MINI REVIEW

Drug-food interactions of commonly available juices of Pakistan

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Abstract: Medicines are often consumed concurrently with food; sometimes to improve its absorption and efficacy. However, certain foods may modify the function of drug metabolizing enzymes or transport mechanisms that are crucial determinants of systemic drug availability. Extensive work has been reported on certain juices like grapefruit that affects the bioavailability of more than 60 medications. However, relatively less work has been reported on certain other commonly used fruit juices, especially in Pakistan, such as mango, strawberry, apple, banana, pomegranate and grape etc. Present review has taken an account of the current work done in this area.

Keywords: Fruit juices, drug interaction, Pakistan

INTRODUCTION

A drug-food interaction is "The result of a physical, chemical, physiological or pathophysiological relationship between a drug and a nutrient, multiple nutrients, food in general, or nutrition status (Rodriguez-Fragoso *et al*., 2011; Genser, 2008; Boullata and Hudson, 2012). Patient nutrition status, food composition, dietary habits, along with the wide spread use of medicines; increase the risk for potential drug-food interactions. However, there are a finite number of documented vegetable/ fruit-drug interactions, necessitating the need for further clinical evaluation. In order to optimize the clinical efficacy of drugs, health care providers like clinicians, pharmacists, dietitians and nurses should be aware of important drug-food interactions. Patients who are at high risk of adverse events, resulting from drug-food interactions include children, older patients, patients with gastrointestinal disorders, cancer, acquired immunodeficiency syndrome (AIDS) and other chronic diseases, where multiple drug regimen as well as dietary/nutritional supplements are advised. The adverse effects resulting from these interactions can vary in severity, depending upon the extent to which oral drug bioavailability increases, the effect of dose related toxicity, the circumstances under which the vegetable/ fruit is consumed and the susceptibility of the patient to the interaction (Bailey *et al*., 2013). The predominant mechanism for drug-food interaction is the induction or inhibition of cytochrome *P*-450 iso-enzymes in the small intestine and liver. Another mechanism involves induction or inhibition of uptake and efflux transport proteins. Fig. 1 and 2 shows the major drug metabolizing enzymes and transporters, respectively. An interaction may have two types of clinical consequences *i.e*. decrease in drug bioavailability leading to treatment failure or increase in bioavailability leading to potential drug toxicity (Singh, 1999; Singh and Malhotra, 2004; Custodio *et al*., 2008). The subsequent paragraphs elaborate some of these interactions.

Pomegranate juice

Pomegranate (*Punica granatum L*.), a seeded or granular apple, is a delicious fruit consumed worldwide in different forms, such as fresh fruit, beverages (juice and wine), and extracts (Jaiswal *et al*., 2010). The fruit is native to Afghanistan, China, Iran and is widely cultivated in Pakistan, India, Russia, Japan and the United States (California) (Haidari *et al*., 2009). Pomegranate juice is a rich source of several phytochemicals including flavonoids (catechins, anthocyanins and other complex flavonoids) (Zahra *et al*., 2018), hydrolysable tannins (ellagitannins and gallotannins) and condensed tannins (proanthocyanidins) (Jiao *et al*., 2015; Syed *et al*., 2007). It has been used for several centuries for the treatment of various ailments such as dysentery, helminthiasis, memory problems, microbial infections and respiratory tract pathologies (Azra *et al*., 2014; Dey *et al*., 2012). In addition, the juice has nutritional values and may provide protection against cardiovascular diseases and also shows potential in chemoprevention of various types of tumors (Stowe, 2011; Ismail *et al*., 2012). table 1 summarizes the major constituents and potential health benefits of pomegranate. The nutritional and beneficial health-related properties make this fruit increasingly popular as a dietary supplement by the public. However, owing to its

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abilities to modulate drug metabolizing enzymes and membrane transporters, the emphases on interactions with drugs have increased. It has been investigated that both pomegranate juice and grapefruit juice caused 50% inhibition of in vitro CYP3A activity at very low juice concentration 0.61 and 0.55% strength, respectively. Pomegranate juice almost completely inhibited midazolam 1′-hydroxylase and carbamazepine 10, 11-epoxidation activity in human liver microsomes to similar extent as grapefruit juice in a dose dependent manner (Hidaka *et al*., 2005; Meng *et al*., 2018). Furthermore, pomegranate juice has been shown to inhibit the sulfoconjugation of 1-naphthol in Caco-2 cells. It has been suggested that punicalagin is the major constituent of pomegranate juice which may impair the metabolic functions of the intestine and therefore, alter the bioavailability of several drugs (Saruwatari *et al*., 2008).

