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Effects of sinapic acid on hepatic cytochrome P450 3A2, 2C11, and intestinal P-glycoprotein on the pharmacokinetics of oral carbamazepine in rats: Potential food/herb-drug interaction

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ABSTRACT

Dietary supplements, herbal medicines, and other foods may affect the pharmacokinetics and/or pharmacodynamics of carbamazepine (CBZ), which may possibly lead to potential drug–drug/herb–drug interactions, as CBZ has a narrow therapeutic window. Sinapic acid (SA) is a bioactive phytoconstituent used as a dietary supplement for the treatment of epilepsy. This study determined the effects of SA on the pharmacokinetics of CBZ and proposed a possible interaction mechanism in twenty-four male wistar rats (180–210 g). A single CBZ dose (80 mg/kg) was administered orally to rats with or without SA pretreatment (20 mg/kg p.o. per day for 7 days, n = 6). The CBZ concentration in plasma samples was determined by using a sensitive reversed-phase high-performance liquid chromatography assay. The pharmacokinetic parameters were calculated by using non-compartmental analysis. Significance was determined through Dunnett's multiple comparison test or one-way analysis of variance as appropriate; $p < 0.05$ were considered significant. The change in the pharmacokinetic parameters (C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $T_{½}$, and k_{el}) of CBZ was evaluated after the administration of CBZ alone or after CBZ co-administration with SA pretreatment. The plasma concentration of CBZ was higher after SA pretreatment than that without pretreatment. The pharmacokinetics of orally administered CBZ were found to be significantly altered ($p < 0.05$) in rats pretreated with SA compared to those in rats administered CBZ alone. The increases in the C_{max}, AUC_{0-t}, $T_{1/2}$, and MRT of CBZ were 29.79%, 57.18%, 77.18%, and 58.31%, respectively, whereas the k_{el} and apparent oral CL/F were significantly reduced ($p < 0.05$) in rats pretreated with SA compared to those in rats not pretreated with SA (43.87% and 42.50%, respectively). However, no significant change was observed in the T_{max} of CBZ in rats pretreated with SA compared to that in rats that did not receive pretreatment. The enhancement in Cmax, AUC_{0-t}, $T_{1/2}$, and MRT and the reduction in K_{el} and CL/F values resulted from the significant inhibition of CYP3 A2, the CYP2C11-mediated metabolism of CBZ in the liver, and the inhibition of intestinal P-glycoprotein/MDR1, which enhanced the rate of CBZ absorption. Further studies are required to determine the clinical relevance of these observations.

1. Introduction

Epilepsy is a predominant neural illness regarded as episodic seizures. The anti-epileptic drug Carbamazepine (CBZ) is prescribed worldwide and has been recognized as effective for the management of epileptic seizures, convulsion, neuralgia of trigeminal nerves and manic-depressive illness (Bielen et al., 2009; Hsieh and Huang, 2009; Moran et al., 2004) (Grzesiak et al., 2003; Okuma and Kishimoto, 1998;

Abbreviations: CBZ, carbamazepine; SA, sinapic acid; p.o, per oral; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; IS, internal standard; AUC, area under concentration time curve; AUMC, area under the moment curve; MRT, mean residence time; Vd, volume of distribution; CL, total clearance; kel, elimination rate constant; T1/2, half-life; Cmax, maximum concentration; Tmax, time to maximum concentration; P-gp, P-glycoprotein; MDR, multiple drug resistance protein; SEM, standard error of mean; CYP, cytochrome P450 protein; HPLC, high performance liquid chromatography

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Tolou-Ghamari et al., 2013). The commonly used oral maintenance dose range of CBZ for the treatment of epilepsy and Trigeminal Neuralgia is 10.66–16 mg/kg (800–1200 mg daily for human average weight 75 kg) (Alkharfy et al., 2013; Raish et al., 2017). In addition to its clinical reputation, CBZ has some pharmacokinetic characteristics that subject to interaction with drugs, herbs, supplements, and diet (Ketter et al., 1991a). CBZ is potent inducer of various drug metabolizing enzymes, such as CYP450 3 A and 2B in the liver (Roujeau et al., 1995). P-glycoprotein (Pgp) and multidrug resistance-associated protein 2 (MRP-2) are efflux pumps and thought to be linked with the metabolism of CBZ (Hudson et al., 2000). CYP3 A biotransforms CBZ into CBZ-10,11-epoxide, 3-hydroxy CBZ, and its intermediate catabolic product in vitro (Sullivan and McElhatton, 1977). CBZE has anticonvulsant activity and may cause hepatotoxicity upon accumulation in the liver (Owen et al., 2006). The prolonged use of CBZ can lead to liver injuries commonly demonstrated by the elevation in Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT), which result from the induction of CYP450 enzymes. CBZ-induced hepatotoxicity has two forms: hypersensitive granulomatous hepatitis and an acute hepatitis (Raish et al., 2017). In patients with epilepsy that require long-term therapy, clinicians should administer hepatoprotective dietary supplements.

Sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid; SA) occurs in free and ester forms as glycosides or esters of several organic moieties. Two common sinapoyl esters are found in leaves, and sinapine (sinapoyl choline) occurs in roots (Chapple et al., 1992; Tzagoloff, 1963). SA is a dietary supplement with good oral bioavailability, present in spices, fruits, vegetables, cereals, and vegetables of the Brassicaceae family (Chen, 2016). It is recognized to have potent therapeutic effects, including antioxidant, hepatoprotective, antimutagenic, anti-inflammatory, anticancer, antihyperglycemic, neuroprotective, and antibacterial activities (Chen, 2016). Several studies have demonstrated the antioxidant, anti-inflammatory, and hepatoprotective effects of SA (Kikuzaki et al., 2002; Zou et al., 2002). This may lead to potential drug–drug/herb–drug interactions owing to the narrow therapeutic window of CBZ. Phenolic acids are known for antioxidant, antidepressant, anti-epileptic and anti-inflammatory activity (Szwajgier et al., 2017). SA, a phenolic acid abundantly present in human foods such as berries (Mattila et al., 2006), citrus fruits, nuts (Grosso and Estruch, 2016), coffee and tea (Crozier et al., 2009) and whole grains (Van Hung, 2016) and in tradition herbs rich in sinapic acid used as sedative, anticonvulsant, antidepressant and antiepileptic (*Brassica juncea*, *Brassica Chinensis*, *Brassica Nigra*, *Brassica oleracea*, *Anacyclus pyrethrum*, *Ipomoea reniformis*, *Viscum album*, *Zea mays)* (Gupta et al., 2012; Okomolo et al., 2011; von Schoen-Angerer et al., 2015; Zou et al., 2002). CBZ interactions with co-administered food, herbal medicines are commonly pharmacokinetic in nature may lead alteration in absorption, distribution, metabolism and elimination. CBZ is a potent enzyme inducer and is a subject to auto-induction. The consumption of SA containing food or traditional herbal medicine unknowingly along with prescribe narrow therapeutic index drug CBZ. Therefore, it is mandatory to study the safety concerns of such concomitant usage (Chen et al., 2000; Liow et al., 2007). Possible pharmacokinetic SA-CBZ interactions are still uninvestigated and to resolve the probable interaction mechanism.

2. Experimental

2.1. Materials

Omeprazole, SA and CBZ, were obtained from Sigma-Aldrich (USA). Acetonitrile and methanol (HPLC grade) were acquired from BDH, Pool, (UK) and potassium phosphate monobasic was acquired from Win Lab Ltd (UK). Anti-CYP3 A2 (LS-C36108), anti-CYP2C11 (LS-C86039), anti-Pgp (LS-B1448), and anti-β-actin (LS-C147034) antibodies were purchased from LifeSpan Biosciences, Inc. (USA).

2.2. Animals and pharmacokinetic studies

Male wistar rats (180–210 g) were acquired from the Central Animal House Facility of the College of Pharmacy, King Saud University (Riyadh, Saudi Arabia) and maintained in plastic animal cages; six animals were housed per cage with a 12-h light/dark cycle, at 25 °C ± 2 °C, in accordance with the animal facilities guidelines. The rats were allocated into four groups (total 24 rats; 6 rats in each group) and fasted for 12 h prior to the study. Rats in group I (Vehicle control) were orally administered normal saline for 6 days. The rats in Group II were orally administered normal saline for six days and CBZ (80 mg/kg) on day 7. The rats in group III were co-administered CBZ with SA, SA (20 mg/kg) for 7d and CBZ (80 mg/kg *po*) on day 7, 2 h after SA administration. The rats in group IV were orally administered SA (20 mg/kg) for 7 days continuously. All groups were fasted overnight prior to study, but were provided free access to water.

Blood (0.5 ml) was procured from the left eye retro-orbital plexus in heparinized tubes at chosen time intervals (0, 0.5, 1, 1.5, 2, 3, 4, 6, 12, and 24 h) after CBZ administration. Blood was subjected to centrifugation at 3000 ×g for 10 min to get plasma and transferred to 1.5 ml tubes for following HPLC analysis of CBZ. Lastly, the rats were decapitated and samples of the liver and intestine tissue were removed for western blotting.

2.3. CBZ HPLC analysis

The CBZ analyses in plasma were estimated by previously establish HPLC method (Alkharfy et al., 2013; Raish et al., 2017). Concisely, the Shimadzu HPLC system (Shimadzu, Kyoto, Japan) equipped with a SIL 20 A with model LC 20 AD dual piston pump, an auto-sampler, dual UV detector model SPD 20 A. The mobile phase comprised a (methanol: acetonitrile: potassium phosphate buffer (20 mM) in a 65:2:33 (*v/v/v*) ratio, which was filtered through a 0.45-μm filter. CBZ was quantified at a γ 285 nm at 25 °C ± 1 °C. A Symmetry® C18 (5 μm, 3.9 × 150 mm) column was employed to separate the CBZ with a λ_{max} = 285 nm. Analysis of the signal output was conducted by using Lab Solutions32 software, version 3.05 (Shimadzu, Tokyo, Japan). The limit of quantification of CBZ was found to be 0.5 μg/mL.

