Title Grapefruit-drug interaction: Isolation, synthesis, and biological activities of furocoumarins and their variation due to pre- and post-harvest factors

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Abstract

The health maintaining properties of citrus consumption are attributed to the wide assortment of bioactive compounds. Consumption of grapefruit along with certain medications, however, is posing a risk of drug toxicity and side reactions. The first study involved isolation of bioactive furocoumarins with a combination of chromatographic techniques and synthesis. Five furocoumarins namely, dihydroxybergamottin, paradisin A, bergamottin, bergaptol and geranylcoumarin were isolated from grapefruit and series of furocoumarin monomers and paradisin A were synthesized. The second study involved influence of pre- and post-harvest factors on the levels of furocoumarins in grapefruit juice. Considerable differences were observed in the levels of these compounds in different grapefruit cultivars. Ray Red showed the lowest levels of all three furocoumarins and Duncan contains the highest amount of DHB and bergamottin, where as the highest levels of paradisin A was observed in Star Ruby. The highest levels of DHB and bergamottin were found in Flame cultivar grown in California. The changes in the levels of these furocoumarins during the season in Rio Red and Marsh White grapefruit cultivars were evaluated.

The third study investigated biological activities of grapefruit juices and furocoumarins. Grapefruit and Pummelo juices were found to be potent inhibitors of cytochrome CYP3A4 and CYP2C9 isoenzymes at 5% concentration while CYP2D6 was less affected. Among the five furocoumarins tested, the inhibitory potency was in the order of paradisin A > dihydroxybergamottin > bergamottin > bergaptol > geranylcoumarin at 0.1 μM to 0.1 mM concentrations. A fourth study investigated the effect of furocoumarins on bacterial auto-inducer signaling, and found that furocoumarins are potent inhibitors of AI-1 and AI-2 activities at 0.01% concentration. In a fifth study, involving synthesized furocoumarin monomers and dimer on anti-proliferative activities on normal and cancer cell lines, furocoumarins found to be non-toxic to normal cells. However, bergamottin showed a significant anti-proliferative activity in HT-29 and MCF-7 cell lines.

This dissertation indicates that furocoumarins are bioactive compounds from grapefruit juice with potent inhibitory property of major drug metabolizing cytochrome P450 isoenzymes. Furocoumarins show a considerable variation between varieties, location and season. These results corroborate the involvement of furocoumarins in grapefruit drug interaction.