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Research Article
Influences of Ferulic Acid on Pharmacokinetics of Carbamazepine in Rats: Possible Mechanism of Herb/food-drug Interactions

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Abstract

Background and Objective: Carbamazepine (CBZ), an antiepileptic drug, possesses pharmacokinetic properties that make it susceptible to interaction with co-administered ingredients, such as dietary and herbal supplements and drugs. Ferulic acid (FA) possesses anti-epileptogenic, antidepressant and antioxidant activity and is used as adjuvant therapy for epilepsy. In this study, we evaluated the effects of concomitant administration of FA on CBZ pharmacokinetics and explored a possible interaction mechanism. **Materials and Methods:** Rats received a single CBZ dose (80 mg kg^{-1} orally [p.o.]) with and without pretreatment with FA (40 mg kg^{-1} p.o. every day for 7 days). Plasma CBZ levels were determined using a reversed-phase-high performance liquid chromatography bioassay. Pharmacokinetic parameters were estimated using non-compartmental analysis. **Results:** Following pretreatment with FA, CBZ exhibited increases in area under concentration-time curve (AUC_{0-t}) (100.32%), half-life ($T_{1/2}$) (212%) and mean residence time (MRT) (180%) compared with the group treated with CBZ alone ($p<0.05$). In contrast, the elimination constant (Kel), volume of distribution (Vz) and clearance (CL/F) values decreased by 69.23, 7.54 and 65.60%, respectively. The enhanced bioavailability of CBZ was accompanied by down regulated expression of cytochrome (CYP) 3A2, CYP2C11 and permeability-glycoprotein 1 (P-gp 1) (also known as multidrug resistance 1 [MDR1]) at the protein level in hepatic and intestinal tissues and increased intestinal absorption. **Conclusion:** The study findings indicate that metabolic inhibition of CYP450 and P-gP (MDR1) leads to a reduced rate of CBZ elimination and interactions with FA in the intestine. Therefore, patients who receive concomitant administration of FA and CBZ should be monitored carefully.

Key words: Carbamazepine, CYP450, ferulic acid, pharmacokinetics, herb drug interaction, anti-epileptic drug, psychiatric disorders

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Carbamazepine (CBZ), a tricyclic molecule (dibenzazepine), is a drug choice for the management of epilepsy, psychiatric disorders, bipolar disorders and trigeminal neuralgia[1]. Despite extensive clinical use, CBZ is predisposed to interaction with co-administered agents, such as drugs, phytoconstituents and other dietary components[2]. CBZ is a narrow therapeutic index drug commonly used in prolonged antiepileptic therapy and monitoring of the drug concentration is necessary to reduce CBZ-induced toxicity[3]. Serious toxic effects reported for CBZ include toxic epidermal necrolysis, Stevens-Johnson syndrome and hepatic toxicity[4,5]. People may be unaware of the possibility of herb-drug interactions and, since many do not use herbs as for medical purposes, they do not report use to their clinician[6].

Ferulic acid (FA), an omnipresent phenolic phytoconstituent of plants, exists in free form and coupled with glycoprotein, polysaccharides, polyamines, hydroxy fatty acids and lignin. FA has anti-cancer and vasodilatation effect along with modulation of transcriptional factors and biological pathways. FA is a key phytoconstituent of various herbs with "activation of the blood circulation" effects and widely employed in traditional medicine. It possesses a wide range of pharmacological activities such as antioxidant, anti-inflammatory and antimicrobial[7-12]. The CBZ completely metabolized in the liver of humans and animals[13]. In humans, this process is catalyzed by hepatic (85%) and intestinal (5%) CYP3A4 and CYP2C9 and, in rats, by the orthologous isoforms[4,14] CYP3A2 and CYP 2C11. The CBZ stimulates the expression of auto induction genes CYP3A4 and CYP2B6 via NR1I2 (PXR) and NR1I3 (CAR)[15-17] Drug-drug interactions[18] via CYP3A4, CYP2B6[19] and CYP2C9[20] have been widely reported and can restrict the use of combination therapy.

