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Original Research Article

Effect of Fruit/Vegetable-Drug Interactions on CYP450, OATP and p-Glycoprotein: A Systematic Review

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Abstract

Purpose: *To review the concomitant use of certain drugs with fruit/vegetable juices that may lead to drug-juice interactions resulting in medication-related problems.*
Method: *In this systematic review, online databases (PubMed, Google Scholar and Science Direct) were searched for information on juices derived from fruits and vegetables that are reported to have inhibitory effects on cytochrome P450, p-glycoprotein and organic anion transporting polypeptides (OATPs).*
Results: *Fruits can inhibit CYP1A1, CYP1A2, CYP1A4, CYP3A1, CYP3A4, CYP2C6, CYP2C9, CYP2E1 and drug transporters (P-glycoprotein, OATP). On the other hand CYP1A1, CYP1A2, CYP2A2, CYP3A1, CYP1B1, CYP2B1, CYP2B2, CYP2C1, CYP2C6, CYP2E1 can be inhibited by some vegetables. Antihypertensives, antidiabetics, statins, analgesics and antipsychotics were the most common drugs interacting with fruits and vegetables. The inhibition of their metabolism by fruits and vegetables can cause serious toxic effects, e.g., hypertension, poor glycemic control, rhabdomyolosis and drug overdose-related toxic effects. Overall, active components of fruits and vegetables can interact with many drugs leading to adverse effects.*
Conclusion: *Screening of fruits/vegetables for possible risk of interaction, and patient counseling are some effective strategies for preventing such interactions for optimal patient care.*

Keywords: *Fruits and vegetables, Cytochrome P450, Drug interactions, p-Glycoprotein, Organic anion transporting polypeptides*

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INTRODUCTION

Drugs are essential components of medical therapy but concomitant consumption of other substances with drugs can cause unintended and unwanted outcomes which may lead to significant harm in some cases. The risk of drug interactions increases with number of drugs being taken by the patient. For example, the risk of interactions with 6-10 drugs may just be 7 % but with 16-20 drugs, the risk may increase up to 40 % [1]. High risk patients, such as elderly patients taking three or more medications for chronic conditions are more susceptible to suffer from such interactions. Many of such patients also use herbs, fruits, vegetables and other nutrients due to their traditional and folk benefits.

Nutritional status and diet can affect drug action by altering metabolism and function [2].

The global market of fruits and vegetable juices has been forecast to reach 72.29 billion liters by the year 2017 due to their therapeutic potential [3]. About 42.1 % of US population takes dietary supplements and 18.4 % of the population takes these supplements with their medications. Likewise, 73.1 % of Italian cancer patients take their prescribed drugs concomitantly with dietary supplements [4].

The concomitant use of multiple drug regimens along with different herbs and nutrients makes the users more prone to drug-fruit interactions. Such interactions can either lead to loss of therapeutic efficacy of drug or result in drug toxicities e.g. inhibition of metabolism of cilostazol by grapefruit juice leads to purpura [2]. The various mechanisms by which drug interactions can occur are summarized in Figure 1.

Inhibitory effect of grapefruit on cytochrome P_{450} was accidentally discovered when grapefruit juice was used to mask the taste of ethanol in assessing the effects of alcohol on felodipine. Cytochrome P_{450} is responsible for metabolism of several drugs, steroids and carcinogens. The members of this family are represented as CYP followed by Arabic numeral (family), capital letter (subfamily) and Arabic numeral (gene) e.g. CYP3A4. Six enzymes of this family (CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5) are responsible for 90 % of oxidation processes [5]. Drug efflux transporters (e.g. p-glycoprotein) and influx transporters (e.g. organic anion transporting polypeptide, OATP), located in human intestine (enterocytes), are present in several fruit juices. OATP is responsible for influx of anionic drugs such as HMG CoA reductase inhibitors, angiotensin receptor blockers (ARBs), several beta blockers and fexofenadine. It has similar classification pattern as cytochrome P_{450} i.e. OATP-A and OATP-B in brain and intestine respectively. They are further sub-classified as OATP1A2 and OATP2B1 [6]. Commonly used substrates for CYP450, p-glycoprotein and OATP are given in Table 1.

The current review aims to summarize research studies investigating general or specific interactions between clinically used drugs and fruits/vegetables in humans.

