

## Original Research Article

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

Tauqeer Hussain Mallhi<sup>1\*</sup>, Azmi Sarriff<sup>1</sup>, Azreen Syazril Adnan<sup>2</sup>, Yusra Habib Khan<sup>1</sup>, Muhammad Imran Qadir<sup>4</sup>, Azhar Amir Hamzah<sup>3</sup> and Amer Hayat Khan<sup>1</sup>

<sup>1</sup>Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Penang 11800, <sup>2</sup>Chronic Kidney Disease Resource Centre, School of Medical Sciences, Health Campus, University Sains Malaysia, <sup>3</sup>Urology Unit, Department of Surgery, Hospital University Sains Malaysia, Kelantan 16150, Malaysia, <sup>4</sup>Institute of Molecular Biology & Biotechnology, Bahauddin Zakariya University, Multan, Pakistan

\*For correspondence: **Email:** [tauqeer.hussain.mallhi@hotmail.com](mailto:tauqeer.hussain.mallhi@hotmail.com); **Tel:** +60105644191

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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, rhabdomyolysis 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.

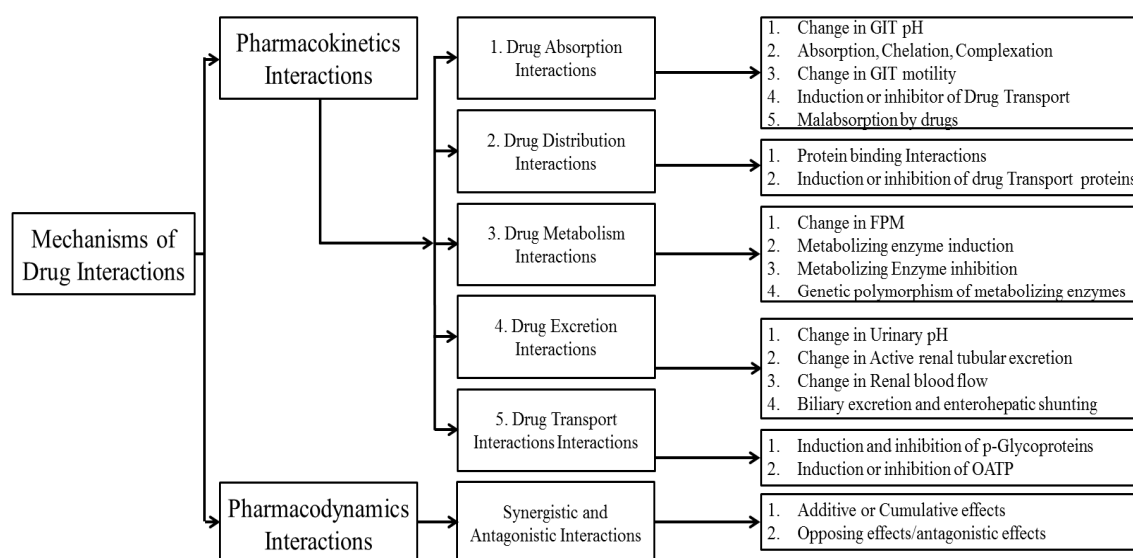
Inhibitory effect of grapefruit on cytochrome P<sub>450</sub> was accidentally discovered when grapefruit juice was used to mask the taste of ethanol in assessing the effects of alcohol on felodipine. Cytochrome P<sub>450</sub> is responsible for metabolism of several drugs, steroids and carcinogens. 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<sub>450</sub> 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<sub>450</sub> drug interactions, vegetable juice drug interactions, pharmacodynamics drug interactions, pharmacokinetics drug interactions, and drug transporters (OATP/p-glycoprotein) were excluded. Figure 2 illustrates the

