JOURNAL OF FOOD AND DRUG ANALYSIS XXX (2018) 1–11

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.jfda-online.com

Review Article

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

Meng Chen [a], *Shu-yi Zhou* [b], *Erlinda Fabriaga* [b], *Pian-hong Zhang* [c], *Quan Zhou* [a,*]

[a] *Department of Pharmacy, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310009, Zhejiang Province, People's Republic of China*
[b] *ULink College of Shanghai, Shanghai 201615, People's Republic of China*
[c] *Department of Clinical Nutrition, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang Province, People's Republic of China*

ARTICLE INFO

Article history:
Received 19 October 2017
Received in revised form
5 January 2018
Accepted 8 January 2018
Available online xxx

Keywords:
Drug metabolism
Fruit juices
Food–drug interaction
Randomized controlled trials
Transporters

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.

* *Corresponding author*. Department of Pharmacy, The Second Affiliated Hospital, School of Medicine, Zhejiang University, Jiefang Road No 88, Shangcheng District, Hangzhou 310009, Zhejiang Province, People's Republic of China. Fax: +86 571 8702 2776.
E-mail address: zhouquan142602@zju.edu.cn (Q. Zhou).

https://doi.org/10.1016/j.jfda.2018.01.009

Please cite this article in press as: Chen M, et al., Food-drug interactions precipitated by fruit juices other than grapefruit juice: An update review, Journal of Food and Drug Analysis (2018), https://doi.org/10.1016/j.jfda.2018.01.009

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

Please cite this article in press as: Chen M, et al., Food-drug interactions precipitated by fruit juices other than grapefruit juice: An update review, Journal of Food and Drug Analysis (2018), https://doi.org/10.1016/j.jfda.2018.01.009