Modulation of hepatic drug metabolizing enzymes by the natural polyphenol curcumin

Authors

Shuli Chen

Rhonda J. Rosengren*****

Affiliation

Department of Pharmacology and Toxicology, School of Biomedical Sciences, University of Otago, Dunedin 9016, New Zealand

Correspondence to:

Professor Rhonda J. Rosengren

Department of Pharmacology and Toxicology, 18 Frederick St, University of Otago, Dunedin 9016, New Zealand

E-mail:
rhonda.rosengren@otago.ac.nz

Abstract

Curcumin, the yellow pigment found in turmeric, has potent chemopreventative properties towards cancer in both *in vivo* and *in vitro* models. Phase I cytochrome P450 (CYP) enzymes and phase II conjugation enzymes play a critical role in carcinogen metabolism and hence could be an important target for cancer chemoprevention and treatment. Various studies have been undertaken to evaluate the effects of curcumin on the activity of phase I and phase II enzymes. Phase I enzymes are functionalization enzymes and Phase II enzymes perform conjugative reactions. This review summarizes the studies on curcumin modulation of phase I and II activities in the last decade. Various studies have shown that curcumin inhibits the activity of different CYPs including CYP1A1 and CYP1B1 CYP1A1, CYP1A2, CYP2A6, CYP3A4, CYP2B1 and CYP2E1 *in vitro* and *in vivo*. However, a few studies have also reported the induction of CYPs. Curcumin also modulates the activity of phase II enzymes. Phase II enzymes have attracted much less attention than CYPs, especially in clinical pharmacology. Most studies focus on the inhibition or induction of glutthione S-transferase (GST). Also modulating of sulfotransferases (SULTs) and glucuronosyltransferases (UGTs) has been reported. However, more studies in humans following oral adminstration of curcumin are required in order to fully elucidate the potential for curcumin to be used as an effective potential chemopreventative.

Key words: curcumin, phase II enzymes, CYP450s, inhibition, in vitro

I. Introduction

Curcumin (diferuloylmethane), a polyphenol phytochemical extracted from the plant *Curcuma longa*, is a yellow pigment and widely used in cooking and in the preparation of traditional medicines in Southeast Asia, China and India. Commercially available curcumin, collectively called curcuminoids, is generally composed of about 77% curcumin, 17% demethoxycurcumin, and 3% bisdemethoxycurcumin (Figure 1). In recent years, curcumin has emerged as a compound with multiple biologic properties for health maintenance and cancer prevention. It has been reported that curcumin is able to inhibit the cellular transformation, proliferation, invasion, angiogenesis and metastasis of tumors (1, 2). Curcumin has also shown antioxidant, anti-inflammatory and antimicrobial activities as well as chemopreventive and therapeutic potential against a wide variety of cancers including leukemia, lymphoma, melanoma, and sarcoma, as well as gastric, colon, pancreatic, breast, prostate, ovarian, cervical, lung, hepatic, and neurological cancers (2-6). Due to its lack of toxicity in humans, low molecular weight and affordability, curcumin is an ideal candidate for use as a chemopreventative agent. It has been suggested that curcumin's chemopreventative action is also related to the modulation of the activities of drug metabolizing enzymes, both phase I cytochrome P450 (CYP) and phase II conjugation enzymes.

