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Review Article

Food-drug interactions precipitated by fruit juices other than grapefruit juice: An update review

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ABSTRACT

This review addressed drug interactions precipitated by fruit juices other than grapefruit juice based on randomized controlled trials (RCTs). Literature was identified by searching PubMed, Cochrane Library, Scopus and Web of Science till December 30 2017. Among 46 finally included RCTs, six RCTs simply addressed pharmacodynamic interactions and 33 RCTs studied pharmacokinetic interactions, whereas seven RCTs investigated both pharmacokinetic and pharmacodynamic interactions. Twenty-two juice-drug combinations showed potential clinical relevance. The beneficial combinations included orange juice-ferrous fumarate, lemon juice-^{99m}Tc-tetrofosmin, pomegranate juice-intravenous iron during hemodialysis, cranberry juice-triple therapy medications for H. pylori, blueberry juice-etanercept, lime juice-antimalarials, and wheat grass juice-chemotherapy. The potential adverse interactions included decreased drug bioavailability (apple juice-fexofenadine, atenolol, aliskiren; orange juice-aliskiren, atenolol, celiprolol, montelukast, fluoroquinolones, alendronate; pomelo juice-sildenafil; grape juice-cyclosporine), increased bioavailability (Seville orange juice-felodipine, pomelo juice-cyclosporine, orange-aluminum containing antacids). Unlike furanocoumarin-rich grapefruit juice which could primarily precipitate drug interactions by strong inhibition of cytochrome P450 3A4 isoenzyme and P-glycoprotein and thus cause deadly outcomes due to co-ingestion with some medications, other fruit juices did not precipitate severely detrimental food–drug interaction despite of sporadic case reports. The extent of a juice-drug interaction may be associated with volume of drinking juice, fruit varieties, type of fruit, time between juice drinking and drug intake, genetic polymorphism in the enzymes or transporters and anthropometric variables. Pharmacists and health professionals should properly screen for and educate patients about potential adverse juice-drug interactions and help minimize their occurrence. Much attention should be paid to adolescents and the elderly who ingest medications with drinking fruit juices or consume fresh fruits during drug treatment. Meanwhile, more researches in this interesting issue should be conducted.

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1. Introduction

According to *Joint Commission International (JCI) Accreditation Standards for Hospitals (6th Edition)*, the hospital should provide information about any medications associated with food interactions and list foods that are contraindicated according to the patient's care needs. Also, actual or potential food–drug interactions should be checked during appropriateness review of prescriptions [1].

Fruit juice is a beverage produced by squeezing or crushing fresh fruit (e.g., apple, orange, grape, cranberry, grapefruit, pomegranate, blueberry), and often consumed for its perceived health benefits. Meanwhile, medications may be ingested with common fruit juices by patients. It is an interesting and practical issue regarding whether fruit juice could precipitate drug interactions.

Grapefruit juice (GFJ)-drug interactions have received extensive interests from the scientific, medical, regulatory and general communities because GFJ can strongly interfere with the disposition of substrates of cytochrome P450 (CYP)3A and/or P-glycoprotein (P-gp). More than 85 medications are known to interact with GFJ, and about one-half of these interactions have the potential to cause serious adverse events [2]. For example, when simvastatin was ingested with GFJ, the mean peak serum concentration (C_{max}) (indicator of the rate of absorption) and the area under the serum concentration–time curve (*AUC*) (indicator of the extent of absorption) of simvastatin were increased 12.0-fold and 13.5-fold, respectively, compared with water control [3]. In other words, one tablet of simvastatin with a glass of GFJ can be like taking 12 tablets with a glass of water, increasing the risk of liver and muscle damage. Recently, a new update from the U.S. Food and Drug Administration advises against taking some medications with GFJ [4].

In terms of fruit juices other than GFJ, there are a few sporadic case reports of food–drug interactions which are vital for pharmacovigilance and serve to stimulate practitioners to be alert for potential adverse outcomes. For example, lime juice could significantly increased the bioavailability, antiepileptic activity and toxicity of carbamazepine [5]. An elderly man receiving usual maintenance dose of warfarin experienced fatal internal hemorrhage after co-ingestion of cranberry juice for two weeks. The adverse event was assumed to be associated with cranberry flavonoids competition for the enzymes that normally inactivate warfarin [6]. Kang et al. reported a case of unsafe interaction between a commercial product of noni (*Morinda citrifolia L*) juice and phenytoin. Persistent subtherapeutic phenytoin levels (<10 mg/L) and poor seizure control were observed in a epileptic patient who coadministered noni fruit juice daily. However, the level of phenytoin raised to 25.34 mg/L after noni juice was stopped for one week and dropped to 17.82 mg/L two weeks after restarting with usual daily consumption of noni juice under the same dose of phenytoin. The possible mechanism was the inducible effect of noni juice on CYP2C9 which primarily accounted for phenytoin elimination [7]. Because noni juice is a popular beverage for some consumers, clinicians should be aware of this clinically significant juice-drug interaction and request epileptic patients not use noni juice while receiving phenytoin therapy.

