# Modulation of drug-metabolizing enzymes by extracts of a herbal medicine Evodia rutaecarpa in C57BL/6J mice

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## Abstract

Evodia rutaecarpa is a traditional Chinese medicine used for the treatment of gastrointestinal disorders and headache. To assess the possible drug interactions, effects of methanol and aqueous extracts of E. rutaecarpa on drug-metabolizing enzymes, cytochrome P450 (CYP), UDP-glucuronosyl transferase (UGT), and glutathione S-transferase (GST) were studied in C57BL/6J mice. Treatment of mice with methanol extract by gastrogavage caused a dose-dependent increase of liver microsomal 7-ethoxyresorufin O-deethylation (EROD) activity. In liver, methanol extract at 2 g/kg caused 47%, 7-, 8-, 4-fold, 81% and 26% increases of benzo(a)pyrene hydroxylation (AHH), EROD, 7-methoxyresorufin O-demethylation (MROD), 7-ethoxycoumarin O-deethylation (ECOD), benzphetamine N-demethylation, and N-nitrosodimethylamine N-demethylation activities, respectively. Aqueous extract at 2 g/kg caused 68%, 2-fold, and 83% increases of EROD, MROD, and ECOD activities, respectively. For conjugation activities, methanol extract elevated UGT and GST activities. Aqueous extract elevated UGT activity without affecting GST activity. Immunoblot analyses showed that methanol extract increased the levels of CYP1A1, CYP1A2, CYP2B-, and GSTYb-immunoreactive proteins. Aqueous extract increased CYP1A2 protein level. In kidney, both extracts had no effects on AHH, ECOD, UGT, and GST activities. Three major bioactive alkaloids rutaecarpine, evodiamine, and dehydroevodiamine were present in both extracts. These alkaloids at 25 mg/kg increased hepatic EROD activity. These results demonstrated that E. rutaecarpa methanol and aqueous extracts could affect drug-metabolizing enzyme activities. Rutaecarpine, evodiamine, and dehydroevodiamine contributed at least in part to the increase of hepatic EROD activity by extracts of E. rutaecarpa. Thus, caution should be paid to the possible drug interactions of E. rutaecarpa and CYP substrates.