

# Resveratrol Enhances the Bioavailability of Fexofenadine in Healthy Human Male Volunteers: Involvement of P-Glycoprotein Inhibition

Satish Kumar Bedada<sup>1</sup>, Sudhakar Akul Yakkanti<sup>2</sup> and Prasad Neerati<sup>1\*</sup><sup>1</sup>DMPK and Clinical Pharmacology Division, Department of Pharmacology, University College of Pharmaceutical Sciences, Kakatiya University, Warangal, Telgana, India  
<sup>2</sup>Cell Signaling and Matrix Biology Center, Foster City, CA, 94404, USA

## Abstract

**Objective:** The purpose of the present study was to assess the influence of resveratrol on P-glycoprotein mediated drug disposition in humans using fexofenadine as a P-glycoprotein substrate.

**Methods:** A non-blinded, an open label crossover study was conducted in twelve healthy male volunteers aged between 26 and 31 years. A single dose of fexofenadine hydrochloride 120 mg was given to volunteers during control phase and treatment phases. A single dose of resveratrol 500 mg was given to volunteers once daily for period of 10 days. The blood samples were collected at predetermined time intervals during control and treatment phases. The plasma samples containing fexofenadine hydrochloride were analyzed by LC-MS/MS. The pharmacokinetic parameters were computed by non-compartmental method and the mean pharmacokinetic parameter differences during control and treatment phases were assessed.

**Results:** Treatment with resveratrol significantly increased the area under the plasma concentration-time curve (AUC) and maximum plasma concentration ( $C_{max}$ ) of fexofenadine to 76.7% (2520.92.48 versus 4454.48 ng.h/mL) and 65.2% (415.08 versus 685.58 ng/mL) respectively when compared to control phase. On other hand, apparent clearance (CL/F) and apparent volume of distribution (Vd/F) of fexofenadine were significantly decreased by 42.6% (49.46 versus 28.37 L/h) and 42.1% (591.73 versus 342.62 L) respectively. However, there was no significant change was observed in  $T_{1/2}$ ,  $K_{el}$  and  $T_{max}$  of fexofenadine upon treatment with resveratrol when compared to control phase.

**Conclusion:** The results of the present study showed that multiple doses of resveratrol enhanced the bioavailability of fexofenadine probably by the inhibition of P-glycoprotein mediated drug efflux in humans.

**Keywords:** Fexofenadine; Resveratrol; P-glycoprotein; Pharmacokinetics; Bioavailability

## Introduction

Resveratrol (RSV) (3,4',5-trihydroxystilbene) is a naturally occurring polyphenolic phytoalexin is naturally present in fruits, vegetables, grape skins and especially in red wine. RSV possesses diverse biochemical and physiological properties including anti-inflammatory, immune modulatory activities as well as wide range of health benefits ranging from chemoprevention to cardio protection [1]. It is produced by the plants in response to stress, injury, ultraviolet irradiation and fungal infection as part of their defense mechanism. In addition, it is synthesized by grapes in response to fungal infections and found in red wine at levels between 1 and 10  $\mu$ M [2].

RSV modulates the synthesis of hepatic apolipoprotein, lipids, inhibits platelet aggregation and eicosanoid production in human platelets and neutrophils [3]. Moreover, RSV inhibits events associated with tumor initiation, promotion and progression [4]. It has been reported that RSV increased the accumulation of daunorubicin (a P-glycoprotein substrate) in KB-C2 cells in a concentration dependent manner by inhibiting P-gp (P-glycoprotein) [5]. Additionally, RSV has been found to reverse the multidrug resistance in KBv200 cells by inhibiting the multidrug resistant gene expression [6]. It has been previously reported that RSV enhanced the chemosensitivity of doxorubicin in multidrug resistant human breast cancer cells by increasing the cellular influx of doxorubicin [7]. In addition, RSV has been found to potentiate the cytotoxic activity P-gp substrates such as docetaxel and doxorubicin due to enhanced intracellular levels by

inhibition of P-gp and down regulation of *mdr1* gene [8]. Furthermore, *in vivo* studies in rats demonstrated that RSV was able to increase the bioavailability of P-gp substrates through the inhibition of P-gp mediated drug efflux [9,10]. Since RSV is a P-gp inhibitor and may potentially inhibit efflux transporter responsible for the poor absorption of P-gp substrates, the influence of RSV treatment on the pharmacokinetics of known P-gp substrate, fexofenadine hydrochloride (FEX) in healthy volunteers is the subject of current investigation.