Farkas et al. observed the discrepancies between in vitro and clinical studies regarding the interactions between prescription drugs and over ten fruit beverages [8]. Dolton, Bailey, and An reviewed the literature on interactions between clinically used OATP substrates and fruit juice consumption [9–11]. These reviews have enriched international community knowledges on fruit juice-drug interactions. However, many randomized controlled trials (RCTs) of drug interactions precipitated by fruit juices other than GFJ have been conducted in recent years; however, a review on these RCTs has not been available. RCTs are considered to provide the most reliable evidence on the effectiveness of interventions because the processes used during the conduct of an RCT can minimize the risk of confounding factors affecting the results [12]. Therefore, we present an update narrative review, based on RCTs rather than sporadic case reports and non-RCTs, to investigate whether fruit juices other than GFJ could precipitate significant food–drug interactions.

2. Methods

Relevant literature was identified by searching PubMed, Cochrane Library, Scopus and Web of Science till December 30 2017. For PubMed, the query was "title/abstract: juice or juices" and "all fields: drug or medication or pharmacokinetics or drug interaction or combination therapy", with a filter of "language: English; article type: randomized controlled trials". For Cochrane Library, the query was "record title: juice or juices" and "all text: drug or medication or pharmacokinetics or drug interaction or combination therapy", with a filter of "publication type: randomized controlled trials". For Scopus, the query was "article title, abstract, keywords: juice or juices", "all fields: drug or medication or pharmacokinetics or drug interaction or combination therapy" and "article title, abstract, keywords: randomized controlled trials", with a filter of "language: English; publication type: article". For Web of Science, the query was "topic: juice or juices", and "topic: drug or medication or pharmacokinetics or drug interaction or combination therapy", with a filter of "language: English; "document type: clinical trial". The number of articles identified in PubMed, Cochrane Library, Scopus and Web of Science was 532, 361, 192 and 318, respectively. After eliminating

duplicate documents, five hundred and thirty-two articles were further screened.

Inclusion criteria included fruit juices other than GFJ-drug interaction studies. Exclusion criteria were articles with title containing GFJ but not other fruit juices, and articles actually irrelevant to the juice-drug interaction topics. After reviewing the summary of each article, 481 articles were directly excluded because of actually irrelevant topics ($n = 370$) and only discussing GFJ-related juice-drug interactions ($n = 111$). Forty-six articles were finally included under this search strategy and inclusion/exclusion criteria. The full text of each included article was critically reviewed, and valuable information was summarized by data interpretation.

3. Results

3.1. General information

Eight RCTs were conducted in true patients whereas 38 RCTs were carried out in healthy volunteers. Six RCTs addressed juice-related pharmacodynamic interactions and 33 RCTs studied pharmacokinetic juice-drug interactions, whereas seven RCTs investigated both pharmacokinetic and pharmacodynamic juice-interactions.

Twenty-two juice-drug combinations showed potential or actual clinical relevance (Table 1). The potential beneficial juice-drug interactions included orange juice-ferrous fumarate, lemon juice-^{99m}Tc-tetrofosmin, pomegranate juice-intravenous iron during hemodialysis, cranberry juice-triple therapy medications for H. pylori, blueberry juice-etanercept, lime juice-antimalarials, and wheat grass juice-chemotherapy. The potential adverse interactions included decreased drug bioavailability (apple jucie-fexofenadine, atenolol, aliskiren; orange juice-aliskiren, atenolol, celiprolol, montelukast, fluoroquinolones, alendronate; pomelo juice-sildenafil; grape juice-cyclosporine), and increased bioavailability (Seville orange juice-felodipine, pomelo juice-cyclosporine, orange-aluminum containing antacid).

Different from the fact that drinking GFJ with some medications can be deadly, other fruit juices did not precipitate severe adverse juice-drug interaction in this review. For drugs with narrow therapeutic window, only cyclosporine was confirmed to have drug interactions with fruit juices other than GFJ (i.e., bioavailability of cyclosporine was moderately increased by pomelo juice and moderately decreased by grape juice).

3.2. Fruit juice-drug combination

3.2.1. Apple juice

One-time ingestion of 400 ml 10% apple juice could significantly decrease the *AUC* for (R)- and (S)-fexofenadine by 49% and 59%, respectively, and prolonged the time to reach the maximum plasma concentration (T_{max}) of both enantiomers ($P < 0.001$) in healthy Japanese volunteers. The underlying mechanism is that apple juice probably inhibits intestinal organic anion transporting polypeptide 2B1 (OATP2B1)-mediated transport of fexofenadine, and that the OATP2B1 inhibition effect does not require repeated ingestion or a large volume of apple juice [13]. Although the authors did not examine which apple juice ingredients were responsible for the observed effects, their previous in vitro study showed that a mixture of four flavonoids at concentrations present in apple juice (i.e., phloridzin 16.8 μmol/L, phloretin 0.20 μmol/L, hesperidin 0.25 μmol/L, and quercetin 0.50 μmol/L) could significantly inhibit OATP2B1-mediated uptake of estrone-3-sulfate [14]. Luo et al. revealed dose-dependent apple juice–fexofenadine interaction in healthy subjects. A moderate to large juice-drug interaction is caused by a larger volume of apple juice (e.g., 300–600 ml), whereas the effect of a small volume (e.g., 150 ml) appears to be minimal [15]. Drinking apple juice (1200 ml/day) could significantly decrease fexofenadine *AUC* compared with water (1342 ± 519 vs. 284 ± 79.2 ng h/ml, $P < 0.05$) and the decrease in fexofenadine *AUC* was significantly less in subjects carrying the solute carrier organic anion transporter family member 2B1 (*SLCO2B1*) c.1457C > T allele [16]. In vitro drug transport studies and human volunteer study showed that apple juice at 5% of normal strength markedly reduced human OATP activity rather than P-gp activity and decreased the *AUC* and C_{max} of fexofenadine, to 30%–40% of those with water [17]. Taken together, to maximize the effects of fexofenadine, it is recommended that fexofenadine should be taken with water.

