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Original Article

Effect of sinapic acid on aripiprazole pharmacokinetics in rats: Possible food drug interaction

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ABSTRACT

Dietary supplements and foods can interact with various drugs, leading to possible clinical concerns. This study aimed to investigate the effect of orally administered sinapic acid (SA) on the pharmacokinetics of aripiprazole (APZ) in rats and its possible modulatory effects on hepatic cytochrome P450 (CYP3A2 and CYP2D6) expression in the liver tissues. Single dose and multiple dose parallel groups of wistar rats were categorized into six groups (n = 6 each) which abstained from food for 12 h prior to the experiment, while water was allowed *ad libitum*. The investigation was carried out for single dose: Group I was treated with normal saline orally for 15 days (normal control). Group II was administered normal saline orally for 15 days and received APZ (3 mg/kg p.o.) on day 15. Group III received SA (20 mg/kg p.o.) for 15 days and received APZ (3 mg/kg p.o.) on day 15. Group IV was treated with SA (20 mg/kg p.o.) for 15 days. For the multiple dose study, Group I was treated with normal saline orally for 15 days (normal control); Group II received APZ (3 mg/kg p.o.) daily for 15 days; Group III was administered with SA (20 mg/kg p.o.) and APZ (3 mg/kg p.o.) for 15 days and Group IV received SA (20 mg/kg p.o.) for 15 days. The group I and IV were kept common in single and multiple dose groups. After last APZ dose, plasma samples were collected and APZ concentrations were determined using an UPLC-MS/MS technique. The pharmacokinetic parameters were calculated using a non-compartmental analysis. The concomitant administration of APZ with SA (as single or multiple dose) resulted in an increase in APZ absorption and a decrease on its systemic clearance. This was associated with a reduction in

Abbreviations: Aripiprazole, APZ; Sinapic acid, SA; Imipramine, IMP; Ultra Performance Liquid Chromatography mass spectrometer, UPLC-MS; oral, P.O.; area under plasma concentration–time curve, AUC; area under the first moment curve, AUMC; mean residence time, MRT; total clearance, CL; volume of distribution, Vd; terminal elimination rate constant, Ke; elimination half-life, T1/2; maximum plasma concentration, C_{max}; time to maximum concentration, T_{max}.

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CYP3A2 and CYP2D6 protein expressions by 33–43% and -71–68% after the single and multiple co-administration, which are two enzymes responsible of the metabolism of APZ. Therefore, a reduction in the metabolic clearance appears to be the mechanism underlying the drug interaction of dietary supplement containing SA with APZ. Therefore, the concomitant administration of SA and APZ should be carefully viewed. Further investigations are required to assess the clinical significance of such observations in humans.

1. Introduction

Aripiprazole (APZ), 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril (Fig. 1A), is an atypical or second-generation antipsychotic agent with a partial agonist activity for D(2)-dopamine and 5-hydroxytryptamine (5-HT) 1A serotonin receptors, as well as an antagonist action of the 2A serotonin receptor [1]. APZ is used alone or in combination with other therapies to treat psychotic illness such as bipolar disorders (manic-depressive illness), major depressive disorders, and schizophrenia [2]. APZ exhibits linear kinetics and has a long elimination half-life and therefore delayed steady-state plasma concentrations [3]. *In vitro* studies demonstrated that the enzymes CYP3A4 and CYP2D6 are responsible for dehydrogenation and hydroxylation of APZ, while N-alkylation is catalysed by CYP3A4 [4,5]. Since antipsychotic regimens are generally designed for a long-term use, the potential for significant clinical interactions between APZ and co-administered substances is considerably high.

A polyphenol, sinapic acid (SA), or 3,5-dimethoxy-4-hydroxycinnamic acid (Fig. 1B), is a bioavailable phytoconstituent present in various plant-like spices, citrus and berry fruits, and vegetables [6–9]. Interestingly, the use of SA in the pharmaceutical, food, and cosmetic industries is becoming widespread because of its potent antioxidant, antinflamatory, preservative and antimicrobial activities [10]. Furthermore, SA has been shown to prevent or slow down the progression of a wide range of diseases, including cancer, diabetes, cardiovascular disease, ischemic injuries, and Alzheimer's disease [11–13]. Moreover, *in vitro* studies revealed that SA has a significant inhibitory potential towards CYP3A4 [14]. Consequently, the concurrent use of herbal supplements and food products that contain SA could be associated with a potential clinical risk. However, it is not known whether SA has the capacity to alter protein expressions of important hepatic enzymes (e.g., CYP3A2 and CYP2D6) and/or interact with APZ. Therefore, the present study was conducted to examine the effect of SA on the disposition of APZ *in vivo* and to determine a possible mechanism, if any.