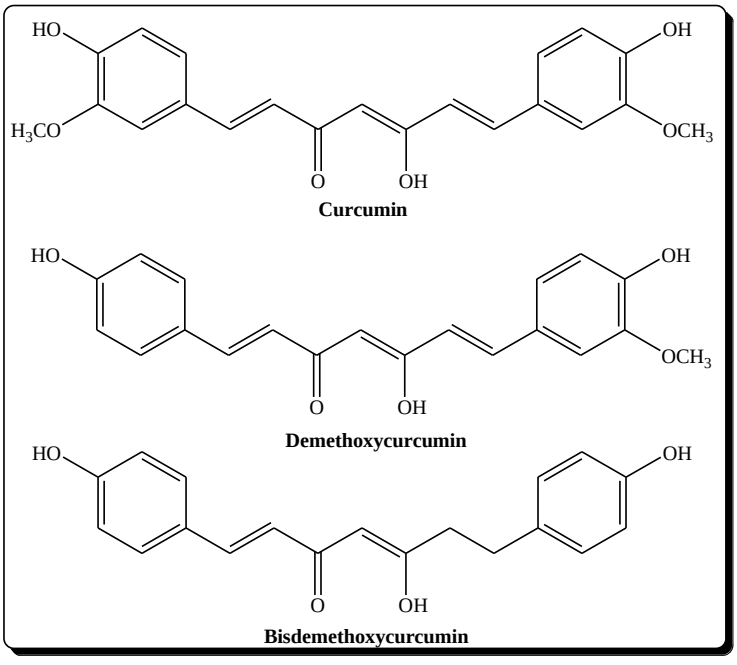

Figure 1. Chemical structures of curcuimoids

CYP enzymes, a heme containing superfamily of mono-oxygenases, play a critical role in modulating the phase I metabolism of various drugs and other lipophilic xenobiotics via oxidative biotransformation such as hydroxylation, epoxidation, or heteroatom oxidation (7-9). CYPs have been identified both in rodent

and human tissues and 18 families and 44 subfamilies of CYPs have been identified and categorized according to amino acid sequence similarity (9). It has been reported that 11 families of CYPs - CYP1A2, CYP2A6, CYP2B6, CYP2C8/9/18/19, CYP2D6, CYP2E1, and CYP3A4/5- are expressed in the human liver with five of them (CYPs 1A2, 2C9, 2C19, 2D6 and 3A4) mediating 95% of drug metabolism (10, 11). In addition, CYPs are also found in the small intestine, lung, kidney, brain, adrenal gland, gonads, heart, nasal and tracheal mucosa, and skin (12). Drug treatment can cause CYP enzyme inhibition or CYP enzyme induction. Inhibition or induction of CYP enzymes may lead to an increase or decrease of drug plasma level resulting in toxicity or adverse reactions (13). Many drugs are metabolized by CYP oxidation followed by conjugation. Phase II conjugation enzymes include a set of transferase enzymes: uridine-diphosphate-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), glutathione S-transferases (GSTs), N-acetyltransferases (NATs), methyltransferases, catechol O-methyl transferase (COMT) and acyltransferases (14). These enzymes perform conjugative reactions including glucuronidation, sulfation, methylation, acetylation, glutathione and amino acid conjugation and thus conjugate a wide variety of chemical structures (15). Therefore, the resulted conjugated metabolites with more hydrophilic and polar properties are efficiently excreted from the body. Although bioactivation of xenobiotics by phase II enzymes most often result in detoxifying of xenobiotics, toxic metabolites and adverse effects can also occur (16). Phase I and II enzymes have been observed to play an important role in carcinogen metabolism and hence could be an important target for chemoprevention. Curcumin exhibits chemopreventive efficacy via modulating the transcriptional regulators of phase I and phase II enzymes in various experimental models.

II. Modulation effects of curcumin on Phase I and II enzymes

1. Effects of curcumin on phase I metabolizing enzymes

Curcumin was found to inhibit the CYP1A1 and CYP1B1 induced by 2,3,7,8-tetrachlorodibenzop-dioxin (TCDD) via its modulatory effects on both the aryl hydrocarbon receptor (AhR) and AhR nuclear translocator (ARNT) *in vitro* (17). CYP1A1 and CYP1B1 were reported to produce quinine containing 2- or 4-hydroxyestradiol by hydroxylation of 17-β-estradiol, and quinine is classified as a tumor initiator (18). It was observed that curcumin inhibited CYP1A1 and CYP1B1 induced by TCDD in Hep3B and MCF7 cell lines. Western blotting analysis indicated that 250 pM of TCDD induced CYP1A1 and CYP1B1 in both cell lines, specifically a significant increase of CYP1A1 in MCF7 cells and CYP1B1 in Hep3B cells. Furthermore, after treatment with 20 μM of curcumin for 24 h, the TCDD-induced protein expression and mRNA levels of CYP1A1 and CYP1B1 was significantly decreased (17). This suggests that curcumin was able to supress CYP1A1 induction by preventing AhR binding to its response element.

