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A Review On Drug Interaction With Nutrients Obtained From Commonly Used Fruits And Vegetables

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Abstract: Health Organisation (WHO) and the Food and Agriculture Organisation of the United Nations (FAO) in order to help avoid chronic diseases like heart disease, cancer, diabetes, and obesity. As a result, there is a rise in the demand for fruits and vegetables on a global scale. Some people choose to buy organic foods because they believe they are healthier. On the other hand researcher are proving that without knowing that the person is on medication or not these statements should not be taken as universal. Commonly used fruits like grape and apple are known to inhibit the pharmacodynamic and pharmacokinetic properties of drug substances hence resulting in the inhibition of their therapeutics effects. Hence this study is suggesting that not every fruit and vegetable is going to provide nutrients to the person. The medical condition of patient the type medication he or she is on needs to considered previously.

1. INTRODUCTION

Food effect, also known as food–drug interactions, is a common phenomenon associated with orally administered medications and can be defined as changes in absorption rate or absorption extent. The mechanisms of food effect and their consequences can involve multiple factors, including human post-prandial physiology, properties of the drug, and how the drug is administered. Therefore, it is essential to have a thorough understanding of these mechanisms when recommending whether a specific drug should be taken with or without food. According to epidemiologic data, eating fruits and vegetables frequently may lower your risk of developing certain diseases, such as cancer (Liu 2004). Foods that are abundant in various bioactive components, such as phytochemicals, have been linked to these qualities (Milner 2004). People who appear to be "healthy" may be able to prevent various diseases by altering their diet of particular foods and/or their bioactive components (Liu 2003). Potential issues may arise when patients who frequently take medications also eat specific fruits or vegetables, as will be covered in Thousands of drugs are commercially available and a great percentage of the population takes at least one pharmacologically active agent on a regular basis. Given this magnitude of use and variability in individual nutritional status, dietary habits, and

food composition, there is a high potential for drug–nutrient interactions. However, there is a relatively short list of documented fruit/vegetable–drug interactions, necessitating further, and extensive clinical evaluation. Healthcare providers, such as physicians, pharmacists, nurses, and dietitians, have to be aware of important food–drug interactions in order to optimize the therapeutic efficacy of prescribed and over-the-counter drugs. Food–drug interactions can be clinically relevant, especially when they must be avoided to prevent undesirable effects or exploited to optimize medication therapy. This review conducts a literature search that examined studies on food effect. We summarized the literature and identified and discussed common nutrient drug interection . Furthermore, we highlighted common nutrient that have a clinically significant effect and discussed the corresponding mechanisms. In addition, this review analyzes the effects of high-fat food or standard meals on the oral drug absorption effect. The impact of food on successful delivery of promising new drug candidates via the oral route poses a major challenge during drug development. Consequently, understanding FDIs has the potential to assist physicians, researchers, and patients in reducing adverse drug events (ADEs). The current review provides an update on dietary substance–drug interaction research also we review some of the most widely consumed fruits and vegetables to inform healthcare providers of possible nutrient–drug interactions and their potential clinical significance.

Cheminformatics studies have achieved remarkable results in drug-drug interactions (DDIs), drug-target interactions (DTIs), and new drug discovery. Multiple computational models have been developed for detecting how a particular drug pair interacts towards the discovery of new drugs. The adoption of different machine learning models is rapidly increasing in drug discovery19. These models have been used for the discovery of novel DDIs. For instance, a deep learning model was implemented to predict the pharmacological effects of DDIs using the structural similarity profile (SSP), target gene similarity profiles, and gene ontology (GO) term similarity profiles of known drug pairs20. Recently, Deep DDI was developed as a multi-label classification model that calculates structural similarity profiles (SSP) of DDIs21. Deep DDI employs principal components analysis to reduce the feature set size before feeding the rotated data into a feed-forward deep neural network (DNN)21. Another predictive model was trained to distinguish unknown biological effects of inactive ingredients that are recognized as safe compounds in food22. A general-purpose method, named Alternative Drug-Drug Interaction, was developed for DDI predictions23. Three combined methods were used, including text mining, deep learning, and graph clustering. Feng et al. proposed DPDDI to predict DDIs without considering biological and chemical properties24. The authors used graph convolution networks (GCN) and DNN for prediction. GCN explores low-dimensional feature representations of drugs by identifying the topological association of drugs in the DDI network. The impact of food on successful delivery of promising new drug candidates via the oral route poses a major challenge during drug development.

There are numerous patients who encounter increased risks of adverse events associated with drug–nutrient interactions. These include elderly patients, patients with cancer and/or malnutrition, gastrointestinal tract dysfunctions, acquired immunodeficiency syndrome, and chronic diseases that require the use of multiple

drugs, as well as those receiving enteral nutrition or transplants. Therefore, the main reason for devoting a major review to nutrient–drug interactions is the enormous importance of fruits and vegetables used for their beneficial

