In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes.

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OBJECTIVES: Phytochemical-mediated modulation of cytochrome P450 (CYP) activity may underlie many herb-drug interactions. Single-time point phenotypic metabolic ratios were used to determine whether long-term supplementation of goldenseal (Hydrastis canadensis), black cohosh (Cimicifuga racemosa), kava kava (Piper methysticum), or valerian (Valeriana officinalis) extracts affected CYP1A2, CYP2D6, CYP2E1, or CYP3A4/5 activity. METHODS: Twelve healthy volunteers (6 women) were randomly assigned to receive goldenseal, black cohosh, kava kava, or valerian for 28 days. For each subject, a 30-day washout period was interposed between each supplementation phase. Probe drug cocktails of midazolam and caffeine, followed 24 hours later by chlorzoxazone and debrisoquin (INN, debrisoquine), were administered before (baseline) and at the end of supplementation. Presupplementation and postsupplementation phenotypic trait measurements were determined for CYP3A4/5, CYP1A2, CYP2E1, and CYP2D6 by use of 1-hydroxymidazolam/midazolam serum ratios (1-hour sample), paraxanthine/caffeine serum ratios (6-hour sample), 6-hydroxychlorzoxazone/chlorzoxazone serum ratios (2-hour sample), and debrisoquin urinary recovery ratios (8-hour collection), respectively. The content of purported "active" phytochemicals was determined for each supplement. RESULTS: Comparisons of presupplementation and postsupplementation phenotypic ratio means revealed significant inhibition (approximately 40%) of CYP2D6 (difference, -0.228; 95% confidence interval [CI], -0.268 to -0.188) and CYP3A4/5 (difference, -1.501; 95% CI, -1.840 to -1.163) activity for goldenseal. Kava produced significant reductions (approximately 40%) in CYP2E1 only (difference, -0.192; 95% CI, -0.325 to -0.060). Black cohosh also exhibited
statistically significant inhibition of CYP2D6 (difference, -0.046; 95% CI, -0.085 to -0.007), but the magnitude of the effect (approximately 7%) did not appear to be clinically relevant. No significant changes in phenotypic ratios were observed for valerian. CONCLUSIONS: Botanical supplements containing goldenseal strongly inhibited CYP2D6 and CYP3A4/5 activity in vivo, whereas kava inhibited CYP2E1 and black cohosh weakly inhibited CYP2D6. Accordingly, serious adverse interactions may result from the concomitant ingestion of goldenseal supplements and drugs that are CYP2D6 and CYP3A4/5 substrates. Kava kava and black cohosh may interact with CYP2E1 and CYP2D6 substrates, respectively. Valerian appears to be less likely to produce CYP-mediated herb-drug interactions.