METHOD

In a systematic review, interactions of juices derived from fruits and vegetables with drugs were evaluated using online databases (PubMed, GoogleScholar, ScienceDirect). The search terms used were grapefruit juice, fruit juice-drug interactions, citrus juice drug interactions, drug metabolism, drug food interactions, p-glycoprotein interactions, tropical juice-drug interactions, OATP, cytochrome P_{450} drug interactions, vegetable juice drug interactions, pharmacodynamics drug interactions, pharmacokinetics drug interactions, and drug transporters (OATP/p-glycoprotein) were excluded. Figure 2 illustrates the

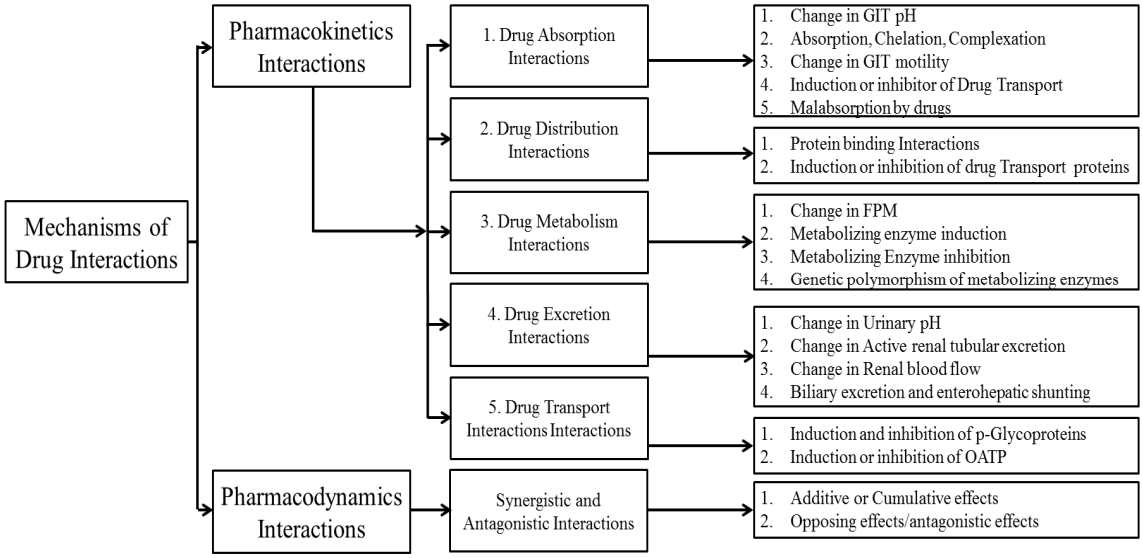

Figure 1: Types of drug interactions, GIT: Gastrointestinal tract, FPM: First pass metabolism, OATP: Organic anion transporting polypeptide

Table 1: Commonly used substrates for cytochrome P_{450}, p-glycoprotein and OATP [7,8]

CYP1A2	CYP2B6	CYP2C19	CYP2C9
Propranolol, Naproxen, Ondansetron, Theophylline, Verapamil	Buproproion, Cyclophosphamide	Amitriptyline, Citalopram, Cyclophosphamide, Diazepam, Indomethacin, PPIs, Phenobarbitone, Progesterone, Propranolol, Warfarin	Celecoxib, Diclofenac, Fluoxetine, Fluvastatin Glipizide, Ibuprofen, Naproxen, Phenytoin, Piroxicam, Rosiglitazone, ARBs, Tolbutamide, Warfarin
CYP2D6	**CYP2E1**	**CYP3A4/ CYP3A5/ CYP3A7**	**p-Glycoprotein Substrates**
Amitriptyline, Nortriptyline, Ondansetron Paroxetine, Phenacetin, Lidocaine, Metoclopramide, Tamoxifen, Venlafaxine, Beta blockers	Acetaminophen, Enflurane, Ethanol, Halothane, Isoflurane, Theophylline	Macrolides, calcium channel blockers, statins, beta blockers, anti HIV drugs, benzodiazepine, cisapride, dextromethorphan, estradiol, hydrocortisone, lidocaine, progesterone, quinidine, quinine, tamoxifen, vincristine	Vinblastine, vincristine, doxorubicin, dexamethasone, morphine, digoxin, loperamide, cimetidine
			OATP Substrates
			Cephalosporins, anticancer, lipid lowering drugs, HIV protease inhibitors, ARBs, enalapril, valsartan, fexofenadine

ARBs: angiotensin receptor blockers, PPIs: proton pump inhibitors, OATP: Organic anion transporting polypeptide.

