Journal of Intercultural Ethnopharmacology
www.jicep.com
DOI: 10.5455/jice.20170511061624

Letter to the Editor

Grapefruit: Some perspectives in pharmacology and nutrition

Dear Editor,

Among others, the aim of this letter has been discussion of some publications that might create a biased vision and damage the trade and production of citrus fruit. Soviet citizens, who lived in conditions of relatively high prices and shortage of citrus fruits, grapefruit (Gr) in particular, know their value. Citrus fruits, along with tomatoes and potatoes, are major contributors of vitamin C to the American diet [1]. Gr is a source of ascorbic and folic acid, magnesium, vitamin B6, and thiamin, which are supplied in greater proportion than the calories [2].

It is known that Gr has the potential for interactions with certain drugs enhancing their bioavailability. This has been discussed as a reason for contraindications to the consumption of Gr during pharmacotherapy with the interacting drugs [3]. According to the concept discussed in this letter, the Gr-drug interactions can be used to decrease drug dosages. Doses of analgesic, hormonal, psychoactive, immunosuppressive, and other medications should generally be kept as low as reasonably possible. The enhanced bioavailability means that the same therapeutic effect is achieved by a lower dose and correspondingly lower levels of metabolites of the drug. Metabolites, having no desirable therapeutic action, may cause side effects.

The main Gr-drug interaction mechanism is inactivation of the enzyme CYP3A4 by furanocoumarins. CYP3A4 enzyme participates in the inactivation of various drugs; it is located in the intestinal epithelium and the liver. This mechanism explains for the increase in the plasma concentration of certain orally taken drugs under the impact of Gr. Although some studies have tested unusually high quantities, a usual amount (200-250 ml juice or a whole Gr) has sufficient potency to cause a pertinent pharmacokinetic interaction [3]. Bitter oranges, limes, and pomelos also produce such interactions although weaker than Gr. Some sorts of sweet oranges do not cause the interaction. Apart from CYP3A4, constituents of Gr, for example, furanocoumarins or bergamottin, can inhibit other cytochrome P450 isoenzymes (CYP3A4, CYP2C9, and CYP2D6) and transporters in the intestine such as P-glycoproteins [4-6]. Genetic variability of the enzymes can influence patients' susceptibility to the effects of Gr [7], prediction being a potential field of future research.

Medications currently documented or predicted to augment the oral bioavailability if ingested with Gr are listed [3] and include certain calcium channel blockers, beta blockers, analgesics, corticosteroids, estrogens, benzodiazepines, statins, anticancer, and antiallergic medications [3,8-11]. The interaction between medications and Gr is drug specific and is not a class effect. The interacting drugs are generally characterized by the oral intake, low to intermediate bioavailability, and inactivation by the CYP3A4 enzyme. Patients with higher levels of CYP3A4 determined in intestinal biopsies may require higher doses of corresponding drugs, the size of the Gr effect being generally higher in such patients. However, routine intestinal biopsy for this purpose is impractical [3].

Potential adverse events result from the enhanced bioavailability, i.e. effective overdose of interacting drugs. Apparently, there is a tendency to exaggerate the Gr-associated side effects, for example, by applying the term "vulnerability" [3] instead of "susceptibility" to Gr-drug interactions, although they are not necessarily harmful and can be favorable. An exaggerated impression of risk may be created, for example, by the eye-catching subheadings such as "breast cancer," under which a questionable risk elevation due to the increased bioavailability of estrogens (ethinylestradiol and 17-β-estradiol) taken together with Gr is discussed [3]. In fact, Gr can be used for the dose reduction of estrogens as well as of other interacting medications. It would be logical to prevent the Gr-related side effects by reducing the drug dosage, which is of particular importance at an older age. Elderly patients may have a decreased capacity to compensate for excessive systemic drug concentrations. The predicted interaction risk can be used by clinicians to adjust doses and to decide about contraindications. For example, torsades de pointes induced by some anticancer or antiarrhythmic drugs taken together with Gr are regarded as contraindications for the Gr intake during the pharmacotherapy [3]. With regard to "Rhabdomyolysis" (another subheading in reference 3) due to the effective overdose of statins, the increased risk from Gr juice is considered to be minimal; Gr is not deemed contraindicated in people taking statins [12]. A possibility of dose lowering of statins if taken together with Gr should be investigated.

In patients receiving interacting drugs, the doses can be tentatively lowered if Gr is regularly consumed. Considering large individual variations, the approach must be cautious. The effect of Gr may depend on the sort of the fruit, storage time and temperature, and geographical and environmental conditions. Relevant measurable indices (e.g., blood pressure and heart rate in case of calcium channel or beta blockers) should be monitored; if technically feasible, the drug concentration in blood might be determined. During the pharmacotherapy, the intake of Gr must remain stable using possibly the same sort of the fruit. The Gr-drug interactions should be discussed with patients to achieve a stable intake of Gr. Patients on multiple

drug therapy need special precautions; however, the dosages of drugs known to interact with Gr can be tentatively lowered by small degrees within the therapeutic window.