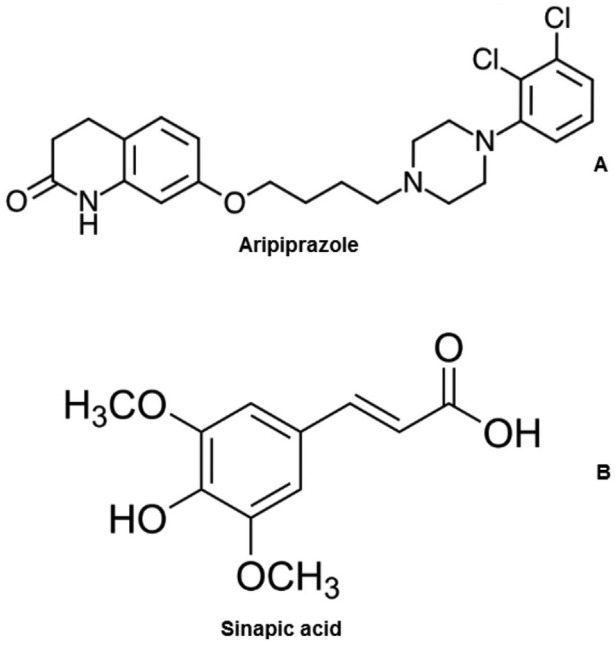

Fig. 1 – Chemical structure of Aripiprazole (A) and sinapic acid (B).

2. Materials and methods

2.1. Chemicals and reagents

SA, APZ, and imipramine (IMP) were purchased from Sigma–Aldrich (St Louis, MO, USA). Acetonitrile and methanol (UPLC grade) were obtained from Panreac Chemicals (Barcelona, Spain), while potassium dihydrogen phosphate was procured from Winlab Ltd. (Maidenhead, Berkshire, UK). Milli-Q water was prepared in the laboratory by a purification system (Millipore Corp., Billerica, MA, USA). Anti-CYP3A2 (LS-C36108), CYP2D6 (PA1397) and anti β-Actin (sc-47778) antibodies were purchased from Lifespan Biosciences, Inc. (Seattle, WA, USA), Boster Bio, (Pleasanton, CA, USA) and Santa Cruz Biotechnology, Inc. (Dallas, Texas U.S.A), respectively. HRP-linked secondary antibodies were procured from Santa Cruz Biotechnology, Inc. (Santa Cruz, CA, USA), and Luminata Forte Western HRP substrate was obtained from Millipore (Billerica, MA). All other chemical reagents used were of an analytical grade.

2.2. Animals and treatment

Wistar rats (190–210 g) were obtained from the Central Animal House Facility of the College of Pharmacy, King Saud University (Riyadh, Saudi Arabia) and were categorised into five groups (n = 6 each) and placed in plastic animal cages with

a 12-h light/dark cycle (25 ± 2 °C). The animals were acclimatized to laboratory conditions for a week prior to experiments. The study was approved by the college's Ethic Committee (Clearance No. 5986; October, 2016). The rats were fed standard rat chow diet and provided water *ad libitum* except 12 h prior to the experiment where food was pulled out. In the single dose study, treatments were as follows:

Group I was treated with normal saline orally for 15 days (normal control); Group II was received normal saline orally for 15 days and administered APZ (3 mg/kg p.o.) on day 15; Group III received SA (20 mg/kg p.o) for 15 days and received APZ (3 mg/kg p.o.) on day 15; and Group IV was administered SA (20 mg/kg p.o.) for 15 days. The study protocol of the multiple dose study was as follows: Group I was treated with normal saline orally for 15 days (normal control); Group II received APZ (3 mg/kg p.o.) daily for 15 days; Group III was administered with SA (20 mg/kg p.o.) and APZ (3 mg/kg p.o.) for 15 days. Group IV received SA (20 mg/kg p.o) for 15 days; As Groups 1 and IV are common in the single and multiple dose studies.