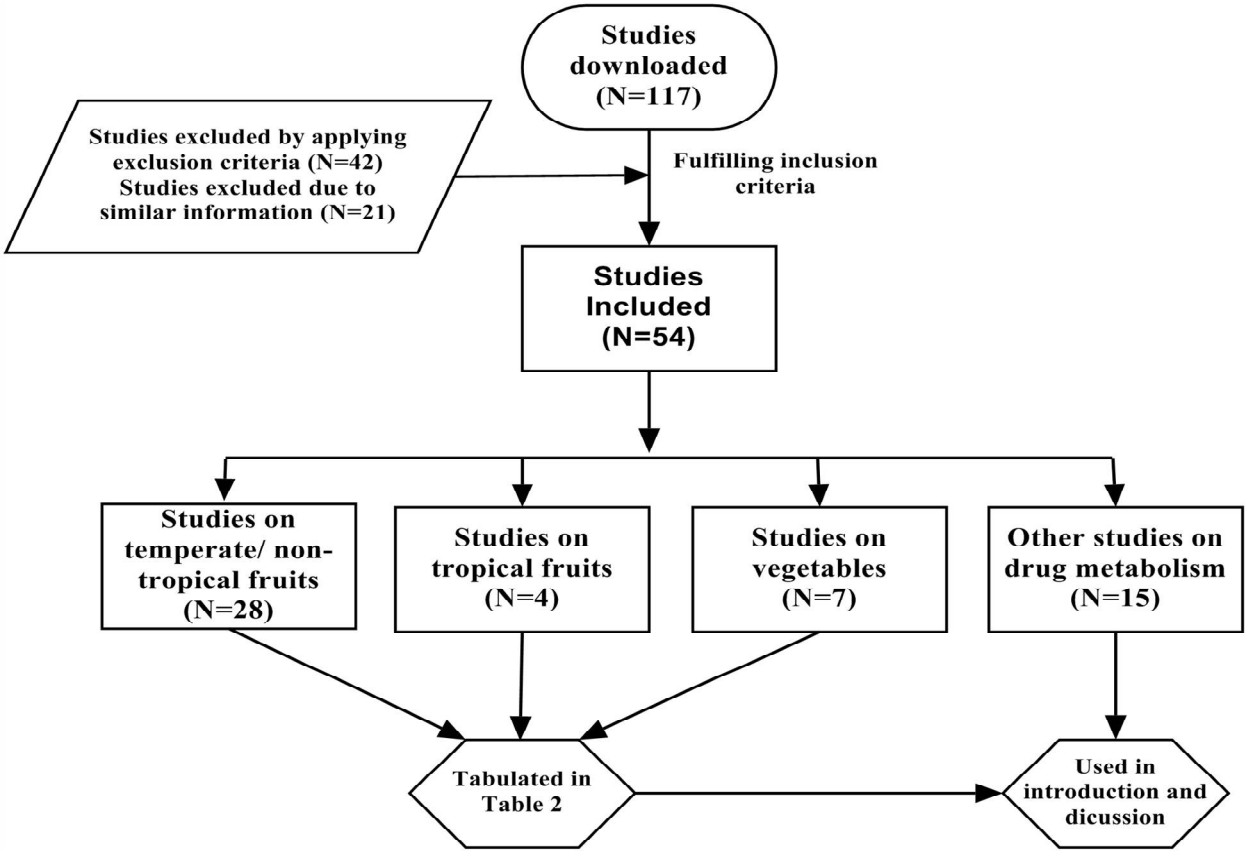

Figure 2: Flow chart of review process

CYP3A4 fruit juices, fruit juice and fruit juices warnings,. All studies (*in vitro* and *in vivo*) demonstrating interactions between drugs and juices from fruits and vegetables involving inhibition of cytochrome P_{450} (CYP450), p-glycoprotein (p-gp) and organic anion transporting polypeptides (OATPs) were included in the review. The articles included were those published from 1992 to 1013. However, personal communications, conference proceedings, un-published work, drug interactions that do not involve CYP450 system methodology adopted for the review process.

RESULTS AND DISCUSSION

Findings of literature search (Table 2) showed that CYP1A1, CYP1A2, CYP1A4, CYP3A1, CYP3A4, CYP2C6, CYP2C9 and CYP2E1 are more commonly inhibited metabolizing enzymes by fruits and their juices. On the other hand CYP1A1, CYP1A2, CYP2A2, CYP3A1, CYP1B1, CYP2B1, CYP2B2, CYP2C1, CYP2C6, CYP2E1 were inhibited by vegetables. We found no studies demonstrating inhibition of drug transporters by tropical fruits and vegetables while fruits and their juices caused significant inhibition of P-glycoprotein and OATPs in our reviewed studies. Fruits and vegetables inhibit metabolism of antidiabetics, calcium channel blockers and statins resulting in hypoglycemia, hypotension and rhabdomyolosis respectively [9–47].

Fruits and vegetables are frequently used for their nutritional and medicinal potential e.g. use of cranberry and mulberry juice for UTIs and diabetes respectively [28,32]. Comprehensive studies have been conducted to illustrate inhibitory effects of temperate fruits on cytochrome P_{450} and drug`s transporters. Limited data demonstrate inhibition of such enzymes by tropical fruits and vegetables. Moreover, there is still paucity of literature explaining the effect of tropical fruits and vegetables on drugs transporters.