Curcumin has been reported to decrease aflatoxin B1 (AFB1) toxicity by

modulating CYP450 activities (19). AFB1 treatment in male broilers for 2 weeks induced the activity of CYP1A1 (270.6%), CYP1A2 (99.4%), CYP2A6 (184.5%), and CYP3A4 (29.2%) compared to liver microsomes from control chickens (20). However, dietary AFB1 and curcumin co-administration in male broilers for the same period resulted in a significant inhibition on the above CYP450 isozyme activities by 37, 43, 48 and 35% for CYP1A1, CYP1A2, CYP2A6, and CYP3A4, respectively, compared to the AFB1 treated group alone (20). Since CYP450 isozymes are crucial for the bioactivation of AFB1 to highly toxic epoxide metabolites, this result suggested that dietary curcumin has the potential to decrease AFB1-induced liver injury. The over expression of CYP2A6 has been correlated with a greater risk of liver cancer, cirrhosis and chronic inflammation (21). A similar study on CYP2A6 also indicated its relation to bioactivation of AFB1 and the biotransformation of AFB1 into AFBO (22). Speficially, Arbor Acres broilers were fed dietary AFB1 (5 mg/kg) for 28 days and a significant increase in CYP2A6 compared to control was observed. However, the broiler group treated with curcumin (150, 350 and 450 mg/kg) and AFB1 (5 mg/kg) exhibited a decrease in CYP2A6 compared to the AFB1 fed group with a maximum inhibition of liver CYP2A6 enzyme activity by 450 mg/kg of curcumin. Since curcumin treatment inhibited CYP2A6 at the mRNA and protein levels in AFB1 treated broilers in a dose-dependent manner, this study indicates that curcumin protects the liver from AFB1 toxicity (22).

It was concluded that the extent of CYP inhibition was concentration-dependent with higher concentrations of curcumin resulting in greater suppression of the enzyme activities. For example, another study reported that curcumin (2-120 μM) was able to effectively inhibit human CYP3A4, CYP1A2, CYP2C9 and CYP2D6 (23). It should be noted that CYP1A2, CYP2C9, CYP2D6, and CYP3A4 collectively mediate approximately 70% of 95% of drug metabolism (24). The results indicated that curcumin is a strong inhibitor of CYP2C9 and CYP3A4 as the activity of CYP3A4 was completely supressed under the curcumin concentrations ≥ 60 μM, while that of CYP2C9 was inhibited more than 70% with the curcumin concentrations ≥ 90 μM (23). It was less effective against CYP1A2 and CYP2D6, as the inhibition was approximately 50% for CYP1A2 and CYP2D6 at 120 μM of curcumin (23).

Curcumin was also reported to inhibit the carcinogen- and solvent-induced activities of other CYPs *in vivo*. A study in male Swiss albino mice showed that dietary curcumin (0.01% and 0.05%) significantly inhibited phenobarbital (PB)- and acetone-induced hepatic CYP2B1 by 26-32% and hepatic CYP2E1 by 12-39% (25). Moreover, immunoblotting and RT-PCR analysis indicated that dietary curcumin (0.01% and 0.05%) significantly inhibited PB-induced CYP2B1 protein expression by 21-32% and mRNA level by 33-62%, as well as acetone-induced CYP2E1 protein expression by 11-40% in mouse liver (25). As CYP2B1 and CYP2E1 modulate the oxidative bio-activation of nitrosamines, this result also suggested that curcumin may decrease the generation

of DNA reactive species in N-nitrosamines associated hepatocellular carcinogenesis (25). Curcumin also showed the inhibition of N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis via a decrease in the expression of the CYPs. A study on the activities in F344 rats after treatment with curcumin for 6 weeks indicated that curcumin (0.05% and 0.2%) decreased esophageal CYP2B1 and 2E1 by up to 60% relative to controls (26). However, contradictory results have been reported regarding curcumin's action on CYP2E1. Specifically, the catalytic activity of heaptic CYP2E1 was unchanged following treatment with curcumin (200 mg/kg or 400 mg/kg) for 2 weeks in female Swiss Webster mice (27). It is possible that the effects are sex-dependent as the majority of studies are conducted in male mice. Regardless, more studies in both sexes and in multiple species as well as human volunteers are required to elucidate the effect of curcumin on CYP2E1.

