PRP Pharmacology Research & Perspectives Open Access

ORIGINAL ARTICLE

UGT concentrations in human rectal tissue after multidose, oral curcumin

Gary N. Asher[1], John K. Fallon[2] & Philip C. Smith[2]

[1]Department of Family Medicine, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599
[2]Division of Molecular Pharmaceutics, Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599

Keywords
Clinical trial, curcumin, quantitative-targeted absolute proteomics (QTAP), uridine diphosphate glucuronosyltransferase (UGT)

Correspondence
Gary N. Asher, Department of Family Medicine, CB# 7595, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7595. Tel: 919 966 7269; Fax: 919 966 6125; E-mail: gasher@med.unc.edu

Funding Information
This study was funded in part by grants from the National Institutes of Health National Center for Advancing Translational Sciences (KL2TR000084), National Institute of Diabetes and Digestive and Kidney Diseases (P30DK034987), National Cancer Institute (P50CA106991), and National Center for Research Resources (S10RR024595).

Received: 13 November 2015; Revised: 5 January 2016; Accepted: 20 January 2016

Pharma Res Per, 4(2), 2016, e00222, doi: 10.1002/prp2.222

doi: 10.1002/prp2.222

This work was previously presented at the 19th North American ISSX/29th JSSX Meeting in San Francisco, CA, October 19-23, 2014.

Abstract

In vitro studies have demonstrated that curcumin is a substrate for uridine diphosphate glucuronosyltransferase (UGTs), with a putative ability to both induce expression and inhibit function, highlighting the potential for interaction with some drugs. Therefore, we sought to evaluate the effect of oral curcumin on intestinal UGT expression. Healthy volunteers, ages 40–80 years, who had received recent screening colonoscopy were recruited. Participants did not have any gastrointestinal or bleeding disorders, lab abnormalities, or recent antibiotic use. All participants received daily curcuminoid extract, 4 g, for 30 days. Untreated, rectal mucosal pinch biopsies were obtained at baseline and at 30 days. Microsomes were prepared from biopsy samples, using sequential centrifugation. Quantification of 14 UGT 2As and 2Bs was performed by LC-MS/MS(MS, mass spectrometry), using quantitative- targeted absolute proteomics. Lowest LODs were ~0.1 pmol/mg protein. Comparisons were performed using Wilcoxon signed-rank test. Paired baseline and 30 days biopsy samples were available for 38 participants. UGTs 1A10 and 2B17 were detected in 35 and 33 paired samples, respectively, while all other UGTs were below the limit of quantification (BLOQ). Median baseline UGT1A10 concentration was 0.60 pmol/mg (95% CI:0.32–0.92), and 0.60 pmol/mg (95% CI:0.43–1.00) after 30 days ($P = 0.23$). For UGT2B17, median baseline concentration was 0.83 pmol/mg (95% CI:0.32–1.62), and 1.18 pmol/mg (95% CI:0.39–1.77) after 30 days ($P = 0.24$). We found no differences in rectal mucosal UGT concentrations before and after 30 days of oral curcumin administration, indicating that daily curcumin use is unlikely to alter colonic UGT expression. Distal gut biopsies may not accurately reflect the proximal gut environment where UGT expression and curcumin concentrations may be higher.

Abbreviations

BLOQ, below limit of quantification; LLOQ, lower limit of quantification; MRM, multiple reaction monitoring; MS, mass spectrometry; SIL, stable isotope-labeled; UGT, uridine diphosphate glucuronosyltransferase; UPLC, ultra performance liquid chromatography.

Introduction

Dietary supplement use is common among cancer patients. Over half of cancer patients report taking a dietary supplement after diagnosis (Ferrucci et al. 2009). Importantly, patients using complementary and alternative medicines, including supplements, often do not report their use to their medical providers (Mehta et al. 2008). Although often perceived as innocuous, supplements can interact with various metabolic enzymes

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

including cytochrome P450s (CYPs), UDP glucuronosyltransferases (UGTs), and drug transporters (e.g., P-gp, MRP, OATP), giving rise to potential herb–drug interactions (Izzo and Ernst 2009).

