endogenous compounds like hormones in the body. These enzymes take involvement in phase I drug metabolism reactions as well as oxidation reactions[45]. They need a reducing agent like NADPH and molecular oxygen; they are often referred to as mixed function oxidases or monooxygenases [50].

Their patterns of substrate specificity differ; for instance, acetaminophen is a substrate of CYP2E1 and CYP1A2, but halogenated anesthetics are only a substrate of CYP2E1 [51]. Numerous tissues, including the kidney, lung, skin, brain, adrenal cortex, placenta, testicles, and other tissues, have this enzyme system; nevertheless, the organs with the highest concentration of CYP450 are the liver and small intestine [52].

Methodology

The global literature that is directly relevant to the ethnomedicinal usage, phytochemical, pharmacological, and mechanism of natural products of fruit and vegetable origins was searched between January 2023 and March 2024 for this review. Libraries and online databases (PubMed, Web of Science, Elsevier, Scopus, SciFinder, China National Knowledge Internet, Baidu Scholar, Google Scholar, and Springer) were used to gather all of the data regarding the fruits and vegetables. There were several keywords in the bibliography

Impact of fruit and vegetable-derived bioactive substances on CYP450 activity

There is a wealth of information regarding the ability of drugs to either activate or inhibit specific CYP450 isoenzymes in the literature. The population uses herbal medicine in traditional practice and consumes foods with nutraceutical properties, either to prevent or control any

disease, so there has been an increase in research recently on the impact of some phytochemical components found in fruits and vegetables on the activity of CYP450.

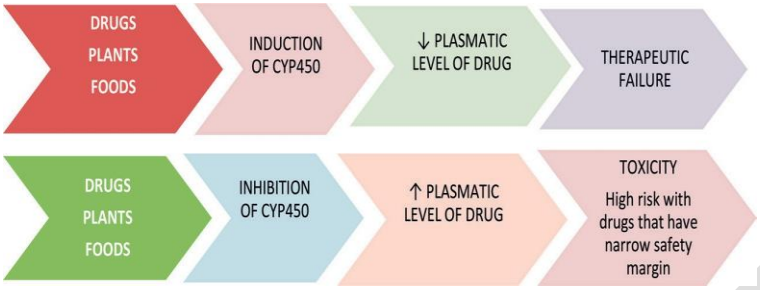

Figure 2. Impact of meals derived from vegetables and medicinal herbs on CYP450 activity

Table 1. Fruits and vegetables' impact on CYP450 activity

Fruit or vegetable	Phytochemistry compound	Activity on CYP450	Clinical effect on substrates of CYP450	References
Broccoli Brassica oleracea varitalica	Isothiocyanate sulforaphane, glucosinolate glucoraphanin, glucosinolates, phenolic acid, indol, and dithiolthiones	↑CYP1A2 ↓CYP2D6	↓Plasmatic concentration of I ↑Plasmatic concentration of II	[1]
Grapefruit *Citrus paradisi*, *Citrus reticulata*	Bergamottin, flavonoids (nobilein, tangeretin, quercetin, diosmin, naringenin, naringin, and kaempferol), and furanocoumarins	↓CYP3A4	↑Plasmatic concentration of	[2]

			III	
Pomegranate *Punica granatum*	Phenolic acids (punicalagin and tannins), flavonoids (anthocyanins), and pectin	↓CYP2C9 ↓CYP3A4	↑Plasmatic concentration of IV ↑Plasmatic concentration of III	[3]
Sevillian orange *Citrus sinensis*	Furanocoumarin	↓CYP3A4	↑Plasmatic concentration of III	[4]
Star fruit	Catechin Epicatechin	↓CYP3A4	↑Plasmatic concentration of III	[5]
Onion	Flavonoids organosulfur	↑CYP1A ↑CYP2B	↓Plasmatic concentration of I ↓Plasmatic concentration of I	[6]
Cauliflower *Brassica oleracea var. botrytis*	Isothiocyanate, glucosinolate, indole-3-carbinol, sulforaphane, indol	↑CYP1A2	↓Plasmatic concentration of I	[7]

