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ORIGINAL ARTICLE

Modulation of Hepatic Cytochrome P450 Enzymes by Curcumin and its Pharmacokinetic Consequences in Sprague–dawley Rats

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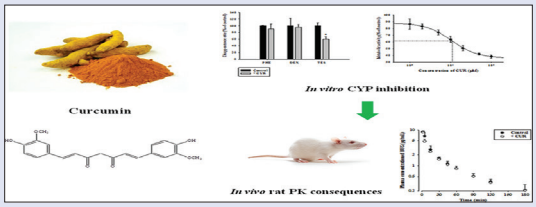
ABSTRACT

Background: Curcumin (CUR) is a polyphenolic component derived from an herbal remedy and dietary spice turmeric (*Curcuma longa*). **Objective:** The aim of this study was to investigate inhibitory effects of CUR on *in vitro* cytochrome P450 (CYP) activity and *in vivo* pharmacokinetic consequences of single CUR dose in rats. **Materials and Methods:** An *in vitro* CYP inhibition study in rat liver microsomes (RLM) was conducted using probe substrates for CYPs. Then, an *in vivo* pharmacokinetics of intravenous buspirone (BUS), a probe substrate for CYP3A, was studied with the concurrent administration of oral CUR in rats. **Results:** In the *in vitro* CYP inhibition study, CUR inhibited the CYP3A-mediated metabolism of testosterone (TES) with a half maximal inhibitory concentration of 11.0 ± 3.3 μM. However, the impact of a single oral CUR dose on the pharmacokinetics of BUS in rats is limited, showing that CUR cannot function as an inhibitor for CYP3A-mediated drug metabolism *in vivo*. **Conclusion:** To the best of our knowledge, our results are the first reported data regarding the inhibition of *in vitro* CYP3A-mediated metabolism of TES and the *in vivo* impact of a single CUR dose on the pharmacokinetics of BUS in rats. Further study is required to draw a confirmative conclusion on whether CUR can be a clinically relevant CYP3A4 inhibitor.

Key words: Buspirone, curcumin, cytochrome P450, hepatic metabolism, rat

SUMMARY

- CUR can inhibit the in vitro CYP3A-mediated metabolism of TES in RLM. However, the impact of a single oral CUR dose on the pharmacokinetics of BUS in rats is limited, showing that CUR cannot function as an inhibitor for CYP3A-mediated drug metabolism *in vivo*.



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INTRODUCTION

Many herbal products and phytochemicals have been regarded as complementary and alternative medicines during the past decades.[1] In the United States, the concomitant use of herbal medicines and drugs occurred in about 20–30% of total prescription.[2-4] However, some phytochemicals contained in herbal products may be metabolized by the enzyme systems, which are the same as those responsible for the metabolism of prescription drugs. Therefore, metabolic interactions between drugs and herbs (or phytochemicals) could occur frequently, some of which may lead to therapeutic failure.[1]

Among drug metabolizing enzymes, cytochrome P450 (CYP) is commonly involved in clinically significant pharmacokinetic herb (or phytochemicals)–drug interactions.[5,6] Indeed, grapefruit (*Citrus paradisi*), St. John's wort (*Hypericum perforatum*), and ginkgo (*Ginkgo biloba*) have been reported to influence CYP-mediated metabolism and/or efficacy of several concurrent drugs such as anticoagulants, anti-cancer drugs, anti-hyperlipidemic drugs, anti-retroviral drugs, immunosuppressants, and anti-depressants.[6-8] However, many herbs and phytochemicals still remain unexplored for their CYP-modulating effects, which necessitate further investigation.