Blood samples were collected from the retro-orbital plexus at 0, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72 h after the last APZ dose and transferred into tubes containing di-sodium EDTA. Plasma was immediately separated by centrifugation at 2500 g for 10 min and transferred into labelled Eppendorf tubes for the determination of APZ concentrations. At the end of the experiments, the rats were euthanized under light ether, and liver tissue samples were excised for Western blotting analysis.

2.3. *APZ assay and pharmacokinetic analysis*

APZ plasma concentrations were measured using an UPLC-MS/MS technique according to a previously reported method [15]. The chromatography was carried out using Acquity™ UPLC triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA) equipped with an electrospray ionization source. A non-compartmental pharmacokinetic analysis was performed using PK Solver software (version 1.0). The calculated parameters include AUC, area under the concentration–time curve; AUMC, area under the first moment curve; MRT, mean residence time; Vd, volume of distribution; CL, total clearance and Ke terminal elimination rate constant, $T_{1/2}$, apparent elimination half-life. The Cmax, maximum plasma concentration and Tmax, time to maximum concentration were determined empirically directly from the time–concentration curve.

2.4. *Western blotting*

Specific antibodies were used for the estimation of CYP3A2, CYP2D6, and β-actin protein expression by an immunoblot analysis. Briefly, denatured hepatic protein (25 μg per well) was loaded onto a 10% polyacrylamide gel containing 0.1% SDS and electrophoresed at 120 V for 60 min. Protein samples were then transferred to a PVDF membrane at 100 V for 60 min, and immunoblots were incubated overnight at 4 °C with primary antibodies, washed with PBS containing 0.1% tween and incubated with secondary antibodies linked to horseradish peroxidase (HRP) for 60 min. The following primary antibodies were used: Anti-CYP3A2 (LS-C36108), CYP2D6 (PA1397) and anti β-Actin (sc-47778). The western blot bands were visualized using "Luminata™ Western Chemiluminescent HRP Substrates" (Millipore, Billerica, MA, USA) and a densitometric analysis of the immunoblots was accomplished using LI-COR C-DiGit Blot Scanners (Lincoln, NE, USA).

2.5. *Statistical analysis*

The data are expressed as mean ± standard deviation (SD). The significance was determined by applying a paired T-test or ANOVA followed by Dunnet test.; p values of <0.05 were considered statistically significant.

3. Results

The plasma-time concentration profiles of APZ after the single or multiple dose alone and in combination with SA are shown in Figs. 2 and 3. The estimated pharmacokinetic parameters of APZ are given in Tables 1 and 2. The C_{max} of a single oral APZ dose in rats was found to be 10.34 ± 0.41 ng/ml with a T_{max} at 8 h. Other parameters include: $AUC_{0\text{-}t}$, 163.88 ± 6.65 ng/ml × h; T1/2 17.88 ± 0.04 h; CL 0.17 ± 0.01 ml/kg/h; and Vd, 44.91 ± 1.88 ml/kg. The co-administration of SA for 15 days increased the absorption and metabolism of APZ significantly as evident from the C_{max} and $AUC_{0\text{-}t}$ values by 33.07% and 25.42%, respectively. Correspondingly, the calculated Vz/F and Cl/F were reduced by 34.57% and 33.48%, respectively, compared with animals treated with APZ alone ($p < 0.05$) without a significant change in $T_{1/2}$ (Table 1).

The C_{max} of APZ with a multiple daily dose was 7.08 ± 0.89 ng/ml. Other parameters were as follows: $AUC_{0\text{-}t}$, 122.38 ± 3.45 ng/ml × h; T1/2 19.83 ± 2.51 h; CL 2.28 ± 0.09 ml/kg/h; and Vd, 65.01 ± 6.53 ml/kg. The chronic co-administration of SA with APZ for 15 days further increased the C_{max} by 337.46% and $AUC_{0\text{-}t}$ by 318.58%. Inversely, the calculated T1/2, Vz/F, and Cl/F decreased by 32.14%, 82.84%, and 74.78%, respectively, as compared to rats treated with multiple doses of APZ alone (p <0.05).