Apple juice ingestion could greatly reduce the plasma concentrations by 84% and renin-inhibiting effect of aliskiren, probably by inhibiting its OATP2B1-mediated influx in the small intestine. Concomitant intake of aliskiren with apple juice is best avoided [18].

Apple juice could markedly reduce atenolol *AUC* in a dose-dependent manner [i.e., the geometric mean *AUC* ratios of apple juice versus water were 0.18 (1200 ml) and 0.42 (600 ml)]. The apple juice–atenolol interaction is not assumed to involve OATP2B1 because atenolol is not an OATP2B1 substrate and genetic variation of *SLCO2B1* c.1457C > T had a negligible effect on the pharmacokinetics of atenolol [19]. Very recently, the specific mechanism was uncovered, i.e., plasma membrane monoamine transporter (PMAT/SLC29A4) was involved in intestinal atenolol absorption and it was sensitive to the flavonoids contained in apple juice. Phloretin, quercetin and quercetin-3ß-d-glucoside were found to extensively inhibit PMAT-specific atenolol uptake whereas rutin (a diglycoside of quercetin) and phlorizin (a monoglycoside of phloretin) showed weaker inhibitory activity [20]. PMAT seemed more sensitive to unglycosidated or less glycosidated forms of flavonoids.

Drinking apple juice (1200 ml/day) has little effect on the pharmacokinetics of midazolam (CYP3A probe), indicating the lack of modulatory effect on CYP3A activity [16].

Some patients are unable to ingest the intact pills, so the feasibility of taking the drug by dispersion in fruit juice should be investigated. Sprinkling the contents of ramipril capsule into apple juice had no effects on the pharmacokinetics and pharmacodynamics in the healthy elderly volunteers [21]. The bioavailability of deferasirox and cyclosporine microemulsion oral solution were unaltered when the drug was dispersed with orange or apple juice compared with dispersion in water [22,23]. Lansoprazole capsules could be administered by mixing the capsule contents with apple juice for nasogastric administration [24].

Table 1 – Significant drug interactions precipitated by fruit juices based on RCTs.

Juices	Object drugs	PK/PD effects
Apple juice	Fexofenadine [13–16], aliskiren [18], atenolol [19]	Great decrease (↓) in drug bioavailability and potential lower (↓) efficacy
Orange juice	Aliskiren [18], atenolol [25], celiprolol [27], montelukast [28], alendronate [35], clofazimine [36]	Great decrease (↓) in drug bioavailability and potential lower (↓) efficacy
	Fluoroquinolones [31–34]	Great decrease (↓) in drug bioavailability, potential higher (↑) risk of therapeutic failures and subsequent bacterial resistance
	Ferrous fumarate [29]	Substantially enhanced (↑) iron absortption and its anti anemia efficacy
	Aluminum-containing antacid [30]	Greatly enhanced (↑) aluminum absorption and increased (↑) aluminum toxicity
Seville orange juice	Felodipine [40]	Significant increase (↑) in *AUC* of felodipine and decrease (↓) in the dehydrofelodipine-felodipine *AUC* ratio (an index of CYP3A4 activity)
Pomelo juice	Cyclosporine [42]	Significant increase (↑) in *AUC* and C_{max}, and potential higher (↑) risk of supratherapeutic concentrations of cyclosporine
	Sildenafil [43]	Significantly reduced (↓) bioavailability and potential reduced (↓) efficacy
Grape juice	Cyclosporine [44]	Significantly decreased (↓) bioavailability and potential higher (↑) risk of subtherapeutic concentrations of cyclosporine
	Phenacetin [45]	Marked reduction (↓) in *AUC* and C_{max}, and a delay in time to peak concentration
Lemon juice	^{99m}Tc-tetrafosmin [47]	Enhanced (↑) hepatobiliary excretion and improved (↑) myocardial SPECT image quality
Pomegranate juice	Intravenous iron during hemodialysis [51]	Attenuation (↓) in oxidative stress and inflammation induced by intravenous iron
Cranberry juice	Triple therapy medications for H. pylori [55]	Higher (↑) eradication rate of H. pylori eradication in females
Blueberry juice	Etanercept [56]	Significantly improved (↑) efficacy and reduced (↓) side effects of etanercept
Lime juice	Antimalarials (artemether and camoquine) [57]	Improved (↑) antimalarial efficacy
Wheat grass juice	Chemotherapy (fluorouracil, adriamycin and cytoxan) [59]	Significantly reduced (↓) side effects of chemotherapy

Notes: PK, pharmacokinetics; PD, pharmacodynamics; CYP, cytochrome P450; SPECT, single photon emission computed tomography; C_{max}, peak serum concentration; *AUC*, area under the serum concentration–time curve.