Results from our review showed more frequent interactions with temperate fruits as compared to tropical fruits and vegetables which might be due to extensive research conducted on temperate fruit juices as compared to tropical fruits and vegetables. CYP3A4 and CYP2C9 are most widely inhibited metabolizing enzymes causing elevated serum levels in the presence of calcium channel blockers, anti-diabetics, warfarin, midazolam and diclofenac [9–17,23–34]. Such interactions cause toxic effects e.g. hypoglycemia with antidiabetics [11–13,18,19] and bleeding tendencies with warfarin [23–31]. Dahan & Altman reported that inhibition of metabolism of statins, felodipine and rapaglinide can cause rhabdomyolosis, hypotension and hypoglycemia respectively [9]. Both influx and efflux drug transporters were significantly inhibited by temperate fruit juices. In an earlier report, FDA search on adverse events caused by concomitant use of grapefruit juice and drugs have resulted in identification of 36 potential interaction cases. Examples include hypotension resulting from calcium channel blockers and muscle pain with statins [48,49].

Sadeque *et al* [51] has indicated that inhibition of p-glycoprotein causes increases drug delivery towards brain. Inhibition of p-glycoprotein by grapefruit juice may lead to accumulation of loperamide in the brain resulting in respiratory depression. Similarly, the inhibition of OATPs by apple juice increases bioavailability of rosuvastatin resulting in rhabdomyolosis [20,21]. Furthermore, fruit juices inhibit metabolizing enzymes (CYP450, glucuronosyl transferase), drug transporters (OATP, P-gp) and other multiple resistance proteins [MRP]. This in turn increases plasma levels of drugs metabolized by these systems. One widely studied example of such inhibition is grapefruit juice which is reported to inhibit cytochrome P_{450}, p-glycoprotein and OATP [9,10]. Even a single glass (250 ml) of regular strength grapefruit juice can cause potential inhibition of drug metabolizing enzymes [9,10]. Inhibition of CYP3A4 by grapefruit juice increases the risk of toxicity from calcium channel blockers (tachycardia, hypotension), statins (myopathy, headache, rhabdomyolosis), antihistamines (arrhythmias, prolongation of QT intervals) and immunosuppressant's (renal and hepatic dysfunction) [52].

The active components of fruits and vegetables are involved in inhibition of CYP450 and drug transporters. Findings of literature search showed that polyphenols [16], disomin [15], punicalagin [18], resveratrol [22], qurecetin, glycosylated xanthones, mangiferin [23-25], bromelin [26] and anthocyanins [34] are compounds of fruits and vegetables responsible for inhibition of CYP450 and drug transporters.

Although flavonoids (naringenin) and furanocoumarins (bergamottin) in fruits and vegetables have been reported to inhibit CYP450 but their protective effect against cardiovascular diseases and cancer is known [49]. Moreover, there is also potential therapeutic benefit of using active constituents of fruits as they increase drug bioavailability [53]. Concomitant administration of grapefruit juice with cyclosporine is one of the examples of drug sparing effect (reduction of amount of drug being taken with the help of another agent). It reduces repeated dosing of cyclosporine leading to reduction in dose-related side effects and increase patient compliance. Moreover, improvement have been reported in efficacy of antihypertensives and anti-psoriosis therapy by using grapefruit juice as drug sparing agent [53,54].

Table 2: Inhibition of CYP450 and drug transporters by common/temperate fruit juices