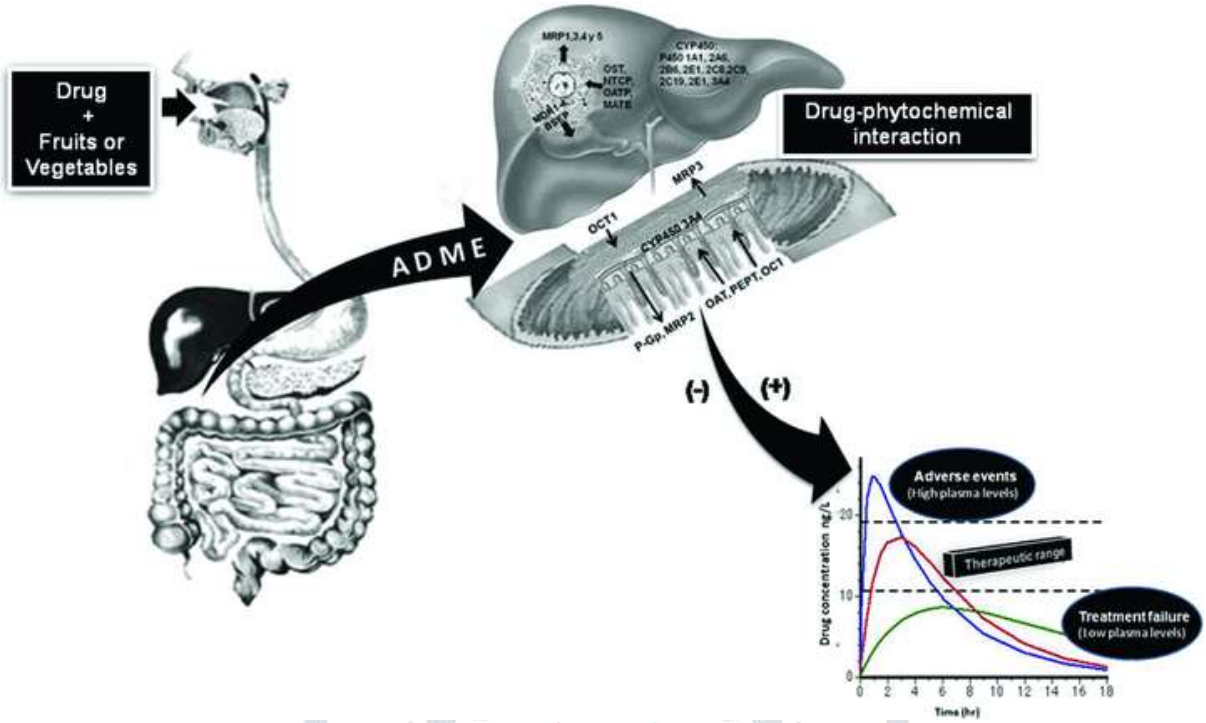

Figure 1–

Drug–fruit/vegetable interaction and effects on bioavailability of drugs. During the consumption of drugs with fruits or vegetables, the ADME properties of drug (absorption, distribution, metabolism, and excretion) can be modified by drug–phytochemical interaction. As a result of this, interaction can be increased or decreased plasma concentrations of a drug that can lead to the presence of adverse events or treatment failure.

According to epidemiologic data, eating fruits and vegetables frequently may lower your risk of developing certain diseases, such as cancer (Liu 2004). Foods that are abundant in various bioactive components, such as phytochemicals, have been linked to these qualities (Milner 2004). People who appear to be "healthy" may be able to prevent various diseases by altering their diet of particular foods and/or their bioactive components (Liu 2003). Potential issues may arise when patients who frequently take medications also eat specific fruits or vegetables, as will be covered in Thousands of drugs are commercially available and a great percentage of the population takes at least one pharmacologically active agent on a regular basis. Given this magnitude of use and variability in individual nutritional status, dietary habits, and food composition, there is a high potential for drug–nutrient interactions. However, there is a relatively short list of documented fruit/vegetable–drug interactions, necessitating further, and extensive clinical evaluation. Healthcare providers, such as physicians, pharmacists, nurses, and dietitians, have to be aware of important food–drug interactions in order to optimize the therapeutic efficacy of prescribed and over-the-counter drugs.

Nutrient–Drug Interactions: Examples with Clinical Relevance

Since fruits have low energy density and are sources of vitamins, fibre, and other substances with functional qualities known as phytochemicals, fruits and vegetables are well-known to be significant parts of a balanced diet . Consumption of fruits and vegetables can also aid in replacing foods heavy in salt, sugar, or saturated fat. One of the top 10 risk factors for death is a low consumption of fruits and vegetables. Increased daily consumption of fruits and vegetables may help prevent serious chronic noncommunicable diseases, according to the World Health Organisation (WHO) (WHO 2003). There is growing evidence that certain phytochemical combinations may be much more potent than single substances at warding off particular diseases (Tables 1 and 2). observed interactions between dietary micronutrients and drugs, as well as drug-phytochemical interactions.

Table 1–. Commonly consumed fruits.

Fruit	Phytochemicals	Cultural uses
Grapefruit *Citrus paradisi, Citrus reticulata*	Bergamottin, flavonoids (nobilein, tangeretin, quercetin, diosmin, naringenin, naringin, and kaempferol), and furanocoumarins	Insomnia and anxiety or nervousness
Orange *Citrus sinensis, Citrus aurantium*	Flavonoids as tangeretin, nobiletin, diosmin, and hesperetin.	Inflammatory ailments in respiratory tract, arthritis, gastrointestinal tract ailments, and others
Tangerine *Citrus reticulata, Citrus deliciosa*	Flavonoids as diosmin, tangeritin, nobilein, and quercetin	Inflammatory ailments in respiratory tract, arthritis, gastrointestinal tract ailments, and others
Grapes *Vitis vinifera*	Stilbens (resverestrol, viniferin) and flavonoids.	Antianemic, inflammatory ailments in respiratory tract, and others

Fruit	Phytochemicals	Cultural uses
Cranberry *Vaccinium macrocarpon Vaccinum myrtillus*	Flavonoids as anthocyanidin (cyaniding and poenidin) and flavonols (quercetin) and carotenoids	Genitourinary ailments, nephrolithiasis, wound healing, and others
Pomegranate *Punica granatum*	Phenolic acids (punicalagin and tannins), flavonoids (anthocyanins), and pectin	Inflammatory ailments in respiratory tract and others Gastrointestinal tract ailments and others
Apple *Malus domestica*	Phenolic acids (tannins), flavonoids (including quercetin), glycosylated xanthones (mangiferin), and saponins	Diuretic, genitourinary ailments, inflammatory ailments in respiratory tract, and others
Mango *Mangifera indica*	Phenolic acids (tannins), flavonoids (anthocyanins), carotenoids, essential oils, fatty acids, lectins, phenols, saponins, alkaloids, and triterpenes	Recommended to combat heart disease. It is also a laxative and diuretic
Black raspberry *Rubus coreanus, Rubus idaeus, Rubus fruticosus*	Phenolic acids (ellagic acid, gallic acid), flavonoids (quercetin, anthocyanins, pelargonidins, kaempferol and cyanidins), catechins, and salicylic acid	Antianemic, antiinfectious, inflammatory ailments in respiratory tract, gastrointestinal tract ailments, and others
Black mulberry *Morus nigra*	2-arylbenzofuran derivative, flavones (mornigrol D, mornigrol G, mornigrol H, and norartocarpetin), flavonol	Genitourinary ailments, inflammatory ailments in

Fruit	Phytochemicals	Cultural uses
	(dihydrokaempferol), albanin A, albanin E, stilbenes (moracin M), and albafuran	respiratory tract, gastrointestinal tract ailments, and others
Guava *Psidium guajava*	Flavonoid as quercetin and phloretin	Genitourinary ailments, hypertension

- Data from: Takanaga and others (2000), Harris and Jeffery (2008), Satoh and others (2005), Kim and others (2006), Sica (2006), Pham and Pham (2007), Yoo and others (2007), Schmidt and Dalhoff (2002), Chieli and others (2009), and Wang and Leung (2010).

Table 2–. Commonly consumed vegetables.