3.2.2. *Orange juice*

Orange juice could reduce the C_{max}, *AUC* and renin-inhibiting effect of aliskiren by 80%, 62% and 87%, probably by inhibiting the OATP2B1-mediated aliskiren influx in the small intestine [18]. Concomitant intake of aliskiren with orange juice is best avoided.

Orange juice three times daily for 3 days could decrease the C_{max} and *AUC* of atenolol by 49% and 40%, respectively ($P < 0.01$), but it did not change the elimination half-life of atenolol. Meanwhile, volunteers exhibited significantly higher average heart rate during the orange juice phase than during the water phase ($P < 0.01$) [25]. Coadministration of atenolol with orange juice may need drug dose adjustment; otherwise they should be ingested separately. Considering the latest finding that atenolol is a substrate of PMAT which is sensitive to apple juice [20], it is very necessary to confirm whether orange juice–atenolol interaction involves PMAT-mediated intestinal transport.

Orange juice three times daily for 3 days could greatly reduce the bioavailability of celiprolol (i.e., C_{max} and *AUC* decreased by 89% and 83%, respectively whereas T_{max} increased from 4 to 6 h despite of insignificant difference in the hemodynamic variables between the juice phase and water phase) [26]. The concentrations of celiprolol are so substantially decreased that this interaction is likely to be of clinical relevance. The mechanisms for this interaction may be as follows: (1) Intake of acidic orange juice (pH approximately 3.5) may lower the pH in the intestinal lumen and thus decrease the amount of un-ionized celiprolol (the absorbable form) because celiprolol is a relatively hydrophilic base with a pKa of 9.5. (2) Chemical constituents in orange juice may modulate the function of transporters in the intestinal wall. Hesperidin contributes predominantly to the inhibition of OATP2B1-mediated estrone-3-sulfate uptake by orange juice, with the ratio of inhibitor concentration in the juice to the inhibitor concentration giving half-maximum inhibition ([C]/IC_{50}) being 124 [14]. Considering the clearly confirmed effect of *SLCO2B1* polymorphism on the *AUC* of celiprolol at the therapeutic dose [27], and the inhibitory effect of orange juice on OATP2B1 [14,18], the orange juice–celiprolol interaction probably involves OATP2B1-mediated mechanism.

Compared with co-ingestion with sports drink Gatorade control, co-ingestion with orange juice had a minimal effect on the *AUC* of montelukast in adolescents and young adults 15–18 years old with asthma. However, a significant reduction in *AUC* of montelukast was detected with orange juice relative to Gatorade in *SLCO2B1* c.935G/G homozygote [28]. The underlying mechanism may be that montelukast is a substrate of OATP2B1 and subjects carrying *SLCO2B1* c.935 wild homozygote are more susceptible to intestinal uptake inhibition by orange juice.

Orange juice could significantly enhance the absorption of ferrous fumarate in young children [29], and vitamin C in the juice is likely responsible for this effect. Orange juice could greatly enhance aluminum absorption (i.e., about 10-fold increase in 24 h urinary aluminum excretion following coadministration of aluminum-containing antacids). Citric acid in orange juice may primarily account for substantially enhancing the absorption of aluminum [30]. To avoid the toxicity of excessive intake of aluminum, orange juice should not be concomitantly taken with aluminum containing antacids.

Calcium-fortified orange juice could lead to lack of bioequivalence of fluoroquinolones (e.g., levofloxacin, gatifloxacin and ciprofloxacin) in healthy volunteers when drug and juice are coadministered [31–33]. The underlying mechanism may involve chelating interactions and/or competition between fluoroquinolone and components of the orange juices for intestinal transporters. Another study compared the bioequivalence of single doses of oral ciprofloxacin in healthy volunteers when coadministered with water, orange juice, or calcium-fortified orange juice. The C_{max} and *AUC* of ciprofloxacin significantly decreased in the presence of both forms of the orange juice, carrying the potential to significantly decrease clinical efficacy and increase antibiotic resistance. Therefore ingestion of the orange juice with fluoroquinolones should be discouraged [34].

Orange juice could reduce the bioavailability of alendronate and clofazimine by approximately 60% and 18%, respectively [35,36]. Orange juice had no potential risk of interactions with deferasirox, cycloserine, ethionamide, and diltiazem [22,37–39].