Curcumin, an extract of turmeric root, is widely available and is a top-selling supplement (Blumenthal et al. 2011). In preclinical studies, curcumin affects important tumor initiation and proliferation pathways (Pari et al. 2008). Trials using colorectal cancer models have demonstrated promising results, leading patients to use the supplement as a treatment adjunct.

In vitro studies have demonstrated that curcumin is a substrate for UGTs with a putative ability to both induce their production and inhibit their function, highlighting the potential for drug interaction (Basu et al., 2004; Hoehle et al. 2007; Iwuchukwu et al. 2011). Although clinical trial evidence does not support a meaningful interaction with hepatic UGTs, little is known about clinically relevant interactions within the gut (Volak et al. 2012). Irinotecan toxicity, for example, may be mediated by intestinal UGTs (Tallman et al. 2007), and an agent such as curcumin might alter that toxicity. Because of the high stakes of cancer chemotherapy, we wished to investigate the impact of curcumin on intestinal UGT expression. We have previously shown UGTs 1A1, 1A10, 2B7, and 2B17 to be measurable in human intestinal microsomes (Fallon et al. 2013a). If curcumin has clinically meaningful regulatory action on UGT concentrations, it may be possible to infer an effect on other UGT substrates.

Materials and Methods

Study population and sampling

Healthy volunteers were recruited from a previously identified cohort to study the association between diet and colorectal adenoma (Diet and Health Study V), which enrolled patients undergoing an outpatient screening colonoscopy at the University of North Carolina Hospitals in Chapel Hill, NC between 2009–2010 (n = 805) (Peery et al. 2012). Participants completing the cohort study were contacted by letter and phone until 42 volunteers were enrolled. Eligibility for the current study included: good general health, age 40–80 years, willingness to follow the study protocol, and provision of informed consent. Volunteers were excluded if they had a familial history of colorectal cancer syndromes or a personal history of inflammatory bowel disease, bowel resection, bleeding disorders, or therapeutic anticoagulation with warfarin, or narcotic or alcohol dependence. Other exclusions included currently pregnant or breastfeeding, ALT, AST, or creatinine above 1.5 times upper limit of normal, allergy to curcumin, or use of antibiotics within prior 3 months. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board at the University of North Carolina. All participants provided written informed consent.

Curcumin supplement

Standardized curcumin extract (C3, Sabinsa Corp., Piscataway, NJ) was formulated into 1 g tablets containing: 730 mg curcumin, 220 mg demethoxycurcumin, and 50 mg bisdemethoxycurcumin. Four tablets were taken every morning for 30 days providing 2920 mg curcumin daily. All doses were administered from a single lot, and the manufacturer provided a certificate of analysis that was independently verified by our laboratory.

Biopsy

Rectal mucosal biopsies were obtained through a rigid disposable sigmoidoscope (KleenSpec® Disposable Sigmoidoscope with Obturator, Welch Allyn, Inc., Skaneateles Falls, NY) coated with gel and inserted to approximately 10 cm with the patient in the left lateral position. A disposable flexible biopsy forcep (EndoJaw Alligator Jaw-Step, Olympus Corporation, Shinjuku, Tokyo, Japan) was used to obtain mucosal pinches from two separate sites. Biopsy samples were placed into cryovials and snap-frozen in liquid nitrogen prior to storage at −80°C. Individual pinch biopsy samples weighed 10–15 mg average. Participants underwent rectal mucosal pinch biopsy and plasma sampling at enrollment and after 30 days. No oral preparation (e.g., polyethylene glycol) was taken by participants prior to biopsy.