Herbal dietary supplements or herbs might interact with CBZ pharmacodynamically and/or pharmacokinetically, prompting caution in the clinical application of this drug[3]. The daily consumption of FA is estimated at approximately 500-1,000 mg in humans, with vegetables, cereal bran, fruits, beer and coffee as sources[21]. Monocarboxylic acid transporters are implicated in the absorption of free phenolic acids from the gastrointestinal mucosa. The therapeutic dose of oral FA is in the range of 20-40 mg kg^{-1} (body weight) in rats[22]. The use of phytomedicines or phytosupplements has gained increasing popularity; thus, with the increasing prevalence of people be treated with CBZ in combination with dietary and herbal supplements, reports of safety concerns associated with concomitant use are now obligatory[23,24]. There are no previous reports about the possible pharmacokinetic interactions between FA and CBZ and FA supplementation for management of depression, antithrombotic, antidiabetic, hypolipidemic and anti-epileptogenic therapy[25,26] may be taken simultaneously with CBZ in some clinical conditions. Thus, in this study, we investigated the impact of FA on the pharmacokinetics of CBZ and assessed the potential mechanism of interactions between FA and CBZ.

MATERIAL AND METHODS

Drugs and chemicals: Omeprazole (IS), FA and CBZ were obtained from Sigma-Aldrich (St Louis, MO, USA). Methanol and acetonitrile were acquired from PanReac Chemicals (Barcelona, Spain).

Animals: Total of 24 Wistar rats (200-226 g) were acquired from the Central Animal House, Collage of Pharmacy, King Saud University (Riyadh, Saudi Arabia) and were maintained in 4 cages (6 rats per cage) under a 12 h light/dark cycle (24±2°C) in accordance with the animal ethics guidelines at Department of Pharmaceutics, College of Pharmacy, King Saud University (Riyadh, Saudi Arabia) in month of October, 2018. The rats were provided with food (standard pellet diet) and water *ad libitum* and acclimated to their surroundings for 1 week before the study.

Pharmacokinetic studies: The rats were fasted for approximately 12 h prior to the study but allowed free access to water. The rats were allocated to the following groups (n = 6/group): Group 1 was administered normal saline (Normal control), Group 2 was administered normal saline orally for 6 days and on day 7 CBZ (80 mg kg^{-1}) was administered orally (CBZ alone), Group 3 was orally pretreated with FA (40 mg kg^{-1}) for 7 successive days and on day 7 CBZ (80 mg kg^{-1}) was administered 1 h after FA dosing (CBZ+FA) and Group 4 was orally treated with FA (40 mg kg^{-1}) for 7 successive days (FA alone). Blood samples were obtained from the retro-orbital plexus in heparinized tubes at various time-points. Plasma was separated by centrifugation (3,000×g for 10 min) and was transferred to tubes (1.5 mL) for subsequent analysis of CBZ levels by RP-HPLC. At the end of the study, animals were euthanized by using ether anesthetic overdose and liver tissues were excised for proteins expression analysis.

RP-HPLC bioassay: Plasma CBZ levels were evaluated using a validated RP-HPLC analytical process previously reported by Alkharfy *et al.*[27]. Briefly, the mobile phase consisting of (methanol:potassium dihydrogen phosphate buffer (20 mM): acetonitrile in a volumetric ratio of 65:33:2) was passed through a 0.45 µm filter and sonicated before use. The CBZ was assayed at a λ_{max} = 254 nm using a flow rate of 0.8 mL min^{-1}. The HPLC quantification and identification were carried out at room temperature (25±1°C). A Symmetry® C18 (5 µm, 3.9×150 mm) column was used to elude the CBZ at a λ_{max} = 254 nm. The CBZ quantification was carried out by determining the peak area relative to that of omeprazole as the internal standard using Lab Solutions32 version 3.05 (Shimadzu, Japan).

Pharmacokinetic analysis: The non-compartmental pharmacokinetic estimates were obtained using PK Solver (version 1.0). The following parameters were calculated: Maximum plasma concentration (C_{max}), area under plasma concentration-time curve (AUC), total clearance (CL), mean residence time (MRT), terminal elimination rate constant (λz), volume of distribution (Vz), time to maximum concentration (T_{max}) and apparent elimination half-life ($T_{1/2}$)[28].

Analysis of CYP3A2, CYP2C11 and MDR1expression: Total protein levels of liver tissues were assessed using the Lowry method[29]. Protein expression of CYP3A2, CYP2C11 and MDR1proteins in liver and intestinal tissues was evaluated by immunoblot analysis according to the method described by Towbin *et al.*[30]. A detailed and comprehensive description of the methods used for this analysis has been published previously[31].

Statistical analysis: Data were presented as arithmetic means±standard error (SEM). Statistical significance was determined by one-way analysis of variance followed by Dennett's test. The $p<0.05$ was considered to indicate statistical significance.