Vegetable	Phytochemicals	Cultural uses
Broccoli *Brassica oleracea var. italica*	Isothiocyanate sulforaphane, glucosinolate glucoraphanin, glucosinolates, phenolic acid, indol, and dithiolthiones	Antioxidant, anticancer, antiseptic, antiulcerous, hypoglycemic, antianemic, gastrointestinal tract ailments, and others
Cauliflower *Brassica oleracea var. botrytis*	Isothiocyanate, glucosinolate, indole-3-carbinol, sulforaphane, indol	Antioxidant
Spinach *Spinacia oleracea*	Flavonoids and *p*-coumaric acid derivatives, α-lipoic acid, poliphenols, lutein, zeaxantin, betaine	Diuretic, inflammatory ailments, gastrointestinal tract ailments, inflammatory ailments in respiratory tract, and others
Watercress *Nasturtium officinale*	Phenylethyl isothiocyanate (PEITC) and methylsulphinylakyl isothiocyanates (MEITCs), flavonoids such as quercetin, hydroxycinnamic acids, and carotenoids such as β-carotene and lutein	Antioxidants, diuretic, gastrointestinal tract ailments, inflammatory ailments in respiratory tract, and others
Tomato *Lycopersicum esculentum*	Carotenoids phytofluene, phytoene, neurosporene, γ-carotene, and ζ-carotene lycopene, phytoene, phytofluene, quercetin, polyphenols, kaempferol	Antioxidant, hydratant, hypocholesterolemic

Vegetable	Phytochemicals	Cultural uses
Carrot *Dactus carrota*	Polyphenols, α- and β-carotene, quercetin, myrecetin, and panaxynol	Constipation
Avocado *Persea americana*	Persin, carotenoids (zeaxanthin, α-carotene, and β-carotene), lutein, β-sitosterol, glutathione	Genitourinary ailments, inflammatory ailments in respiratory tract, gastrointestinal tract ailments, and others

- Data from: Bergman and others (2001), Lomnitski and others (2003), Roberts and others (2007), Telang and others (2009), Velasco and others (2011), and Wang and Leung (2009).

Table 3–. Fruit–drug interactions.

Fruit	Molecular target	Drug interactions in humans and others
Grapefruit	Inhibits: CYP3A4, CYP1A2, MRP2, OATP-B, and P-glycoprotein (Dresser and others2002; Honda and others 2004; Flanagan 2005; Saito and others 2005; Satoh and others 2005; Kim and others 2006; Sica 2006; Greenblatt 2009)	In humans: reports of more than 40 drug interactions: calcium-channel antagonists (Sica 2006), central nervous system modulators (Pawełczyk and Kłoszewska 2008), HMG-CoA reductase (Reamy and Stephens 2007), immunosuppressants (Paine and others 2008), antivirals (Van den Bout-van den Beukel and others 2006), phosphodiesterases-5 inhibitor (Bailey and Dresser 2004), antihistamines (Dresser and others 2005), antiarrythmics (Bailey and Dresser 2004), and antibiotics (Amory and Amory 2005)
Sevilla orange	Inhibits: CYP3A4, P-glycoprotein, OATP-A, OATP-B (Takanaga and others 2000; Malhotra and others 2001; Harris and Jeffery 2008; Dresser d others 2005; Kamath and others 2005; Greenblatt 2009)	*In vitro* system: vinblastine (Takanaga and others 2000), fexofenadine (Dresser and others 2005), glibenclamida (Satoh and others 2005) In humans: atenolol, ciprofloxacine, ciclosporine, celiprolol, levofloxacin, and pravastatin (Lilja and others 2005; Greenblatt 2009)
Tangerine	Stimulates CYP3A4 activity and inhibits P-glycoprotein (Yoo and others 2007; Nowack 2008)	*In vitro* system: nifedipine (Backman and others 2000), digoxina (Yoo amd others 2007)
Grapes	Inhibits: CYP3A4 and CYP2E1 (Chan and Delucchi 2000)	In humans: cyclosporine (Piver and others 2001)

Fruit	Molecular target	Drug interactions in humans and others
Cranberry	Inhibits: CYP3A and CYP2C9 (Zhou and others 2004; Izzo 2005; Ushijima and others 2009)	In humans: warfarin (Izzo 2005; Pham and Pham 2007) *In vitro* system: Diclofenac (Ushijima and others 2009)
Pomegranate	Inhibits: CYP3A and phenolsulfotransferase activity (Hidaka and others 2005; Saruwatari and others 2008)	Animals: carbamacepine (Hidaka and others 2005)
Mango	Inhibits: CYP1A1, CYP1A2, CYP 3A1, CYP2C6, CYP2E1, P-glycoprotein (ABCB1) (Chieli and others 2009)	*In vitro* system: midazolam, diclofenac, chlorzoxazone (Rodeiro and others 2008; Rodeiro and others 2009); verapamil (Chieli and others, 2009).
Guava	Inhibits: P-glycoprotein (Junyaprasert and others 2006)	Not documented
Black raspberry	Inhibits: CYP3A (Kim and others 2006)	*In vitro* system: midazolam
Apple	Inhibits: CYP1A1, OATP family (Oatp-1, Oatp-3, and NTCP) (Dresser and others 2002; Pohl and others 2006)	*In vitro* system: fexofenadine (Dresser and others 2005

Table 4–. Vegetable–drug interactions.

Vegetable	Molecular target	Drug interactions in humans and others
Broccoli	Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, glucorosytransferases, sulfotransferases, quinone reductases phenolsulfotransferases (Fimognari and others 2008; Anwar-Mohamed and El-Kadi 2009; Telang and others 2009) Induces: UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and quinone reductases (QRs) (Telang and others 2009)	Not documented
Cauliflower	Inhibits: CYP1A1, CYP2B1/2, CYP3A 4, CYP2E1, hGSTA1/2, MRP-1, MRP-2, BCRP, UDP, glucorosytransferases, sulfotransferases, quinone reductases phenolsulfotransferases (Fimognari and others 2008; Anwar-Mohamed and El-Kadi 2009; Telang and others 2009)	Not documented

Vegetable	Molecular target	Drug interactions in humans and others
	Induces: UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and quinone reductases (QRs) (Telang and others 2009)	
Spinach	Possible inhibition of CYP1A2 (Platt and others 2010)	In humans: chlorzoxazone
Tomato	Inhibits: CYP1A1, CYP1B1, UGP (Wang and Leung 2010) Increases: UGT and CYP2E1 (Veeramachaneni and others 2008)	*In vitro* system: diethylnitrosamine, N-methyl-N-nitrosourea, and 1,2-dimethylhydrazine
Carrot	Induces: phenolsulfotransferases and ethoxycoumarin O-deethylase (ECD) (Bradfield and others 1985; Velasco and others 2011; Yeh and Yen 2005) Inhibits: CPY2E1 (Harris and Jeffery 2008)	Not documented
Avocado	Unknown	Humans: warfarin