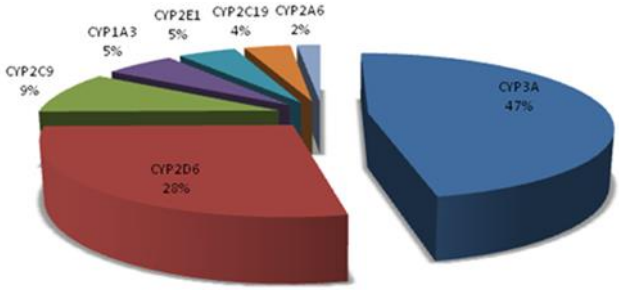

Fig. 1: Human Cytochromes P450 and their relative contribution to hepatic drug metabolism (Ulrich and Matthias, 2013)

In recent years, in vivo studies have revealed the effect of pomegranate juice on CYP3A4. It has been reported that pomegranate juice significantly increased the oral bioavailability of carbamazepine in rats. The authors attributed the increased bioavailability of carbamazepine to the inhibition of CYP3A4 activity in the intestine (Hidaka *et al*., 2005). Pomegranate juice also has been shown to alter the area under the concentration-time curve of tolbutamide and nitrendipine in rats (Voruganti *et al*., 2012).

The literature review covering both *in vitro* and *in vivo* studies indicate, that pomegranate juice may have very high potential to inhibit CYP3A-mediated drug metabolism. Drugs that are affected by pomegranate or its components are summarized in table 2.

Grape juice

Grapes (*Vitis vinifera* L.) are one of the most valued conventional fruits consumed worldwide in different forms, such as fresh fruit, beverages (juice and wine), and extracts (Yadav *et al*., 2009). World top ten grape producing countries include Italy, France, USA, Spain, China, Turkey, Iran, Argentina, Chili and Australia. In Pakistan grapes are produced in Balochistan and some districts of Khyber Pakhtunkhwa and central Punjab (Khair *et al*., 2009). Grape juice is a rich source of several phytochemicals including polyphenols, sugars (Emanuela *et al*., 2018), flavonoids, stilbenes, coumarins and tannins (Garrido and Borges, 2013; Capanoglu *et al*., 2013). The most active and well-characterized polyphenolic compound from the grapes is resveratrol (Rotches-Ribalta *et al*., 2012) that manifested antibacterial (Maddox *et al*., 2010), antioxidation (Meherzia *et al*., 2016; Mikstacka *et al*., 2010), anti-inflammation (Kang et al., 2009) and protection against ischemic injuries (Wang *et al*., 2012). Furthermore, grape juice has nutritional values and is a rich source of essential elements (Lachman *et al*., 2013). Because of high nutritional and health beneficial effects, grapes are widely consumed throughout the world (>consumption 68 million tons). However, owning to its abilities to modulate CYPs and P-gp, the attentions on interactions with substrate drugs have increased.

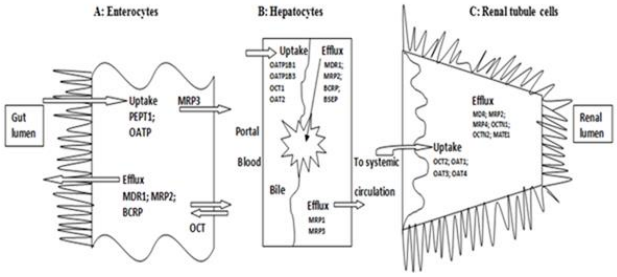

Fig. 2: Selected efflux & uptake transporters in the gut wall (a), liver (b), and kidney (c) (Sarah S and Leslie. 2009)