Materials

Materials were as previously described (Fallon et al. 2013b). BCA Protein Assay Kit was purchased from Pierce (Rockford, IL). PCR tubes (0.2 mL) (in which the digestion reaction was done) were purchased from Fisher Scientific (Pittsburg, PA). Trypsin Gold mass spectrometry (MS) grade was purchased from Promega (Madison, WI). Solutions of stable isotope-labeled (SIL) proteotypic peptides (1 nmol/L per 200 μL in water and 5 or 20% acetonitrile) were purchased from Thermo Biopolymers (Ulm, Germany) (>97% purity).

Preparation of microsomes and determination of total protein concentrations

Two pinch biopsies (~25 mg) were used to prepare microsomes for each participant from both baseline and

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

30 days samples. Frozen tissue was placed into centrifuge tubes with 2.8 mm ceramic beads (Cayman Chemical Company, Ann Arbor, MI) and 300 μL buffer solution (250 mmol/L sucrose, 1 mmol/L EDTA, 10 mmol/L KPhos, pH 7.0) and placed on wet ice for 15 min. Tissue homogenization was performed using a bead homogenizer (Precellys®24, Bertin Technologies, Bertin Corp, Rockville, MD) at 6500 rpm for two 30 sec cycles with a 15 sec rest between cycles. Sample tubes were returned to wet ice, and the homogenate was then transferred to polycarbonate tubes and centrifuged at 10,000*g* for 10 min at 4°C. Supernatant was transferred to polycarbonate ultracentrifuge tubes (Beckman Coulter, Brea, CA) and centrifuged at 100,000*g* for 70 min at 4°C. The pellet was recovered and resuspended in 100 μL of buffer solution, using a glass rod, vortexed for 60 sec and stored at −80°C. Total protein concentration was determined using the Pierce BCA Protein Assay Kit. Microsomes were thawed at room temperature, and 6 μL was diluted 10-fold with PBS for use in the assay.

Determination of UGT concentrations by multiplexed-targeted quantitative proteomic analysis

Sample analysis was as previously described (Fallon et al. 2013a,b; Margaillan et al. 2015a,b). Samples were analyzed in duplicate using 20 μg of microsomal protein in each duplicate if available. For samples where <20 μg was used, this was accounted for in final calculations. Samples were randomly divided into 4 groups and batch processed by group. Microsomes were denatured with heat, reduced with dithiothreitol, and then alkylated with iodoacetamide. Trypsin digestion (4 h) was stopped with cold acetonitrile and SIL peptides were then added. Supernatant was dried and reconstituted in modified mobile phase A (contained 2% acetonitrile) for injection onto the nanoLC-MS/MS system (nanoACQUITY–AB SCIEX QTRAP 5500 [Fallon et al. 2013b;]). The mass spectrometer was operated in the multiple reaction monitoring (MRM) mode, with two MRMs being acquired per peptide (i.e., two per unlabeled peptide and two per heavy labeled peptide). Two proteotypic tryptic peptides were used per UGT isoform where available (Fallon et al. 2013b). Peaks were smoothed prior to integration and area (2 MRMs summed) ratios of unlabeled/SIL peptides were used to determine peptide concentrations. One peptide was used for reporting isoform concentrations.

Statistical analysis

Demographics are described using standard measures. Normality of the UGT data was tested using the skewness and kurtosis test for normality (sktest), which indicated some variables were not normally distributed. Therefore, comparison of UGT concentrations was performed using the Wilcoxon signed-rank test (Stata v12.1, Statacorp, College Station, TX). UGT results are reported as medians with binomial 95% confidence intervals (CI). Our primary analysis of medians included all evaluable samples. For sensitivity analyses, samples that had a final UGT concentration <0.5 pmol/mg protein were evaluated individually for signal-to-noise (S/N) ratio and were labeled ‘rejected’ if the ratio was <5 by visual inspection. Sensitivity analyses were performed replacing measured values for ‘rejected’ samples alternately with 0 and 0.22 pmol/mg (our lower limit of quantification [LLOQ] for the reporting peptides of the two isoforms detected). Additionally, we tested datasets with rejected values for the baseline samples set to 0 and posttreatment values set to 0.22, which would have potentially created the greatest spread between samples, and vice versa (baseline 0.22, posttreatment 0). We also performed a sensitivity analysis removing participants with plasma curcumin concentrations at follow-up that were below our level of quantitation to remove participants who may have been nonadherent, since that might have led us to falsely conclude that there were no between-group differences. Lastly, evaluation of UGT concentrations using subgroups was performed by dividing the study population into two groups, one with plasma 30 days curcumin concentrations >9 ng/mL (high) and one with concentrations <9 ng/mL (low). Curcumin plasma concentrations were measured using previously published methods (Vareed et al. 2008).

