

Curcumin, a component of turmeric, and piperine, a component of black pepper, inhibit human cytochrome P450 (CYP) enzymes *in vitro*.

L. Volak, D. Greenblatt, M. Court

Tufts University School of Medicine, Boston, MA

Purpose.

Turmeric extracts containing high levels of curcumin are currently being evaluated in several clinical trials for the treatment of advanced cancers and Alzheimer's disease. However, limited data have been generated examining curcumin's potential for herb-drug interactions due to inhibition of the major drug metabolizing enzymes. Because of limited bioavailability, curcumin is frequently co-administered with piperine to enhance its bioavailability, which also may increase the probability of herb-drug interactions. The purpose of this study was to determine whether curcumin and piperine can interfere with cytochrome P450 (CYP)-mediated metabolism *in vitro*.

Methods.

Both curcumin and piperine were evaluated for their effects on the metabolism of marker substrates of CYP3A (triazolam), CYP2C9 (flurbiprofen), CYP2C19 (S-mephenytoin), CYP2D6 (dextromethorphan), CYP1A2 (phenacetin), CYP2E1 (chlorzoxazone), and CYP2B6 (bupropion) measured using human liver microsomes (HLMs) and recombinant CYPs. The compounds were also investigated for their mechanism of inhibition, specifically, whether they displayed mechanism-based or time-dependent inhibition of CYP3A.

Results.

Curcumin inhibited CYP3A, CYP2C9, CYP2C19, and CYP2B6 in HLMs with IC_{50} values of $25.3 \pm 1.3\mu\text{M}$, $13.5 \pm 1.4\mu\text{M}$, $7.4 \pm 1.2\mu\text{M}$, and $9.4 \pm 1.9\mu\text{M}$, respectively, but had less of an effect on other CYPs ($IC_{50} > 60\mu\text{M}$). Piperine was a relatively selective inhibitor of CYP3A with an IC_{50} value of $6.2 \pm 1.2\mu\text{M}$, whereas other CYPs were less potently inhibited ($IC_{50} > 29\mu\text{M}$). Preincubation of HLMs with curcumin but not with piperine enhanced inhibition of triazolam hydroxylation consistent with mechanism-based inhibition of CYP3A by curcumin. Effects on recombinant CYPs indicated that both curcumin and piperine were more potent inhibitors (by 4- to 10-fold) of CYP3A4 compared with CYP3A5.

Conclusion.

Based on these data, we predict that a combination of curcumin and piperine has a high likelihood of inhibiting CYP-mediated drug metabolism *in vivo*. Further studies are ongoing to assess whether a combination of curcumin and piperine can inhibit CYP3A and CYP2C9-mediated metabolism in healthy human volunteers.