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 oxcodone [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.

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