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Effects of spice constituents on P-glycoprotein-mediated transport and CYP3A4-mediated metabolism in vitro.

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Abstract

The effects of eight components from six commonly consumed spices on P-glycoprotein (P-gp) transport and CYP3A4 metabolism were evaluated in vitro. P-gp-mediated [(3)H]digoxin fluxes across the L-MDR1 (LLC-PK1 cells transfected with human MDR1 gene) and Caco-2 (human colon carcinoma) cell monolayers showed a marked asymmetry compared with that in the LLC-PK1 (porcine kidney epithelial cells) cell monolayers. Curcumin (from turmeric) at 30 to 60 microM and 6-gingerol (from ginger) at 100 to 500 microM were observed to inhibit P-gp-mediated [(3)H]digoxin transport in L-MDR1 and Caco-2 cells. Effects of spices on midazolam (MDZ) 1'-hydroxylation and 4-hydroxylation of CYP3A4 activity were determined in pooled human liver microsomes (HLM). The following IC(50) values for effects of spices on MDZ 1'-hydroxylation in HLM were obtained: 29 microM for curcumin, 1.17 mM for allyl methyl disulfide (AMD) (from Chinese chive), 1.02 mM for 1,8-cineole (from coriander), and 1.28 mM for beta-caryophyllene (from curry leaf). CYP3A4-mediated 4-hydroxylation of MDZ was inhibited by curcumin at 30, 45, and 60 microM (4-hydroxy-MDZ formation was decreased to 52, 30, and 29%, respectively, compared with control), by 6-gingerol at 60, 100, and 500 microM (71, 68, and 38%), by AMD at 1 and 4 mM (29 and 14%), by d-limonene (from coriander) at 4 mM (65%), by 1,8-cineole at 0.5, 1, and 4 mM (74, 64, and 59%), and by citral (from lemongrass) at 1 mM (59%). Among the spices that showed inhibitory effect on MDZ metabolism in HLM, only AMD showed a preincubation time-dependent inhibitory effect on MDZ metabolism in HLM, suggesting the AMD as an irreversible CYP3A4 inhibitor.

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