2.4. Pharmacokinetic analysis

Non-compartmental model of pharmacokinetic variables was executed by using PK Solver software (version 1.0). The calculated variables were as follows: The area under concentration time curve (AUC), the area under the moment curve (AUMC); the mean residence time (MRT), the volume of distribution (Vd), the total clearance (CL), the elimination rate constant (k_{el}), the half-life ($T_{1/2}$), the maximum concentration (Cmax) and time to maximum concentration (Tmax) were determined.

2.5. Protein expression analysis

Western blotting was performed by using a previously described method (Towbin et al., 1979), with minor modifications, to measure the effect of sinapic acid on the hepatic CYP3 A2 and CYP2C11 isoenzymes and intestinal P-glycoprotein/MDR1 protein expression (Raish et al., 2017).

2.6. Statistical analysis

All data are expressed as the mean ± standard error of mean (SEM). The significance was determined through the application of Dunnett's multiple comparison test or one-way analysis of variance as appropriate; $p < 0.05$ were considered significant.

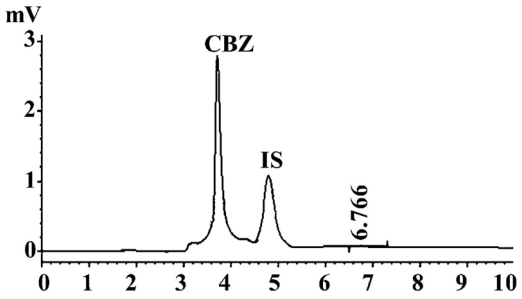

Fig. 1. HPLC Chromatograms showing separation of carbamazepine (CBZ) and internal standard (IS) extracted from rat plasma.

Table 1
Pharmacokinetic variables of CBZ (80 mg/kg) administration with or without SA (20 mg/kg) in rats (mean ± SEM; n = 6 in each group).

Parameter (n = 6)	CBZ (80 mg/kg)	CBZ + SA (20 mg/kg)	% Change	*p* value
k_{el} (1/h)	0.16 ± 0.02	0.09 ± 0.004	43.877	0.0012
$T_{1/2}$ (h)	4.33 ± 0.42	7.67 ± 0.380	−77.18	0.0007
Tmax (h)	2.00 ± 0.00	2.00 ± 0.000	0	–
Cmax (μg/mL)	4.94 ± 0.37	6.40 ± 0.109	−29.79	0.0065
$AUC_{0\text{-}t}$ (μg/mL•h)	34.51 ± 3.11	54.24 ± 1.193	−57.18	0.0001
$AUC_{0\text{-}\infty}$ (μg/mL•h)	35.60 ± 3.57	61.447 ± 1.559	−72.58	0.0001
$AUMC_{0\text{-}\infty}$ (μg/mL•h^2)	243.23 ± 43.87	660.41 ± 31.65	−171.5	0.0002
$MRT_{0\text{-}\infty}$ (h)	6.79 ± 0.57	10.74 ± 0.295	−58.31	0.001
Vd ((mg/kg)/(μg/mL))	14.05 ± 0.19	14.41 ± 0.438	−2.584	0.1823
CL ((mg/kg)/(μg/mL)/h)	2.27 ± 0.23	1.30 ± 0.033*	42.506	0.0005

Area under concentration time curve (AUC); Area under the moment curve (AUMC); Mean residence time (MRT), Volume of distribution (Vd); Total clearance (CL); Elimination rate constant (k_{el}), Half-life (T1/2); Maximum concentration (Cmax); Time to maximum concentration (Tmax).

3. Results

The representative chromatograms (Fig. 1), and plasma concentration–time plots of CBZ (80 mg/kg) and SA (20 mg/kg) after oral administration in the rats are described and illustrated in Table 1 and Fig. 2. The changes in pharmacokinetic parameters (Cmax, Tmax, AUC0-t, AUC0-∞, T½, and Kel) of CBZ were determined with and without SA pretreatment. The plasma concentrations of CBZ were higher after SA pretreatment than without pretreatment. The pharmacokinetics of orally administered CBZ were found to be significantly altered ($p < 0.05$) in rats pretreated with sinapic acid compared to those in rats that did not receive pretreatment. The increases in C_{max}, AUC_{0-t}, $t_{1/2}$, and MRT of CBZ were 29.79%, 57.18%, 77.18%, and 58.31%, respectively, whereas the k_{el} and apparent oral CL were significantly reduced ($p < 0.05$) in rats pretreated with SA compared to those in rats not pretreated (43.87% and 42.50%, respectively). However, no significant change was observed in the T_{max} of CBZ in rats pretreated with SA compared to that in rats not pretreated with SA. The enhancement in Cmax, AUC_{0-t}, $T_{1/2}$, and MRT and the reduction in k_{el} and CL resulted from the significant inhibition of CYP3 A2, CYP2C11-mediated metabolism of CBZ in the liver, and the inhibition of intestinal Pgp/MDR1, which enhanced the absorption rate of CBZ.