Results

Paired baseline and 30 days biopsy samples were available for 38 participants (Fig. 1). Plasma curcumin concentrations were available for 34 of those participants. The mean age was 57 years (SD 5.8) and mean BMI was 30.5 (SD 6.4). Most participants were female (55%), white (82%), and non-Latino (95%). Sixty-seven percent reported a lifetime smoking history of less than 100 cigarettes.

Quantifiable concentrations of UGTs 1A10 and 2B17 were detected in 35 (92%) and 33 (87%) paired samples, respectively. For 66 of the 152 sample chromatograms (43%) required visual evaluation of the S/N ratio and 16 samples (10.5% of the total number) were ultimately labeled ‘rejected’. Of the reevaluated samples, all accepted samples had quantifiable UGT isoform concentrations >0.22 pmol/mg, which was taken as our LLOQ. UGT1A1 was detected at a very low concentration in 1 participant. No other UGT was detected in any sample.

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

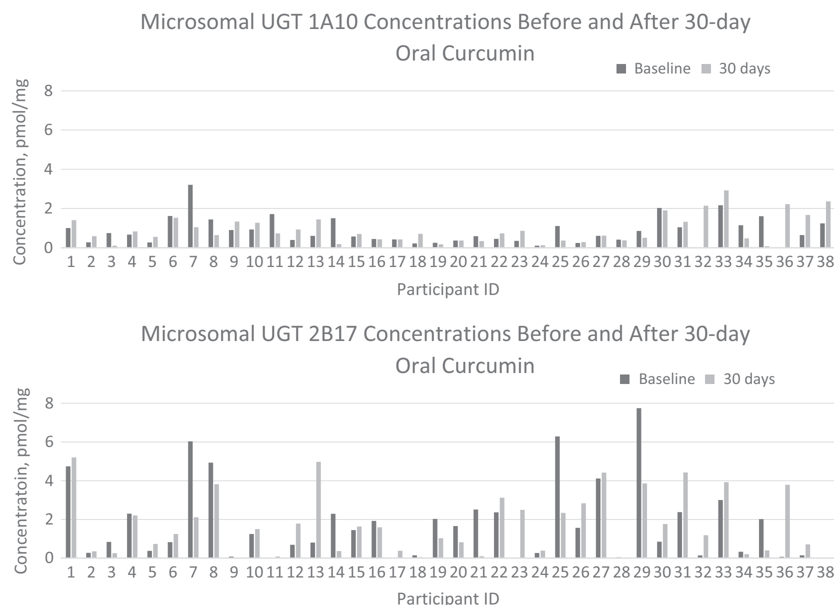

Figure 1. Uridine diphosphate glucuronosyltransferase (UGT) 1A10 and 2B17 concentrations before and after 30-day curcumin administration for all individual study participants.

Median concentration for UGT1A10 was 0.60 pmol/mg at baseline and 0.60 pmol/mg at day 30 ($P = 0.23$) (Table 1). For UGT2B17, median baseline concentration was 0.83 pmol/mg and 1.18 pmol/mg at day 30 ($P = 0.24$). No statistically significant difference in UGT concentration before and after curcumin administration was detected for any sensitivity analysis (Table 1).