Curcumin [diferuloylmethane, CUR; Figure 1] is a polyphenolic component derived from a herbal remedy and dietary spice turmeric (*Curcuma longa*).[9] Generally, it is regarded as the most active constituent of most turmeric preparations. CUR possesses potent antioxidant, anti-inflammatory, and anti-cancer activities.[9] It, thus, exhibits beneficial health effects on various diseases, including multiple myeloma, pancreatic cancer, myelodysplastic syndromes, colon cancer, psoriasis, arthritis, major depressive disorder, and Alzheimer's disease.[10-12] Oral CUR dose of 3600 mg/day has been typically used in clinical trials, but dosages of CUR up to 8000 mg/day have been used.[13]

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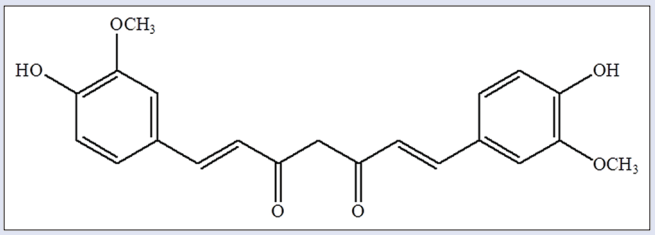

Figure 1: Chemical structure of curcumin

In the intestine and liver, CUR is metabolized primarily to glucuronide and sulfate conjugates and then excreted mainly into bile or urine.[14,15] It also exhibits a limited oral bioavailability (about 1% in rats), likely due to extensive intestinal and hepatic first-pass effects.[9,16,17] CUR has been reported to inhibit *in vitro* CYP1A2, 2B6, 2C9, 2D6, and 3A4 activities in human cDNA-expressed CYP enzymes.[18] Moreover, repeated doses of CUR caused a down-regulation of intestinal CYP3A expression but an induction of hepatic and renal CYP3A expression in rats.[19] However, there are few studies on *in vivo* CYP3A-related pharmacokinetic consequences of a single CUR dose in rats. Therefore, further investigation on this issue is required to improve the understanding of the drug interactions with turmeric or CUR. Herein, we report on the direct effect of CUR on hepatic CYP-mediated drug metabolism in rats. The inhibitory effect of CUR on CYP activity in rat liver microsomes (RLM) was evaluated for its inhibition constants half maximal inhibitory concentration (IC_{50}). The pharmacokinetics of buspirone (BUS), a probe substrate of rat CYP3A, with a single oral administration of CUR was further evaluated as well.

MATERIALS AND METHODS

Materials

BUS, CUR, dextromethorphan (DEX), phenacetin (PHE), testosterone (TES), and the reduced form of β-nicotinamide adenine dinucleotide phosphate (NADPH; as a tetrasodium salt) were purchased from Sigma–Aldrich Co. The purity of CUR was 94%, and that of the other compounds was higher than 98%. Other chemicals were of reagent grade or high-performance liquid chromatography (HPLC) grade.

Animals

Protocols for the animal studies were handled in accordance with the guidelines for the Institutional Animal Care and Use Committee of Seoul National University (date of approval 22/07/2013; approval number SNU-130722-1). Male Sprague–Dawley rats (7–9 weeks old; 230–300 g) were purchased from Orient Bio, Inc. They were retained in a clean room (Animal Center for Pharmaceutical Research, College of Pharmacy, Seoul National University) at a temperature of 20–23°C with 12-h light (07:00–19:00) and dark (19:00–07:00) cycles, and a relative humidity of 50% ± 5%. The rats were housed in metabolic cages (Tecniplast USA, Inc.) under filtered, pathogen-free air, with food (Agribrands Purina Korea, Inc.) and water available *ad libitum*.

Preparation of rat liver microsomes

RLMs were prepared using a previously reported method.[20] In brief, the liver of an overnight fasted rat was homogenized using a 15-mL Pyrex glass homogenizer (Ultra-Turrax T25; IKA Korea, Ltd.) in an ice-cold buffer of 0.154 M KCl/50 mM Tris–HCl in 1 mM EDTA (pH 7.4). The homogenate was centrifuged (16,000 × *g*, 30 min), and then the supernatant fraction was centrifuged (100,000 × *g*, 90 min). The resultant microsomal pellet was resuspended in a buffer of 0.154 M KCl/50 mM Tris–HCl in 1 mM EDTA (pH 7.4). The microsomal preparations were stored at −80°C until use.