RESULTS

Influence of FA on the pharmacokinetics of CBZ: The pharmacokinetic parameters of CBZ with and without FA pretreatment are shown in Fig. 1 and Table 1. The C_{max} of orally administered CBZ in rats was 5.24±0.14 mg mL^{-1}, with T_{max} at 2 h, however, in animals pretreated for 7days with FA, C_{max} of CBZ increased to 8.03±0.24 mg mL^{-1}, with the T_{max} remaining at approximately 2 h. Pretreatment with FA significantly increased the CBZ AUC_{0-t} (100.32%), $T_{1/2}$ (212%) and MRT (180%) compared with the values in the CBZ group ($p<0.05$). In contrast, the elimination constant (Kel), volume of distribution (Vz) and clearance (CL/F) values decreased by 69.23, 7.54 and 65.60%, respectively.

Influence of FA on CYP3A2 and CYP2C11 protein expression in hepatic intestinal tissues: The CBZ is potent inducer of CYP3A2 and CYP2C11, therefore, we hypothesized that these changes in the pharmacokinetics of CBZ following FA pretreatment were due to inhibition of CYP3A2 and CYP2C11 protein expression. As illustrated in Fig. 2a and b, hepatic expression of CYP3A2 and CYP2C11 proteins was significantly increased (3.55- and 2.75-fold, respectively) in the CBZ group compared with the levels detected in the normal control group ($p<0.05$). The FA treatment alone significantly inhibited (0.71- and 0.37-fold, respectively) the expression of CYP3A2 and CYP2C11 at the protein level compared to the levels detected in the normal control group ($p<0.05$). In the CBZ+FA group, protein expression of CYP3A2 and CYP2C11 was significantly decreased (1.75- and 1.12-fold, respectively) compared to that in the CBZ group ($p<0.05$). As shown in Fig. 2c and d, intestinal protein expression of CYP3A2 and CYP2C11 was significantly higher (2.5-and 1.87-fold, respectively) in the CBZ group compared to that in the normal control group ($p<0.05$). The FA treatment alone significantly inhibited (0.65- and 0.48-fold) intestinal protein expression of CYP3A2 and CYP2C11 compared to that in the normal control group ($p<0.05$). In the CBZ+FA group, intestinal protein

Table 1: Pharmacokinetic parameters of CBZ administered orally with and without and FA pretreatment in rats

Parameters	CBZ (Mean±SEM)	CBZ+FA (Mean±SEM)	Change (%)
Kel (1/h)	0.13±0.00	0.04±0.00	69.23
$T_{1/2}$ (h)	5.27±0.17	16.45±0.00	-212.14
T_{max} (h)	2.00±0.00	2.00±0.00	0.00
C_{max} (µg mL^{-1})	5.24±0.14	8.03±0.24	-53.24
AUC_{0-t} (µg mL^{-1}×h)	39.87±0.89	79.87±2.42	-100.32
$AUMC_{0-inf}$_obs (µg mL^{-1}×h^2)	346.13±22.15	2823.56±85.68	-715.75
MRT_{0-inf}_obs (h)	8.12±0.27	22.78±0.00	-180.54
Vz/F_obs (mg kg^{-1})/(µg mL^{-1})	14.32±0.16	15.40±0.47	-7.54
CL/F_obs (mg kg^{-1})/(µg mL^{-1})/h	1.89±0.05	0.65±0.02	65.60

All values represent Mean±SEM, $p<0.05$ (Control), ANOVA, followed by paired test, negative sign (up regulation), positive sign (down regulation)

