P.O. Box 144345 Austin, TX 78714-4345 ▪ 512.926.4900 ▪ Fax: 512.926.2345 ▪ www.herbalgram.org

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File: ■ Turmeric (*Curcuma longa*, Zingiberaceae)
■ Curcumin
■ Pharmacokinetics
■ Drug Metabolism

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RE: Reviewed Data Indicate Potential for Curcumin to Affect Pharmacokinetics of Some Pharmaceutical Drugs

Bahramsoltani R, Rahimi R, Farzaei MH. Pharmacokinetic interactions of curcuminoids with conventional drugs: A review. *J Ethnopharmacol*. September 2017;209:1-12.

Curcumin is extracted from turmeric (*Curcuma longa*, Zingiberaceae) rhizome, a spice commonly used worldwide. Turmeric has been used for centuries to treat many conditions including cancer, gastrointestinal disorders, and inflammatory conditions. Curcumin also has anti-inflammatory, antimicrobial, antioxidant, and hepatoprotective properties. Modern-day studies have reported numerous benefits.

While curcumin has a wide therapeutic index, it may affect the safety of other drugs with which it is taken. Curcumin can affect drug metabolism pathways, including cytochrome P450 (CYP) isoenzymes, which metabolize drugs, and P-glycoprotein (P-gp), an efflux pump that rids the intracellular compartment of drugs. Curcumin may also alter pharmacokinetics of some drugs, including the maximum serum concentration (C_{max}) and area under the curve (AUC), an indicator of total exposure. The purpose of this review was to summarize information on the potential effects of curcumin on concurrently used drugs.

To identify relevant studies, the authors searched PubMed, Scopus, and ScienceDirect using the following terms: drug interaction, drug metabolism, cytochrome, P450, P-glycoprotein, and pharmacokinetic. The authors searched 50 years of results from 1966 to October 2016. They included full-text, English, in vitro, in vivo, and clinical studies addressing the effects of purified curcuminoids or turmeric extracts on drug pharmacokinetics or the activity of drug-metabolizing or transporting enzymes including but not limited to CYP enzymes and P-gp. Articles were excluded if they were review articles, not in English, not full text, did not include a drug substance or address changes to the drug's pharmacokinetics, or if the study included curcuminoids mixed with other materials. Ultimately, 33 papers were included in the review.

In Table 1 (Effect of curcuminoids on different cytochrome P450 isoenzymes), the following study parameters were summarized: CYP isoenzyme, compound/preparation, model, duration, and outcome. The following 12 CYP isoenzymes were evaluated in at least one study: CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP2E1, CYP3A, CYP3A4, and CYP450 (isoform not specified). Results were most frequently reported for CYP3A4 (which is one of the most important CYP enzymes since it metabolizes over 50% of all drugs), CYP1A1, CYP2C9, and CYP2A6. Tested preparations included curcumin, curcumin nanoformulated micellar dispersion, demethoxycurcumin, curcuminoid extract, *C. longa* extracts, single curcuminoids, and *C. zedoaria*; dosages were expressed in terms of µM, mg/day, µmol/L, mg/mL, and 2% included in diet. Almost all studies used in vitro isolated enzymes or liver cells; there was one trial in healthy human participants and one in rats. Treatment duration ranged from 10 minutes to 10 weeks or was not determined.

The curcumin preparations frequently inhibited the studied CYP enzymes; the next most common outcome was "no significant interaction" or "no significant effect on mRNA [messenger RNA] expression." However, in a clinical trial of 16 healthy subjects, curcumin 1000 mg/day for 14 days induced, rather than inhibited, CYP2A6. [Note: One explanation for the inhibition observation in microsomes and induction in vivo is that microsomes cannot be used to study induction.]

The review also addressed curcumin's effect on P-gp. A substance that enhances P-gp could prematurely rid the body of a drug, diminishing clinical response. A P-gp inhibitor could cause drug toxicity by increasing exposure. Five in vitro studies evaluated a variety of curcumin preparations (curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin, and *C. longa* extract) under a variety of conditions. The results were not consistent. At times, P-gp activity increased, as did mRNA levels for multidrug resistance 1 (MDR1), the gene that encodes P-gp; at other times, both P-gp activity and mRNA decreased. This is likely due to the variety of products, concentrations, and models used.

Curcumin is also reported to inhibit multidrug resistance protein 1 (MRP1), a transporter that pumps drugs out of cells, and the following drug-metabolizing enzymes, all based on in vitro studies: uridine dinucleotide phosphate glucuronosyltransferases (UDPG), sulfotransferase, and glutathione *S*-transferase (GST). An in vivo study in rats showed no effect on UDPG. Curcumin could also alter organic-anion-transporting polypeptide (OATP) transporter pharmacokinetics, as curcumin is both a substrate and inhibitor of OATPs.

In Table 2 (Pharmacokinetic alterations of conventional drugs in concomitant use with curcumin), the studies' curcumin compound/preparation, concomitant drug, pharmacokinetic model, duration, outcome, and mechanism were compared. Curcumin was most commonly evaluated, followed by curcuminoid/piperine (one study) and turmeric extract (one study). Curcumin dosages ranged widely as did models. These studies were necessarily conducted in vivo; most studies used rodents, though three used human subjects and one included dogs. Study duration ranged from a single dose to seven days. Concomitant drugs included antidepressants, cardiovascular agents, antihistamines, antineoplastic drugs, anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and antibiotics. Outcome parameters included C_{max}, total AUC, bioavailability, and clearance.

In most of these tests, C_{max} and AUC increased, although in others, there was no effect or an opposite effect. In one "self-controlled, two-period experiment with a randomized, open-labeled design … " where healthy human subjects took curcumin 300 mg/day orally and talinolol 50 mg orally, C_{max} and total AUC decreased while total clearance increased. In a study where Sprague-Dawley rats received a single dose of curcumin 50 or 100 mg/kg by mouth and everolimus 0.5 mg/kg by mouth, C_{max} and AUC decreased. Many of the rodent studies used quite large doses of curcumin, and one reported that effects were seen only at the highest of three doses.

The authors conclude that curcumin itself is safe, but it can interact with many drug categories and change drug metabolism, thus altering other drugs' levels and safety. However, the level of evidence contained in the in vivo and in vitro studies they reviewed is insufficient to make clinical recommendations; clinical trials are needed. Many in vitro activities of botanicals on CYP enzymes reported in literature have been found to be clinically nonsignificant when tested in humans; however, this is due in large part to the lack of physiologically relevant in vitro models that are used. While dietary turmeric, according to the authors, "does not show a significant influence on the pharmacokinetics of conventional drugs," they recommend close monitoring of patients taking curcumin and drugs with narrow therapeutic windows and serious adverse effects, especially drugs that are P-gp substrates. The authors also suggest that improving curcumin's bioavailability could lower curcumin doses and drug interaction potential.

The authors declare no conflict of interest.

—Heather Anderson, MD

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