Fruit juice	Botanical name	Interacting system (CYP450/OATP/P-gp)	Interacting drug
Grapefruit juice [9, 10]	*Citrus paradisi*	Inhibits CYP3A4, CYP1A2, MRP2, OATP-B, p-glycoprotein	CCBs, CNS modulators, HMG CoA reductase, immunosuppressant, antiviral, antihistamines, PDE-5 inhibitors, antiarrhythmic drugs and several antibiotics
Seville orange juice [11-13]	*Citrus aurantium*	Inhibits p-glycoprotein, CYP3A4, CYP2C9, OATP	Fexofenadine, glibenclamide, vinblastine, atenolol, ciprofloxacin, levofloxacin, pravastatin, aliskirin, felodipine, montelukast
Navel & Valencia Orange Juice [14]	*Citrus sinensis cv. Valencia*	No reported interactions it might be due to absence of furanocoumarins	*In vitro* and *in vivo* studies are required to determine its potential of drug interactions
Tangerine juice [15]	*Citrus reticulata*	Inhibits p-glycoprotein, stimulate CYP3A4 (Disomin in tangerine also inhibit CYP3A4 and CYP1A2 *in vitro*)	Digoxin, nifedipine (no influence on midazolam pharmacokinetics)
Lemon juice [16, 17]	*Citrus limon*	Inhibits CYP3A4, CYP2C9, possibly OATP (because of presence of same polyphenols as in grapefruit juice)	Diclofenac sodium, tolbutamide, glibenclamide and drugs inhibited by grape fruit juice
Lime juice [18, 19]	*Citrus aurantiifolia*	Inhibits CYP3A4, CYP2C9 (because of presence of same polyphenols as in grapefruit juice)	Diclofenac sodium, Tolbutamide, possibly glibenclamide, same as grapefruit juice, studies are needed for *in vivo* documentation
Pomegranate juice [18, 19]	*Punica granatum*	Inhibits CYP3A4, CYP2C9, contains punicalagin that inhibit intestinal sulfo-conjugation	Tolbutamide, Possibly carbamazepine (*in vitro*), other CYP^{450} substrates not yet known
Apple juice [20, 21]	*Malus domestica*	Inhibits CYP1A1, OATP family (OATP 1, OATP 3, NTCP) due to presence of polyphenols	Estrone-3-sulphate, deltrophin II, fexofenadine, vasopressin, rosuvastatin
Grape juice [22]	*Vitis vinifera*	Inhibits CYP3A1, CYP2E1 (due to Resveratrol)	Cyclosporin (*in vivo*), same as red wine
Mango juice [23-25]	*Mangifera indica*	Inhibits CYP1A1, CYP1A2, CYP3A1, CYP2C6, CYP2E1, p-glycoprotein (ABCB1) due to qurecetin, glycosylated xanthones, mangiferin	Diclofenac, midazolam, chlorzoxazone, Verapamil, warfarin
Pineapple juice [26, 27]	*Ananas comosus*	Inhibits CYP2C9 (due to bromelain)	Diclofenac, tolbutamide, warfarin & other blood thinners
Cranberry juice [28-31]	*Vaccinium macrocarpon*	Inhibits CYP3A4, CYP2C9	Warfarin, CCBs (nifedipine), calcineurin inhibitors, possibly diclofenac and fluribiprofen (only *in vivo*)
Mulberry juice [32, 33, 17]	*Morus nigra*	Inhibits CYP3A1, OATP-B, also modulate (activate) CYP3A1 and p-glycoprotein	Midazolam (*in vitro*), cyclosporin, further studies are required to determine in vivo drug interactions
Black raspberry juice [34]	*Rubus coreanus*	Inhibits CYP3A1, Further studies are required to determine interactions of other species of raspberry e.g. *R. idaeus* and *R. fruticosus*	Midazolam (*in vitro*), further studies are required to determine in vivo drug interactions
Blue berry juice [34]	*Vaccinium corymbosum*	Weak inhibitor of CYP3A4 due to anthocyanins	*In vitro* and *In vivo* studies are needed for documentation
Guava juice [35, 36]	*Psidium guajava*	Weak inhibitor p-glycoprotein, CYP3A4	Midazolam, not well documented, further studies are required for p-glycoprotein substrates
Pineapple juice [26, 27]	*Ananas comosus*	Inhibits CYP2C9 (due to bromelain)	Diclofenac, tolbutamide, warfarin & other blood thinners

Table 3: Inhibition of CYP450 and drug transporters by tropical fruit juices

Plum juice [33]	*Prunus mume*	No inhibition	More *in vivo* and *in vitro* studies are required
Kiwi juice [37, 27]	*Actinidia chinensis*	Inhibits CYP3A4	Midazolam, diclofenac, tolbutamide (no clinically significant interactions have reported)
Pamelo juice 38, 27]	*Citrus grandis*	Inhibits CYP2C9, CYP3A4 (no effect on P-glycoprotein)	Diclofenac, tolbutamide, cyclosporine, tacrolimus
Star fruit juice [39]	*Averrhoa carambola*	Inhibits CYP3A4 (stronger than grape fruit)	Midazolam, CYP3A4 substrates,
Passion fruit juice [40, 39, 37]	*Punica granatum*	Inhibits CYP2C9, CYP3A4	Midazolam, Diclofenac, Tolbutamide (no clinically significant interactions have reported)
Dragon fruit juice [40, 39, 37]	*Hylocereus undatus*	Inhibits CYP3A4	Midazolam (no clinically significant interactions have been reported)
Rambutan juice [40, 39, 37]	*Passiflora edulis*	Inhibits CYP3A4	Midazolam (no clinically significant interactions have been reported)
Litchi juice [27]	*Lichi chinensis*	Inhibits CYP2C9	Midazolam, Diclofenac