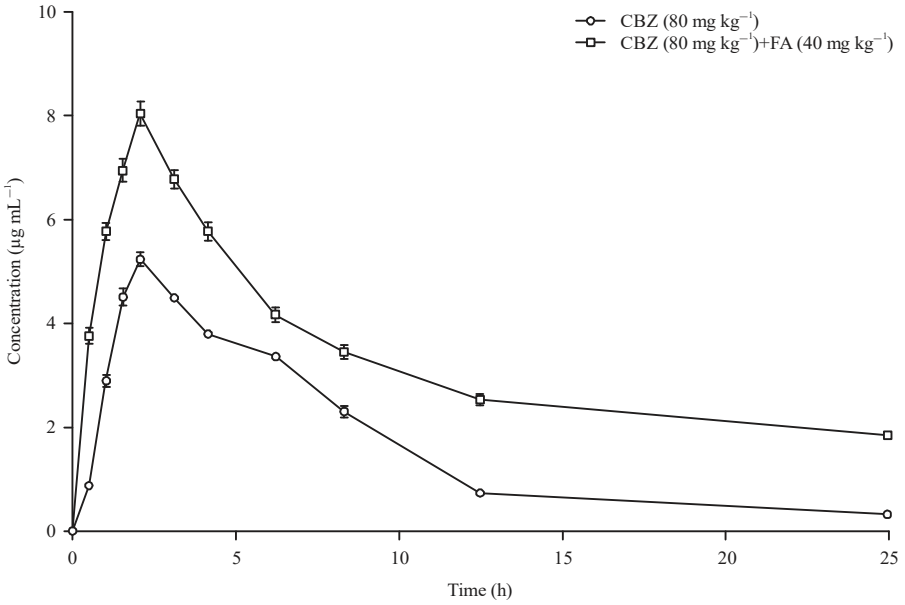

Fig. 1: A typical plasma concentration-time curve of CBZ (80 mg kg^{-1} p.o.) administered with/without FA (40 mg kg^{-1} p.o. for 7 days) in rats