There follow several examples when Gr might become a useful component of the pharmacotherapy. Cyclosporine prevents rejection after transplantation; the drug is expensive and must be taken for long time. Several studies have indicated that Gr enhances the bioavailability of cyclosporine [13-16]. Artemether is an effective medication against malaria; however, relapses may occur presumably as a result of the drug metabolism by CYP3A4. Gr was reported to increase the oral bioavailability of artemether [17]. Gr doubled the bioavailability of saquinavir putatively protecting against damage to pancreatic β-cells by protease inhibitors used in the treatment of HIV-1 infection [18,19]. Gr augmented concentrations and potentially also analgesic effects of morphine in rats. Also in rats, Gr juice potentiated anti-inflammatory action of diclofenac. In humans, Gr juice increased the bioavailability of oxycodone [8-10]. Presumably, Gr can find its place in the management of chronic pain reducing doses of analgesics. Moreover, regular intake of Gr juice was reported to enhance the bioavailability of budesonide and methylprednisolone [11,20], which indicates a perspective of its use for the dose reduction of corticosteroids and other hormonal medications, for example, estrogens. Favorable action of naringin and naringenin (flavonoids in Gr) and Gr juice in diabetes mellitus and obesity has been discussed [21-28]. Further research on potential interactions of Gr with anti-diabetic drugs and insulin is needed.

In conclusion, the capacity of Gr to potentiate effects of drugs can be used in practice for reduction of drug doses. The basic requirement for a bioavailability enhancing agent is the absence of toxicity. Gr is known as a safe and valuable foodstuff. Understanding of Gr-drug interactions would be useful for the planning of drug therapy [29]. Further studies free of conflicts of interest are needed. However, in the author's opinion, medical practitioners may attempt dose lowering of interacting drugs within the therapeutic window in patients regularly consuming Gr. To enable more exact dosage, development of drugs and dietary supplements on the basis of Gr seems to be a promising field of future research.

Sergei V. Jargin,
Peoples' Friendship University of Russia, Russia.

Address for correspondence:
Sergei V. Jargin, Peoples' Friendship University of Russia, Russia. E-mail: sjargin@mail.ru