2. LITERATURE REVIEW

2.1 Cuciureanu et ,al (2010) Revealed that Two decades ago, grapefruit's medication interactions were accidently found (Flanagan 2005). The impact of grapefruit and its constituents on CYP450 drug oxidation and transportation has since been the subject of multiple. Epidemiologic studies reveal that approximately 2% of the population in the United States consumes at least one glass of regular strength grapefruit juice per day. This becomes pertinent if we consider that many people suffer from chronic metabolic diseases (including hypertension, hyperlipidemia, and cardiovascular diseases) and receive calcium-channel antagonis therapy and HMG-CoA reductase inhibitors. Patients with mental disorders also chronically receive central nervous system modulators. In the case of many drugs, an increase in serum drug concentration has been associated with increased frequency of dose-dependent adverse effects (Saito and others 2005; Kiani and Imam 2007Epidemiologic studies reveal that approximately 2% of the population in the United States consumes at least one glass of regular strength grapefruit juice per day. This becomes pertinent if we consider that many people suffer from chronic metabolic diseases (including hypertension, hyperlipidemia, and cardiovascular diseases) and receive calcium-channel antagonis therapy and HMG-CoA reductase inhibitors. Patients with mental disorders also chronically receive central nervous system modulators. In the case of many drugs, an increase in serum drug concentration has been associated with increased frequency of dose-dependent adverse effects (Saito and others 2005; Kiani and Imam 2007; Pillai

and others 2009). In light of the wide ranging effects of grapefruit juice on the pharmacokinetics of various drugs, physicians need to be aware of these interactions and should make an attempt to warn and educate patients regarding the potential consequences of concomitant ingestion of these agents.

In light of the wide ranging effects of grapefruit juice on the pharmacokinetics of various drugs, physicians need to be aware of these interactions and should make an attempt to warn and educate patients regarding the potential consequences of concomitant ingestion of these agents.

2.2 Orange (Citrus sinensis) Takanaga et.al (2000) Suggested that orange juice made from Seville oranges appears to be somewhat similar to grapefruit juice and can affect the pharmacokinetics of CYP3A4 substrates (Ho and others 2000). It has been previously shown that consumption of a single 240-mL serving of Sevilla orange juice resulted in a 76% increase in felodipine exposure, comparable to what is observed after grapefruit juice consumption Presumably, the mechanism of this effect is similar to that of grapefruit juice-mediated interactions, because Sevilla orange contains significant concentrations of flavonoids, mainly bergamottin and 6′,7′-dihydroxybergamottin (Kamath and others 2005). Orange juice has also been shown to exert inhibitory effects on Pgp-mediated drug efflux. Takanaga and others showed that 3,3′,4′,5,6,7,8-heptamethoxyflavon and tangeretin were the major Pgp inhibitors present in orange juice and showed that another component, nobiletin, was also a Pgp inhibitor (Takanaga and others 2000). Therefore, the intake of orange juice might inhibit the efflux transporters by Pgp, which could enhance the bioavailability of drugs and thus lead to an increase in the risk of adverse events (Yoo and others 2007).

It has also been observed that components of orange juice—naringin in particular—are in vitro inhibitors of OATP transport activity (Farkas and Greenblatt 2008). Dresser and others have previously reported that orange juice inhibits the function of human OATP-A (OATP1A2, gene symbol SLC21A3/SLCO1A2) in vitro (Dresser and others 2002). OATP-A, however, is predominantly expressed in the brain, but not in the intestine. On the other hand, Satoh and others reported that OATP-B-mediated uptake of glibenclamide as well as estrone-3-sulfate was significantly inhibited by 5% orange juice (Satoh and others 2005). Orange juice might reduce the intestinal absorption of substrates of OATP-B (for example, digoxin, benzylpenicillin, and hormone conjugates), resulting in a decrease in concentration in the blood.

Previous studies in humans using fexofenadine as a probe showed that oral coadministration with orange juice decreased the oral bioavailability of fexofenadine (Dresser and others 2005). Orange juice and its constituents were shown to interact with members of the OATP transporter family by reducing their activities. The functional consequences of such an interaction are reflected in a significant reduction in the oral bioavailability of fexofenadine, possibly by preferential direct inhibition of intestinal OATP activity. Other reports indicate that orange juice slightly reduced the absorption of ciprofloxacin, levofloxacin, and celiprolol (Saito and others 2005). A study of an interaction between orange juice and pravastatin showed an increase in area under curve (Greenblatt 2009). Orange juice also moderately reduces the bioavailability of atenolol, which may necessitate a dose adjustment (Lilja and others 2004, 2005).

2.3 Tangerine (Citrus reticulata) Obermeier et. al (1995) It was demonstrated that angeretin inhibits P450 1A2 and P450 3A4 activity in human liver microsomes (Obermeier and others 1995). Tangeretin is a potent regioselective stimulator of midazolam 1′-hydroxylation by human liver microsomes CYP3A4. Although clinical studies have shown no influence on midazolam pharmacokinetics in vivo, further studies are needed to evaluate its effects on other drugs (Backman and others 2000). Diosmin is one of the main components of citrus fruits, such as tangerine. Diosmin may increase the absorption or bioavailability of coadministered drugs able to serve as Pgp substrates. As a result, some caution may be required with its clinical use (Yoo and others 2007).

2.4 Grapes (Vitis vinifera) Yadav et, al 2009 Suggested that Grapes are one of the most valued conventional fruits worldwide. The grape is considered a source of unique and potentially useful medicinal natural products; they are also used in the manufacturing of various industrial products. The main biologically active and well-characterized constituent from the grape is resveratrol, which is known for various medicinal properties in treating human diseases (Yadav and others 2009). Resveratrol was shown to be an irreversible (mechanism-based) inhibitor of CYP3A4 and a noncompetitive reversible inhibitor for CYP2E1 in microsomes from rat liver and human liver cells containing cDNA-expressed CYPs (Chan and Delucchi 2000; Piver and others 2001). Resveratrol is an electron-rich molecule with 2 aromatic benzene rings linked by an ethylene bridge. CYP3A-mediated aromatic hydroxylation and epoxidation of resveratrol are possible, resulting in a reactive p-benzoquinone methide metabolite that is capable of binding covalently to CYP3A4, leading to inactivation, and potential drug interactions.

2.5 Cranberry (Vaccinium macrocarpon) Rossi et, al 2010 Suggested that American cranberry is a fruit used as a prophylactic agent against urinary tract infections (Rossi and others 2010). Drug interactions with cranberry juice might be related to the fact that the juice is rich in flavonol glycosides, anthocyanins, proantho cyanidins, and organic and phenolic acids (Côté and others 2010). Izzo (2005) described a total of 8 cases of interaction between cranberry juice and warfarin, leading to changes in international normalized ratio (INR) values, and bleeding. The mechanism behind this interaction might be the inhibition by cranberry flavonoids of CYP3A4 and/or CYP2C9 enzymes, which are responsible for warfarin metabolism (Zhou and others 2004; Izzo 2005; Pham and Pham 2007).