		↓CYP2D6	↑Plasmatic concentration of II	
Spinach *Spinacia oleracea*	Flavonoids and *p*-coumaric acid derivatives, α-lipoic acid, poliphenols, lutein, zeaxantin, betaine	↑CYP1A2	↓Plasmatic concentration of I	[8]
Tomato *Lycopersicum esculentum*	Carotenoids phytofluene, phytoene, neurosporene, γ-carotene, and ζ-carotene lycopene, phytoene, phytofluene, quercetin, polyphenols, kaempferol	↓CYP1A1 ↓CYP1B1	↑Plasmatic concentration of III ↑Plasmatic concentration of III	[9]
Avocado *Persea americana*	Persin, carotenoids (zeaxanthin, α-carotene, and β-carotene), lutein, β-sitosterol, glutathione			[10]
Watercress *Nasturtium officinale*	Phenylethyl isothiocyanate (PEITC) and methylsulphinylakyl isothiocyanates (MEITCs), flavonoids such as quercetin, hydroxycinnamic acids, and carotenoids such as β-carotene and lutein	↑CYP4501A	↓Plasmatic concentration of	[11]
Carrot	beta-carotene and panaxynol	↓CYP1A2	↑Plasmatic concentration of I	[12]

I: Warfarin, caffeine, verapamil, amitriptyline, phenacetin, tacrine, theophylline, tamoxifen, Propanolol, ondansetron, naproxen, and haloperidol.

II: phenformin, paroxetine, risperidone, metoprolol, clozapine, timolol, tamoxifen, tramadol, seleglinide, fluoxetine, oxycodone, codeine, dextromethorphan, and tricyclic antidepressants.

III: Astemizole, cocaine, amiodarone, cisapride, dapsone, diltiacem, felodipine, nifedipine, erythromycin, indinavir, lidocaine, methadone, miconazole, quinidine, paclitaxel, mifepristone, spironolactone, verapamil, trazolam, desametaxone, ritonavir, lovastatin, and hydrocortisone.

IV: Amitriptyline, phenytoin, tolbutamide, glipizide, glibenclamide, fluoxetine, hexobarbital, meloxicam, ibuprofen, diclofenac, tamoxifen, fluvastation, phenytoin, and losartan.

Discussion

Grapefruit (Citrus paradisi): Two decades ago, it was inadvertently discovered that grapefruit and some medications interact [65]. Numerous studies on the impact of grapefruit and its constituents on CYP450 drug oxidation and transportation have been published since then [66]. According to a number of studies, grapefruit juice mostly affected the intestine CYP system while having a little impact on the liver [67]. The main mechanism underlying this interaction is the small intestine's suppression of cytochrome P450 3A4, which significantly lowers drug presystemic metabolism [65]. Consuming grapefruit juice has been shown to reduce CYP3A4 mRNA activity via a post transcriptional mechanism, maybe by promoting the enzyme's breakdown [68]. The inhibition of Pgp- and MRP2-mediated drug efflux, which is the transfer of medicines from enterocytes back to the gut lumen, may be another mechanism [69]. This would lead to an even higher fraction of medications ingested and greater systemic drug bioavailability. Additionally, it has been noted that the main components of grapefruit considerably reduce the function of OATP-B in vitro [54].

Several components may be involved in the interaction between grapefruit juice and medications [68]. Drug interactions may be caused by flavonoids, which are key constituents of grapefruit and include naringin, naringenin, quercetin, and kaempferol [70]. Other fruit juices also include some of these compounds.

Furanocoumarins, also known as PSoralens, are another class of chemicals found in grapefruit juice that are known to be mechanism-based CYP450 inactivators [71]. The main furanocoumarin found in grapefruit is bergamottin, which has been shown to inactivate CYP enzymes in vitro in a concentration- and time-dependent manner [72]. An intriguing feature of this interaction is that grapefruit juice can cause the medication to interact without having to be consumed at the same time. It has been claimed that grapefruit juice doubles the bioavailability of medications, even when taken 12 hours after eating. Grapefruit juice, both colored and white, has the same potency in causing medication interactions [73].

Prescriptions for medications metabolized by CYP3A4 should take this inhibitory interaction into consideration. Calcium-channel antagonists, such as diltiazem, nisoldipine, amlodipines, and pravastatin [74], modulators of the central nervous system, such as diazepam, triazolam, midazolam, atorvastatin, and pravastatin [75], immunosuppressants, such as cyclosporine [Paine and others 2008], antivirals, such as saquinavir [76]; a phosphodiesterases-5 inhibitor, such as

sildenafil [77]; antihistamines, such as terfenadine and fexofenadine [78]; antiarhythmics, such as amiodarone [77]; and antibiotics, such as eritromicine [15].