Table 1. Comparison of uridine diphosphate glucuronosyltransferase (UGT) concentrations in human rectal microsomes after 30 days exposure to oral curcumin ($n = 38$).

UGT	Visit	Median (pmol/mg)	95% CI	*P* value
1A10 ($n = 35$)	Baseline	0.60	0.32–0.92	0.23
	30 days	0.60	0.43–1.00	
	Baseline[1]	0.60	0.32–0.92	0.29
	30 days[1]	0.60	0.43–1.00	
	Baseline[2]	0.60	0.32–0.92	0.24
	30 days[2]	0.60	0.43–1.00	
2B17 ($n = 33$)	Baseline	0.83	0.32–1.62	0.24
	30 days	1.18	0.39–1.77	
	Baseline[1]	1.44	0.32–1.62	0.29
	30 days[1]	1.57	0.39–1.77	
	Baseline[2]	1.51	0.32–1.62	0.28
	30 days[2]	1.62	0.39–1.77	

Findings from additional sensitivity analyses were no different than those reported in the table (data not reported).
[1]sensitivity analysis with rejected values set to 0 pmol/mg.
[2]sensitivity analysis with rejected values set to 0.22 pmol/mg (LLOQ).

For 34 available plasma samples, the mean curcumin plasma concentration (SD) was 1.6 ng/mL (6.3) at baseline and 13.5 ng/mL (16.5) at follow-up ($P < 0.001$). Eight participants (21%) at follow-up had plasma curcumin concentrations that were below our LLOQ (2 ng/mL). After removal of these eight participants, the results of the UGT analysis were unaltered. There were 17 participants in each of the two subgroups (plasma concentration above or below 9 ng/mL). Mean plasma curcumin concentration (SD) for the low concentration group was 3.6 ng/mL (±3.4) and 22.3 ng/mL (±18.6) for the high concentration group ($P < 0.001$). No statistically significant differences were found between baseline and 30 days UGTs 1A10 or 2B17 concentrations in either subgroup (Table 2).

Table 2. Subgroup comparisons of uridine diphosphate glucuronosyltransferase (UGT) concentrations in human rectal microsomes by plasma curcumin concentration (CC) ($n = 34$).

UGT	Plasma CC concentration	Visit	Median (ng/mL)	95% CI	*P* value
1A10	High ($n = 17$)	Baseline	1.11	0.28–1.61	0.46
		30 days	0.47	0.37–1.44	
	Low ($n = 17$)	Baseline	0.58	0.25–0.90	0.01
		30 days	0.71	0.55–1.33	
2B17	High ($n = 17$)	Baseline	0.80	0.11–1.56	0.65
		30 days	0.83	0.37–2.11	
	Low ($n = 17$)	Baseline	1.25	0.14–2.36	0.19
		30 days	1.21	0.40–2.33	

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

Discussion

There is strong interest in curcumin as a chemotherapeutic agent for colorectal cancer. However, little is known about its interaction with current chemotherapy agents. Because curcumin is a UGT substrate, the potential for drug interaction is high. However, we found no differences in rectal mucosal UGT concentrations at baseline and after 30 days. Therefore, curcumin is unlikely to alter intestinal UGT concentrations.

Curcumin has been reported to both induce UGT production and inhibit UGT activity. Independent teams have reported that 40 μmol/L curcumin causes a modest twofold increase in UGT1A1 mRNA (Naganuma et al. 2006; Iwuchukwu et al. 2011). Because irinotecan gut toxicity is likely mediated by intestinal UGTs, UGT induction may reduce its toxicity (Tallman et al. 2007). Additionally, curcumin (50 μmol/L) can reduce glucuronidation of capsaicin, mycophenolic acid, bilirubin, and acetominophen in preclinical models (Basu et al. 2003, 2004a; Naganuma et al. 2006; Volak et al. 2008). In healthy human volunteers, there does not appear to be any clinically significant interaction between curcumin and UGTs on acetaminophen metabolism (Volak et al. 2012). However, acetaminophen is primarily metabolized by UGT1A9, which is found in the liver but not in the intestine (Court et al. 2001). Therefore, curcumin's effects on intestinal UGT function remain unclear. Our findings suggest curcumin has minimal impact on intestinal UGT production, at least in the rectum.