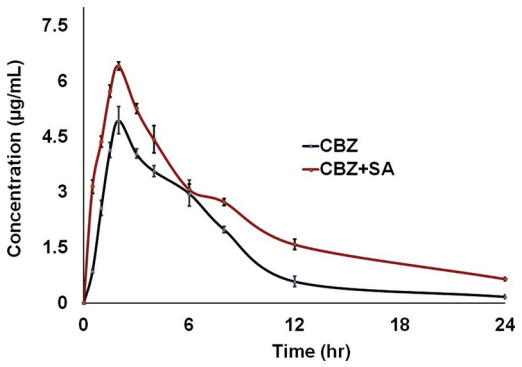

Fig. 2. A representative mean plasma concentration-time curve of carbamazepine (CBZ) (80 mg/kg p.o.) administered with/without sinapic acid (SA) (20 mg/kg p.o. for seven days) in rats (n = 6).

We assessed the status of CYP3 A and CYP2C11 by quantifying the hepatic protein expression of CYP3 A2 and CYP2C11 in rats pretreated with SA and the normal control rats. Hepatic protein expression of CYP3 A and CYP2C11 was significantly upregulated in CBZ administered rats (3.2- and 2.4-fold, respectively) ($p < 0.05$). The SA pretreatment (20 mg/kg) significantly downregulated the hepatic expression of CYP3 A and CYP2C11 in the CBZ-treated groups and SA-alone treated group by approximately 46.87%; we only analyzed CYP3 A and CYP2C11 expression in the liver tissue as 95% CBZ is metabolized in the liver, only 5% of the drug eliminated unaltered (Fig. 3).

The inhibitory mechanisms of SA on P-gp function have been studied and illustrated in Fig. 4 have been suggested. Intestinal MDR1 protein expression was markedly reduced after SA pretreatment compared to that in normal rats. CBZ administration resulted in a significant induction in the intestinal protein expression of MDR1 compared to that in normal rats (1.8-fold or 80%, respectively) ($p < 0.05$). The SA-pretreated rats showed a significant inhibition of the CBZ-induced MDR1 protein that is (˜ 0.8 and 0.23 fold or 55.5% and 87.7% inhibition, respectively) as compare to CBZ alone ($p < 0.05$).

4. Discussion

The co-administration of herbal drugs may mimic, heighten, or decrease the pharmacological activity of drugs (Fugh-Berman and Ernst, 2001). CBZ has complex drug interaction potentials and is known to interact with a wide variety of herbs and drugs. Its narrow therapeutic window and potency as an inducer of CYP3 A, CYP2C11 (Raish et al., 2017), Pgp/MDR1 (Owen et al., 2006) make it imperative to monitor the drug concentrations to reduce the risk of side effects (Fong et al., 2013; Ketter et al., 1991b). Patients may often be ignorant of the probable herb/drug reactions and some do not contemplate herbal supplements as drugs. Thus, clinicians are unaware of concomitant use of herbal supplements, which may lead to potential toxicities (Tarirai et al., 2010), including epidermal necrolysis, teratogenic effects, and Stevens-Johnson syndrome (Roujeau et al., 1995; Sullivan and McElhatton, 1977). For patients with epilepsy who need long-term therapy, the clinician should administer hepatoprotective dietary supplements. In traditional Indian, Iranian and Chinese medicine several herbs viz, *Brassica juncea*, *Brassica Chinensis*, *Brassica Nigra*, *Brassica oleracea*, *Anacyclus pyrethrum*, *Ipomoea reniformis*, *Viscum album*, *Zea* mays have been used as antioxidant, antiepileptic and anxiolytic agent (Gupta et al., 2012; Okomolo et al., 2011; von Schoen-Angerer et al., 2015; Zou et al., 2002). In addition sinapic acid is integral part of human food in form of fruits (citrus and berries), nuts, coffee and tea, whole grains and vegetables (Crozier et al., 2009; Grosso and Estruch, 2016; Mattila et al., 2006; Van Hung, 2016).

The efficacy of SA has been established against several pathological illness such as oxidative stress (Kikuzaki et al., 2002), inflammation (Zou et al., 2002), diabetes (Hudson et al., 2000), neurodegeneration (Sun et al., 2007), and anxiety (Yoon et al., 2007). Furthermore, owing to its chemopreventive effects, SA is extensively used as a dietary supplement.

The co-administration of SA and prescribed medicine can potentially lead to significant pharmacokinetic herb–drug interactions. SA is an established anxiolytic agent in mice (Yoon et al., 2007). The commonly used oral dose for SA chemo preventive activity is 20 mg/kg b.w.