Approximately 2% of Americans, according to epidemiologic research, drink at least one glass of regular strength grapefruit juice each day [74]. This becomes relevant when we take into account the large number of individuals who get calcium-channel antagonist medication and HMG-CoA reductase inhibitors for chronic metabolic illnesses, such as hypertension, hyperlipidemia, and cardiovascular diseases [79]. Central nervous system modulators are also routinely administered to patients with mental illnesses. An rise in serum drug concentration has been linked to a higher frequency of dose-dependent side effects in the case of numerous medications [80]. Physicians should be aware of these interactions and try to warn and educate patients about the possible implications of concurrent administration of these medicines due to the wide-ranging effects of grapefruit juice on the pharmacokinetics of different pharmaceuticals.

Orange (Citrus sinensis): It doesn't seem that consuming the majority of orange juice varieties will change CYP3A4 activity in vivo [81]. On the other hand, grapefruit juice and orange juice from Seville oranges seem to be quite comparable, and they both have an impact on the pharmacokinetics of CYP3A4 substrates [82]. A single 240-mL serving of Sevilla orange juice has been demonstrated to raise felodipine exposure by 76%, which is similar to the rise seen after consuming grapefruit juice [83]. The mechanism of action of Sevilla orange is presumably comparable to grapefruit juice-mediated interactions because it includes notable amounts of flavonoids, primarily bergamottin and 6′,7′-dihydroxybergamottin [84]. It has also been demonstrated that orange juice inhibits Pgp-mediated drug efflux. Tangeretin and 3,3′,4′,5,6,7,8-heptamethoxyflavon were demonstrated by Takanaga and colleagues to be the main Pgp inhibitors in orange juice. They also demonstrated that nobiletin was a Pgp inhibitor. [81]. As a result, consuming orange juice may prevent Pgp from inhibiting the efflux transporters, increasing the bioavailability of medications and raising the possibility of side effects [85].

Additionally, it has been noted that some of the ingredients in orange juice, particularly naringin, have been shown to decrease OATP transport activity in vitro [86]. Orange juice has been shown to impair human OATP-A (OATP1A2, gene symbol SLC21A3/SLCO1A2) function in vitro [87]. On the other hand, OATP-A is not expressed in the intestine but rather primarily in the brain. On the other hand, 5% orange juice was found to strongly block OATP-B-mediated absorption of glibenclamide and estrone-3-sulfate by Satoh and colleagues [87]. Orange juice may lessen the intestinal absorption of OATP-B substrates (such as hormone conjugates, digoxin, and benzylpenicillin), which would lower the levels in the blood.

Orange juice oral coadministration reduced the oral bioavailability of fexofenadine, according to prior human investigations using fexofenadine as a probe [15]. It has been demonstrated that the components of orange juice interact with the OATP transporter family by decreasing their activity. A considerable decrease in the oral bioavailability of fexofenadine is indicative of the functional ramifications of this interaction, which may be caused by favored direct suppression of intestine OATP activity. According to other research, orange juice lowered ciprofloxacin, levofloxacin, and celiprolol absorption just a little bit [88]. An increase in the area under the curve was observed in a study examining the interaction between pravastatin and orange juice

[89]. Additionally, atenolol's bioavailability is somewhat decreased by orange juice, which may call for a dose modification [90].

Pomegranate (Punica granatum): Pomegranates are widely consumed worldwide and have been utilized for a wide range of medicinal uses in traditional medicine [91]. Numerous compounds, including pectin, tannins, flavonoids, and anthocyanins, are abundant in pomegranates.According to Hidaka et al. (2005), pomegranate juice inhibited intestinal CYP3A activity, which affected the pharmacokinetics of carbamazepine in rats. A single exposure to pomegranate juice appears to suppress intestinal CYP3A activity for around three days [92].Pomegranate juice was discovered by Nagata et al. (2007) to increase tolbutamide bioavailability in rats and to decrease human CYP2C9 activity [93]. Pomegranate juice has recently been demonstrated to potently block 1-naphthol's sulfoconjugation in Caco-2 cells [94]. Some pomegranate juice ingredients—most likely punicalagin—have been reported by Saruwatari et al. to potentially affect intestinal metabolism, particularly sulfoconjugation, which in turn may affect a drug's bioavailability [94].