3.2.3. *Seville orange juice*

Seville orange is also commonly known as bitter orange or sour orange. Compared with common orange juice, Seville orange juice could increase felodipine *AUC* by 76% and the metabolite-parent *AUC* ratio most probably by inactivation of intestinal CYP3A4 [40]. Different from significant interaction between GFJ and cyclosporine, Seville orange juice had no significant effect on cyclosporine disposition [41]. The underlying mechanism may be that GFJ inhibits both intestinal-mediated CYP3A4 metabolism and P-gp efflux of cyclosporine whereas Seville orange juice only selectively "knocks out" intestinal CYP3A4 and does not alter the enterocyte concentration of P-gp. It indicates that only drugs whose bioavailability is more significantly determined by enterocyte CYP3A4 and less dependent on P-gp are susceptible to drug interactions induced by Seville orange juice ingestion.

3.2.4. *Pomelo juice*

Pomelo juice could increase the bioavailability of cyclosporine, possibly by inhibiting CYP3A or P-gp activity (or both) in the intestine [42]. For sildenafil, pomelo juice produced an effect opposite to that expected (i.e., the bioavailability of CYP3A4-metabolized sildenafil is assumed to be increased by pomelo juice, however, it was reduced by 40% by co-ingestion). The reduced bioavailability of sildenafil may be attributed to an effect of pomelo juice on uptake transporters or a physicochemical interaction between sildenafil and some constituents in pomelo juice [43]. To avoid the reduced efficacy of sildenafil, consumers should be advised not to drink pomelo juice before or immediately after taking sildenafil.

3.2.5. *Grape juice*

Grape juice is different from GFJ although some people may erroneously substitute grape juice for GFJ. Purple grape juice (200 ml) could significantly decrease oral cyclosporine *AUC* by

30% and C_{max} by 28% in healthy volunteers while not altering the elimination half-life, indicating that this juice-drug interaction probably occurred in the absorption process (bioavailability) rather than in the elimination process [44]. The underlying mechanism may involve CYP3A4 activation by grape juice or physicochemical interaction (e.g., constituents in grape juice bound to cyclosporine) in the gastrointestinal tract. To avoid blood cyclosporine level below the therapeutic window, the co-ingestion of cyclosporine with purple grape juice should be discouraged.

Ingestion of 200 ml grape juice could reduce plasma concentrations of phenacetin and increase paracetamol to phenacetin *AUC* ratios (CYP1A2 probe) following a single oral dose of 900 mg phenacetin. The pharmacokinetic changes may be attributed to enhanced first-pass metabolism of phenacetin due to CYP1A2 activation by flavonoids in grape juice or desaturation of CYP1A2 secondary to a slower rate of phenacetin absorption [45].

Although grape juice could impair CYP2C9 activity in vitro, it did not alter the clearance of flurbiprofen (CYP2C9 probe) in humans, making a pharmacokinetic interaction with warfarin unlikely [46]. Grape juice has no significant influence on the pharmacokinetics and pharmacodynamics of diltiazem extended release in healthy subjects [39].

3.2.6. *Lemon juice*

Drinking 250 ml of diluted lemon juice could accelerate the transit of tetrofosmin through the liver parenchyma and improve image quality on ^{99m}Tc-tetrafosmin myocardial single photon emission computed tomography (SPECT) in male patients. A drink of lemon juice may be recommended as a simple technique to decrease extra-cardiac activity on ^{99m}Tc-tetrafosmin cardiac SPECT [47]. The mechanism may be that lemon juice is rich in vitamin C with a pH as low as 2.0 and its acidic characteristics could facilitate bile secretion and hepatic clearance of tetrofosmin by increasing the secretion of secretin.

3.2.7. *Pomegranate juice*

Despite of CYP2C9 inhibition in vitro, pomegranate juice did not impair oral clearance of flurbiprofen and CYP2C9 activity in human volunteers, and can be consumed by patients taking CYP2C9 substrates with negligible risk of pharmacokinetic interaction [48]. Two weeks' consumption of pomegranate juice did not significantly alter the pharmacokinetics of single subtherapeutic doses of midazolam compared with water [49]. Compared to GFJ, pomegranate juice did not impair clearance of oral or intravenous midazolam, suggesting the lack of inhibitory effect on CYP3A activity [50]. Pomegranate juice intake could attenuate the increase in systemic oxidative stress and inflammation induced by intravenous iron during hemodialysis. Such beneficial effects are probably due to the pomegranate juice's potent antioxidant contents such as polyphenols [51].

3.2.8. *Cranberry juice*

Daily ingestion of cranberry juice for 10 days did not alter the pharmacokinetics of warfarin, tizanidine and midazolam, a cocktail of probes of CYP2C9, CYP1A2, and CYP3A4 [52]. Cranberry juice did not impair the CYP2C9-mediated clearance of flurbiprofen and plasma levels of warfarin enantiomers in humans [46,53]. Drinking a glass of cranberry juice did not significantly affect the disposition of cyclosporine [42].

In patients with atrial fibrillation on a stable dose of warfarin for 3 months, daily consumption of 250 ml cranberry juice had no significant effect on prothrombin time [54]. Cranberry juice 240 ml once daily for 2 weeks had no effect on plasma levels of warfarin in patients on stable warfarin anticoagulation despite that international normalized ratio (INR) temporally elevated significantly at a single time point. The augmented warfarin anticoagulation following cranberry juice ingestion in case reports may represent a chance temporal association [53].