Studies indicated that dietary exposure of benzo[a]pyrene (B[a]P), a polycyclic aromatic hydrocarbon, can cause colorectal cancer in humans (28). CYP1A is responsible for the metabolism of B[a]P into benzo[a]pyrene 7,8-diol-9,10-epoxide (BPDE), a highly carcinogenic and mutagenic electrophile (29). Treatment with dietary curcumin (0.01%) inhibited B[a]P-induced CYP1A1 and CYP1A2 activities by 20–30% in liver and 26–34% in lungs, while a dose of 0.05% resulted in a suppression of both phase I enzyme activities by 43–50% in liver and 59–65% in lungs (30). Moreover, curcumin (0.05%) significantly inhibited the B[a]P-induced CYP1A1 and CYP1A2 mRNA levels in both the liver and lungs, while curcumin (0.01%) pretreatment significantly decreased B[a]P-induced CYP1A1 mRNA in lungs and CYP1A2 mRNA in liver (30). Furthermore, treatment of female Swiss Webster mice with curcumin (200 mg/kg or 400 mg/kg) for 2 weeks resulted in a 25% decrease in the catayltic activity and polypeptide levels of hepatic CYP1A1 compared to control following both doses (27). These studies suggest that curcumin's modulation of CYP1A1 can decrease carcinogen-induced stress and DNA adducts by inhibitiing CYP1A1 and CYP1A2 activity and protein expression *in vivo*.

The effect of curcumin is also tissue-specific. For example, treatment of male Sprague-Dawley rats with 60 mg/kg curcumin for 4 days resulted an inhibition of intestinal CYP3A protein level by 42%, whereas the hepatic and renal CYP3A protein level was increased by 91% and 41%, respectively (31). It should be noted that in this study curcumin significantly induced hepatic and renal CYP3A levels. This result also implicated the presence of differential regulatory mechanisms for protein expression in the various organs. It also reported that curcumin (0-100 μM, IC_{50} = 11.0 ± 3.3 μM) was able to inhibit the *in vitro* CYP3A-mediated metabolism of testosterone in rat liver microsomes in which curcumin (10 μM) treatment led to the highest inhibitory effect by 40% compared to control (32).

The inhibitory potential of curcumin on the five important human drug-metabolizing CYPs, CYP1A2, CYP3A4, CYP2B6, CYP2C9 and CYP2D6, was also investigated (33). It was observed that

curcumin (300 μM) almost completely inhibited the activities of CYP3A4, CYP2C9, and CYP1A2 in the decreasing order of potency CYP2C9 > CYP3A4 > CYP2B6. At the same time, the same concentration of curcumin inhibited the activities of CYP2D6 and CYP2B6 by 72 and 69%, respectively (33). Additionally, competitive inhibition after curcumin treatment was observed with CYP1A2, CYP2B6 and CYP3A4, while non-competitive occurred with CYP2C9 and CYP2D6 (33). CYP2C9 is the second highest CYP in the human liver making up approximately 20% of total hepatic CYP450 content (34, 35). Due to its oxidation of endogenous and exogenous compounds including therapeutic drugs, CYP2C9 plays an important role for drug therapy in the clinic (36). Curcumin (50 mmol/l) also inhibited CYP2C9 in human liver microsomes by 87% (37). The observations imply that curcumin has the potent inhibitory effects on CYP2C9 activity in humans. Moreover, curcumin showed a more potent inhibitory effect of CYP2C9 in human liver microsomes than that of rat liver microsomes.