Leafy vegetables

Among the typical cruciferous vegetables, broccoli (Brassica oleracea var. italica) and cauliflower (B. oleracea var. botrytis) are special because they have large concentrations of the aliphatics glucosinolate and glucoraphanin [59]. The bioactive isothiocyanate sulforaphane is one of the compounds that glucoraphanin hydrolyzes to create [95]. Depending on food handling practices, hydrolysis conditions, and preparation methods, these vegetables may contain varying percentages of isothiocyanate sulforaphane [96]. Dietary freeze-dried broccoli has been shown to provide protection against several malignancies in animal trials [97]. On the other hand, undamaged liver cells from rats and humans have been demonstrated to stimulate phase I and phase II drug-metabolizing enzymes in response to broccoli, cauliflower, and their glucosinolate hydrolysis products [98]. In a dose-dependent manner, the isothiocyanate sulforaphane lowered the hepatocytes' activity of the enzymes ethoxyresorufin-O-deethylase and pentoxyresorufin-O-dealkylase, which are linked to CYP1A1 and 2B1/2 [99]. Human hepatocytes treated with isothiocyanate sulforaphane showed an increase in hGSTA1/2 mRNA, while CYP3A4, the predominant CYP in the human liver, showed a significant drop in both mRNA and activity levels [100]. On the other hand, it was recently demonstrated that in primary hepatocytes and

Caco-2 cells, sulforaphane increases the levels of MRP1 and MRP2 mRNA [101]. Broccoli has also been discovered to have the ability to activate phenolsulfotransferases (PST) [102]. According to these findings, watercress (Nasturtium officinale), a very valuable cruciferous vegetable, is also a good source of other bioactive phytochemicals, including glucosinolates [103]. A remarkably abundant dietary source of beta-phenylethyl isothiocyanate (PEITC) is watercress [104]. A single consumption of watercress suppresses the hydroxylation of chlorzoxazone, an in vivo probe for CYP2E1, in healthy volunteers, according to earlier research by Leclercq et al. (1998) [105]. Additionally, it has been demonstrated that watercress is a bifunctional drug that can stimulate phase II (CYP450) and I enzymes [63]. Human liver cells treated with watercress juice increased the activity of NAD (P)H-quinone reductase, ethoxyresorrufin-O-deethylase, and CYP4501A [88]. Because PEITC can either activate or inhibit phase II enzymes as well as phase I enzymes, findings suggest that it also has a number of anticarcinogenic actions [106]. In vitro and in vivo, watercress juice can raise the levels of the enzymes SOD and GPX in blood cells [107]. Additionally, isothiocyanates interact with Ppg, MRP1, MRP2, and BCRP, among other ABC efflux transporters, and they may have an impact on the pharmacokinetics of these transporters' substrates [108]. Current research suggests that isothiocyanate and watercress may have clinical effects by altering the bioavailability of some medications [109].

Spinach, or Spinacia oleracea, is a vegetable that is high in antioxidants and is often boiled before being eaten [110]. It has been observed that freshly cut spinach leaves have at least 10 flavonoid glycosides and contain about 1000 mg of total flavonoids per kilogram [111]. These are 6-oxygenated flavonol methylated and methylene dioxide derivatives as glucuronides and acylated di-and triglycosides [112]. Although the nutritional benefits and safety of spinach consumption are supported by epidemiological and preclinical research, there is a lack of published information about spinach's impact on drug-metabolizing enzymes and drug transporters. The effects of these substances in vivo on the bioavailability of xenobiotics, whose clearance and/or tissue distribution are dictated by active transport and biotransformation, are

presently poorly understood.Platt et al. (2010) revealed that spinach's interaction with CYP1A2 as an antigenotoxicity mechanism protects against the genotoxic effects of 2-amino-3-methylimidazo [4,5-f] quinoline (IQ). Further research is necessary to assess potential nutrient–drug interactions due to its high amount of flavonoids and isothiocyanates [113].