A single dose of APZ caused a significant enhancement in CYP3A2 protein expression by 90%. Similarly, the CYP2D6 expression was increased by 82% compared with normal controls (Fig. 4; p <0.05). Furthermore, multiple dose of APZ

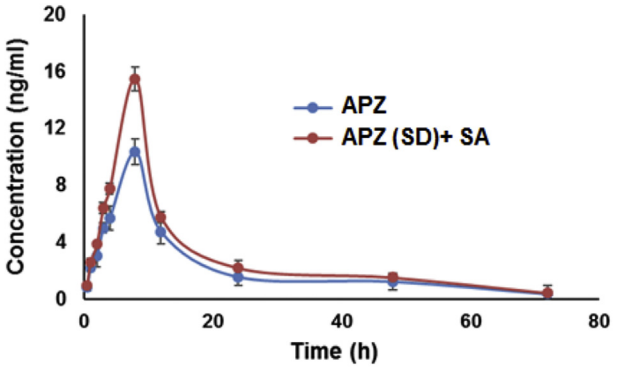

Fig. 2 – Mean plasma concentration time profiles of APZ (3 mg/kg) and APZ with SA (20 mg/kg) dose in rats after single oral administration. Each value is expressed as mean ± SD (n = 6).

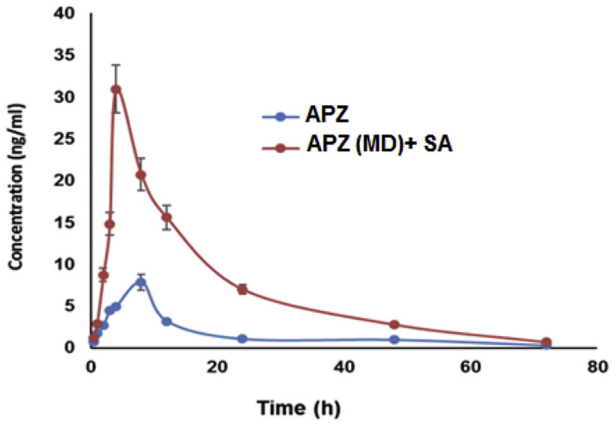

Fig. 3 – Mean plasma concentration time profiles of APZ (3 mg/kg) and APZ with SA (20 mg/kg) dose in rats for 15 days daily. Each value is expressed as mean ± SD (n = 6).

caused a significant enhancement in the liver expressions of CYP3A2 by 135.29% and CYP2D6 by 91.17% compared to normal controls ($p < 0.05$). On the contrary, animals treated with SA for 15 days showed 31.57% and 34.06% reduction of CYP3A2 and CYP2D6 hepatic proteins, respectively, as compared to that of rats treated with a single dose of APZ. The administration of SA was associated with a reduction in hepatic expressions of CYP3A2 by 54.68% and CYP2D6 by 65.76% in contrast to rats treated with multiple doses of APZ ($p < 0.05$). Rat received SA demonstrated a significant reduction of CYP3A2 and CYP2D6 proteins of 50.52% and 53.84% in the single dose study, and 73.75% and 71.15% in the multiple dose study compared with rats received APZ alone ($p < 0.05$).

4. Discussion

The concomitant administration of herbal products with prescribed medications may mimic, increase, or decrease the pharmacological activity of drugs. Indeed, herbal products are an important cause of drug–drug interactions (DDIs) and toxicity [16,17]. SA is a wide bioavailable phytoconstituent present in wheat bran, canola (*Sinapis alba*), rapeseed (*Brassica napus*), mustard seed (*Brassica nigra*), citrus and berry fruits [7,18,19]. Several studies have demonstrated that SA treatment reduced $A\beta_{1\text{-}42}$ protein-induced hippocampal neuronal cell death and that the neuroprotective nature of SA results from its anti-apoptotic, anti-inflammatory, and radical-scavenging properties, which make it a potent neuroprotective compound [12,20,21].

Psychiatric disorders are generally chronic illnesses that require a prolonged drug therapy with close monitoring in order to avoid or decrease the risk of side effects [22]. The widespread use of SA for the proposed therapeutic benefits makes it a suitable candidate as a health supplement in many countries [23,24]. Therefore, the risk of SA interaction

Table 1 – Pharmacokinetic parameters for APZ single dose treatment with or without SA.