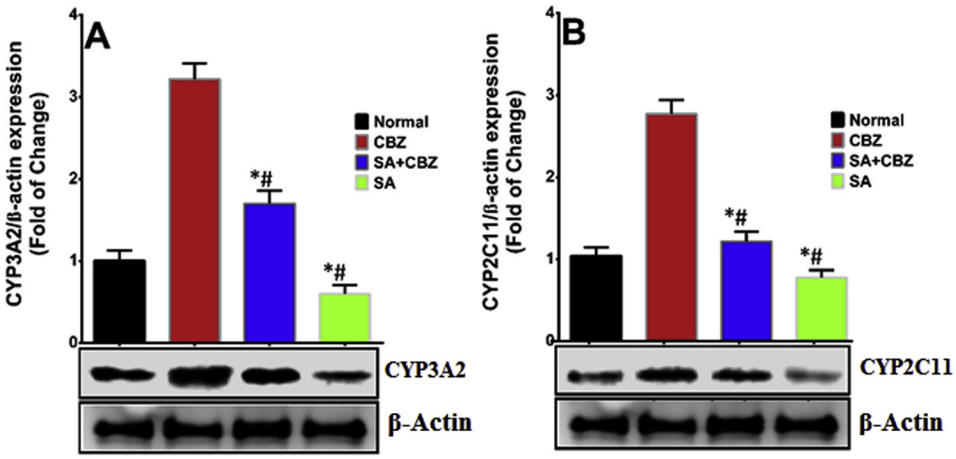

Fig. 3. Expression of hepatic CYP3 A2 and CYP2C11 protein expression in rats (n = 6) following carbamazepine (CBZ) (80 mg/kg p.o.) administration with/without sinapic acid (SA) (20 mg/kg p.o. for seven days' treatment in rats. All values represent mean ± SEM. *p < 0.05 (Control); #p < 0.05 (CBZ); ANOVA, followed by Dunnett's multiple comparison test.

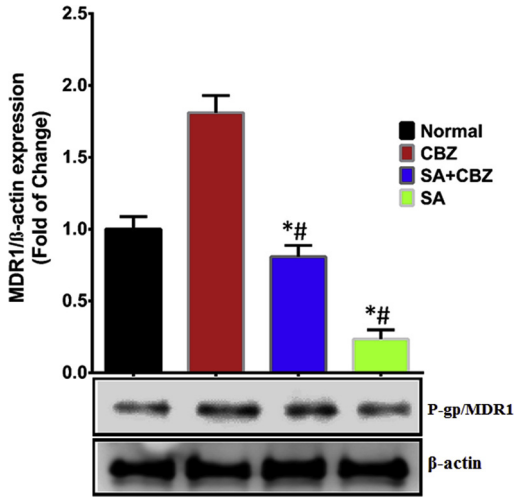

Fig. 4. Expression of Intestinal P-glycoprotein/MDR1 in rats (n = 6) following carbamazepine (CBZ) (80 mg/kg p.o.) administration with/without sinapic acid (SA) (20 mg/kg p.o. for seven days' treatment in rats. All values represent mean ± SEM. *p < 0.05 (Control); #p < 0.05 (CBZ); ANOVA, followed by Dunnett's multiple comparison test.

this is first report that explore the single dose SA and CBZ herb drug interaction in rats. CBZ primarily metabolized (95%) in the liver (Kim et al., 2005). Most of CBZ is metabolized into CBZ-E that is mostly catalyzed by CYP3 A4 and CYP2C9 in humans, CYP3 A2, and CYP2C11 in rats (Kerr et al., 1994; Pearce et al., 2008; Tateishi et al., 1999). The rate bioconversion of CBZ is markedly different from humans; as the rate clearance is 10-times higher in rats (Faigle, 1995; Hidaka et al., 2005). The enzymes CYP3 A4 and CYP2C9 are liable for first-pass metabolism and alteration in the drug distribution, absorption and metabolism of many oral administered medicines, including CBZ (Wilkinson 1996). Therefore, the current study design used 24-h experiments in rats.