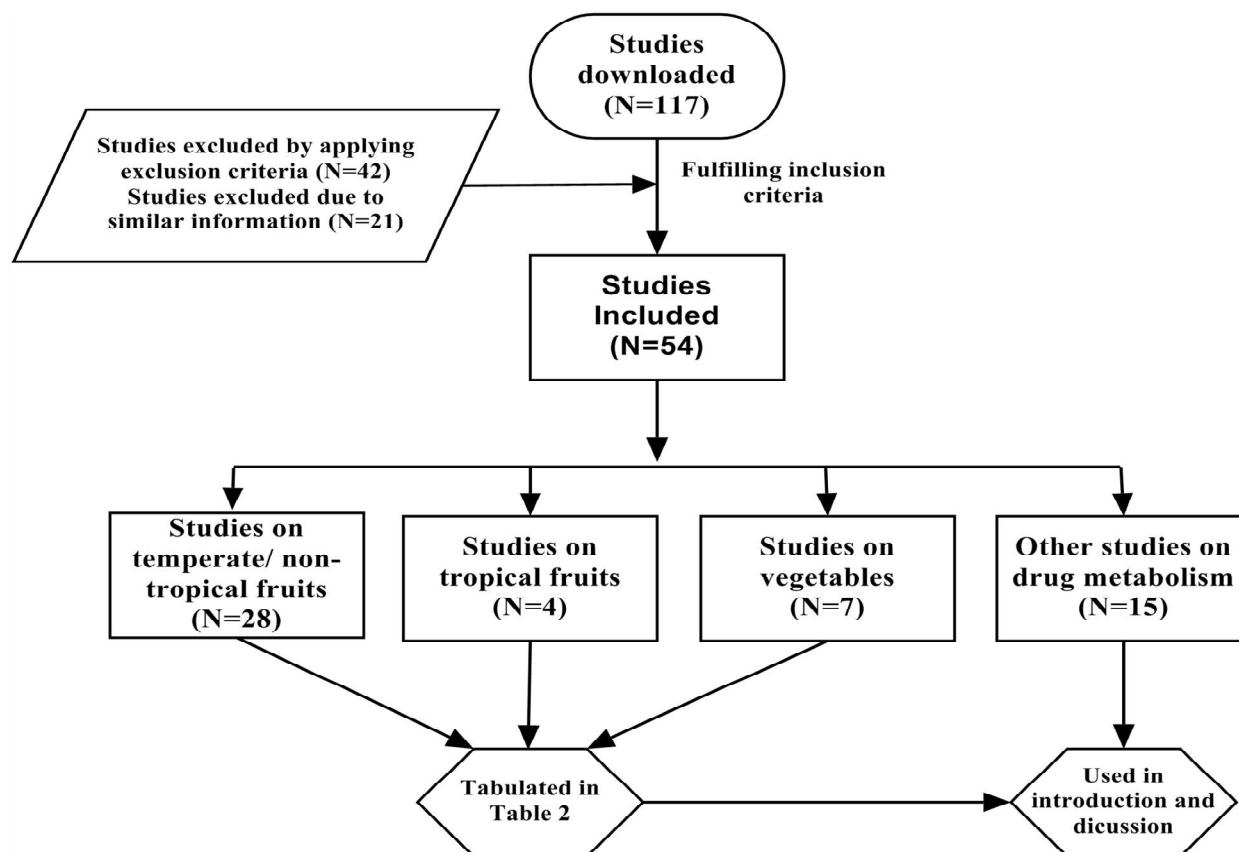


**Figure 1:** Types of drug interactions, GIT: Gastrointestinal tract, FPM: First pass metabolism, OATP: Organic anion transporting polypeptide