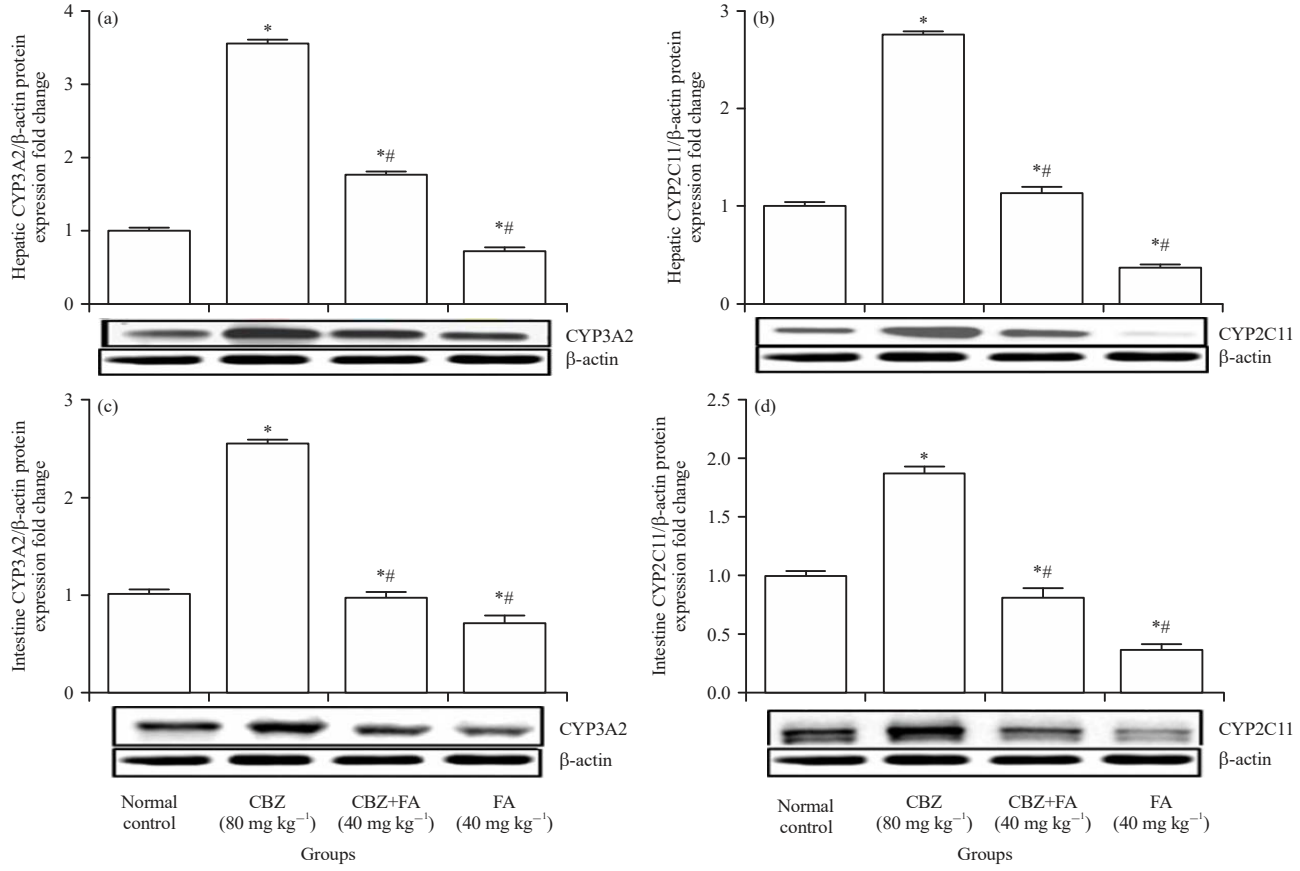

Fig. 2(a-d): (a-b) Expression of CYP3A2 and CYP2C11 proteins in rat liver following CBZ administration with/without FA pretreatment, (c-d) Expression of CYP3A2 and CYP2C11 proteins in rat intestine following CBZ administration with/without FA pretreatment

Data represent Mean±SEM, *p<0.05 (Control), #p<0.05 (CBZ), ANOVA, followed by Dunnett's multiple comparison test

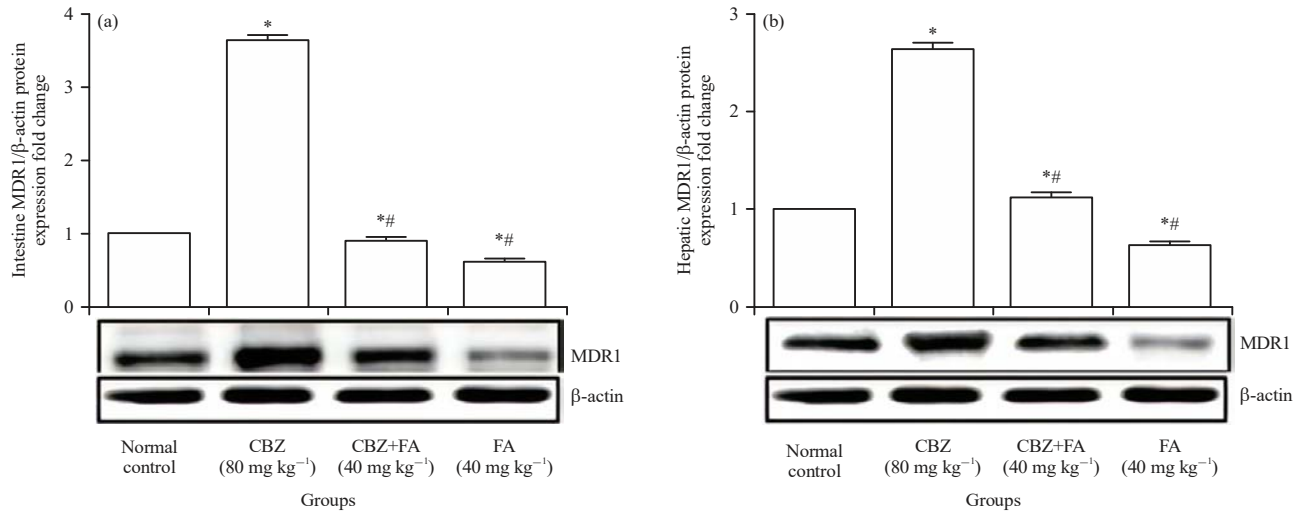

Fig. 3(a-b): (a) Expression of P-glycoprotein (MDR1) proteins in rat intestine and (b) Expression of P-glycoprotein (MDR1) proteins in rat liver following CBZ administration with/without FA pretreatment
Data represent Mean±SEM, *p<0.05 (Control), #p<0.05 (CBZ), ANOVA, followed by Dennett's multiple comparison test

expression of CYP3A2 and CYP2C11 was significantly decreased (0.97- and 0.82-fold, respectively) compared to that in the CBZ group (p<0.05).

Effect of FA on P-gp 1 (MDR1) protein expression in hepatic and intestinal tissues: To investigate the mechanisms underlying the influence of FA on the pharmacokinetics of CBZ, we investigated the effects of FA on P-gp 1 expression in hepatic and intestinal tissues (Fig. 3a, b). Compared with the normal control group, hepatic and intestinal expression of P-gp 1 (MDR1) was significantly reduced (0.74- and 0.61-fold, respectively) by treatment with FA alone (p<0.05). In contrast, hepatic and intestinal expression of P-gp 1 (MDR1) in the CBZ group was significantly increased (3.55- and 2.63-fold, respectively) compared with the normal control group. In the CBZ+FA group, hepatic and intestinal expression of P-gp 1 (MDR1) was significantly reduced (1.12- and 0.81-fold or 57.30 and 77.46% inhibition) compared to that in the CBZ group (p<0.05).