Table 4: Inhibition of CYP450 and drug transporters by vegetable juices fruits

Tomato [41, 42]	*Lycopersicum esculentum*	Inhibit CYP1A1, CYP1B1, UGP	N-methyl nitrosourea, dimethyl nitrosamine, dimethylhydrazine
Carrot [43]	*Dactus carrota*	Inhibit CYP2E1	Not documented
Avocado [44]	*Persea Americana*	Unknown	Warfarin (*in vivo*)
Red pepper [45-46]	*Capsicum annuum*	Inhibit CYP1A1, CYP2A2, CYP3A1, CYP2C1, CYP2B1, CYP2B2, CYP2C6	Theophylline, Xanthine oxidase, Salicylates, Hypoglycemic drugs
Spinach [47]	*Spinacia oleraceae*	Inhibit CYP1A2	Heterocyclic aromatic amines (*in vitro*)

CYP_{450}: cytochrome P_{450}, OATP: organic anion transporting polypeptide, P-gp: p-gylcoprotein, CCBs: calcium channel blockers, CNS: central nervous system, HMG CoA! hydroxyl methyl glutaryl coenzyme A, PDE-5: phosphodiesterase type 5, NTCP: sodium taurocholate cotransporting peptide

Few studies have been conducted on tropical fruits and vegetables to elaborate their potential in inhibition of metabolizing enzymes and drug transporters. Tropical fruits are most commonly used in tropical and subtropical countries and screening of these fruits can avoid drug related complications among patients. More studies are required to find out the safety and risk profile of concomitant use of tropical fruits/vegetables with drugs.

CONCLUSION

As a number of drugs are approved by FDA each year, there is less information available about their adverse effects and interactions when the drugs reach the market. It is imperative for physicians and pharmacists to be well aware of interactions of drugs with fruits and vegetables because such interactions can be more complicated than drug–drug interactions. Screening of fruits and vegetables for possible risk of interactions will ensure success of treatment and avoid detrimental effects. Fruits/vegetables containing active components reported to affect metabolizing enzymes or drug transporters must be screened for interactions. It will aid health care professionals during patient counseling. Since it is difficult to create public awareness of the fact that despite offering curative and nutritional benefits, fruit juices can also confer health risk, and therefore, avoidance of concomitant use of fruits/vegetables juices and drugs where required, can be an effective strategy for preventing such interactions.

REFERENCES

1. *Smith JW, Seidl LG, Cluff LE. Studies on the epidemiology of adverse drug reactionsV. Clinical factors influencing susceptibility. Ann Intern Med 1966; 65(4): 629-640.*
2. *Rodríguez-Fragoso L, Martínez-Arismendi JL, Orozco-Bustos D, Reyes-Esparza J, Torres E, Burchiel SW. Potential Risks Resulting from Fruit/Vegetable–Drug Interactions: Effects on Drug-Metabolizing Enzymes and Drug Transporters. J Food Sci 2011; 76(4): R112-R124.*
3. *Neves MF, Trombin VG, Lopes FF, Kalaki R, Milan P. World consumption of fruit juices, nectars, and still drinks. In The orange juice business. Wageningen Acad Publishers 2012: 118-119.*
4. *Fuchikami H, Satoh H, Tsujimoto M, Ohdo S, Ohtani H, Sawada Y. Effects of herbal extracts on the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos 2006; 34(4): 577-582.*
5. *Guengerich FP. Characterization of human cytochrome P450 enzymes. The FASEB J 1992; 6(2): 745-748.*
6. *Dolton, M. J., Roufogalis, B. D., & McLachlan, A. J. Fruit Juices as Perpetrators of Drug Interactions: The Role of Organic Anion–Transporting Polypeptides. Clin Pharmacol Ther 2012; 92(5): 622-630.*
7. *Niemi M., Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. Pharmacol Rev 2011; 63(1): 157-181.*
8. *Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. Curr Drug Metab 2002; 3(6): 561-597.*
9. *Dahan A, Altman H. Food–drug interaction: grapefruit juice augments drug bioavailability—mechanism, extent and relevance. Eur J Clin Nutr 2004; 58(1): 1-9.*
10. *Greenblatt DJ. Analysis of drug interactions involving fruit beverages and organic anion-transporting polypeptides. J Clin Pharmacol 2009, 49(12), 1403-1407.*
11. *Malhotra S, Bailey DG, Paine MF, Watkins PB. Seville orange juice-felodipine interaction: Comparison with dilute grapefruit juice and involvement of furocoumarins&ast. Clin Pharmacol Ther 2001; 69(1): 14-23.*
12. *Lilja JJ, Juntti-Patinen L, Neuvonen PJ. Orange juice substantially reduces the bioavailability of the β-adrenergic–blocking agent celiprolol&ast. Clin Pharmacol Ther 2004; 75(3): 184-190.*
13. *Lilja JJ, Raaska K, Neuvonen PJ. Effects of orange juice on the pharmacokinetics of atenolol. Eur J Clin Pharmacol 2005; 61(5-6): 337-340.*
14. *Simonne AH, Ritenour MA, Terry LA. Citrus [orange, lemon, mandarin, grapefruit, lime, and other citrus fruits]. Health-Promoting Properties of Fruit & Vegetables. Terry L (ed). 2011; CABI, Cambridge, MA, USA: 90-117.*
15. *Backman JT, Mäenpää J, Belle DJ, Wrighton SA, Kivistö KT, Neuvonen PJ. Lack of correlation between in vitro and in vivo studies on the effects of tangeretin and tangerine juice on midazolam hydroxylation&ast. Clin Pharmacol Ther 2000; 67(4): 382-390.*
16. *Xu J, Go ML, Lim LY. Modulation of digoxin transport across Caco-2 cell monolayers by citrus fruit juices: lime, lemon, grapefruit, and pummelo. Pharm Res 2003; 20(2): 169-176.*
17. *Satoh H, Yamashita F, Tsujimoto M, Murakami H, Koyabu N, Ohtani H, Sawada Y. Citrus juices inhibit the function of human organic anion-transporting polypeptide OATP-B. Drug Metab Dispos 2005; 33(4): 518-523.*
18. *Hidaka M, Okumura M, Fujita KI, Ogikubo T, Yamasaki K, Iwakiri T, Setoguchi N, Arimori K. Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. Drug Metab Dispos 2005; 33(5): 644-648.*
19. *Srinivas NR. Is pomegranate juice a potential perpetrator of clinical drug–drug interactions? Review of the in vitro, preclinical and clinical evidence. Eur J Drug Metab Ph 2013; 2013: 1-7.*

