ENDOCRINE ACTIVE SUBSTANCES IN CITRUS FRUITS AND DRUGS

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The dietary exposure to endocrine active substances concerns the general population, which includes a conspicuous fraction of subjects who undergo prolonged or continuous pharmacological treatment(s).

Recently an important issue has surfaced to the attention of public opinion: chemicals present in citrus fruits, and above all in grapefruit, with the potential to interfere with drug metabolism, increasing the risk of serious side effects.

It’s a matter of metabolic potentiation, which enhances the bioavailability of molecules that - usually - undergo a high intestinal metabolism by the enzyme CYP 3A4 of the cytochrome P450 family, critical for metabolism of both endogenous and exogenous compounds. Involved drugs include antiarrhythmics agents, immunosuppressive agents, statins and calcium channel blockers. (Stump et al., 2006).

A number of furanocoumarins, naturally present in citrus fruits, have been found to inhibit CYP3A4 activity (Row et al., 2006). Furanocoumarins, and other compounds in citrus fruits, interact with the expression and activity of aryl hydrocarbon receptor (AhR) (Baumgart et al., 2005; Van Ede et al., 2008). The interaction with AhR, a specific target for dioxins and polycyclic aromatic hydrocarbons, is a well known endocrine disruption mechanism. CYP 3A4 is not directly regulated by AhR, instead there are cross-talk mechanisms between other receptors, such as PXR, CYP3A4 and AhR (Gerbal-Chaloin et al., 2006).

Gene expression profiles induced by compounds found in citrus juice were comparable to those by the xenobiotic AhR agonists 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and benzo[a]pyrene (De Waard et al., 2008a). Moreover several furocoumarins are able to modulate hepatic drug-metabolizing enzymes, interacting directly with PXR in murine liver (Kleiner et al., 2008).

De Waard et al. (2008b) evaluated Ah receptor agonist activity in frequently consumed food items. Overall consumer exposure to natural AhR agonists could be even greater than exposure to dioxins and dioxin-like compounds: grapefruit juice was identified as a major source of such compounds. In conclusion, the authors suggests that AhR natural agonists should be considered in dioxins and dioxin-like surveillance as well as in risk-to-benefit analysis of relevant foods.

In anticipation of better explicating the interaction mechanisms between substances present in citrus fruits and drugs, the choice strategies for risk management would be to select other pharmacological treatments (Stump et al., 2006); since citrus fruits do provide significant nutritional benefits, the reduction or even cessation of citrus intake should be considered as a last resort.

References