As an important human metabolizing enzyme, CYP3A4, expressed in the intestine and liver, is responsible for the metabolism of more than 50% of clinically used drugs (38). Everolimus (EVL) is a substrate of P-glycoprotein (P-gp) and is primarily metabolized by CYP3A4 (39). A study investigated the effect of coadministration of curcumin on the pharmacokinetics of EVL in rats and the underlying mechanisms. After oral administration of EVL alone and coadministrations with 50 or 100 mg/kg of curcumin, the area under the blood concentration–time curve from 0 to 540 min (AUC_{0-540}) of EVL was significantly decreased by 71% and 72%, respectively, and both dosages reduced the peak plasma concentration (C_{max}) of EVL by 77%. 5 and 10 μM of curcumin treatment caused significant inhibition of CYP 3A4 activity by 93% and 90%, respectively. The efflux function of P-gp was significantly reduced by 13, 17 and 173%, respectively. Mechanism studies revealed that CYP3A4 was markedly activated by curcumin metabolites, which appeared to override the inhibitory effects of curcumin on P-gp. This study suggested that curcumin was able to significantly decreased the bioavailability of EVL via marked activation on CYP 3A4 (40). This finding was confirmed in another species as 2 weeks of curcumin treatment (400 mg/kg) decreased the catalytic activity and polypeptide levels of hepatic CYP3A compared to vehicle control in female Swiss Webster mice (27).

2. Effects of curcumin on phase II metabolising enzymes

As drug-drug and/or drug–food interactions involving phase II enzymes are relatively sparse phase II enzymes have attracted much less attention than CYPs, especially in clinical pharmacology. One of the most important enzymes of this group is GST, which plays a critical role in the detoxication of epoxides derived from PAHs and alpha-beta unsaturated ketones and in providing protection against electrophiles and products of oxidative stress (14). Induction of GSTs has long been suggested to be one of the critical actions of an effective cancer preventative agent. For example, the combined

chemopreventive potential of curcumin and resveratrol towards B[a]P-induced lung carcinogenesis in mice was investigated (41). A significant decrease of 26% in the B[a]P-treated group was observed for GST compared to control (41). In addition, individual treatment with curcumin and resveratrol resulted in a significant increase of 14 and 15% of GST compared to B[a]P-treated mice, respectively. However, simultaneous administration of curcumin and resveratrol to the B[a]P-treated animals significantly increased the GST by 18% compared to B[a]P-treated mice (41). These results suggested that coadministration of curcumin and resveratrol was able to upregulate GST. Furthermore, these results were confirmed in a study that reported that 2 weeks of curcumin treatment (400 mg/kg) in female Swiss Webster mice caused a 20% increase in heaptic GST activity (27).

Curcumin also induced the expression and activity of GST enzymes and increased the presence of reactive oxygen species in *Dictyostelium discoideum*, a eukaryotic model, (42). Curcumin selectively induced only two of five gstA genes with a significant increases of 127 and 35% in gstA2 and gstA3 genes compared to control in the *Dictyostelium discoideum*. In addition, total GST enzyme activity was also increased by more than 30% after treatment with 10 μM of curcumin (42). This result suggested that there was specialized regulation and function of GSTs in *Dictyostelium*. Furthermore, the lack of GSTP1 expression in human prostate cells was likely to result in oxidative DNA damage, which is an important contributor to prostate carcinogenesis (43-45). Therefore, a rational prevention strategy against prostate cancer could be to compensate for GSTP1 loss by induction of phase II enzymes especially GST within the prostate. To this end, F344 rats were fed for 5 days with 45 mg/kg of curcumin and the total GST and GST-mu activities in prostate tissues over control levels were increased by 14 and 73% compared to control animals (46). This suggests that curcumin is an effective inducing agent and has the potential for use in prostate cancer prevention.

Curcumin and curcuminoid extract were reported to inhibit the catalytic activity of SULT and UGT *in vitro*. Inhibition of UGT enzymatic activity was reported to be related to prostate cancer by modulation of hormone levels (47). SULTs are responsible for the transfer of a sulfuryl group to hydroxyl or amine groups, particularly in the liver, intestine, adrenal gland, brain, and skin (48). Experiments have shown that curcuminoid extract inhibited UGT and SULT activity with IC_{50} values of 12.1 and 5.2 μmol/l in LS180 colon adenocarcinoma cells, while 0.99 μmol/l of curcuminoid extract and 5.9 μmol/l of curcumin lead to 50% inhibition SULT in HLC cells. 2.6 and 2.2 μmol/l of curcumin resulted in 50% inhibition of SULT and UGT activity in LS180 cells, respectively (49). On the other hand, curcumin was also able to induce UGT enzyme activity *in vivo.* For example, 1% of curcumin was fed to male Wistar rats for 2 weeks and intestinal and liver microsomes were then prepared. The results showed that curcumin induced UGT activity by 1.5- and 3.1- fold in the large intestine and liver, respectively,

while proximal, middle and distal sections of the small intestine were increased by 5.4-, 6.7- and 7.2-fold, respectively (50).