In a previous study, our research group noted wide variation in steady-state plasma curcumin concentrations among healthy volunteers (unpublished data). Geometric mean curcumin area under the curve (AUC) values ranged from ~100 to 1900 h×ng/mL. Similarly, in the same participants, the interquartile range for deconjugated curcumin in rectal tissue was 18–58 ng/mL per mg tissue. However, we observed little correlation between plasma and tissue curcumin concentrations (e.g., high plasma concentration did not always correlate with high tissue concentration in the same participant). Given the absence of correlation between plasma and tissue curcumin concentrations, we hypothesized in the current study that the effect of curcumin on UGT concentrations would not be mediated by curcumin plasma concentration. Indeed, we found no differences in levels of UGTs 1A10 and 2B17 between baseline and 30 days follow-up regardless of whether participants had low or high plasma curcumin concentrations..

It is possible that rectal tissue curcumin concentrations were not high enough to alter UGT concentration. We were unable to measure tissue curcumin concentrations in our sample, which leaves this question unanswered. Previously, Garcea et al. demonstrated that at steady state, proximal and distal colon tissue samples contained 34 μmol/L and 20 μmol/L curcumin, respectively, which is below the 40 μmol/L concentration reported to cause UGT induction (Garcea et al. 2005; Iwuchukwu et al. 2011). Given the curcumin concentrations reported in Garcea et al., it is unlikely curcumin will induce UGT production in the colon, which is consistent with our findings. Nonadherence is an unlikely explanation for our findings since nearly all participants (84%) had detectable plasma curcumin, indicating they had taken the supplement.

We sampled tissue from the rectum where both UGT and curcumin concentrations may be lower than in the proximal gastrointestinal tract. For example, concentration of UGT1A10, which may have the highest affinity for curcumin, is estimated to be about 20% greater in the small intestine compared to the colon (Hoehle et al. 2007). As previously noted, steady-state curcumin concentrations drop by about 40% between the proximal and distal colon (Garcea et al. 2005). It is conceivable that the higher curcumin concentrations in the more proximal GI tract might induce UGT production proximally, but not distally.

Dietary curcumin does not alter UGT concentrations in the rectum. Although our findings suggest curcumin is unlikely to alter intestinal UGT function, we did not measure UGT activity in our samples, and it is still unknown if curcumin has an effect in the proximal intestine.

Disclosure

None declared.

Author Contributions

Asher and Smith participated in research design. Asher and Fallon conducted experiments, while Fallon and Smith contributed new reagents or analytic tools. Asher, Fallon, and Smith performed data analysis and wrote or contributed to the writing of the manuscript.

References

Basu NK, Kole L, Owens IS (2003). Evidence for phosphorylation requirement for human bilirubin UDP-glucuronosyltransferase (UGT1A1) activity. Biochem Biophys Res Commun 303: 98–104.

Basu NK, Kole L, Kubota S, Owens IS (2004a). Human UDP-glucuronosyltransferases show atypical metabolism of mycophenolic acid and inhibition by curcumin. Drug Metab Dispos 32: 768–773.

Blumenthal M, Lindstrom A, Lynch M, Rea P (2011). Herb sales continue growth. HerbalGram 90: 64–67.

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.

Court MH, Duan SX, von Moltke LL, Greenblatt DJ, Patten CJ, Miners JO, et al. (2001). Interindividual variability in acetaminophen glucuronidation by human liver microsomes: identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 299: 998–1006.

