The alkaloid rutaecarpine is a selective inhibitor of cytochrome P450 1A in mouse and human liver microsomes

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摘要

Abstract

Rutaecarpine, evodiamine, and dehydroevodiamine are quinazolinocarboline alkaloids isolated from a traditional Chinese medicine, Evodia rutaecarpa. The in vitro effects of these alkaloids on cytochrome P450 (P450)-catalyzed oxidations were studied using mouse and human liver microsomes. Among these alkaloids, rutaecarpine showed the most potent and selective inhibitory effect on CYP1A-catalyzed 7-methoxyresorufin O-demethylation (MROD) and 7-ethoxyresorufin O-deethylation (EROD) activities in untreated mouse liver microsomes. The IC50 ratio of EROD to MROD was 6. For MROD activity, rutaecarpine was a noncompetitive inhibitor with aKi value of 39 ± 2 nM. In contrast, rutaecarpine had no effects on benzo[a]pyrene hydroxylation (AHH), aniline hydroxylation, and nifedipine oxidation (NFO) activities. In human liver microsomes, 1 μM rutaecarpine caused 98, 91, and 77% decreases of EROD, MROD, and phenacetinO-deethylation activities, respectively. In contrast, less than 15% inhibition of AHH, tolbutamide hydroxylation, chlorzoxazone hydroxylation, and NFO activities were observed in the presence of 1 μM rutaecarpine. To understand the selectivity of inhibition of CYP1A1 and CYP1A2, inhibitory effects of rutaecarpine were studied using liver microsomes of 3-methylcholanthrene (3-MC)-treated mice and Escherichia coli membrane expressing bicistronic human CYP1A1 and CYP1A2. Similar to the CYP1A2 inhibitor furafylline, rutaecarpine preferentially inhibited MROD more than EROD and had no effect on AHH in 3-MC-treated mouse liver microsomes. For bicistronic human P450s, the IC50 value of rutaecarpine for EROD activity of CYP1A1 was 15 times higher than the value of CYP1A2. These results indicated that rutaecarpine was a potent inhibitor of CYP1A2 in both mouse and human liver microsomes.