In recent years, in vitro and in vivo studies have revealed the effect of resveratrol on CYP3A4 and *P*-gp (Chan and Delucchi, 2000; Piver *et al*, 2001). It has been reported that resveratrol irreversibly inhibits CYP3A4 and reversibly inhibits CYP2E1 in a non-competitive manner (Piver *et al*., 2001). It also strongly inhibited the activity of CYP3A4 in insect microsomes containing human CYPs (Chan and Delucchi, 2000). Resveratrol has also been shown to increase the AUC of nicardipine and diltiazem and its metabolite, desacetyldiltiazem in rats (Capanoglu *et al*., 2013; Rotches-Ribalta *et al*., 2012). It has been reported that grape seed extract strongly inhibited the activities of CYP2D6, CYP2C9 and CYP3A4 in human liver microsomes (Nishikawa *et al*., 2004). Grape seed extract decreased the bioavailability of midazolam in rats that may be due to the induction of CYP3A in the liver (Nishikawa *et al*., 2004). The effect of purple grape juice on the oral bioavailability of cyclosporine was studied in healthy male volunteers. It was reported that purple grape juice significantly decreased the bioavailability of cyclosporine C_{max} (by 28%). The authors attributed the decreased bioavailability of cyclosporine to the induction of CYP3A4 and or *P*-gp in the intestine (Oliveira-Freitas *et al*., 2010). In another study, red wine, obtained from black grapes caused a significant decrease for the oral bioavailability of cyclosporine. It was concluded that red wine enhanced the

Table 1: Commonly consumed fruits, their constituents and uses

Fruit	Phytochemicals	Therapeutic use	References
Pomegranate	Flavonoids (quercetin , anthocyanins), phenolic acids (tannins and punicalagin), and pectin	Respiratory and gastrointestinal tract diseases.	Harris and Jeffery, 2008
Grapes	Stilbenes (resverestrol and viniferin) and flavonoids	Respiratory tract diseases, anti anemic, antimicrobial.	Schmidt and Dalhoff, 2002
Mango	Flavonoids (anthocyanins), saponins, phenols, essential oils , carotenoids and fatty acids	Diuretic, laxative, used to combat heart disease.	*Chieli et al*., 2009
Apple	Flavonoids (quercetin), phenolic acids (tannins), saponins, and glycosylated xanthones (magniferin)	Genitourinary diseases, diuretic, respiratory tract inflammation	Kim *et al*., 2009
Guava	Flavonoid (phloretin, quercetin)	Hypertension and genitourinary ailments,	Rodríguez-Fragoso *et al*., 2011
Orange	Flavonoids (diosmin, , nobiletin, tangeretin, and hesperidin)	Respiratory tract diseases, gastrointestinal disorders, and arthritis	Yoo *et al*., 2007
Strawberry	Flavonoids (mainly anthocyanins), hydrolyzable tannins (gallotannins and ellagitannins), phenolic acids (hydroxycinnamic acids and hydroxybenzoic acids)	Inflammation, cardiovascular disease, cancer, type 2 diabetes, obesity and oxidative stress	Francesca *et al*., 2012; Lopes-da-Silva *et al*., 2002
Banana	Phenolic compounds, such as gallic acid, catechin, epicatechin, tannins and anthocyanins, Carotenoids, biogenic amines, such as serotonin, dopamine and norepinephrine, ascorbic acid, rutin, carotenes, tocopherols and catecholamines	Cancer, diabetes, heart problems, Antioxidant, hepatoprotective, antimicrobial, anti-inflammatory, antiallergic, anticarcinogenic, modulation of enzyme activity, antiviral, vasodilatory actions	Mattila *et al*., 2006; Krinsky and Johnson, 2005; Balwinder *et al*., 2016

activities of *P*-gp and CYPs in the intestine (Tsunoda *et al*., 2001).

The literature showed (Capanoglu *et al*., 2013; Rotches-Ribalta *et al*., 2012; Oliveira-Freitas *et al*., 2010; Tsunoda *et al*., 2001; Nishikawa *et al*., 2004) both inhibition and induction of CYP3A4 and *P*-gp in the intestine by the grape juices however, in all cases, the pharmacokinetic profile of the drugs that are substrates of these enzymes is significantly altered. These studies indicate that grape juice had a very high potential to alter the pharmacokinetic profile of CYP3A4 and *P*-gp substrates. The chemical constituents of grapes and the relevant metabolic enzymes and drug transporters are summarized in table 1 and 2, respectively.