The pharmacokinetics of the co-administration of CBZ and SA were analyzed. Pretreatment with SA at 20 mg/kg for 7 days induced significant augmentation of the C_{max}, AUC_{0-t}, $t_{1/2}$, and MRT of CBZ and reductions in k_{el} and the apparent oral CL/F compared with that after CBZ alone, which suggests that the administration of SA significantly increased the oral bioavailability of CBZ and may increase the anti-epileptic effect, most likely through the inhibition of CYP3 A4 and CYP2C9 in the liver and the inhibition of P-gp in the intestine. These results are similar to those of previous studies, where herbal supplementation with grapefruit, kinnow, pomegranate, and star fruit juice have been shown to have the ability to increase the C max and the AUC of CBZ owing to the inhibition of CYP3 A4 (Garg et al., 1998a, b; Hidaka et al., 2005, 2006). These results also corroborated our previous reports that *Paeonia emodi* inhibited CYP3 A and CYP2C11, and thereby enhanced the bioavailability of CBZ (Raish et al., 2017). The P-glycoprotein pump, which is present in the brush border of the intestinal wall, transports many substrates of CYP3 A4 and CYP2C9 and is known to be inhibited by polyphenols (Amin, 2013; Zhou et al., 2004). Dietary supplements such as thymoquinone, resveratrol, and diosmin are potent inhibitors of CYP3 A2 and CYP2C11 (Ahmad et al., 2015; Guthrie et al., 2017). To explain the possible mechanisms involved, we executed western blotting, which evidently revealed a significant inhibition of hepatic CYP3 A2 and CYP2C11 and intestinal Pgp protein expression in SA-pretreated rats. SA is a bioactive polyphenol that may have the ability to modulate CYP3 A and CYP2C11 in the liver and P-gp in the intestine; therefore, we evaluated CYP3 A and CYP2C11 expression in the liver and Pgp expression in the intestine. The expression data showed that CBZ significantly increased CYP3 A and CYP2C11 expression in the liver and Pgp expression in the intestine. The SA pretreatment significantly downregulated CYP3 A2 and CYP2C11 expression in the liver and Pgp expression in the intestine of rats co-administered CBZ and SA and SA alone compared to the expression in normal control. It is established that CBZ induces CYP3 A2, CYP2C11, and Pgp protein expression (Amin, 2013; Ohnishi et al., 1999; Pearce et al., 2008). This investigation has established that SA modulates the pharmacokinetics of CBZ through an increase in C_{max}, AUC_{0-t}, and $T_{1/2}$, and a decrease in CL. This result substantiates pharmacokinetic studies, where CBZ bioavailability increased by interactions with CYP3 A and CYP2C11 inhibitors (Garg et al., 1998b; Hidaka et al., 2005). The increase in intestinal absorption of CBZ with concomitant use of SA in rats due to inhibition of P-gp/MDR1 expression (Basheer and Kerem, 2015; Wang et al., 2002)

5. Conclusion

The present study demonstrated that the oral administration of SA (20 mg/kg) has the potential to change the CBZ pharmacokinetics through a significant decrease in the hepatic expression of CYP3 A2, CYP2C11 and intestinal expression of Pgp/MDR1. This was linked to an extensive decrease in CBZ-CL, an escalation in its AUC and $T_{1/2}$, and increased intestinal absorption owing to the inhibition of Pgp/MDR1. Therefore, the parallel consumption of SA containing food or traditional herb with CBZ should be employed with caution.

Conflict of interest

The authors declare that they have no conflicts of interest.

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References

Ahmad, A., Khan, R.M., Alkharfy, K.M., Raish, M., Al-Jenoobi, F.I., Al-Mohizea, A.M., 2015. Effects of thymoquinone on the pharmacokinetics and pharmacodynamics of glibenclamide in a rat model. Nat. Prod. Commun. 10, 1395–1398.

Alkharfy, K.M., Al-Jenoobi, F.I., Alam, M.A., Al-Mohizea, A.M., Al-Suwayeh, S.A., Korashy, H.M., Khan, R.M., Muzaffar, I., 2013. Lepidium sativum but not Nigella sativa affects carbamazepine disposition in an animal model. Drug Metab. Lett. 7, 47–51.

Amin, M.L., 2013. P-glycoprotein inhibition for optimal drug delivery. Drug Target Insights 7, 27–34.

Basheer, L., Kerem, Z., 2015. Interactions between CYP3A4 and dietary polyphenols. Oxid. Med. Cell. Longev 854015.

Bielen, I., Sruk, A., Planjar-Prvan, M., Cvitanovic-Sojat, L., Kosicek, M., Bergman-Markovic, B., Baraba, R., Butkovic-Soldo, S., 2009. Age-related pattern of the anti-epileptic drug utilization in active epilepsy: a population-based survey. Coll. Antropol. 33, 659–663.

Chapple, C.C., Vogt, T., Ellis, B.E., Somerville, C.R., 1992. An Arabidopsis mutant defective in the general phenylpropanoid pathway. Plant Cell 4, 1413–1424.

Chen, C., 2016. Sinapic acid and its derivatives as medicine in oxidative stress-induced diseases and aging. Oxid. Med. Cell. Longev., 3571614.

Chen, L.C., Chen, Y.F., Yang, L.L., Chou, M.H., Lin, M.F., 2000. Drug utilization pattern of antiepileptic drugs and traditional Chinese medicines in a general hospital in Taiwan - a pharmaco-epidemiologic study. J. Clin. Pharm. Ther. 25, 125–129.

Crozier, A., Jaganath, I.B., Clifford, M.N., 2009. Dietary phenolics: chemistry, bioavailability and effects on health. Nat. Prod. Rep. 26, 1001–1043.

Faigle, J., 1995. Carbamazepine: chemistry and biotransformation. Antiepileptic Drugs 499–513.

Fong, S.Y., Gao, Q., Zuo, Z., 2013. Interaction of carbamazepine with herbs, dietary supplements, and food: a systematic review. Evid. Complement. Alternat. Med 898261.

Fugh-Berman, A., Ernst, E., 2001. Herb-drug interactions: review and assessment of report reliability. Br. J. Clin. Pharmacol. 52, 587–595.