Parameter	Unit	APZ (Mean ± SD)	APZ + SA (Mean ± SD)	%Change
Ke	1/h	0.04 ± 0.001	0.039 ± 0.001	0.83
T1/2	h	17.88 ± 0.04	17.740 ± 0.41	0.79
Tmax	h	8.00 ± 0.00	8.00 ± 0.00	0.00
Cmax	ng/ml	10.34 ± 0.41	15.45 ± 0.83[a]	33.08
AUC 0-t	ng/ml × h	163.88 ± 6.65	219.74 ± 12.48[a]	25.42
AUC 0-∞	ng/ml × h	172.56 ± 7.001	230.64 ± 13.35[a]	25.18
AUMC 0-∞	ng/ml × h^2	4060.90 ± 165.67	5250.16 ± 394.43[a]	22.65
MRT 0-∞	h	23.53 ± 0.011	22.75 ± 0.57	3.48
Vd	ml/kg	44.91 ± 1.88	33.37 ± 1.94[a]	34.57
CL	ml/kg/h	0.17 ± 0.01	0.13 ± 0.01[a]	33.48

[a] Indicate $p < 0.05$.

Table 2 – Pharmacokinetic parameters for APZ multiple doses treatment with or without SA.

Parameter	Unit	APZ (Mean ± SD)	APZ + SA (Mean ± SD)	%Change
Ke	1/h	0.04 ± 0.005	0.05 ± 0.001[a]	45.39
T1/2	h	19.83 ± 2.52	13.46 ± 0.04[a]	32.14
Tmax	h	8.00 ± 0.00	4.00 ± 0.00[a]	50.00
Cmax	ng/ml	7.08 ± 0.89	30.95 ± 2.55[a]	337.46
AUC 0-t	ng/ml × h	122.38 ± 3.45	512.28 ± 39.36[a]	318.59
AUC 0-∞	ng/ml × h	131.78 ± 4.85	525.50 ± 40.45[a]	298.76
AUMC 0-∞	ng/ml × h^2	3443.83 ± 234.17	10559.08 ± 805.37[a]	206.61
MRT 0-∞	h	26.11 ± 1.01	20.09 ± 0.04[a]	23.04
Vd	ml/kg	65.01 ± 6.53	11.15 ± 0.91[a]	82.84
CL	ml/kg/h	2.28 ± 0.09	0.57 ± 0.05[a]	74.78

[a] Indicate $p < 0.05$.