FEX is a non-sedating antihistamine drug which is indicated for treatment of seasonal allergic rhinitis and chronic urticaria [11]. It has been demonstrated that after oral administration of [<sup>14</sup>C] FEX to healthy subjects, 92% of the total dose was recovered, 12% in urine and 80% in the feces in unchanged form [12]. It has been reported that FEX is a P-gp substrate and the low passive membrane permeability of FEX makes the absorption of this drug to be P-gp related. The low

**\*Corresponding author:** Neerati Prasad, Assistant Professor, DMPK and Clinical Pharmacology Division, Department of Pharmacology, University College of Pharmaceutical Sciences, Kakatiya University, Warangal-506009, Telgana, India, Tel: +91 9494812120; Fax: +91 8702453508; E-mail: [prasadneerati@gmail.com](mailto:prasadneerati@gmail.com)

Received August 17, 2014; Accepted August 25, 2014; Published October 03, 2014

**Citation:** Bedada SK, Yakkanti SA, Neerati P (2014) Resveratrol Enhances the Bioavailability of Fexofenadine in Healthy Human Male Volunteers: Involvement of P-Glycoprotein Inhibition. J Bioequiv Availab 6: 158-163. doi:10.4172/jbb.1000198

**Copyright:** © 2014 Bedada SK, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

intestinal permeability and almost no metabolism of FEX *in vivo* make it a suitable model substrate to evaluate the role of P-gp in drug efflux. The pharmacokinetic profile of FEX primarily depends on the activity of P-gp, an efflux transporter which is expressed in the small intestine mucosa, hepatocytes, kidney and blood-brain barrier [13,14].

In this study, we hypothesized that if RSV acts as an inhibitor of P-gp mediated efflux, possibly in the intestine, it will increase the bioavailability of FEX, a P-gp substrate. To our knowledge, there are no available data that show any inhibitory effect of RSV on P-gp mediated disposition in humans. Therefore, we investigated the possible effect of RSV on P-gp mediated efflux using FEX as a P-gp substrate in healthy male volunteers.

## Materials and Methods

### Materials

FEX and Diphenhydramine (DPH) were obtained from Matrix Labs Limited (Hyderabad, India). RSV 500 mg capsules were procured from Zenith Nutritions (Bangalore, India). FEX 120 mg tablets (Allegra) were purchased from Aventis Pharma Ltd (Mumbai, India). Solvents used for quantitative analysis (Merck, India) and all other chemicals, reagents which were used in the study are of analytical grade.

### Subjects

Twelve healthy male volunteers with an age of  $28.17 \pm 1.59$  (range 26-31) years, weight of  $68.3 \pm 7.95$  (range 52-82) kg, height of  $173.2 \pm 7.33$  (range 165-188) cm and body mass index (BMI) of  $22.76 \pm 2.02$  (range 17.99-24.95) were participated in the study (Table 1). All participants gave their written informed consent prior to the study. The participants were confirmed as healthy by their medical history, physical examination and routine laboratory tests before enrollment. All the subjects were nonsmokers, ate a normal diet and were not taking any herbal dietary supplements. The subjects were instructed to abstain from taking any medication for at least 2 weeks prior to and during the study period. All the subjects were asked to abstain from alcohol, caffeine-containing beverages, tea and fruit juices during the study period.

### Study design

The study protocol was approved by the institutional human ethical committee (UCPSC/KU/BA/2012-08) of University College of pharmaceutical sciences, Kakatiya University, Warangal, India. A non-blinded, open-label, two-way crossover study was performed. The study phases were divided into control and treatment separated by a 2-week washout period. The general study design was identical in control and treatment phases. The participants were administered with oral RSV 500 mg capsules once daily for duration of 10 days (Zenith Nutritions, Bangalore, India). A single oral dose of FEX 120 mg (Allegra, Aventis Pharma Ltd, India) was administered during control phase and on eleventh day after RSV treatment with 240 mL water under fasting conditions of more than 10 h. The doses of RSV and FEX were selected based on the marketed formulations. The drugs used in this study were given in the sitting position and the subjects remained seated for 4 h after administration of FEX. Standardized meals were given at 4 and 10 h after dosing. Blood samples were drawn immediately before as well as 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48 h after FEX administration. Blood samples were collected in heparinized vacutainers and centrifuged at 4,000 rpm for 15 min and these separated plasma samples were stored at  $-70^{\circ}\text{C}$  until the assay was performed.