The addition of cranberry juice (250 ml twice daily) to triple therapy with omeprazole, amoxicillin and clarithromycin could improve the rate of H. pylori eradication in female patients [55]. Although cranberry constituents had antiadhesion activity on H. pylori in vitro, the underlying mechanism for synergistic effect of cranberry juice is still unclear.

3.2.9. *Blueberry juice*

A combination therapy of blueberry juice and etanercept in patients with juvenile idiopathic arthritis under the age of 16 years could significantly reduce the disease severity and side effects caused by etanercept, and thus it is a potential method for the therapy of this disease. This clinically beneficial juice-drug interaction may attribute to the reduced levels of interleukin-1 alpha and beta, and the increased level of interleukin-1 receptor antagonist brought by blueberry [56].

3.2.10. *Lime juice*

Malaria parasite clearance in children with acute uncomplicated malaria could be enhanced when lime juice was coadministered with World Health Organization recommended antimalarials (artemether and camoquine). The mechanism of lime juice–antimalarials interaction may be related to high antioxidant property of vitamin C and flavonoid compounds, and the alkalinizing effects of juice rich in vitamin C [57]. Considering that lime juice could inhibit CYP3A4 [5], and CYP3A4 plays an important role in drug metabolism of artemether, mefloquine, and lumefantrine [58], it is necessary to conduct pharmacokinetic interaction study of lime juice and these CYP3A4-metabolized antimalarials.

3.2.11. *Wheat grass juice*

A pilot RCT revealed that wheat grass juice 60 ml orally daily taken during chemotherapy (fluorouracil, adriamycin and cytoxan) in breast cancer patients could reduce myelotoxicity and need for granulocyte colony-stimulating factors support, without any substantial compromise in the efficacy of chemotherapy [59]. The beneficial effects of wheat grass juice may be due to its high antioxidant activity of phenolic compounds and several flavonoids [60].

4. Discussion

4.1. *Mechanism of drug interaction*

The possible mechanisms of juice-drug interactions were illustrated in Table 2. This review showed that apple juice and

orange juice had no substantial inhibitory effects on CYP3A4 and P-gp compared with GFJ. Interestingly, in the case of OATP2B1, apple juice and orange juice, but not GFJ, had long-lasting inhibitory effect on OATP2B1-mediated drug absorption [61]. The reduced bioavailability of aliskiren in the presence of both apple juice and orange juice is due to OATP2B1 inhibition, whereas the decreased aliskiren absorption caused by GFJ involved OATP1A2 inhibition [62].

Among constituents of GFJ, furanocoumarins (bergamottin and 6′,7′- dihydroxybergamottin) and flavonoid (naringin) are known to inhibit CYP3A and OATP1A2, respectively [63]. Naringin and naringenin in GFJ can inhibit transport by P-gp. Pomelo contains as much 6′,7′- dihydroxybergamottin as grapefruit, but it has significantly less bergamottin than grapefruit. The inhibitory effects of Seville orange juice on CYP3A are probably due to the high concentration of bergamottin (5 μmol/L) and 6′,7′- dihydroxybergamottin (36 μmol/L) in the juice. Orange juice and apple juice only contain trace amounts of furanacoumarins so that they do not have capability of interacting with CYP3A [8]. A mixture of phloridzin, phloretin, hesperidin, and quercetin at the concentrations present in apple juice could significantly inhibit OATP2B1. Hesperidin is the major OATP2B1 inhibitor in orange juice [14].

Currently, OATP2B1 exhibits an increasing number of drug substrates, including fexofenadine, aliskiren, celiprolol, montelukast, some HMG-CoA reductase inhibitors (statins), glibenclamide, and SN-38 (active metabolite of irinotecan) [13,18,27,28,64–66]. In vitro study confirmed the inhibitory effect of orange juice on intestinal absorption of glibenclamide [65]. OATP2B1 contributes to the uptake of SN-38 by intestinal tissues, triggering gastrointestinal toxicity observed in irinotecan therapy (e.g., late-onset diarrhea). Co-ingestion of apple juice may provide an innovative method for prophylaxis of troublesome late-onset diarrhea in irinotecan therapy by inhibition of OATP2B1. This assumption has been confirmed in mice study but human studies have not yet been carried out among cancer patients [66]. A non-RCT study showed that orange juice (800 ml over 3 h) could significantly increase the bioavailability of pravastatin in healthy volunteers [67]. It is necessary to conduct more clinical trials to address whether alterations of intestinal OATP2B1 function by apple juice and orange juice could result in clinically significant interactions with OATP2B1 substrates.

Intestinal CYP3A4 activation, rather than CYP3A4 induction, was assumed to involve in interaction between one-time ingestion of grape juice and cyclosporine [44]. Similarly, grape juice–phenacetin interaction may involve enhanced first-pass metabolism of phenacetin due to CYP1A2 activation by grape juice [45]. It is necessary to further investigate whether and how grape juice exerts the effects of metabolizing enzyme activation.