Mango juice

Mango is a phytochemically dense fruit and has been used worldwide for many healthful benefits. Pakistan is the fifth largest producer of mango in the world followed by India, China, Mexico and Thailand. In addition, Pakistan is the third largest exporter of mangoes in the world, with an export of about 90,000 tons till September 2016 and expected to reach 100,000 tons by the end of the current export season. In Pakistan, mango is mainly produced in Sindh and Punjab, producing 32% and 67% of the total production, respectively (Akhtar *et al*., 2009; Schieber *et al*., 2001; Sluis *et al*., 2002). Mango is a rich source of flavonoids (quercetin), carotenoids, polyphenols and xanthones such as magniferin (Berardini *et al*., 2005; Dorina *et al*., 2017). The effect of mango juice on drug metabolizing enzymes and drug transporters has been studied (Rodeiro *et al*., 2009; Gomez-Lechon *et al*., 2008). Magniferin has been shown to reduce the activities of CYP3A1, CYP2C6 and CYP2E1 enzymes. Similarly, mango-derived polyphenols have been shown to inhibit the activity of P-gp ABCB1 (Chieli *et al*., 2009). Drug metabolizing enzymes and the relevant transporters that may be affected by mango or its components are summarized in table 2.

Apple juice

Apple has a wide range of health beneficial effects and is helpful in the treatment of cardiac diseases, pulmonary dysfunction, asthma, obesity, diabetes and cancer (Boyer and Liu, 2004). Apple contains high amounts of flavonoids (quercetin, phlorizin, epicatechin, kaempferol), anthocyanins and triterpenoids (Schieber *et al*., 2001; Sluis *et al*., 2002; Awad *et al*., 2000). It has been reported that apple juice inhibits CYP1A1- mediated drug

Table 2: The effect of fruit juices on drug metabolizing enzymes and their substrates

Fruits	Molecular target	Drug interactions in humans and others	References
Pomegranate	Inhibits: CYP3A and phenol sulfotransferase activity	In humans: carbamazepine, midazolam, In rates: tolbutamide	Farkas D and Greenblatt, 2008; Misaka *et al*., 2011
Grapes	Inhibits: CYP3A4, and CYP2E1,CYP1A1,CYP1B1, CYP2D6,CYP2C9,CYP2C19 Inhibit *P*-glycoprotein ,MRP2	In humans: cyclosporine	Chan and Delucchi, 2000; Piver et al., 2001
Mango	Inhibits: CYP 3A1, CYP1A1, CYP1A2, CYP2E1,CYP2C6,P-glycoprotein (ABCB1)	*In vitro* system: verapamil midazolam, chlorzoxazone, diclofenac	Gomez-Lechon *et al*., 2008
Apple	Inhibits: CYP1A1,minimal effect on CYP3A activity, strongly inhibits OATP family (Oatp-1, Oatp-3, and NTCP)	*In vitro* system: fexofenadine In humans: fexofenadine and midazolam	Pohl *et al*., 2006; Ming *et al*., 2011; Mougey *et al*., 2009
Guava	Inhibits: *P*-glycoprotein	Not documented	Junyaprasert *et al*., 2006
Orange	Inhibits: CYP3A4, OATP-A, OATP-B and P-glycoprotein,	*In vitro* system: fexofenadine, vinblastine, glibenclamida In humans: pravastatin, celiprololciclosporine, ciprofloxacin, levofloxacin, atenolol	Takanaga *et al*., 2000; Harris *et al*., 2008; Greenblatt, 2009
Strawberry	Not documented		
Banana	Not documented		

metabolism (Pohl *et al*., 2006). On the other hand, phlorizin strongly inhibits the hepatic drug transporter OATP1B1 while quercetin and kaempferol are potent inhibitors of OATP1A2 and OATP2B1 (Mandery *et al*., 2010).