It has also been shown that cranberry juice inhibits diclofenac metabolism in human liver microsomes, but this has not been demonstrated clinically in human subjects (Ushijima and others 2009). Cranberry juice may increase the bioavailability of CYP3A4 substrates (for example, calcium antagonists or calcineurin inhibitors) as discussed by Van den Bout-Van den Beukel and others (2006). Uesawa and Mohri have demonstrated that nifedipine metabolism in rat intestinal and human hepatic microsomes are inhibited by preincubation with cranberry juice. Furthermore, cranberry juice increased the nifedipine concentration in rat plasma. These findings suggest that cranberry juice might affect the plasma concentration of nifedipine in humans as well (Uesawa and Mohri 2006).

2.6 Pomegranate (Punica granatum) **Oliveira et, al 2010** Suggested that Pomegranate is commonly eaten around the world and has been used in folk medicine for a wide variety of therapeutic purposes. Pomegranate is a rich source of several chemicals such as pectin, tannins, flavonoids, and anthocyanins. pomegranate juice influenced the pharmacokinetics of carbamazepine in rats by inhibiting enteric CYP3A activity. Such inhibition of the enteric CYP3A activity by a single exposure to pomegranate juice appears to last for approximately 3 d. Nagata and others (2007) found that pomegranate juice inhibited human CYP2C9 activity and increased tolbutamide bioavailability in rats. Recently, pomegranate juice was shown to potently inhibit the sulfoconjugation of 1-naphthol in Caco-2 cells. Saruwatari and others have suggested that some constituents of pomegranate juice, most probably punicalagin, may impair the metabolic functions of the intestine (specifically sulfoconjugation) and therefore might have effects upon the bioavailability of drugs.

2.7 Mango (Mangifera indica) **Knodler et , al 2008** Suggested that the beneficial effects of mango include anti-inflammatory and antimicrobial activities.Preliminary phytochemical screening revealed the presence of flavonoids, including quercetin and glycosylated xanthones such as mangiferin . Quercetin has been shown to possess antioxidant, antimicrobial, antitumor, antihypertensive, antiatherosclerosis, and anti-inflammatory properties (Bischoff 2008). In a series of studies, Rodeiro and others have shown the effects of mango on drug-metabolizing enzymes and drug transporters (Rodeiro and others 2008, 2009). They found that exposure of hepatocytes to mango extract produced a significant reduction (60%) in 7-methoxyresorufin-O-demethylase (MROD; CYP1A2) activity and an increase (50%) in 7-penthoxyresorufin-O-depentylase (PROD; CYP2B1) activity. This group also studied the effect of mangiferin on CYP enzymes and found that mangiferin reduced the activities of 5 P450s: POD (CYP1A2), midazolam 1′-hydroxylation (M1OH; CYP3A1), diclofenac 4′-hydroxylation (D4OH; CYP2C6), S-mephenytoin 4′-hydroxylation (SM4OH), and chlorzoxazone 6-hydroxyaltion (C6OH; CYP2E1). Recently, mango and mango-derived polyphenols have been shown to potentially affect the activity of the multidrug transporter Pgp ABCB1 (Chieli and others 2009). These findings suggest that mango and its components inhibit the major human P450 enzymes involved in drug metabolism and some transporters. The potential for drug interactions with mango fruit should therefore be considered.

2.8 Guava (Psidium guajava L.) **Jouad et, al 2001** xperimented on a number of metabolites, such as phenolics, flavonoid, carotenoid, terpenoid, and triterpene, have been found in this fruit. Extracts and metabolites of this plant, particularly those from the leaves and fruit, possess useful pharmacological activities.There is only one report about the effect of guava extracts on drug transport: guava extract showed a potent inhibitory effect on Pgp-mediated efflux in Caco-2 cells. It was also found to inhibit efflux transport from serosal to mucosal surfaces in the rat ileum .This means that guava could interact with Pgp substrates, such as digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, and paclitaxel, in the small intestine. For this reason, this fruit should be consumed with caution by patients taking medicines.

2.9 Raspberry (Rubus spp.) **Patel et, al (2004)** Suggested that Berries have been shown to have a positive impact on several chronic conditions including obesity, cancer, and cardiovascular and neurodegenerative diseases ,Like other fruits, raspberries contain micro- and macronutrients such as vitamins, minerals, and fiber. Their biological properties, however, have been largely attributed to high levels of various phenolic compounds, as well as the interactive synergies among their natural phytochemical components (for example, ellagic acid, quercetin, gallic acid, anthocyanins, cyanidins, pelargonidins, catechins, kaempferol, and salicylic acid). Raspberry or raspberry constituents have antioxidant and anti-inflammatory properties and inhibit cancer cell growth (Wang and Lin 2000; Juranic and Zixack 2005; Seeram and others 2006; Seeram 2008). Black raspberries (Rubus coreanus) have been called the "king of berries" for their superior health benefits, whereas black mulberry (Morus nigra) is most commonly used for its antioxidants properties and for its high bioactive content of phenolics, anthocyanins, and gallic acid. It has been shown that black raspberry and black mulberry are able to inhibit the human CYP3A-catalyzed midazolam 1-hydroxylation activity in liver microsomes, and the inhibitory effects are somewhat greater than those of pomegranate (Hidaka and others 2005; Kim and others 2006). It has also been reported that black mulberry extract potently inhibits OATP-B function at concentrations that seem to be physiologically relevant in vitro (Satoh and others 2005). These results suggest that black raspberry and black mulberry may decrease the plasma concentrations of concomitantly ingested OATP-B substrate drugs or increase the plasma concentration levels of concomitantly ingested CYP3A-substrate drugs. In vivo studies on the interaction between black mulberry and black raspberry and CYP3A substrates are needed to determine whether inhibition of CYP3A activity by fruit juices is clinically relevant.

2.10 Apple (Malus domestica) **Lewis and Ruud(2004)** Suggested that an apple and its products contain high amounts of polyphenols, which show diverse biological activities and may contribute to beneficial health effects such as protecting the intestine against inflammation due to chronic inflammatory bowel diseases (Lewis and Ruud 2004; Gerhauser 2008). Pohl and others (2006) found that apple juice extract inhibits CYP1A1 at levels of CYP1A1 mRNA, protein, and enzymatic activity. On the other hand, it has also been reported that apple juice and its constituents can interact with members of the OATP transporter family (OATP-1, OATP-3, and NTCP) by reducing their activities in vitro. The functional consequence of such an interaction was a significant reduction in the oral bioavailability of fexofenadine in human plasma levels, possibly by preferential direct inhibition of intestinal OATP activity (Dresser and others 2002). These findings suggest that apple might interact with OATP substrates (for example, estrone-3-sulfate, deltorphin II, fexofenadine, vasopressin, and rosuvastatin).