Garg, S., Bhargava, V., James, H., KuJan-Mar, N., Prabhakar, S., Naresh, K.-M., 1998a. Influence of kinnow juice on the bioavailability of carbamazepine in healthy male volunteers. Neurol. India 46, 229.

Garg, S.K., Kumar, N., Bhargava, V.K., Prabhakar, S.K., 1998b. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. Clin. Pharmacol. Ther. 64, 286–288.

Grosso, G., Estruch, R., 2016. Nut consumption and age-related disease. Maturitas 84, 11–16.

Grzesiak, A.L., Lang, M., Kim, K., Matzger, A.J., 2003. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J. Pharm. Sci. 92, 2260–2271.

Gupta, G., Kazmi, I., Afzal, M., Rahman, M., Saleem, S., Ashraf, M.S., Khusroo, M.J., Nazeer, K., Ahmed, S., Mujeeb, M., Ahmed, Z., Anwar, F., 2012. Sedative, anti-epileptic and antipsychotic effects of Viscum album L. (Loranthaceae) in mice and rats. J. Ethnopharmacol. 141, 810–816.

Guthrie, A.R., Chow, H.S., Martinez, J.A., 2017. Effects of resveratrol on drug- and carcinogen-metabolizing enzymes, implications for cancer prevention. Pharmacol. Res. Perspect. 5 e00294.

Hidaka, M., Okumura, M., Fujita, K., Ogikubo, T., Yamasaki, K., Iwakiri, T., Setoguchi, N., Arimori, K., 2005. Effects of pomegranate juice on human cytochrome p450 3A (CYP3A) and carbamazepine pharmacokinetics in rats. Drug Metab. Dispos. 33, 644–648.

Hidaka, M., Okumura, M., Ogikubo, T., Kai, H., Fujita, K., Iwakiri, T., Yamasaki, K., Setoguchi, N., Matsunaga, N., Arimori, K., 2006. Transient inhibition of cyp3a in rats by star fruit juice. Drug Metab. Dispos. 34, 343–345.

Hsieh, L.P., Huang, C.Y., 2009. Antiepileptic drug utilization in Taiwan: analysis of prescription using National Health Insurance database. Epilepsy Res. 84, 21–27.

Hudson, E.A., Dinh, P.A., Kokubun, T., Simmonds, M.S., Gescher, A., 2000. Characterization of potentially chemopreventive phenols in extracts of brown rice that inhibit the growth of human breast and colon cancer cells. Cancer Epidemiol. Biomarkers Prev. 9, 1163–1170.

Kerr, B.M., Thummel, K.E., Wurden, C.J., Klein, S.M., Kroetz, D.L., Gonzalez, F.J., Levy, R.H., 1994. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. Biochem. Pharmacol. 47, 1969–1979.

Ketter, T.A., Post, R.M., Worthington, K., 1991a. Principles of clinically important drug interactions with carbamazepine. Part I. J. Clin. Psychopharmacol. 11, 198–203.

Ketter, Ta., post, Rm., worthington, K., 1991b. Principles of clinically important drug interactions with carbamazepine. Part I. J. Clin. Psychopharmacol. 11, 198–202.

Kikuzaki, H., Hisamoto, M., Hirose, K., Akiyama, K., Taniguchi, H., 2002. Antioxidant properties of ferulic acid and its related compounds. J. Agric. Food Chem. 50, 2161–2168.

Kim, K.A., Oh, S.O., Park, P.W., Park, J.Y., 2005. Effect of probenecid on the pharmacokinetics of carbamazepine in healthy subjects. Eur. J. Clin. Pharmacol. 61, 275–280.

Liow, K., Ablah, E., Nguyen, J.C., Sadler, T., Wolfe, D., Tran, K.D., Guo, L., Hoang, T., 2007. Pattern and frequency of use of complementary and alternative medicine among patients with epilepsy in the midwestern United States. Epilepsy Behav. 10, 576–582.

Mattila, P., Hellstrom, J., Torronen, R., 2006. Phenolic acids in berries, fruits, and beverages. J. Agric. Food Chem. 54, 7193–7199.

Moran, N.F., Poole, K., Bell, G., Solomon, J., Kendall, S., McCarthy, M., McCormick, D., Nashef, L., Sander, J., Shorvon, S.D., 2004. Epilepsy in the United Kingdom: seizure frequency and severity, anti-epileptic drug utilization and impact on life in 1652 people with epilepsy. Seizure 13, 425–433.

Ohnishi, N., Yonekawa, Y., Nakasako, S., Nagasawa, K., Yokoyama, T., Yoshioka, M., Kuroda, K., 1999. Studies on interactions between traditional herbal and Western medicines. I. Effects of Sho-seiryu-to on the pharmacokinetics of carbamazepine in rats. Biol. Pharm. Bull. 22, 527–531.