Inhibitory effect of curcumin on cytochrome P450 Activity in rat liver microsomes

For the *in vitro* CYP inhibition study, microsomal incubation mixtures (total volume of 1 mL) were prepared as follows: RLM (0.5-mg/mL microsomal protein), 1-mM NADPH, 10-mM MgCl2, 50-mM potassium phosphate buffer, 10-μM CUR, CYP isoform-specific probe substrate (10-μM PHE for rat CYP1A, 5-μM DEX for rat CYP2D, and 30-μM TES for rat CYP3A).[21-23] The probe substrates and CUR were dissolved in acetonitrile, and the spiking volume of the stock solutions was 5 μL. For the construction of dose–response curve and the inhibition of disappearance of TES in the presence of CUR, 30-μM TES and seven different concentrations of CUR (0, 1, 2, 5, 10, 20, 50, and 100 μM) were used. The experiments for dose–response curves were carried out in four separate runs. The microsomal incubation and sample preparation were performed as described previously.[21] In brief, microsomal reactions were initiated by the addition of each CYP probe substrate, and incubation was carried out at 37°C in a shaking water bath. At 0, 5, 10, and 30 min after starting the metabolic reaction, 100 μL of the incubation sample was transferred into a clean 1.5-mL Eppendorf tube containing 100-μL acetonitrile to terminate the metabolic reaction. The experiments for the double reciprocal plot were carried out in a single run. After vortex mixing and centrifugation at 16,000 × *g* for 10 min, a 100-μL aliquot of the supernatant was stored at −80°C until HPLC analysis.

In vivo pharmacokinetic study in rat

The femoral vein and artery of the rats were cannulated with a polyethylene tube (Clay Adams) 4 h before administration of the drug. The rats were anesthetized with zoletil (20 mg/kg, intramuscular injection).[24] Rats were given a single intravenous dose (10 mg/kg) of BUS (dissolved in normal saline) with or without single simultaneous oral CUR (dissolved in an aqueous vehicle containing 60 v/v% polyethylene glycol 400 and 10 v/v% N, N-dimethyl acetamide) at a dose of 200 mg/kg. Blood sampling and sample preparations were performed as described previously.[21] In brief, approximately 150-μL aliquot of a blood sample was collected via the femoral artery at 0, 2, 5, 15, 30, 45, 60, 90, 120, and 180 min after the intravenous injection. After centrifugation of the blood sample at 16,000 × *g* at 4°C for 10 min, a 50-μL aliquot of a plasma sample was stored in a−80°C until HPLC analysis.

High-performance liquid chromatography analysis

The concentrations of BUS in plasma samples and the concentrations of PHE, DEX, and TES in microsomal samples were determined as previously reported.[21] In brief, for plasma samples, a 50-μL aliquot of plasma was deproteinized with 100 μL acetonitrile. After vortex mixing and centrifugation at 16,000 × *g* for 10 min, the supernatant was transferred to a clean 1.5-mL tube, and dried under nitrogen gas at room temperature. The residue was reconstituted with a 100-μL mobile phase and a 70-μL aliquot was injected into a reversed-phase HPLC column (C18 Gemini NX; 150 mm length × 4.6 mm i.d.; particle size 5 μm; Phenomenex) using a HPLC system (Waters e2685; Waters Co., Milford, MA, USA). For microsomal samples, 100-μL microsomal samples prepared as mentioned above were directly injected into the HPLC column. The mobile phase was a mixture of 20-mM phosphate monobasic solution (pH 2.4, solvent A) and acetonitrile (solvent B). For BUS, the mobile phase was composed of 78.5 v/v% solvent A and 21.5 v/v% solvent B. For PHE, the following gradient system was used: Solvent A of 70 v/v% to 30 v/v% during 0-8 min; solvent A of 70 v/v% during 8–11 min. For DEX, the following gradient system was used: Solvent A of 85 v/v% to 45 v/v% during 0-8 min and then solvent A of 85 v/v% during 8–10 min. For TES, the mobile phase was

composed of 50-v/v% solvent C (deionized distilled water 95%, acetonitrile 5%, TFA 0.1%) and 50-v/v% solvent D (deionized distilled water 20%, acetonitrile 80%, TFA 0.1%). The flow rate of the mobile phase was 1.0 mL/min, and the column effluent was monitored by a UV/Vis detector (Waters 2487; Waters Co., Milford, MA, USA) at 245 nm for PHE and 254 nm for the other drugs, at room temperature. The lower limit of quantification of BUS was 0.1 μg/mL. The inter- and intra-day coefficients of variation were below 11.5%.