2.11 Leafy vegetables

Cartea et ,al (2010) suggested that and cauliflower are unique among the common cruciferous vegetables that contain high levels of the aliphatics glucosinolate and glucoraphanin (Cartea and others 2010). Upon hydrolysis, glucoraphanin produces several products that include the bioactive isothiocyanate sulforaphane. The percentage of isothiocyanate sulforaphane present in these vegetables may vary depending on conditions

of hydrolysis, food handling, and preparation . In animal studies, dietary freeze-dried broccoli was found to offer protection against several cancers (Vasanthi and others 2009). However, broccoli, cauliflower, and their glucosinolate hydrolysis products have been shown to induce phase I and phase II drug-metabolizing enzymes in intact liver cells from both rats and humans. The isothiocyanate sulforaphane decreased the enzyme activities hepatocytes associated with CYP1A1 and 2B1/2, namely ethoxyresorufin-O-deethylase and pentoxyresorufin-O-dealkylase, respectively, in a dose-dependent manner (Anwar-Mohamed and El-Kadi 2009). An increase in hGSTA1/2 mRNA has been observed in isothiocyanate sulforaphane-treated human hepatocytes, whereas the expression of CYP3A4, the major CYP in the human liver, markedly decreased at both mRNA and activity levels (Fimognari and others 2008). Conversely, it was recently shown that sulforaphane induces mRNA levels of MRP1 and MRP2 in primary hepatocytes and Caco-2 cells (Harris and Jeffery 2008). It has been additionally reported that broccoli is able to induce the activity of phenolsulfotransferases (PST) (Yeh and Yen 2005). These results suggest that other vegetables with a high content of isothiocyanates, such as those of the family Cruciferae (for example, cabbage, cauliflower, Brussels sprouts, watercress, broccoli, and kale) and the genus Raphanus (radishes and daikons) may have pharmacological and toxicological implications in humans.

atercress is another important member of the cruciferous vegetables, an excellent source for glucosinolates, and other bioactive phytochemicals (Getahun and Chung 1999). Watercress (Nasturtium officinale) is an exceptionally rich dietary source of beta-phenylethyl isothiocyanate (PEITC) (Palaniswamy and others 2003). Previous studies by Leclercq and others (1998) have shown that a single ingestion of watercress inhibits the hydroxylation of chlorzoxazone, an in vivo probe for CYP2E1, in healthy volunteers. It has also been shown that watercress is a bifunctional agent with the ability to induce both phase I (CYP450) and II enzymes. Adding watercress juice to human liver cells induced the activity of CYP4501A and ethoxyresorufin-O-deethylase and NAD(P)H-quinone reductase (Lhoste and others 2004). According to reports, PEITC also has several anticarcinogenic effects given that it can inhibit phase I enzymes and/or activate phase II enzymes. Watercress juice can increase the enzymes SOD and GPX in blood cells in vitro and in vivo (Hofmann and others 2009). Isothiocyanates also interact with ABC efflux transporters such as Ppg, MRP1, MRP2, and BCRP and may influence the pharmacokinetics of substrates of these transporters (Telang and others 2009). According to current data, watercress and isothiocyanate may have clinical repercussions by inducing changes in the bioavailability of some drugs.

2.11 Spinach (Spinacia oleracea) **Schirrmacher and others (2010)** Suggested that spinach is an important antioxidant vegetable usually consumed after boiling the fresh or frozen leaves. Freshly cut spinach leaves contain approximately 1000 mg of total flavonoids per kilogram, and the occurrence of at least 10 flavonoid glycosides has been reported .These are glucuronides and acylated di-and triglycosides of methylated and methylene dioxide derivatives of 6-oxygenated flavonols (Lomnitski and others 2003). While epidemiological and preclinical data support the nutritional benefits of spinach and the safety of its consumption (Lomnitski and others 2003), there are no publications about its effects on drug-metabolizing enzymes and drug transporters. Little is currently known about the in vivo effects these compounds have on

the bioavailability of xenobiotics the clearance and/or tissue distribution of which is determined by active transport and biotransformation. Platt and others (2010) reported the protective effect of spinach against the genotoxic effects of 2-amino-3-methylimidazo[4,5-f]quinoline (IQ) by interaction with CYP1A2 as a mechanism of antigenotoxicity. Its high isothiocyanate and flavonoid content demands additional research to evaluate possible nutrient–drug interactions.

2.12 Vegetable fruits Heber et, al (2014) Suggested that Tomatoes (Lycopersicon esculentum) and tomato-based products are a source of important nutrients and contain numerous phytochemicals, such as carotenoids, that may influence health (carotenoids such as phytofluene, phytoene, neurosporene, γ-carotene, and ζ-carotene) (Heber 2004; Tan and others 2010). Tomatoes are also a source of a vast array of flavonols (for example, quercetin and kaempferol), phytosterols, and phenylpropanoids (Ellinger and others 2006). Lycopene is the most important carotenoid present in tomatoes and tomato products, and their dietary intake has been linked to a decreased risk of chronic illnesses such as cancer and cardiovascular disease (Rao and Rao 2007; Riccioni and others 2008; Waliszewski and Blasco 2010). Studies performed on human recombinant CYP1 showed that lycopene inhibits CYP1A1 and CYP1B1. Lycopene has also been shown to slightly reduce the induction of ethoxyresorufin-O-deethylase activity by 20% by dimethylbenz[a]anthracene in MCF-7 cells (Wang and Leung 2010). It appears to inhibit bioactivation enzymes and induce detoxifying enzymes. It has been suggested that lycopene might have a potential advantage over other phytochemicals by facilitating the elimination of genotoxic chemicals and their metabolites (Wang and Leung 2010). Recent in vitro evidence suggests that high-dose lycopene supplementation increases hepatic cytochrome P4502E1 protein and inflammation in alcohol-fed rats (Veeramachaneni and others 2008).

2.13 Carrots (Daucus carrota) Yeh et, al 2005 Suggested that carrots are widely consumed as food. The active components of carrots, which include beta-carotene and panaxynol, have been studied by many researchers (Surles and others 2004; Sikora and others 2009; Sun and others 2009). Carrots induce PST activity (Yeh and Yen 2005) and decrease CYP1A2 activity (Harris and Jeffery 2008). Bradfield and others have reported that a carrot diet increased the activity of ethoxycoumarin O-deethylase (ECD) activity in a mouse model (Bradfield and others 1985).

2.14 Avocado (Persea americana) Duesteret, al (2001) Suggested that avocadois a good source of bioactive compounds such as monounsaturated fatty acids and sterols. Growing evidence on the health benefits of avocadoes has led to increased consumption and research on potential health benefits (Whiley and Schaffer 2002; Ernst 2003). Phytochemicals extracted from avocado can selectively induce several biological functions (Lu and others 2005; Plaza and others 2009). Two articles published in the 1990s reported avocados interact with warfarin, stating that the fruit inhibited the effect of warfarin. They, however, did not establish the cause of such inhibition .

3. AIM: Review on drug interaction with nutrition obtained from commonly used fruits and vegetables.

4. PLAN OF WORK: The study will be conducted in following steps

1.Study the research work done in the past years on drug interaction with nutrition obtained from commonly used fruits and vegetables.