20. Guyot S, Marnet N, Laraba D, Sanoner P, Drilleau JF. Reversed-phase HPLC following thiolysis for quantitative estimation and characterization of the four main classes of phenolic compounds in different tissue zones of a French cider apple variety (Malus domestica var. Kermerrien). J Agri Food Chem 1998; 46(5): 1698-1705.
21. Zessner H, Pan L, Will F, Klimo K, Knauft J, Niewöhner R, Hümmer W, Owen R, Richling E, Frank N et al. Fractionation of polyphenol-enriched apple juice extracts to identify constituents with cancer chemopreventive potential. Mol Nutr Food Res 2008; 52(S1): S28-S44.
22. Piver B, Berthou F, Dreano Y, Lucas D. Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non-volatile red wine components. Toxicol Lett 2001; 125(1): 83-91.
23. Berardini N, Fezer R, Conrad J, Beifuss U, Carle R, Schieber A. Screening of mango (Mangifera indica L.) cultivars for their contents of flavonol O-and xanthone C-glycosides, anthocyanins, and pectin. J Agri Food Chem 2005; 53(5): 1563-1570.
24. Izzo AA, Di Carlo G, Borrelli F, Ernst E. Cardiovascular pharmacotherapy and herbal medicines: the risk of drug interaction. Intern J Cardiol 2005; 98(1): 1-14.
25. Lam AY, Elmer GW, Mohutsky MA. Possible interaction between warfarin and Lycium barbarum L. Ann Pharmacother 2001; 35(10): 1199-1201.
26. Booth SL, Centurelli MA. Vitamin K: a practical guide to the dietary management of patients on warfarin. Nutr Rev 1999; 57(9): 288-296.
27. Hidaka M, Nagata M, Kawano Y, Sekiya H, Kai H, Yamasaki K, Okumura M, Arimori, K. Inhibitory effects of fruit juices on Cytochrome P450 2C9 activity in vitro. Biosci Biotechnol Biochem 2008; 72(2): 406-411.
28. Pham DQ, Pham AQ. Interaction potential between cranberry juice and warfarin. Am J of Health-system Pharm 2007; 64(5): 490-494.
29. Ushijima K, Tsuruoka SI, Tsuda H, Hasegawa G, Obi Y, Kaneda T, Fujimura A. Cranberry juice suppressed the diclofenac metabolism by human liver microsomes, but not in healthy human subjects. Br J C Pharmacol 2009; 68(2): 194-200.
30. Greenblatt DJ, von Moltke LL, Perloff ES, Luo Y, Harmatz JS, Zinny MA. Interaction of flurbiprofen with cranberry juice, grape juice, tea, and fluconazole: In vitro and clinical studies. Clin Pharmacol Ther 2006; 79(1): 125-133.
31. Uesawa Y, Mohri K. Effects of cranberry juice on nifedipine pharmacokinetics in rats. J Pharm Pharmacol 2006; 58(8): 1067-1072.
32. Hsu PW, Shia CS, Lin SP, Chao PDL, Juang SH, Hou YC. Potential Risk of Mulberry-Drug Interaction: Modulation on P-glycoprotein and Cytochrome P450 3A. J Agr Food Chem 2013; 61(18): 4464-4469.
33. Kim H, Yoon YJ, Shon JH, Cha IJ, Shin JG, Liu KH. Inhibitory effects of fruit juices on CYP3A activity. Drug Metab Dispos 2006; 34(4): 521-523.
34. Dreiseitel A, Schreier P, Oehme A, Locher S, Hajak G, Sand PG. Anthocyanins and their metabolites are weak inhibitors of cytochrome P450 3A4. Mol Nutr Food Res 2008; 52(12): 1428-1433.
35. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview. Adv Drug Deliver Rev 2012; 55(1): 3-29.
36. Kaneko K, Suzuki K, Iwadate-Iwata E, Kato I, Uchida K, Onoue M. Evaluation of Food–drug Interaction of Guava Leaf Tea. Phytotherapy Research 2012; 27(2), 299-305.