DISCUSSION

Parallel use of herbal dietary supplements might mimic, heighten, or decrease the pharmacological effect of drugs[32]. In this study, we investigated the impact of the common phytoconstituent FA on the pharmacokinetics of the antiepileptic drug CBZ in an animal model.

The pretreatment of rats with FA for seven days before administration of CBZ, significantly increased the C_{max} (53.24%), AUC_{0-t} (100.32%), $T_{1/2}$ (212%) and MRT (180%) of plasma CBZ compared with the values detected in the animals treated with CBZ alone (p<0.05). In contrast, the calculated Kel, Vz and CL/F values decreased by 69.23, 7.54 and 65.60%, respectively. This showed a reduction in the metabolism of CBZ following FA pretreatment in rats. The CBZ is primarily bio transformed in the liver to CBZ 10.11-epoxide (CBZ-E), with only small amounts (approximately 5%) of the drug eliminated unchanged[1,33].

The CBZ is potent inducer of CYP3A2, CYP2C11 and P-gp 1, which are involved in CBZ biotransformation in rats[4,14]. In this study, the enhanced bioavailability of CBZ in FA pretreated rats was accompanied by down regulated expression of cytochrome CYP3A2, CYP2C11 and permeability-glycoprotein 1 (P-gp 1) (also known as multidrug resistance 1 [MDR1]) at the protein level in hepatic and intestinal tissues. These observations are consistent with several other reports describing inhibition of CYP3A, CYP2C11 and P-gp 1 (MDR1) protein expression in intestinal and hepatic tissues. Thus, it can be speculated that the enhanced bioavailability CBZ may be due to FA-induced down regulation of CYP3A2, CYP 2C11 and MDR1 protein expression in hepatic and intestinal tissues and increased intestinal absorption. These effects are characteristic of metabolic inhibition and reduced elimination and indicate that CBZ is absorbed and interacts with FA occur in the intestinal mucosa. Hence, elevated oral absorption of CBZ co-administered with FA in rats might be the consequence of a of P-glycoprotein (MDR1) action. In accordance with our results, other studies have shown that FA induces P-gp1 (MDR1) expression in the intestinal and hepatic tissues in both CBZ treated and normal

animals[34,35]. The P-gp 1 (MDR1), which is an efflux pump located in the brush border of the intestine wall and hepatic parenchyma, transports several substrates including CYP3A4 and CYP2C9[36,37]. P-gp 1 and CYP3A4 and CYP2C11 inhibitors/blockers increase the absorption of CBZ in the intestine[38]. Furthermore, previous reports showed that FA inhibits P-gp1 (MDR1) both *in vitro* and *in vivo*[39,40].

The FA is a derivative of hydroxycinnamic acid phenolic acid present in cell walls, where it is conjugated to molecules, such as arabinoxylans[41]. Al-Jenoobi *et al*.[42] showed that Asafetida (FA is the principal constituent) has a significant potent inhibitory activity on CYP3A4 but minimal activity on CYP2D6 *in vitro* and *in vivo*. In accordance with these results, we showed FA pretreatment significantly attenuated the increased expression of CYP3A2 and CYP2C11 proteins in the intestinal and hepatic tissues of CBZ treated rats. CBZ is known to induce CYP3A4 and CYP2C11 protein expression[1,43] and is a substrate for CYP3A4 and CYP2C9 in humans and CYP3A2 and CYP2C11 in rats[1,44]. The biotransformation and metabolic clearance rates in rats are 10-fold higher than those in humans[45], therefore, we used a single dose of CBZ in this study[42,46,47].

CONCLUSION

The pharmacokinetic analysis indicates that FA pretreatment enhances the bioavailability of orally administered CBZ through enhanced intestinal absorption mediated by modulation of P-glycoprotein activity combined with a decreased rate of elimination and clearance due to inhibition of CYP3A2, CYP2C11 and MDR1 in hepatic and intestinal tissues. Therefore, patients who receive concomitant administration of FA and CBZ should be monitored carefully.

SIGNIFICANCE STATEMENT

This investigation shed light on the possible mechanism of herb/food-drug Interactions of carbamazepine with ferulic acid that can be beneficial for patients who receive concomitant administration of FA and CBZ which should be monitored carefully. This investigation will help the researchers to uncover the critical areas of herb food drug interaction of carbamazepine, a narrow therapeutic index drug.

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