2.Categorize the study on the basis of different applications.

3.Conclusion of the study.

5. MATERIAL AND METHODS: The work will be done in the following steps:

A literature review of studies done in the past years which will document the development of drug interaction with nutrition obtained from commonly used fruits and vegetables.

Searching will done through various search engines like Google Scholar, Web of science etc.

1. Collection of Literature and year wise arrangement by using tools like sci-hub, mendeley desktop etc.
2. Documentation of summery of research work studied.

Conclusions of the review by assessment of the importance and application of food drug interaction in increasing or decreasing the pharmacokinetic and pharmacokinetic of drug substances.

6. CONCLUSION /SIGNIFICANCE OF THE STUDY

A daily diet of at least 400 g, or five servings, of fruits and vegetables is advised by the World Health Organisation (WHO) and the Food and Agriculture Organisation of the United Nations (FAO) in order to help avoid chronic diseases like heart disease, cancer, diabetes, and obesity. As a result, there is a rise in the demand for fruits and vegetables on a global scale. Some people choose to buy organic foods because they believe they are healthier. Natural product use for enhancing human health has developed independently in various parts of the world, and there are regional differences in production, use.

Hence WHO and the Food and Agriculture Organization of the United Nations (FAO) recommend a daily intake of at least 400 g or 5 servings of fruits and vegetables to aid in the prevention of chronic illnesses such as heart disease, cancer, diabetes, and obesity. As a consequence, there is an increased global consumer demand for fruits and vegetables, and some consumers purchase organic foods with the understanding that they are healthy. The use of natural products for improving human health has evolved independently in different regions of the world and production, use, attitudes, he governing factors differ everywhere. Folk medicine (phytomedicine), despite the fact that modern medicine may be available in the majority of nations for the treatment of many chronic degenerative diseases, has persisted in popularity due to historical and cultural factors. Although the importance of drug interactions with other pharmaceuticals is generally acknowledged, drug interactions with nutrition have received less attention. Preclinical research account for the majority of the published data on the impact of fruits and vegetables on drug transporters and metabolising enzymes. But it's important to keep in mind that same effects could also happen in people. The results of

numerous clinical research on the interactions between grapefruit juice and medications are impressive. The majority of the fruits and vegetables evaluated in this review have a phytochemical combination . A more consistent approach to the evaluation of nutrient–drug interactions in human beings is therefore needed. Said approach must be systematic in order to (1) assess the influence of nutritional status, foodstuffs, or specific nutrients on a drug's pharmacokinetics and pharmacodynamics, and (2) evaluate the influence of a drug on overall nutritional status or the status of a specific nutrient.

7. REFERENCE

1. Alvarez AI, Real R, Perez M, Mendoza G, Prieto JG, Merino G. 2010. Modulation of the activity of ABC transporters (P-glycoprotein, MRP2, BCRP) by flavonoids and drug response. *Pharm Sci* **99**: 598– 617.
2. Amory JK, Amory DW. 2005. Oral erythromycin and the risk of sudden death. *N Engl J Med* **352**: 301– 4.
3. Anwar-Mohamed A, El-Kadi AO. 2009. Sulforaphane induces CYP1A1 mRNA, protein, and catalytic activity levels via an AhR-dependent pathway in murine hepatoma Hepa 1c1c7 and human HepG2 cells. *Cancer Lett* **275**: 93– 101.
4. Ayrton A, Morgan P. 2001. Role of transport proteins in drug absorption, distribution and excretion. *Xenobiotica* **8**: 469– 97.
5. Backman JT, Maenppa J, Belle DJ, Wrighton SA, Kivisto KT, Neuvonen PJ. 2000. Lack of correlation between in vitro and in vivo studies on the effects of tangeretin and tangerine juice on midazolam hydroxylation. *Clin Pharmacol Ther* **67**: 382– 90.
6. Bailey DG, Dresser GK. 2004. Interactions between grapefruit juice and cardiovascular drugs. *Am J Cardiovasc Drugs* **4**: 281– 97.
7. Berardini N, Fezer R, Conrad J, Beifuss U, Carle R, Schieber A. 2005. Screening of mango (*Mangifera indica* L.) cultivars for their contents of flavonol O- and xanthone C-glycosides, anthocyanins, and pectin. *J Agric Food Chem* **53**: 1563– 70.
8. Bergquist SA, Gertsson UE, Knuthsen P, Olsson ME. 2005. Flavonoids in baby spinach (*Spinacia oleracea* L.): changes during plant growth and storage. *J Agric Food Chem* **53**: 9459– 64.
9. Bergman M, Varshavsky L, Gottlieb HE, Grossman S. 2001. The antioxidant activity of aqueous spinach extract: chemical identification of active fractions. *Phytochemistry* **58**: 143– 52.
10. Bischoff SC. 2008. Quercetin: potentials in the prevention and therapy of disease. *Curr Opin Clin Nutr Metab Care* **11**: 733– 40.
11. Blickstein D, Shaklai M, Inbal A. 1991. Warfarin antagonism by avocado. *Lancet* **337**: 914– 15.
12. Bradfield CA, Chang Y, Bjeldanes LF. 1985. Effects of commonly consumed vegetables on hepatic xenobiotic-metabolizing enzymes in the mouse. *Food Chem Toxicol* **23**: 899– 904.
13. Bressler R. 2006. Grapefruit juice and drug interactions. Exploring mechanisms of this interaction and potential toxicity for certain drugs. *Geriatrics* **61**: 12– 8.
14. . 2010. Phenolic compounds in Brassica vegetables. *Molecules* **16**: 251– 80.