In another study, quercetin significantly increased the oral bioavailability of fexofenadine, possibly as a result of inactivation of *P*-gp (Kim *et al*., 2009). These findings suggest that substrates both for CYP1A1 and OATP may potentially interact with apple juice. Undoubtedly, further investigation is needed to determine possible active compounds in apple juice that may well explain the interactions observed between certain medicines and apple juice.

Guava juice

Guava is an important subtropical fruit and has been used as food and in folk medicine for the treatment of diarrhea and diabetes (Kaneko *et al.*, 2013). Guava contains a number of biologically active compounds such as polyphenols, carotenoids, flavonoids, triterpines and terpenoids (Soares *et al*., 2007; Kombele *et al*., 2018). These compounds particularly the one derived from the leaves, possess potent pharmacological activities (He and Venant, 2004). There is no report whether these phytochemicals have any effect on inducing or inhibiting the activity of drug metabolizing enzymes. However, guava extract has been evaluated for its inhibitory effect on P-gp mediated efflux in Caco-2 cells. The reports suggest that guava is a potent inhibitor of efflux transporter and can interact with P-gp substrates such as fexofenadine, paclitaxel, indinavir, colchicines and vincristine (Junyaprasert *et al*., 2006).

Orange Juice

Orange is primarily used for making marmalade and in herbal medicine to treat various ailments. Seville orange contains flavonoids such as bergamottin, 6,7-dihydroxy bergamottin, diosmin, nobiletin, tangeretin, and hesperidins as the principal constituents (Takanaga *et al*., 2000; Vanessa *et al*., 2018). It has been investigated that orange inhibited enteric CYP3A4 in vitro and in healthy volunteers (Mouly *et al*., 2005). The consumption of a single glass of orange juice resulted in a 76% increase in the bioavailability of felodipine, compared to what is observed after grapefruit juice consumption (Malhotra *et al.*, 2001; Meng *et al*., 2018). The increase in bioavailability may be explained as to the inhibition of CYP3A4 in the gut, presumably by bergamottin and 6, 7-dihydroxy bergamottin. Orange juice also inhibited the activities of P-gp efflux transporters that may be due to the tangeretin and nobiletin, the components of orange juice (Takanaga *et al*., 2000). It has also been reported that naringin, a component of orange juice, inhibit OATP transporter activity (Farkas and Greenblatt, 2008). Thus, orange juice might increase or reduce the oral bioavailability of drugs depending upon whether the drug is a substrate for CYP enzymes and or the drug transporter.

Strawberry juice

Fresh strawberry juice is widely consumed in Pakistan, particularly in summer season. The juice is a rich source of vitamin C, thiamin, riboflavin, pantothenic acid, vitamin B6, vitamin B12, vitamin A, vitamin E, vitamin K, α-tocopherol, calcium, magnesium, potassium, zinc and copper. Similarly, the juice also contains some important phytochemicals such as flavonoids (mainly

anthocyanins), hydrolyzable tannins (gallotannins and ellagitannins) and phenolic acids such as hydroxycinnamic acids and hydroxybenzoic acids (Francesca *et al*., 2012; Lopes-da-Silva *et al*., 2002). The health benefits of strawberry juice consumption include their role in the prevention of inflammation, cardiovascular disease, cancer, type 2 diabetes, obesity and oxidative stress (Francesca *et al*., 2012; Mariel and Edith 2018). Flavonoids may inhibit the activity of CYP-enzymes; however, no data is available regarding the potential interaction of fresh strawberry juice with drug metabolizing enzymes or drug transporters.

Banana juice

Extensive search using keywords; banana juice-drug interaction, effect of banana juice on drug metabolizing enzymes, effect of banana juice on drug transporters and interaction of banana with various isoforms of CYP like CYP3A4, CYP2C19 etc. using Google scholar, PubMed and Science Direct provided no information regarding banana juice interaction.

CONCLUSION

Pomegranate, apple, grape and orange juice significantly inhibit the activities of drug metabolizing enzymes namely CYP3A4, CYP3A1, CYP2C6, CYP2C9, CYP2D6 and CYP2E1 as well as drug transporters such as P-gp, OATP1B1, OATP1A2, OATP2B1 and other OATP transporters in a concentration dependent manner. The inhibition or induction of these enzymes and transporters resulted in a significant change in the AUC of substrate drugs.

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