Data analysis

Noncompartmental analysis (WinNonlin, version 3.1, NCA200 and 201; Certara USA, Inc.) was used to calculate the following pharmacokinetic parameters: The total area under the plasma concentration–time curve from time zero to time infinity (AUC); the total area under the first moment of plasma concentration–time curve (AUMC); the time-averaged total body clearance (CL, calculated as dose/AUC); the mean residence time (MRT, calculated as AUMC/AUC); the terminal half-life ($t_{1/2}$); and the apparent volume of distribution at steady state (V_{ss}, calculated as dose × AUMC/AUC^2). The relative IC_{50} of CUR for the inhibition of CYP activity was determined by nonlinear regression using GraphPad Prism (version 5.01; GraphPad Software, San Diego, CA) according to the following four-parameter logistic equation:[25]

$$Y = Min + \frac{Max - Min}{1 + (X / IC_{50})^{-P}} \quad (1)$$

where X and Y are the inhibitor concentration and response, respectively. Max and Min are the initial and final Y value, respectively, and the power *P* represents the hill coefficient. Control samples (with no inhibitor) were assayed in each analytical run (CV = 5.83%).

Statistical analysis

$P < 0.05$ was considered statistically significant using a *t*-test between two means for unpaired data or a Duncan's multiple range test *posteriori* analysis of variance (ANOVA) among three means for unpaired data. All data were expressed as mean ± standard deviation, except for median ranges for T_{max}, and were rounded to three significant figures.

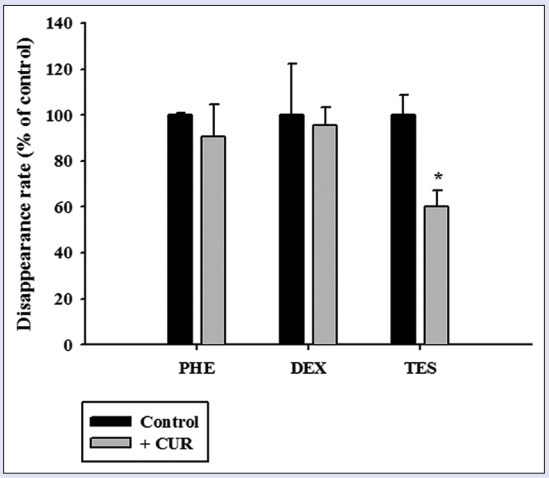

Figure 2: Effects of curcumin on the disappearance rate of model cytochrome P450 substrates (PHE: Phenacetin for cytochrome P450 1A; DEX: Dextromethorphan for cytochrome P450 2D; TES: Testosterone for cytochrome P450 3A) in rat liver microsomes (n = 3–4). *Significantly different from the control group ($P < 0.05$)

RESULTS

Inhibitory effect of curcumin on cytochrome P450 Activity in rat liver microsomes

The effects of CUR on the disappearance rate of the model CYP substrates in RLM were assessed [Figure 2]. The disappearance rate of TES was significantly lower (by 39.9%) in the presence of 10-μM CUR than in the absence of CUR (control group). However, the disappearance rates of PHE and DEX were not significantly changed as compared with the control group. The inhibitory effect of CYR at various concentrations (0–100 μM) on CYP3A activity in RLM was evaluated by the construction of a dose-response curve [Figure 3]. It was well described by the sigmoidal logistic equation (Eq. 1; $R^2 > 0.99$), and the IC_{50} value was estimated to be 11.0 ± 3.3 μM by fitting the data to Eq. 1.