15. Côté J, Caillet S, Doyon G, Sylvain JF, Lacroix M. 2010. Bioactive compounds in cranberries and their biological properties. *Crit Rev Food Sci Nutr* **50**: 666– 79.
16. Cuciureanu M, Vlase L, Muntean D, Varlan I, Cuciureanu R. 2010. Grapefruit juice–drug interactions: importance for pharmacotherapy. *Rev Med Chir Soc Med Nat Iasi* **114**: 885– 91.
17. Custodio JM, Wu CY, Benet LZ. 2008. Predicting drug disposition, absorption/elimination/transporter interplay and the role of food on drug absorption. *Adv Drug Deliv Rev* **60**: 717– 33.
18. Chan LN. 2006. Drug-nutrient interactions. In: ME Shils, M Shike, AC Ross, B Caballero, RJ Cousins, editors. *Modern nutrition in health and sisease*. Baltimore : Lippincott Williams & Wilkins. p 1540– 53.
19. Chan WK, Delucchi BA. 2000. Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4. *Life Sci* **67**: 3103– 12.
20. Chieli E, Romiti N, Rodeiro I, Garrido G. 2009. In vitro effects of *Mangifera indica* and polyphenols derived on ABCB1/P-glycoprotein activity. *Food Chem Toxicol* **47**: 2703– 10.
21. Dangour AD, Lock K, Hayter A, Aikenhead A, Allen E, Uauy R. 2010. Nutrition-related health effects of organic foods: a systematic review. *Am J Clin Nutr* **92**: 203– 10.
22. de Wet H, Nkwanyana MN, van Vuuren SF. 2010. Medicinal plants used for the treatment of diarrhoea in northern Maputaland, KwaZulu-Natal Province, South Africa. *J Ethnopharmacol* **130**(2): 284– 9.
23. Del Rio D, Borges G, Crozier A. 2010. Berry flavonoids and phenolics: bioavailability and evidence of protective effects. *Br J Nutr* **104**: S67– 90.
24. Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ, Kim RB. 2002. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake. *Clin Pharmacol Ther* **71**: 11– 20.
25. Dresser GK, Kim RB, Bailey DG. 2005. Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* **77**: 170– 7.
26. Duester KC. 2001. Avocado fruit is a rich source of beta-sitosterol. *J Am Diet Assoc* **101**: 404– 5.
27. Ellinger S, Ellinger J, Stehle P. 2006. Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care* **9**: 722– 7.
28. Engels C, Knodler M, Zhao YY, Carle R, Ganzle MG, Schieber A. 2009. Antimicrobial activity of gallotannins isolated from mango (*Mangifera indica* L.) kernels. *J Agric Food Chem* **57**: 7712– 8.
29. Ernst E. 2003. Avocado-soybean unsaponifiables (ASU) for osteoarthritis—a systematic review. *Clin Rheumatol* **22**: 285– 8.
30. Farkas D, Greenblatt DJ. 2008. Influence of fruit juices on drug disposition: discrepancies between in vitro and clinical studies. *Expert Opin Drug Metab Toxicol* **4**: 381– 93.

31. Fimognari C, Lenzi M, Hrelia P. 2008. Interaction of the isothiocyanate sulforaphane with drug disposition and metabolism: pharmacological and toxicological implications. *Curr Drug Metab* **9**: 668– 78.
32. Flanagan D. 2005. Understanding the grapefruit-drug interaction. *Gen Dent* **53**: 282– 5.
33. Foti RS, Wienkers LC, Wahlstrom JL. 2010. Application of cytochrome P450 drug interaction screening in drug discovery. *Comb Chem High Throughput Screen* **13**: 145– 58.
34. Franco OH, Bonneux L, de Laet C, Peeters A, Steyerberg EW, Mackenbach JP. 2004. The polymeal: a more natural, safer, and probably tastier (than the Polypill) strategy to reduce cardiovascular disease by more than 75%. *BMJ* **329**(7480): 1447– 50.
35. Genser D. 2008. Food and drug interaction: consequences for the nutrition/health status. *Ann Nutr Metab* **52**: 29– 32.
36. Gerhauser C. 2008. Cancer chemopreventive potential of apples, apple juice, and apple components. *Planta Med* **74**: 1608– 24.
37. Getahun SM, Chung FL. 1999. Conversion of glucosinolates to isothiocyanates in humans after ingestion of cooked watercress. *Cancer Epidemiol Biomarkers Prev* **8**: 447– 51.
38. Greenblatt DJ. 2009. Analysis of drug interactions involving fruit beverages and organic anion-transporting polypeptides. *J Clin Pharmacol* **49**: 1403– 7.
39. Hagenbuch B, Gui C. 2008. Xenobiotic transporters of the human organic anion transporting polypeptides (OATP) family. *Xenobiotica* **38**: 778– 801.
○
40. Hanley MJ, Cancalon P, Widmer WW, Greenblatt DJ. 2011. The effect of grapefruit juice on drug disposition. *Expert Opin Drug Metab Toxicol* **7**: 267– 86.
41. Harris KE, Jeffery EH. 2008. Sulforaphane and erucin increase MRP1 and MRP2 in human carcinoma cell lines. *J Nutr Biochem* **19**: 246– 54.
42. Heber D. 2004. Vegetables, fruits and phytoestrogens in the prevention of diseases. *J Postgrad Med* **50**: 145– 9.
43. Hidaka M, Okumura M, Fujita K, Ogikubo T, Yamasaki K, Iwakiri T, Setoguchi N, Arimori K. 2005. Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. *Drug Metab Dispos* **33**: 644– 8.
44. Ho PC, Saville DJ, Coville PF, Wanwimolruk S. 2000. Content of CYP3A4 inhibitors, naringin, naringenin and bergapten in grapefruit and grapefruit juice products. *Pharm Acta Helv* **74**: 379– 85.
45. Hofmann T, Kuhnert A, Schubert A, Gill C, Rowland IR, Pool-Zobel BL, Glei M. 2009. Modulation of detoxification enzymes by watercress: in vitro and in vivo investigations in human peripheral blood cells. *Eur J Nutr* **48**: 483– 91.
46. Honda Y, Ushigome F, Koyabu N, Morimoto S, Shoyama Y, Uchiumi T, Kuwano M, Ohtani H, Sawada Y. 2004. Effects of grapefruit juice and orange juice components on P-glycoprotein- and MRP2-mediated drug efflux. *Br J Pharmacol* **143**: 856– 64. PMID: 15504753

47. Huang SM Hall SD, Watkins P, Love LA, Serabjit-Singh C, Betz JM, Hoffman FA, Honig P, Coates PM, Bull J, Chen ST, Kearms GL, Murray MD. 2004. Drug interactions with herbal products & grapefruit juice: a conference report. *Clin Pharmacol Ther* **75**: 1– 12.

48. Huang SM, Strong JM, Zhang L, Reynolds KS, Nallani S, Temple R, Abraham S, Habet SA, Baweja RK, Burckart GJ, Chung S, Colangelo P, Frucht D, Green MD, Hepp P, Karnaukhova E, Ko HS, Lee JI, Marroum PJ, Norden JM, Qiu W, Rahman A, Sobel S, Stifano T, Thummel K, Wei XX, Yasuda S, Zheng JH, Zhao H, Lesko LJ. 2008. New era in drug interaction evaluation: US Food and Drug Administration update on CYP enzymes, transporters, and the guidance process. *J Clin Pharmacol* **48**: 662– 70.

49. Junyaprasert VB, Soonthornchareonnon N, Thongpraditchote S, Murakami T, Takano M. 2006. Inhibitory effect of Thai plant extracts on P-glycoprotein mediated efflux. *Phytother Res* **20**: 79– 81.

50. Juranic Z, Zixack Z. 2005. Biological activities of berries: from antioxidant capacity to anti-cancer effects. *BioFactors* **23**: 207– 11.

51. Kamath AV, Yao M, Zhang Y, Chon S. 2005. Effect of fruit juices on the oral bioavailability of fexofenadine in rats. *J Pharm Sci* **94**: 233– 9.