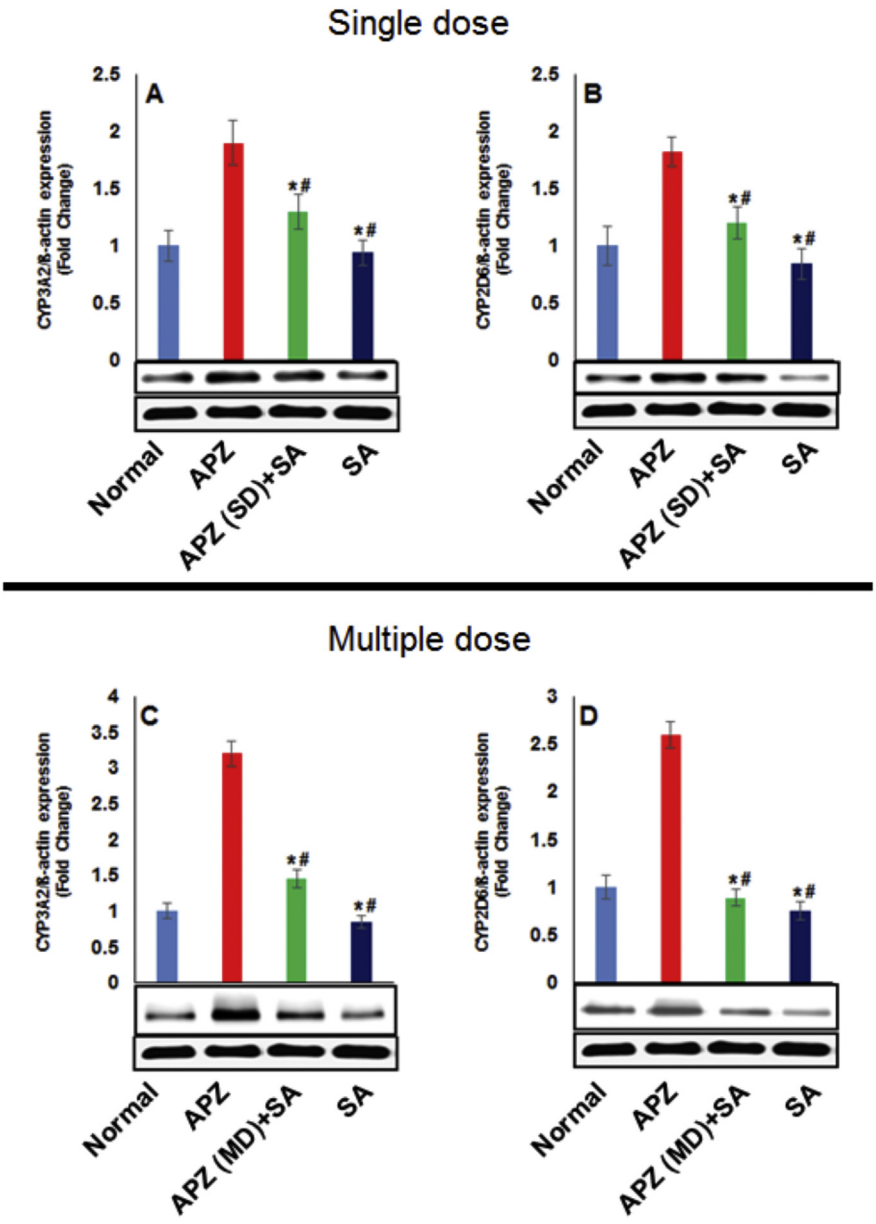

Fig. 4 – Hepatic CYP3A2 and CYP2D6 protein expression in rats after APZ administration with or without sinapic acid (SA) treatment. All values are presented as the mean ± SD. *p < 0.05 (compared to control?); #p < 0.05 (compared to APZ).

with narrow-therapeutic index drugs should not be overlooked. To the best of our knowledge, this is the first report to explore the effect of SA on the pharmacokinetics of APZ using an animal model.

APZ is largely metabolized by CYP3A4 and CYP2D6 to dehydro-aripiprazole (DAPZ), and both enzymes are implicated in the removal of DAPZ [25,26] [5]. At steady state, about 40% of APZ is converted to the major metabolite DAPZ, which is responsible for the overall activity of the drug [4]. APZ exhibits linear kinetics and has a long elimination half-life and delayed steady-state plasma concentrations [3]. Drugs/compounds that inhibit or induce CYP3A4 and/or CYP2D6 activity could potentially alter APZ pharmacokinetics. The results of the current study indicate that SA increases APZ concentrations by reducing drug clearance. The protein expression findings of CYP3A2 and CYP2D6 further support this observation. A polyphenol, SA, reduces CYP3A2 and CYP2D6 protein expression may be due to polyphenolic nature of SA, those are potent inhibitors of cytochromes. APZ cause such a huge increase in CYP3A4 and CYP2D6 protein expression may be due to auto-induction of APZ. SA pretreatment blocks the APZ metabolism as well as able to modulate the pg-p efflux mechanism.

The implication of the absorption site in the intestine may also contribute to the herb–drug interaction. Thus, increased oral absorption of APZ with the concomitant administration of SA may occur because of inhibition of the gut efflux mechanisms. It is known that polyphenolic compounds such as hydroxycinnamic acid, ferulic acid and cumaric acid are P-

glycoproteins (P-gp) inhibitors [14,27–29]. Whether SA is a P-gp inhibitor is not entirely clear and further studies are required to investigate such possibility. The chronic administration of SA (for 15 days) caused further reduction in APZ metabolism and a greater increase in AUC. Therefore, the inhibitory effect of SA on APZ clearance appears to be dependent on the length of treatment. Interestingly, APZ could also induce its own metabolism (i.e., self-autoinduction) as indicated by reductions in C_{max} and AUC following multiple administrations. This is also evident form increases in CYP3A2 and CYP2D6 expressions in hepatic tissues after single or multiple dosing by ~2–3 folds. Finally, SA may also reduce APZ volume of distribution perhaps via a tissue binding displacement mechanism.

5. Conclusion

The concomitant administration of SA with APZ has a significant potential for an herb–drug interaction. The reduction in metabolic clearance, owing to inhibition of CYP3A2 and CYP2D6 protein expression in the liver, appears to be the mechanism underlying this drug interaction. In addition, the possible role of enhanced oral absorption of APZ with the co-administration of SA should be further investigated. Therefore, the consumption of dietary supplement containing SA by patients receiving APZ treatment should be carefully practiced. Additional studies are required to assess the clinical significance of these observations in humans.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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