**Table 1:** Commonly used substrates for cytochrome P<sub>450</sub>, p-glycoprotein and OATP [7,8]

CYP1A2	CYP2B6	CYP2C19	CYP2C9
Propranolol, Naproxen, Ondansetron, Theophylline, Verapamil	Bupropion, 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<sub>450</sub> (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 2013. However, personal communications, conference proceedings, unpublished 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 rhabdomyolysis 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<sub>450</sub> 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 rhabdomyolysis, 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 rhabdomyolysis [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<sub>450</sub>, 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, rhabdomyolysis), 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], quercetin, glycosylated xanthenes, mangiferin [23–25], bromelain [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-psoriasis 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]	<i>Citrus paradisi</i>	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]	<i>Citrus aurantium</i>	Inhibits p-glycoprotein, CYP3A4, CYP2C9, OATP	Fexofenadine, glibenclamide, vinblastine, atenolol, ciprofloxacin, levofloxacin, pravastatin, aliskirin, felodipine, montelukast
Navel & Valencia Orange Juice [14]	<i>Citrus sinensis cv. Valencia</i>	No reported interactions it might be due to absence of furanocoumarins	<i>In vitro</i> and <i>in vivo</i> studies are required to determine its potential of drug interactions
Tangerine juice [15]	<i>Citrus reticulata</i>	Inhibits p-glycoprotein, stimulate CYP3A4 (Disomin in tangerine also inhibit CYP3A4 and CYP1A2 <i>in vitro</i> )	Digoxin, nifedipine (no influence on midazolam pharmacokinetics)
Lemon juice [16, 17]	<i>Citrus limon</i>	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]	<i>Citrus aurantiifolia</i>	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 <i>in vivo</i> documentation
Pomegranate juice [18, 19]	<i>Punica granatum</i>	Inhibits CYP3A4, CYP2C9, contains punicalagin that inhibit intestinal sulfo-conjugation	Tolbutamide, Possibly carbamazepine ( <i>in vitro</i> ), other CYP <sup>450</sup> substrates not yet known
Apple juice [20, 21]	<i>Malus domestica</i>	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]	<i>Vitis vinifera</i>	Inhibits CYP3A1, CYP2E1 (due to Resveratrol)	Cyclosporin ( <i>in vivo</i> ), same as red wine
Mango juice [23-25]	<i>Mangifera indica</i>	Inhibits CYP1A1, CYP1A2, CYP3A1, CYP2C6, CYP2E1, p-glycoprotein (ABCB1) due to quercetin, glycosylated xanthenes, mangiferin	Diclofenac, midazolam, chlorzoxazone, Verapamil, warfarin
Pineapple juice [26, 27]	<i>Ananas comosus</i>	Inhibits CYP2C9 (due to bromelain)	Diclofenac, tolbutamide, warfarin & other blood thinners
Cranberry juice [28-31]	<i>Vaccinium macrocarpon</i>	Inhibits CYP3A4, CYP2C9	Warfarin, CCBs (nifedipine), calcineurin inhibitors, possibly diclofenac and fluribiprofen (only <i>in vivo</i> )
Mulberry juice [32, 33, 17]	<i>Morus nigra</i>	Inhibits CYP3A1, OATP-B, also modulate (activate) CYP3A1 and p-glycoprotein	Midazolam ( <i>in vitro</i> ), cyclosporin, further studies are required to determine <i>in vivo</i> drug interactions
Black raspberry juice [34]	<i>Rubus coreanus</i>	Inhibits CYP3A1, Further studies are required to determine interactions of other species of raspberry e.g. <i>R. idaeus</i> and <i>R. fruticosus</i>	Midazolam ( <i>in vitro</i> ), further studies are required to determine <i>in vivo</i> drug interactions
Blue berry juice [34]	<i>Vaccinium corymbosum</i>	Weak inhibitor of CYP3A4 due to anthocyanins	<i>In vitro</i> and <i>In vivo</i> studies are needed for documentation
Guava juice [35, 36]	<i>Psidium guajava</i>	Weak inhibitor p-glycoprotein, CYP3A4	Midazolam, not well documented, further studies are required for p-glycoprotein substrates
Pineapple juice [26, 27]	<i>Ananas comosus</i>	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]	<i>Prunus mume</i>	No inhibition	More <i>in vivo</i> and <i>in vitro</i> studies are required
Kiwi juice [37, 27]	<i>Actinidia chinensis</i>	Inhibits CYP3A4	Midazolam, diclofenac, tolbutamide (no clinically significant interactions have reported)
Pamelo juice 38, 27]	<i>Citrus grandis</i>	Inhibits CYP2C9, CYP3A4 (no effect on P-glycoprotein)	Diclofenac, tolbutamide, cyclosporine, tacrolimus
Star fruit juice [39]	<i>Averrhoa carambola</i>	Inhibits CYP3A4 (stronger than grape fruit)	Midazolam, CYP3A4 substrates,
Passion fruit juice [40, 39, 37]	<i>Punica granatum</i>	Inhibits CYP2C9, CYP3A4	Midazolam, Diclofenac, Tolbutamide (no clinically significant interactions have reported)
Dragon fruit juice [40, 39, 37]	<i>Hylocereus undatus</i>	Inhibits CYP3A4	Midazolam (no clinically significant interactions have been reported)
Rambutan juice [40, 39, 37]	<i>Passiflora edulis</i>	Inhibits CYP3A4	Midazolam (no clinically significant interactions have been reported)
Litchi juice [27]	<i>Lichi chinensis</i>	Inhibits CYP2C9	Midazolam, Diclofenac

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

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

CYP<sub>450</sub>: cytochrome P<sub>450</sub>, OATP: organic anion transporting polypeptide, P-gp: p-glycoprotein, 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.

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