Fruit vegetables

Lycopersicon esculentum, or tomatoes, provide a wealth of minerals and a variety of phytochemicals, including carotenoids like phytofluene, phytoene, neurosporene, γ-carotene, and ζ-carotene that may have an impact on health [114]. In addition, tomatoes contain a wide variety of phytosterols, phenylpropanoids, and flavonols (such as kaempferol and quercetin) [115]. The primary carotenoid found in tomatoes and tomato-based products is lycopene, which has been associated with a lower risk of long-term conditions like cancer and heart disease [116]. Lycopene suppresses CYP1A1 and CYP1B1, according to research on human recombinant CYP1 [117]. Additionally, lycopene has been demonstrated to somewhat lessen the 20% elevation of ethoxyresorufin-O-deethylase activity in MCF-7 cells caused by dimethylbenz[a]anthracene [118]. It seems to stimulate detoxifying enzymes and inhibit bioactivation enzymes. According to some research, lycopene may be more advantageous than other phytochemicals since it can help remove genotoxic substances and their metabolites [118]. High-dose lycopene supplementation raises hepatic cytochrome P4502E1 protein and inflammation in alcohol-fed rats, according to recent in vitro data [119].

Carrots (Daucus carrota): Carrots are a popular food ingredient. Numerous researchers have examined carrots' active ingredients, which include beta-carotene and panaxynol [120]. Carrots have two effects on CYP1A2 activity [64] and PST activity [88]. In a mouse model, Bradfield et al. observed that feeding carrots boosted the activity of ethoxycoumarin O-deethylase (ECD) [121].

The avocado, or Persea americana, is a good source of bioactive substances such sterols and monounsaturated fatty acids [122]. Avocado consumption and study on potential health benefits have expanded as a result of mounting evidence of its benefits [123]. Avocado phytochemicals have the ability to specifically induce a variety of biological processes [124]. According to a 2015 article, avocados and warfarin interact, with the fruit reducing the medication's effects. They did not, however, identify the reason for this restriction [125].

Clinical Importance

A daily consumption of at least 400 g, or five servings, of fruits and vegetables is advised by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) to help avoid chronic illnesses like diabetes, cancer, heart disease, and obesity. As a result, there is a rise in the demand for fruits and vegetables among customers worldwide, and some of them choose organic food because they know it is healthier. Natural product use to improve human health has developed independently in many parts of the world, and there are regional variations in production, use, attitudes, and regulations.

While the importance of drug-drug interactions is well acknowledged, drug-nutrient interactions have received less attention. Preclinical research provides the majority of the published data regarding fruits' and vegetables' effects on drug transporters and metabolizing enzymes. It is important to keep in mind that these consequences might also apply to people. With remarkable outcomes, a number of clinical investigations on the interactions between medications and grapefruit juice have been carried out. The phytochemical composition of the majority of the fruits and vegetables included in this review is comparable to that of grapefruit juice.Numerous in vitro and animal models have demonstrated the impact of these compounds on drug transporters and enzymes involved in drug metabolism. It is important to consider the possibility that different fruits and vegetables may have the same potential for interactions between drugs and fruits. The majority of medications used by humans are metabolized by the CYP3A4 enzyme, which is affected by fruit, vegetables, or their constituents (phytochemicals) as demonstrated by the evidence presented in this article. Therefore, a more standardized method of assessing nutrient-drug interactions in humans is required. The method must be methodical in order to: (1) determine how foods, nutritional status, or particular nutrients affect a drug's pharmacokinetics and pharmacodynamics; and (2) analyze how a drug affects general nutritional status or the status of a particular nutrient.

Conclusion

The bioavailability of drugs can be altered by the stimulation or inhibition of CYP450 by certain bioactive substances found in natural products derived from fruits and vegetables. The effectiveness and safety of pharmacological management are significantly impacted by changes in bioavailability. It is crucial to remember that a patient receiving pharmacologic treatment should not consume any foods or medicinal plants and fruits that may induce or inhibit any CYP450 isoenzymes.

In particular, patients should not utilize grapefruit or St. John's wort because these plants' phytochemical components have a strong ability to either stimulate or inhibit CYP3A4 activity, which has significant clinical implications. Therefore, physicians, nurses, pharmacists and other allied health workers should take note of this facts.

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