Inhibition of human cytochrome P450 activities by kava extract and kavalactones

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Abstract

The herb kava has recently been associated with numerous drug interactions, but its interaction with cytochrome P450 (P450) enzymes has not been investigated. In the present work the inhibition of P450 enzymes by kava extract and individual kavalactones in human liver microsomes (HLMs) was investigated. Whole kava extract (normalized to 100 microM total kavalactones) caused concentration-dependent decreases in P450 activities, with significant inhibition of the activities of CYP1A2 (56% inhibition), 2C9 (92%), 2C19 (86%), 2D6 (73%), 3A4 (78%), and 4A9/11 (65%) following preincubation for 15 min with HLMs and NADPH; CYP2A6, 2C8, and 2E1 activities were unaffected. The activities of CYP2C9, 2C19, 2D6, and 3A4 were also measured after incubation of HLMs with the major kavalactones kawain (K), desmethoxyyangonin (DMY), methysticin (M), dihydromethysticin (DHM) (each at 10 microM), and NADPH. Whereas K did not inhibit these enzymes, there was significant inhibition of CYP2C9 by DMY (42%), M (58%), and DHM (69%); of 2C19 by DHM (76%); of 2D6 by M (44%); and of 3A4 by DMY (40%), M (27%), and DHM (54%). Consistent with their potency as inhibitors, the two major kavalactones bearing a methylenedioxyphenyl moiety (M and DHM) formed "455 nm" metabolic intermediate complexes after incubation with HLMs and NADPH, but K and DMY did not. These data indicate that kava has a high potential for causing drug interactions through inhibition of P450 enzymes responsible for the majority of the metabolism of pharmaceutical agents.