4.2. *Factors determining the strength of juice-drug interaction*

There are some factors determining the strength of juice-drug interaction:

(1) The amount of co-ingested juice. For example, apple juice had dose-dependent interactions with fexofenadine and atenolol. It may be attributed to concentration-dependent inhibitory effects of constituents present in apple juice on OATP2B1-mediated fexofenadine uptake and PMAT-mediated atenolol

Table 2 – The mechanisms for significant pharmacokinetic interactions between fruit juices and drugs.

Mechanisms	Precipitant juices	Object drugs
Modulation of metabolizing enzymes		
CYP3A4 inhibition	Grapefruit juice	CYP3A4 substrates [2,4]
	Pomelo juice	Cyclosporine [42]
	Seville orange juice	Felodipine [40]
CYP3A activation	Grape juice	Cyclosporine [44]
CYP1A2 activation/desaturation	Grape juice	Phenacetin [45]
Modulation of transporters		
OATP2B1 inhibition	Apple juice	Fexofenadine [13–17], aliskiren [18]
	Orange juice	Aliskiren [18], montelukast [28], celiprolol [26]
OATP1A2 inhibition	Grapefruit juice	Aliskiren [62]
PMAT inhibition	Apple juice	Atenolol [19]
	Orange juice	Atenolol [25]
P-gp inhibition	Grapefruit juice	P-gp substrates [2,4]
	Pomelo juice	Cyclosporine [42]
Physicochemical interaction		
Chelation	Orange juice	Fluoroquinolones [31–34]
Formation of readily absorbable aluminiuml–citrate complexes	Orange juice	Aluminum containing antacid preparations [30]
Formation of soluble vitamin C– iron chelate complex	Orange juice	Ferrous fumarate [29]
Formation of an insoluble complex between drug and some components of the juice in the gastrointestinal tract	Grape juice	Cyclosporine [44]
	Pomelo juice	Sildenafil [43]
pH change	Orange juice	Celiprolol [26]

Notes: OATP, organic anion transporting polypeptide; PMAT, plasma membrane monoamine transporter; CYP, cytochrome P450; P-gp, P-glycoprotein.

[15,19]. Larger volume of fruit juice intake results in higher inhibitor concentration, [C]/IC_{50} value and interaction degree.

(2) Fruit varieties. For example, intake of Seville orange juice could increase felodipine *AUC* by 76% via inactivation of intestinal CYP3A4 [40]. However, common orange juice had no significant effect on felodipine disposition. For tangerine, the most common type of mandarin orange, its juice had no appreciable effect on CYP3A4 in humans because it did not affect the total *AUC* values, elimination half-life, or *AUC* ratios (1′-hydroxymidazolam/midazolam) in healthy volunteers [68].

(3) Type of juice. For example, pomelo juice could increase the bioavailability of cyclosporine whereas purple grape juice could significantly decrease oral cyclosporine bioavailability [42,44].

(4) Time between juice drinking and drug intake. Ingestion of GFJ concomitantly with or 2 h before fexofenadine decreased the drug *AUC* by 52% and 38% respectively whereas GFJ ingested 4 h before the drug intake had no effect [63], indicating that the extent of the interaction may decrease with prolonging time between GFJ and drug intake. It is necessary to investigate how long the inhibitory effect of other fruit juices on intestinal transporters and metabolizing enzymes would persist and whether the interval of drinking other fruit juices and drug intake would affect the extent of juice-drug interaction.

(5) Genetic polymorphism in the enzyme or transporter. For example, apple juice decreased fexofenadine *AUC* more significantly in subjects carrying the *SLCO2B1* c.1457C > T allele and orange juice caused a significant reduction in montelukast *AUC* in *SLCO2B1* c.935G/G homozygotes [16,28].

(6) Anthropometric variables. For example, enhancement of ferrous fumarate absorption in small children by orange juice was significantly positively related to height, weight, and age [29]. A significant beneficial effect of the orange juice was seen only in children older than 6 years of age. For combination use of cranberry juice and triple therapy medications (omeprazole/amoxicillin/clarithromycin) for H. pylori, only female subjects exhibited synergistic therapeutic effect (i.e., the eradication rate was significantly higher in the cranberry coadministration phase than in the placebo-controlled phase) [55].

4.3. *Case reports versus RCTs*

Considering that only seven RCTs were conducted in patients, we retrieved case reports by performing a PubMed search till September 30 2017, using a query "title/abstract: juice or juices" and "all fields: drug or medication or pharmacokinetics or drug interaction or combination therapy", with a filter of "language: English; article type: case reports". One hundred and ten papers were identified. Fourteen case reports of drug interactions precipitated by fruit juices other than GFJ were as follows: noni juice-phenytoin (n = 1), cranberry juice-atorvastatin (n = 1), cranberry juice-warfarin (n = 7), pomegranate juice-warfarin (n = 2), pomegranate juice-rosuvastatin (n = 1), concentrated pomegranate juice-tacrolimus (n = 1), Lycium barbarum (goji) juice-warfarin (n = 1). The adverse clinical outcome due to juice-drug combinations derived from these case reports did not occur in the included RCTs of this review, indicating that RCTs investigating juice-drug interactions in true patients may reflect a realistic clinical scenario and overcome the limitation of RCTs performed in healthy volunteers under standardized conditions. Meanwhile, due to intersubject variability, patients and clinicians should still keep vigilant about the drug effect's changes brought by co-ingestion of fruit juices even if RCTs reveal neutral juice-drug interactions.