In vivo pharmacokinetic study in rats

BUS is a probe substrate for human CYP3A4[26,27] and rat CYP3A.[28,29] Therefore, BUS was selected for the present *in vivo* rat pharmacokinetic study. The plasma concentration–time profiles of BUS after a single intravenous administration of 10 mg/kg with or without 200-mg/kg oral CUR in rats are shown in Figure 4, and relevant pharmacokinetic parameters are listed in Table 1. The plasma concentrations of BUS declined in a multi-exponential manner with a $t_{1/2}$ of 52.0–82.7 min in both rat groups [Figure 4]. Compared with control rats, the AUC, CL, V_{ss}, MRT, and $t_{1/2}$ were not changed significantly in rats with the concurrent administration of oral CUR [Table 1].

Table 1: Pharmacokinetic parameters of BUS after its single intravenous injection at a dose of 10 mg/kg without or with a single 200-mg/kg oral CUR in rats (n=3-4)

Parameter	Control	+ CUR
AUC (μg min/mL)	224±21	208±40
CL (mL/min/kg)	44.9±4.0	49.2±8.5
V_{ss} (×10 mL/kg)	268±53	302±37
MRT (min)	59.3±6.7	63.3±16.4
$t_{1/2}$ (min)	62.5±10.2	65.5±15.7

BUS: Buspirone; CUR: Curcumin; AUC: Total area under the plasma concentration-time curve from time zero to time infinity; CL: Time-averaged total body clearance; V_{ss}: Apparent volume of distribution at steady state; MRT: Mean residence time; $t_{1/2}$: Terminal half-life

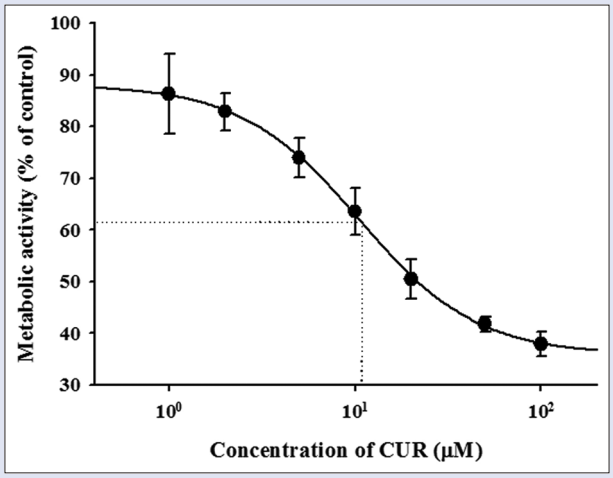

Figure 3: Dose–response curve for the inhibitory effect of curcumin on the disappearance of testosterone in rat liver microsomes (n = 4)

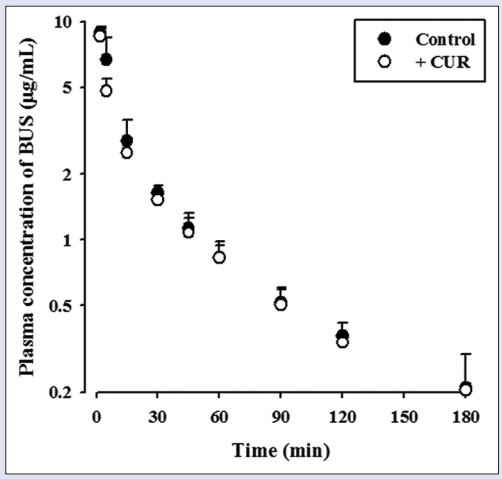

Figure 4: Plasma concentration–time profiles of buspirone after its single intravenous injection at a dose of 10 mg/kg without (●) or with (○) a single 200-mg/kg oral curcumin in rats (n = 3–4)

