Bergamottin and “The Grapefruit Juice Effect”

Some common foods, due to their unique chemical properties, can have dramatic influence on the efficacy of certain medications. Absorption of oral medication into the tissues of the small intestine can be affected by the type of food ingested. Unlike other citrus, grapefruit has been shown to increase the amount of certain drugs in the general circulatory system due to the activity of bergamottin, a coumarin derivative (figure 1). Bergamottin is a potent inhibitor of cytochrome P450, an enzyme that is responsible for the metabolism of approximately 60% of clinically relevant drugs\(^1\). Although much is known about this “grapefruit juice effect,” the exact mechanism of this bergamottin-drug interaction is not clear at this time and warrants further investigation.
Grapefruit contains several furanocoumarins, which are a class of organic chemical compounds composed of a furan ring fused to a coumarin (figure 2) such as 6',7'-dihydroxybergamottin (DHBG) (figure 1), epoxybergamottin and other furanocoumarin dimers, GF-I and GF-I-4\(^2\). Although DHBG and bergamottin are the two major furanocoumarins found in grapefruit juice and responsible for the grapefruit juice–drug interaction\(^2\) the most significant of these is bergamottin\(^3\). Bergamottin (figure 1) is very stable and lipophilic, compared to its related derivatives and dimers\(^2\). Bergamottin is abundant in grapefruit juice extract and segments and is easily absorbed with in the intestinal wall\(^2\). With the exception of Seville orange, no traces of bergamottin are found in other citruses such as lemons and limes. Only the bergamottin in grapefruit reacts with the metabolic enzyme, Cytochrome P450.

Cytochrome P450 (CYP450), a protein containing a heme group, is found in the liver and the cells that line the intestines\(^1\). The basic structure of the protein consists of 12 helices and appears in triangular form, the structural core is formed by a four–helix
bundle, in which the prosthetic heme group is confined between the distal and proximal helix and bound to the adjacent Cys-heme-ligand loop (figure 3)\(^6\) P450 molecules contain 414 amino acid residues and an approximate molecular weight of 45,000 Da\(^4\). In particular, CYP450 3A4, plays an important role in the metabolism of drugs and other foreign chemicals in the intestines. Cytochrome P450 facilitates their removal from the body by oxidation to a more water-soluble form\(^5\). Therefore, CYP450 is important for proper oral drug absorption and dosage levels. Felodipine (Plendil) and midazolam (Versed) are examples of drugs that are significantly metabolized by CYP450\(^4\).

Figure 3. Cytochrome P450 3A4 heme group of the protein on the left and the right is the entire Cytochrome P450 3A4 enzyme.

Intracellular degradation of CYP 450 3A4\(^2\) occurs after the ingestion of grapefruit juice. The bergamottin in the juice inhibits the metabolic activity of CYP 450 3A4 allowing a larger fraction of certain drugs to be absorbed. This bergamottin-CYP450 reaction appears to be mostly at the level of the intestines. It is thought that bergamottin and derivatives may be poorly absorbed or extensively metabolized in the gut so that they have little chance to inactivate or inhibit the liver cytochrome P450’s. The Bergamottin
compound is a mechanism-based inactivator, a subclass of irreversible inhibitors, of cytochrome P450 3A4. A mechanism-based inhibitor such as bergamottin behaves as a substrate in the active site of the enzyme, as the inhibitor reacts in the active site, the inhibitor is converted to a strong electrophile and covalently binds a nucleophile residue in the active site. The bergamottin mechanism-based inactivation of cytochrome is presumed that the furan ring is activated to a reactive intermediate, which covalently modifies a critical part in the active site of the enzyme. Also, studies show that a metabolite of bergamottin is covalently bound to the CYP450 3A4 apoprotein during inactivation by using SDS PAGE and the masses of the apoproteins were analyzed by ESI-LC-MS. It was found that oxidation of a double bond in the furan ring is responsible for inactivation; the irreversible inactivation of CYP450 3A4 catalytic activity is due to a mono-oxygenated reactive metabolite; GSH is conjugated to a mono oxygenated metabolite of furanocoumarins; and a dihydrodiol of the furanocoumarin is formed during metabolism. Through the inactivation, the mass of the apoprotein increased by approximately 400 Da, and could result because of the formation of a covalent adduct with one molecule of bergamottin plus three oxygen groups; this shows that hydroxylation occurred twice on the geranyloxy side chain alone on the bergamottin. The complete inactivation of the cytochrome P450 3A4 molecule has yet to be observed, the highest achievable inactivation has only been approximately 80 percent. One thought is that the binding of a reactive intermediate to an amino acid residue in the active site does not result in complete loss of activity but only wounds the enzyme so that it is less able to catalyze substrate metabolism. Although not fully understood, it appears
that bergamottin modifies a critical functional group in the enzyme CP450 3A4. This “grapefruit juice effect” can cause overdose of certain drugs, like Versed, a sedative.

So, in addition to some herbal medicines, common foods can have significant effects of certain types of oral medication. The case of the “grapefruit juice effect” has usually been viewed negatively due to high drug absorption rates and overdose risks. Perhaps in the future, grapefruit juice could be utilized to lower oral drug dosages. Even though currently in peak season, one may think twice before eating that next delicious slice of grapefruit.
References


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