Okomolo, F.C., Mbafor, J.T., Bum, E.N., Kouemou, N., Kandeda, A.K., Talla, E., Dimo, T., Rakotonirira, A., Rakotonirira, S.V., 2011. Evaluation of the sedative and anticonvulsant properties of three Cameroonian plants. Afr. J. Tradit. Complement. Altern. Med. 8, 181–190.

Okuma, T., Kishimoto, A., 1998. A history of investigation on the mood stabilizing effect of carbamazepine in Japan. Psychiatry Clin. Neurosci. 52, 3–12.

Owen, A., Goldring, C., Morgan, P., Park, B.K., Pirmohamed, M., 2006. Induction of P-glycoprotein in lymphocytes by carbamazepine and rifampicin: the role of nuclear hormone response elements. Br. J. Clin. Pharmacol. 62, 237–242.

Pearce, R.E., Lu, W., Wang, Y., Uetrecht, J.P., Correia, M.A., Leeder, J.S., 2008. Pathways of carbamazepine bioactivation in vitro. III. The role of human cytochrome P450 enzymes in the formation of 2,3-dihydroxycarbamazepine. Drug Metab. Dispos. 36, 1637–1649.

Raish, M., Ahmad, A., Alkharfy, K.M., Jan, B.L., Mohsin, K., Ahad, A., Al-Jenoobi, F.I., Al-Mohizea, A.M., 2017. Effects of Paeonia emodi on hepatic cytochrome P450 (CYP3A2 and CYP2C11) expression and pharmacokinetics of carbamazepine in rats. Biomed. Pharmacother. 90, 694–698.

Roujeau, J.C., Kelly, J.P., Naldi, L., Rzany, B., Stern, R.S., Anderson, T., Auquier, A., Bastuji-Garin, S., Correia, O., Locati, F., et al., 1995. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. N. Engl. J. Med. 333, 1600–1607.

Sullivan, F.M., McElhatton, P.R., 1977. A comparison of the teratogenic activity of the antiepileptic drugs carbamazepine, clonazepam, ethosuximide, phenobarbital, phenytoin, and primidone in mice. Toxicol. Appl. Pharmacol. 40, 365–378.

Sun, X.L., Ito, H., Masuoka, T., Kamei, C., Hatano, T., 2007. Effect of Polygala tenuifolia root extract on scopolamine-induced impairment of rat spatial cognition in an eight-arm radial maze task. Biol. Pharm. Bull. 30, 1727–1731.

Szwajgier, D., Borowiec, K., Pustelniak, K., 2017. The neuroprotective effects of phenolic acids: molecular mechanism of action. Nutrients 9.

Tarirai, C., Viljoen, A.M., Hamman, J.H., 2010. Herb-drug pharmacokinetic interactions reviewed. Expert Opin. Drug Metab. Toxicol. 6, 1515–1538.

Tateishi, T., Asoh, M., Nakura, H., Watanabe, M., Tanaka, M., Kumai, T., Kobayashi, S., 1999. Carbamazepine induces multiple cytochrome P450 subfamilies in rats. Chem. Biol. Interact. 117, 257–268.

Tolou-Ghamari, Z., Zare, M., Habibabadi, J.M., Najafi, M.R., 2013. A quick review of carbamazepine pharmacokinetics in epilepsy from 1953 to 2012. J. Res. Med. Sci. 18, S81–85.

Towbin, H., Staehelin, T., Gordon, J., 1979. Electrophoretic transfer of proteins from polyacrylamide gels to nitrocellulose sheets - procedure and some applications. Proc. Natl. Acad. Sci. U. S. A. 76, 4350–4354.

Tzagoloff, A., 1963. Metabolism of sinapine in mustard plants. I. Degradation of sinapine into sinapic acid & choline. Plant Physiol. 38, 202–206.

Van Hung, P., 2016. Phenolic compounds of cereals and their antioxidant capacity. Crit. Rev. Food Sci. Nutr. 56, 25–35.

von Schoen-Angerer, T., Madeleyn, R., Kienle, G., Kiene, H., Vagedes, J., 2015. Viscum album in the treatment of a girl with refractory childhood absence epilepsy. J. Child Neurol. 30, 1048–1052.

Wang, E.J., Barecki-Roach, M., Johnson, W.W., 2002. Elevation of P-glycoprotein function by a catechin in green tea. Biochem. Biophys. Res. Commun. 297, 412–418.

Yoon, B.H., Jung, J.W., Lee, J.J., Cho, Y.W., Jang, C.G., Jin, C., Oh, T.H., Ryu, J.H., 2007. Anxiolytic-like effects of sinapic acid in mice. Life Sci. 81, 234–240.

Zhou, S., Lim, L.Y., Chowbay, B., 2004. Herbal modulation of P-glycoprotein. Drug Metab. Rev. 36, 57–104.

Zou, Y., Kim, A.R., Kim, J.E., Choi, J.S., Chung, H.Y., 2002. Peroxynitrite scavenging activity of sinapic acid (3,5-dimethoxy-4-hydroxycinnamic acid) isolated from Brassica juncea. J. Agric. Food Chem. 50, 5884–5890.