DISCUSSION

The inhibitory effect of CUR on CYP activity was evaluated by measuring the disappearance rate of specific CYP isoform-selective substrates in the presence of 10-μM CUR. As shown in Figure 2, the disappearance rate of TES was significantly reduced, while those of PHE and DEX were not significantly changed in the presence of CUR. This result and the IC_{50} value of CUR indicate that CUR can inhibit *in vitro* CYP3A activity in RLM, which is consistent with a previous study using HLM.[18] Generally, in the case that a dose–response curve is incomplete and does not reach a bottom plateau, the curve fitting program that used GraphPad Prism (GraphPad Software USA, Inc), tends to estimate unrealistically low bottom plateau (e.g., below zero) and high IC_{50} values (e.g., over thousands or millions). In this study, however, we confirmed that the curve fitting program estimated relatively realistic bottom plateau (33.8% ± 6.3%) and IC_{50} (11.0 ± 3.3 μM) values from the dose-response curve shown in Figure 3.

To investigate the inhibitory effect of CUR on *in vivo* hepatic CYP3A-mediated metabolism, the pharmacokinetics of intravenous BUS with or without the concurrent administration of oral CUR was evaluated in the rat model. The oral dose of CUR was selected based on previous rat pharmacokinetic studies (50–500 mg/kg),[17,30] and the intravenous dose of BUS was selected based on our previous study.[21] BUS is an anxiolytic psychotropic drug of the azapirone chemical class, which functions as a serotonin 5-HT1A receptor partial agonist.[31] It is primarily used for the treatment of generalized anxiety disorder and the short-term relief of the symptoms of anxiety.[32] Since BUS is eliminated primarily *via* hepatic metabolism in rats and humans, the CL listed in Table 1 could represent the hepatic clearance (CL_H) of BUS. Depending on the hepatic extraction ratio (HER) of a drug, the CL_H of the drug can be determined by the following factors; hepatic blood flow rate, unbound fraction of drug in blood, and/or hepatic intrinsic clearance ($CL_{int,\ H}$).[20] The results of the *in vitro* CYP inhibition study using RLM [Figure 2] suggest that 10-μM CUR may reduce the $CL_{int,\ H}$ of CYP3A substrates including BUS in rats. However, the AUC and CL of BUS were not significantly changed by the concurrent administration of oral CUR, suggesting no significant change of the CL_H of BUS. The exact reason for this discrepancy between CL_{int} and CL (CL_H) is not clear, because the HER of BUS in rats is currently unknown, which requires further investigation.

A previous study, reported that the C_{max} value of CUR after its oral administration at a dose of 500 mg/kg in rats was approximately 0.163 μM,[17] which is far below the IC_{50} value obtained from the present RLM study. Moreover, in another rat study, a high dose of CUR mixed into the diet (approximately 1200 mg/kg) for 14 days yielded, low-nanomolar CUR levels in the plasma, with CUR concentrations in the liver and colon mucosa ranging from 0.1 to 1.8 nmol/g tissue.[33] Thus, although the liver-to-plasma concentration ratio of CUR is unknown, it is plausible that the oral CUR dose used (200 mg/kg) may be insufficient to achieve plasma and liver concentrations above the IC_{50} of CUR in rats. Considering that the oral CUR dose used in the present study is higher than its clinically relevant doses (3600–8000 mg/day), the impact of a single oral CUR on the pharmacokinetics of CYP3A substrate drugs could be limited in the clinical setting.

CONCLUSION

The present study demonstrates that CUR can inhibit the *in vitro* CYP3A-mediated metabolism of TES in RLM. However, the impact of a single oral CUR dose on the pharmacokinetics of BUS in rats is limited, showing that CUR cannot function as an inhibitor for CYP3A-mediated drug metabolism *in vivo*. To the best of our knowledge, our results are the first reported data regarding the inhibition of *in vitro* CYP3A-mediated metabolism of TES and the *in vivo* impact of a single CUR dose on the pharmacokinetics of BUS in rats. Further study is required to draw a confirmative conclusion on whether CUR can be a clinically relevant CYP3A4 inhibitor.

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Conflicts of interest

There are no conflicts of interest.

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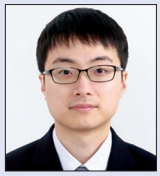

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