Received: February 23, 2017
Accepted: May 02, 2017
Published: May 30, 2017

REFERENCES

1. U.S. Department of Health and Human Services. National Institutes of Health Vitamin C. Fact Sheet for Health Professionals. Available from: https://www.ods.od.nih.gov/factsheets/VitaminC-HealthProfessional. [Last accessed on 2017 May 10].
2. Staroscik JA, Gregorio FU Jr, Reeder SK. Nutrients in fresh peeled oranges and grapefruit from California and Arizona. J Am Diet Assoc 1980;77:567-9.
3. Bailey DG, Dresser G, Arnold JM. Grapefruit-medication interactions: Forbidden fruit or avoidable consequences? CMAJ 2013;185:309-16.
4. Girennavar B, Jayaprakasha GK, Patil BS. Potent inhibition of human cytochrome P450 3A4, 2D6, and 2C9 isoenzymes by grapefruit juice and its furocoumarins. J Food Sci 2007;72:C417-21.
5. Tassaneeyakul W, Guo LQ, Fukuda K, Ohta T, Yamazoe Y. Inhibition selectivity of grapefruit juice components on human cytochromes P450. Arch Biochem Biophys 2000;378:356-63.
6. Ahmed IS, Hassan MA, Kondo T. Effect of lyophilized grapefruit juice on P-glycoprotein-mediated drug transport *in-vitro* and *in-vivo*. Drug Dev Ind Pharm 2015;41:375-81.
7. Li D, Abudula A, Abulahake M, Zhu AP, Lou YQ, Zhang GL. Influence of CYP3A5 and MDR1 genetic polymorphisms on urinary 6 beta-hydroxycortisol/cortisol ratio after grapefruit juice intake in healthy Chinese. J Clin Pharmacol 2010;50:775-84.
8. Nieminen TH, Hagelberg NM, Saari TI, Neuvonen M, Neuvonen PJ, Laine K, *et al*. Grapefruit juice enhances the exposure to oral oxycodone. Basic Clin Pharmacol Toxicol 2010;107:782-8.
9. Mahgoub AA. Grapefruit juice potentiates the anti-inflammatory effects of diclofenac on the carrageenan-induced rat's paw oedema. Pharmacol Res 2002;45:1-4.
10. Okura T, Ozawa T, Ito Y, Kimura M, Kagawa Y, Yamada S. Enhancement by grapefruit juice of morphine antinociception. Biol Pharm Bull 2008;31:2338-41.
11. Seidegård J, Randvall G, Nyberg L, Borgå O. Grapefruit juice interaction with oral budesonide: Equal effect on immediate-release and delayed-release formulations. Pharmazie 2009;64:461-5.
12. Lee JW, Morris JK, Wald NJ. Grapefruit juice and statins. Am J Med 2016;129:26-9.
13. Ducharme MP, Warbasse LH, Edwards DJ. Disposition of intravenous and oral cyclosporine after administration with grapefruit juice. Clin Pharmacol Ther 1995;57:485-91.
14. Hollander AA, van Rooij J, Lentjes GW, Arbouw F, van Bree JB, Schoemaker RC, *et al*. The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. Clin Pharmacol Ther 1995;57:318-24.
15. Sridharan K, Sivaramakrishnan G. Interaction of citrus juices with cyclosporine: Systematic review and meta-analysis. Eur J Drug Metab Pharmacokinet 2016;41:665-73.
16. Hermann M, Asberg A, Reubsaet JL, Sather S, Berg KJ, Christensen H. Intake of grapefruit juice alters the metabolic pattern of cyclosporin A in renal transplant recipients. Int J Clin Pharmacol Ther 2002;40:451-6.
17. El-Lakkany NM, Seif el-Din SH, Badawy AA, Ebeid FA. Effect of artemether alone and in combination with grapefruit juice on hepatic drug metabolising enzymes and biochemical aspects in experimental *Schistosoma mansoni*. Int J Parasitol 2004;34:1405-12.
18. Kupferschmidt HH, Fattinger KE, Ha HR, Follath F, Krähenbühl S. Grapefruit juice enhances the bioavailability of the HIV protease inhibitor saquinavir in man. Br J Clin Pharmacol 1998;45:355-9.
19. Nzuza S, Ndwandwe DE, Owira PM. Naringin protects against HIV-1 protease inhibitors-induced pancreatic β-cell dysfunction and apoptosis. Mol Cell Endocrinol 2016;437:1-10.
20. Varis T, Kivistö KT, Neuvonen PJ. Grapefruit juice can increase the plasma concentrations of oral methylprednisolone. Eur J Clin Pharmacol 2000;56:489-93.
21. Murunga AN, Miruka DO, Driver C, Nkomo FS, Cobongela SZ, Owira PM. Grapefruit Derived flavonoid naringin improves ketoacidosis and lipid peroxidation in Type 1 diabetes rat model. PLoS One 2016;11:e0153241.
22. Jung UJ, Lee MK, Jeong KS, Choi MS. The hypoglycaemic effects of hesperidin and naringin are partly mediated by hepatic glucose-regulating enzymes in C57BL/KsJ-db/db mice. J Nutr 2004;134:2499-503.
23. Mahmoud AM, Ashour MB, Abdel-Moneim A, Ahmed OM. Hesperidin and naringin attenuate hyperglycemia-mediated oxidative stress and proinflammatory cytokine production in high fat fed/streptozotocin-induced Type 2 diabetic rats. J Diabetes Complications 2012;26:483-90.
24. Punithavathi VR, Anuthama R, Prince PS. Combined treatment with naringin and vitamin C ameliorates streptozotocin-induced diabetes in male Wistar rats. J Appl Toxicol 2008;28:806-13.
25. Sirovina D, Oršolić N, Gregorović G, Končić MZ. Naringenin

ameliorates pathological changes in liver and kidney of diabetic mice: A preliminary study. Arh Hig Rada Toksikol 2016;67:19-24.
26. Xulu S, Oroma Owira PM. Naringin ameliorates atherogenic dyslipidemia but not hyperglycemia in rats with Type 1 diabetes. J Cardiovasc Pharmacol 2012;59:133-41.
27. Alam MA, Subhan N, Rahman MM, Uddin SJ, Reza HM, Sarker SD. Effect of citrus flavonoids, naringin and naringenin, on metabolic syndrome and their mechanisms of action. Adv Nutr 2014;5:404-17.
28. Chudnovskiy R, Thompson A, Tharp K, Hellerstein M, Napoli JL, Stahl A. Consumption of clarified grapefruit juice ameliorates high-fat diet induced insulin resistance and weight gain in mice. PLoS One 2014;9:e108408.
29. Bailey DG, Jargin SV. Grapefruit-medication interactions. Ukr Med J 2017;1:XIII-XIV. Available from: http://www.umj.com.ua/article/105072/vzaimodejstvie-grejpfruta-s-lekarstvennymi-preparatami. [Last acessed 2017 May 10].

Source of Support: Nil, Conflict of Interest: None declared.