III. Conclusion

Phase I and II enzymes play an important role in carcinogen metabolism and hence their modulation is an important devlopmental area for cancer chemoprevention. *In vitro* and *in vivo* studies show that curcumin can effectively modulate phase I and phase II enzymes. While there is *in vitro* and *in vivo* evidence regarding the actions of curcumin, further studies in human subjects are required in order to fully elucidate curcumin's potential. While toxicity with curcumin has not been reported, nanoformulations will likely be required to achieve clinically relevant plasma levels.

IV References

1. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23(1A):363-98.
2. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett. 2008;269(2):199-225.
3. Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. Curcumin and cancer: an "old-age" disease with an "age-old" solution. Cancer Lett. 2008;267(1):133-64.
4. Lee W-H, Loo C-Y, Bebawy M, Luk F, Mason RS, Rohanizadeh R. Curcumin and its derivatives: their application in neuropharmacology and neuroscience in the 21st century. Curr Neuropharmacol. 2013;11(4):338-78.
5. Zorofchian Moghadamtousi S, Abdul Kadir H, Hassandarvish P, Tajik H, Abubakar S, Zandi K. A review on antibacterial, antiviral, and antifungal activity of curcumin. BioMed research international. 2014;2014.
6. Sandur SK, Pandey MK, Sung B, Ahn KS, Murakami A, Sethi G, et al. Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism. Carcinogenesis. 2007;28(8):1765-73.
7. Sheweita SA. Drug-metabolizing enzymes mechanisms and functions. Curr Drug Metab. 2000;1(2):107-32.
8. Guengerich FP. Cytochrome p450 and chemical toxicology. Chem Res Toxicol. 2007;21(1):70-83.
9. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103-41.
10. Rendic S, Guengerich FP. Update information on drug metabolism systems—2009, part II. Summary of information on the effects of diseases and environmental factors on human cytochrome P450 (CYP) enzymes and transporters. Curr Drug Metab. 2010;11(1):4-84.
11. Nelson DR. The cytochrome p450 homepage. Human genomics. 2009;4(1):59.
12. Pelkonen O, Turpeinen M, Hakkola J, Honkakoski P, Hukkanen J, Raunio H. Inhibition and induction of human cytochrome P450 enzymes: current status. Arch Toxicol. 2008;82(10):667-715.
13. Koe XF, Muhammad T, Sifzizul T, Chong ASC, Wahab HA, Tan ML. Cytochrome P450 induction properties of food and herbal - derived compounds using a novel multiplex RT - qPCR in vitro assay, a drug ‐ food interaction prediction tool. Food science & nutrition. 2014;2(5):500-20.
14. Jancova P, Anzenbacher P, Anzenbacherova E. Phase II drug metabolizing enzymes. Biomedical Papers. 2010;154(2):103-16.
15. Xu C, Li CY-T, Kong A-NT. Induction of phase I, II and III drug metabolism/transport by xenobiotics. Arch Pharmacal Res. 2005;28(3):249.