37. MacDonald L, Foster BC, Akhtar H. Food and Therapeutic Product Interactions–A Therapeutic Perspective. J Pharm Pharm Sci 2009; 12(3): 367-377.
38. Egashira K, Ohtani H, Itoh S, Koyabu N, Tsujimoto M, Murakami H, Sawada Y. Inhibitory effects of pomelo on the metabolism of tacrolimus and the activities of CYP3A4 and P-glycoprotein. Drug Metab Dispos 2004; 32(8): 828-833.
39. Hidaka M, Fujita KI, Ogikubo T, Yamasaki K, Iwakiri T, Okumura M, Kodama H, Arimori K. Potent inhibition by star fruit of human cytochrome P450 3A (CYP3A) activity. Drug Metab Dispos 2004; 32(6): 581-583.
40. Nekvindova J, Anzenbacher P. Interactions of food and dietary supplements with drug metabolising cytochrome P450 enzymes. Ceska Slov Farm 2007; 56(4): 165.
41. Wang H, Leung LK. The carotenoid lycopene differentially regulates phase I and II enzymes in dimethylbenz anthracene-induced MCF-7 cells. Nutr 2010, 26(11): 1181-1187.
42. Veeramachaneni S, Ausman LM, Choi SW, Russell RM, Wang XD. High dose lycopene supplementation increases hepatic cytochrome P4502E1 protein and inflammation in alcohol-fed rats. J Nutr 2008; 138(7): 1329-1335.
43. Harris KE, Jeffery EH. Sulforaphane and erucin increase MRP1 and MRP2 in human carcinoma cell lines. J Nutr Biochem 2008; 19(4): 246-254.
44. Rodríguez-Fragoso L, Reyes-Esparza J. Fruit/Vegetable-Drug Interactions: Effects on Drug Metabolizing Enzymes and Drug Transporters. Chapter 1 (drug discovery); 2013 (Online: http://dx.doi.org/10.5772/48283)
45. Zhang Z, Hamilton SM, Stewart C, Strother A, Teel RW. Inhibition of liver microsomal cytochrome P450 activity and metabolism of the tobacco-specific nitrosamine NNK by capsaicin and ellagic acid. Anticancer Res 1993; 13(6A): 2341-2346.
46. Bouraoui A, Brazier JL, Zouaghi H, Rousseau M. Theophylline pharmacokinetics and metabolism in rabbits following single and repeated administration of Capsicum fruit. Eur J Drug Metab Ph 1995; 20(3): 173-178.
47. Bergquist SÅ, Gertsson UE, Knuthsen P, Olsson ME. Flavonoids in baby spinach (Spinacia oleracea L.): changes during plant growth and storage. J Agri Food Chem 2005; 53(24): 9459-9464.
48. Huang SM, Lesko LJ. Drug-Drug, Drug—Dietary Supplement, and Drug—Citrus Fruit and Other Food

Interactions: What Have We Learned? J Clin Pharmacol 2004; 44(6): 559-569.

49. Fuhr U. Drug interactions with grapefruit juice: extent, probable mechanism and clinical relevance. Drug Safety 1998; 18(4): 251-272.

50. Spence JD. Drug interactions with grapefruit: Whose responsibility is it to warn the public? Clin Pharmacol Ther 1997; 61(4): 395-400.

51. Sadeque AJ, Wandel C, He H, Shah S, and Wood AJ. Increased drug delivery to the brain by P-glycoprotein inhibition. Clin Pharmacol Ther 2000; 68(3): 231-237.*

52. Maskalyk J. Grapefruit juice: potential drug interactions. Can Med Assoc J 2002; 167(3): 279-280.

53. Taniguchi S, Kobayashi H, Ishii M. Treatment of psoriasis by cyclosporine and grapefruit juice. ArchDermatol 1996; 132(10): 1249-1249.

54. Pisarik P. Blood pressure-lowering effect of adding grapefruit juice to nifedipine and terazosin in a patient with severe renovascular hypertension.Arch Fam Med 1996; 5(7): 413.