4.4. *Fruit juices versus whole fruit*

If there is a clinical concern for a drug interaction with commercial fruit juice, it is worthy to consider this concern might also apply for the whole fruit, and vice versa. For example, both unprocessed grapefruit and commercial GFJ could cause a drug interaction with felodipine (CYP3A4 probe). 6′,7′-Dihydroxybergamottin and naringin are present at higher concentrations in grapefruit segments relative to commercial GFJ while bergamottin is detected at higher level in commercial GFJ [69]. Therefore, any therapeutic concern for a drug interaction with GFJ should be extended to the scenario with whole fruit.

For other fruits, currently there is no direct comparison of whole fruit and fruit juice in the terms of drug interaction potential in human. Anlamlert et al. investigated the effect of pomelo pulp on the pharmacokinetics of cyclosporine in healthy Thai volunteers who received 250 g of pomelo pulp or 250 ml of water 1 h before drug administration and once again 10 min following drug administration. Coadministration of pomelo pulp increased the mean *AUC* and C_{max} values of cyclosporine by 28.8% and 36.1%, respectively [70]. These pharmacokinetic changes were in close agreement with the results derived from the study of pomelo juice–cyclosporine interaction in healthy volunteers [42], suggesting that the active components in pomelo pulp are sufficient to increase oral bioavailability of cyclosporine.

Egashira et al. reported a case of considerable increase in the blood level of tacrolimus after intaking a little less than 100 g of pomelo in a renal transplant recipient. The pharmacokinetic change was attributed to inhibitory effects of pomelo on CYP3A4 and/or P-gp in the small intestine [71]. Although pomelo juice-tacrolimus interaction in human has not been evaluated, it was confirmed in rats with the inhibitory effect of 100% pomelo juice lasting 3 days after ingestion [72].

4.5. *Adolescents and elderly adults*

Self-medication, often without adult guidance, has been reported to be a common practice during adolescence. The prevalence rate of self-medication with prescribed and over-the-counter (OTC) medications was 89.2% among high school students [73]. Westerlund et al. also demonstrated that OTCs and prescription drugs were frequently used in adolescents of high school with a high prevalence of drug-related

problems [74]. Because adolescence is a key period when an individual takes first steps towards self-care and self-medication, and the health care habits developed during adolescence may be carried over into adulthood, early health education strategies for establishing rational medication use in this age group should be applied. Meanwhile, a consumption pattern survey in the U.S. showed that 100% fruit juice consumption was highest among children and declined sharply with age while whole fruit consumption was highest among older adults [75]. A school-based survey conducted by U.S. Centers for Disease Control and Prevention showed that 30.2% of high school students nationwide drank a serving of 100% fruit juices daily [76]. According to the U.S. National Health and Nutrition Examination Survey 2003–2006, consumption of 100% fruit juice is associated with improved nutrient adequacy while 44.5% of adolescents aged 13–18 years are 100% fruit juice consumers [77]. Co-ingestion of medications with drinking fruit juice is possible and potential risk of juice-drug interaction exists in adolescents.

Elderly adults are at great risk for polypharmacy due to medical complexity. Some phytochemicals in fruits have been confirmed as substrates for, or modulators of, transporters and enzyme superfamilies, therefore, elderly adults are potentially susceptible to fruit–drug interactions [78]. Woodward et al. presented a case of clinically relevant and probable interaction between warfarin and scuppernongs (a muscadine grape) in a 73-year-old woman who consumed 75 scuppernongs daily over 2 months and experienced a dramatic elevation of INR to supratherapeutic level [79].

Pharmacological consideration should be especially given to adolescents and elderly adults who ingest medications with drinking fruit juices or consume fresh fruits during drug treatment. It is necessary to develop the interface between pharmacy practitioners and these populations to make them aware of the need for improved knowledge of drugs.

5. Conclusion

Derived from RCTs on juice-drug interactions, some fruit juices other than GFJ could interfere with drug pharmacokinetics to a great extent or produce synergistic effects of drug treatment (e.g., increased efficacy and/or reduced side effects). Unlike furanocoumarin-rich GFJ which could primarily precipitate drug interactions by strong inhibition of CYP3A4 and P-gp and thus cause deadly outcomes due to co-ingestion with some medications, other fruit juices did not precipitate severely detrimental food–drug interaction despite of sporadic case reports. Pharmacists and health professionals should properly educate patients about potential adverse juice-drug interactions and help minimize their occurrence. Much attention should be paid to adolescents and the elderly who ingest medications with drinking fruit juices or consume fresh fruits during drug treatment. Meanwhile, more researches in this interesting issue should be conducted.

Conflicts of interest

All contributing authors declare no conflicts of interest.

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