16. Glatt H. Sulfotransferases in the bioactivation of xenobiotics. Chem-Biol Interact. 2000;129(1):141-70.
17. Choi H, Chun YS, Shin YJ, Ye SK, Kim MS, Park JW. Curcumin attenuates cytochrome P450 induction in response to 2, 3, 7, 8 - tetrachlorodibenzo - p - dioxin by ROS - dependently degrading AhR and ARNT. Cancer Sci. 2008;99(12):2518-24.
18. Hayes CL, Spink DC, Spink BC, Cao JQ, Walker NJ, Sutter TR. 17 beta-estradiol hydroxylation catalyzed by human cytochrome P450 1B1. Proceedings of the National Academy of Sciences. 1996;93(18):9776-81.
19. Firozi P, Aboobaker V, Bhattacharya R. Action of curcumin on the cytochrome P450-system catalyzing the activation of aflatoxin B1. Chem-Biol Interact. 1996;100(1):41-51.
20. Zhang N-Y, Qi M, Zhao L, Zhu M-K, Guo J, Liu J, et al. Curcumin prevents aflatoxin B1 hepatoxicity by inhibition of cytochrome P450 isozymes in chick liver. Toxins (Basel). 2016;8(11):327.
21. Kirby G, Wolf C, Neal G, Judah D, Henderson C, Srivatanakul P, et al. In vitro metabolism of aflatoxin B1 by normal and tumorous liver tissue from Thailand. Carcinogenesis. 1993;14(12):2613-20.
22. Muhammad I, Sun X, Wang H, Li W, Wang X, Cheng P, et al. Curcumin Successfully Inhibited the Computationally Identified CYP2A6 Enzyme-Mediated Bioactivation of Aflatoxin B1 in Arbor Acres broiler. Front Pharmacol. 2017;8.
23. Shamsi S, Tran H, Tan RSJ, Tan ZJ, Lim LY. Curcumin, Piperine, and Capsaicin: A Comparative Study of Spice-Mediated Inhibition of Human Cytochrome P450 Isozyme Activities. Drug Metab Disposition. 2017;45(1):49-55.
24. Williams JA, Hyland R, Jones BC, Smith DA, Hurst S, Goosen TC, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Disposition. 2004;32(11):1201-8.
25. Oesch F, Fabian E, Guth K, Landsiedel R. Xenobiotic-metabolizing enzymes in the skin of rat, mouse, pig, guinea pig, man, and in human skin models. Arch Toxicol. 2014;88(12):2135-90.
26. Mori Y, Tatematsu K, Koide A, Sugie S, Tanaka T, Mori H. Modification by curcumin of mutagenic activation of carcinogenic N - nitrosamines by extrahepatic cytochromes P - 450 2B1 and 2E1 in rats. Cancer Sci. 2006;97(9):896-904.
27. Valentine SP, Le Nedelec MJ, Menzies AR, Scandlyn MJ, Goodin MG, Rosengren RJ. Curcumin modulates drug metabolizing enzymes in the female Swiss Webster mouse. Life Sci. 2006;78(20):2391-8.
28. Banks LD, Amoah P, Niaz MS, Washington MK, Adunyah SE, Ramesh A. Olive oil prevents benzo (a) pyrene [B (a) P]-induced colon carcinogenesis through altered B (a) P metabolism and decreased oxidative damage in Apc Min mouse model. J Nutr Biochem. 2016;28:37-50.
29. Niranjan B, Wilson N, Jefcoate C, Avadhani N. Hepatic mitochondrial cytochrome P-450 system. Distinctive features of cytochrome P-450 involved in the activation of aflatoxin B1 and benzo (a)