Fallon JK, Neubert H, Goosen TC, Smith PC (2013a). Targeted precise quantification of 12 human recombinant uridine-diphosphate glucuronosyl transferase 1A and 2B isoforms using nano-ultra-high-performance liquid chromatography/tandem mass spectrometry with selected reaction monitoring. Drug Metab Dispos 41: 2076–2080.

Fallon JK, Neubert H, Hyland R, Goosen TC, Smith PC (2013b). Targeted quantitative proteomics for the analysis of 14 UGT1As and -2Bs in human liver using NanoUPLC-MS/MS with selected reaction monitoring. J Proteome Res 12: 4402–4413.

Ferrucci LM, McCorkle R, Smith T, Stein KD, Cartmel B (2009). Factors related to the use of dietary supplements by cancer survivors. J Altern Complement Med 15: 673–680.

Garcea G, Berry DP, Jones DJ, Singh R, Dennison AR, Farmer PB, et al. (2005). Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev 14: 120–125.

Hoehle SI, Pfeiffer E, Metzler M (2007). Glucuronidation of curcuminoids by human microsomal and recombinant UDP-glucuronosyltransferases. Mol Nutr Food Res 51: 932–938.

Iwuchukwu OF, Tallarida RJ, Nagar S (2011). Resveratrol in combination with other dietary polyphenols concomitantly enhances antiproliferation and UGT1A1 induction in Caco-2 cells. Life Sci 88: 1047–1054.

Izzo AA, Ernst E (2009). Interactions between herbal medicines and prescribed drugs: an updated systematic review. Drugs 69: 1777–1798.

Margaillan G, Rouleau M, Fallon JK, Caron P, Villeneuve L, Turcotte V, et al. (2015a). Quantitative profiling of human renal UDP-glucuronosyltransferases and glucuronidation activity: a comparison of normal and tumoral kidney tissues. Drug Metab Dispos 43: 611–619.

Margaillan G, Rouleau M, Klein K, Fallon JK, Caron P, Villeneuve L, et al. (2015b). Multiplexed targeted quantitative proteomics predicts hepatic glucuronidation potential. Drug Metab Dispos 439: 1331–5.

Mehta DH, Gardiner PM, Phillips RS, McCarthy EP (2008). Herbal and dietary supplement disclosure to health care providers by individuals with chronic conditions. J Altern Complement Med 14: 1263–1269.

Naganuma M, Saruwatari A, Okamura S, Tamura H (2006). Turmeric and curcumin modulate the conjugation of 1-naphthol in Caco-2 cells. Biol Pharm Bull 29: 1476–1479.

Pari L, Tewas D, Eckel J (2008). Role of curcumin in health and disease. Arch Physiol Biochem 114: 127–149.

Peery AF, Barrett PR, Park D, Rogers AJ, Galanko JA, Martin CF, et al. (2012). A high-fiber diet does not protect against asymptomatic diverticulosis. Gastroenterology 142: e261.

Tallman MN, Miles KK, Kessler FK, Nielsen JN, Tian X, Ritter JK, et al. (2007). The contribution of intestinal UDP-glucuronosyltransferases in modulating 7-ethyl-10-hydroxy-camptothecin (SN-38)-induced gastrointestinal toxicity in rats. J Pharmacol Exp Ther 320: 29–37.

Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, Djuric Z, et al. (2008). Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev 17: 1411–1417.

Volak LP, Ghirmai S, Cashman JR, Court MH (2008). Curcuminoids inhibit multiple human cytochromes P450, UDP-glucuronosyltransferase, and sulfotransferase enzymes, whereas piperine is a relatively selective CYP3A4 inhibitor. Drug Metab Dispos 36: 1594–1605.

Volak LP, Hanley MJ, Masse G, Hazarika S, Harmatz JS, Badmaev V, et al. (2012). Effect of an herbal extract containing curcumin and piperine on midazolam, flurbiprofen, and acetaminophen pharmacokinetics in healthy volunteers. Br J Clin Pharmacol 752: 450–62.

© 2016 The Authors. *Pharmacology Research & Perspectives* published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.