pyrene. J Biol Chem. 1984;259(20):12495-501.
30. Garg R, Gupta S, Maru GB. Dietary curcumin modulates transcriptional regulators of phase I and phase II enzymes in benzo [a] pyrene-treated mice: mechanism of its anti-initiating action. Carcinogenesis. 2008;29(5):1022-32.
31. Zhang W, Tan TMC, Lim L-Y. Impact of curcumin-induced changes in P-glycoprotein and CYP3A expression on the pharmacokinetics of peroral celiprolol and midazolam in rats. Drug Metab Disposition. 2007;35(1):110-5.
32. Kim S-B, Cho S-S, Cho H-J, Yoon I-S. Modulation of Hepatic Cytochrome P450 Enzymes by Curcumin and its Pharmacokinetic Consequences in Sprague–dawley Rats. Pharmacogn Mag. 2015;11(Suppl 4):S580.
33. Appiah-Opong R, Commandeur JN, van Vugt-Lussenburg B, Vermeulen NP. Inhibition of human recombinant cytochrome P450s by curcumin and curcumin decomposition products. Toxicology. 2007;235(1):83-91.
34. Miners JO, Birkett DJ. Cytochrome P4502C9: an enzyme of major importance in human drug metabolism. Br J Clin Pharmacol. 1998;45(6):525-38.
35. Emoto C, Murase S, Iwasaki K. Approach to the prediction of the contribution of major cytochrome P450 enzymes to drug metabolism in the early drug-discovery stage. Xenobiotica. 2006;36(8):671-83.
36. Zhou S-F, Zhou Z-W, Yang L-P, Cai J-P. Substrates, inducers, inhibitors and structure-activity relationships of human Cytochrome P450 2C9 and implications in drug development. Curr Med Chem. 2009;16(27):3480-675.
37. Wang Z, Sun W, Huang C-K, Wang L, ia M-M, Cui X, et al. Inhibitory effects of curcumin on activity of cytochrome P450 2C9 enzyme in human and 2C11 in rat liver microsomes. Drug Dev Ind Pharm. 2015;41(4):613-6.
38. Zhou S-F. Drugs behave as substrates, inhibitors and inducers of human cytochrome P450 3A4. Curr Drug Metab. 2008;9(4):310-22.
39. Zaza G, Tomei P, Ria P, Granata S, Boschiero L, Lupo A. Systemic and nonrenal adverse effects occurring in renal transplant patients treated with mTOR inhibitors. Clin Dev Immunol. 2013;2013.
40. Hsieh Y-W, Huang C-Y, Yang S-Y, Peng Y-H, Yu C-P, Chao P-DL, et al. Oral intake of curcumin markedly activated CYP 3A4: in vivo and ex-vivo studies. Sci Rep. 2014;4.
41. Liu Y, Wu Y, Yu Y, Cao C, Zhang J, Li K, et al. Curcumin and resveratrol in combination modulate drug-metabolizing enzymes as well as antioxidant indices during lung carcinogenesis in mice. Hum Exp Toxicol. 2015;34(6):620-7.
42. Garige M, Walters E. Curcumin inhibits development and cell adhesion in Dictyostelium discoideum: Implications for YakA signaling and GST enzyme function. Biochem Biophys Res Commun. 2015;467(2):275-81.
43. Nelson WG, Angelo M. De Marzo and William B. Isaacs Prostate Cancer NEJM. 2003;349(4):366-81.
44. Lin X, Tascilar M, Lee W-H, Vles WJ, Lee BH, Veeraswamy R, et al. GSTP1 CpG island hypermethylation is responsible for the absence of GSTP1 expression in human prostate cancer cells. The American journal of pathology. 2001;159(5):1815-26.

45. Nakayama M, Bennett CJ, Hicks JL, Epstein JI, Platz EA, Nelson WG, et al. Hypermethylation of the human glutathione S-transferase-π gene (GSTP1) CpG island is present in a subset of proliferative inflammatory atrophy lesions but not in normal or hyperplastic epithelium of the prostate: a detailed study using laser-capture microdissection. The American journal of pathology. 2003;163(3):923-33.
46. Jones SB, Brooks JD. Modest induction of phase 2 enzyme activity in the F-344 rat prostate. BMC Cancer. 2006;6(1):62.
47. Jenkinson C, Petroczi A, Naughton DP. Effects of dietary components on testosterone metabolism via UDP-glucuronosyltransferase. Front Endocrinol (Lausanne). 2013;4.
48. James MO, Ambadapadi S. Interactions of cytosolic sulfotransferases with xenobiotics. Drug Metab Rev. 2013;45(4):401-14.
49. Volak LP, Ghirmai S, Cashman JR. Curcuminoids inhibit multiple human cytochromes P450, UDP-glucuronosyltransferase, and sulfotransferase enzymes, whereas piperine is a relatively selective CYP3A4 inhibitor. Drug Metab Disposition. 2008;36(8):1594-605.
50. Van der Logt E, Roelofs H, Nagengast F, Peters W. Induction of rat hepatic and intestinal UDP-glucuronosyltransferases by naturally occurring dietary anticarcinogens. Carcinogenesis. 2003;24(10):1651-6.