## Determination of fexofenadine hydrochloride concentration in plasma

FEX concentration in plasma samples was assayed using LC-MS/MS method [15] by employing protein precipitation extraction method. Aliquots of plasma samples (100  $\mu\text{L}$ ) were added to 200  $\mu\text{L}$  acetonitrile with DPH (4 ng/mL) as an internal standard, then mixed in a vortex mixer for 3 min and centrifuged at 14,000 rpm for 8 min. Next pipette out 150  $\mu\text{L}$  of supernatant, then 5  $\mu\text{L}$  aliquot was injected into the analytical column. The plasma concentration of FEX was analyzed by LC-MS/MS with Agilent 1200 quaternary pump, auto sampler with thermostat, column oven, online degasser and triple quadrupole mass spectrometer (Mass hunter software version B.03.01) with multimode source (Agilent Technologies, USA). A Symmetry C18 reverse phase column (75 mm  $\times$  4.6 mm, i.d. 3.5  $\mu\text{m}$ ) and the mobile phase (acetonitrile: 10 mM ammonium acetate: 0.1% formic acid = 70:30) at a flow rate of 0.2 mL/min were used. FEX was monitored in positive ion mode with the transition of  $m/z$  502.3 to  $m/z$  466.2 and DPH with the transition of  $m/z$  256.2 to  $m/z$  167.0 respectively. The lower limit of quantification for FEX was 0.5 ng/mL, and the assay range used was 0.5-1000 ng/mL. Correlation coefficient for FEX calibration curves was 0.998. The intra-day and inter-day coefficient of variations for the low and high quality control samples were less than 15%.

### Pharmacokinetic analysis

The pharmacokinetics of FEX was estimated using non-compartmental method using Phoenix WinNonlin 6.2.1 software (Certara, Pharsight Corporation, USA). The maximum plasma concentration ( $C_{\text{max}}$ ) and the time taken to reach  $C_{\text{max}}$  is  $T_{\text{max}}$  were estimated directly from the observed plasma concentration-time data. The elimination rate constant ( $K_{\text{el}}$ ) was determined by linear regression analysis of the log-linear part of the plasma concentration-time curve. The total area under the plasma concentration-time curve (AUC) was calculated using the linear trapezoidal rule. The AUC from 0 to infinity ( $\text{AUC}_{\text{inf}}$ ) was calculated as  $\text{AUC}_{\text{inf}} = \text{AUC} + \text{Ct}/K_{\text{el}}$  (where Ct was the last plasma concentration measured). The half-life ( $T_{1/2}$ ) of FEX was calculated using  $T_{1/2} = \ln 2 / K_{\text{el}}$ . The apparent oral clearance (CL/F) of FEX was calculated as  $\text{CL}/\text{F} = \text{dose}/\text{AUC}_{\text{inf}}$  and the apparent volume of distribution (Vd/F) was calculated using  $\text{Vd}/\text{F} = \text{CL}/\text{F}/\lambda_z$ .

### Statistical analysis

The results are expressed as the mean  $\pm$  SD. The pharmacokinetics of FEX between the control and treatment phases were compared to each other using a paired *t*-test (two-tailed) or the Wilcoxon signed

Subject	Age (Yrs)	Height (cm)	Weight (Kg)	BMI (kg/m <sup>2</sup> )
1	28	175	69	22.53
2	26	185.5	82	23.83
3	26	170	52	17.99
4	28	175	75	24.49
5	28	167.5	65	23.17
6	27	167.5	65	23.17
7	29	175	63	20.57
8	30	167.5	63	22.45
9	31	175	76	24.82
10	28	167.5	70	24.95
11	27	188	75	21.22
12	30	165	65	23.88
Mean	28.17	173.21	68.33	22.76
SD	1.59	7.33	7.95	2.02

Table 1: Demographic characteristics of healthy male volunteers.

rank sum test after normality test using Kolmogorov-Smirnov test. All the data obtained were analyzed using Graph Pad Prism 5.1 software (GraphPad Software Inc., San Diego, CA, USA). A  $P < 0.05$  was considered statistically significant. To determine the possibility of drug interaction between RSV and FEX, we compared calculated individual pharmacokinetic parameters and their ratios (test/reference) using log-transformed data; their geometric means and 90% confidence intervals (CIs) were analyzed. The resulting confidence limits were transformed by exponentiation and reported on the original measurement scale. The statistical limits were set at 0.80–1.25.

## Results

The pharmacokinetic parameters and mean plasma concentration-time profiles of FEX after a 10-day treatment with RSV are shown in Table 2 and Figure 1, respectively. During the study period, no serious adverse effects related to the drugs were reported. When we measured the plasma FEX concentrations after a single oral dose of 120 mg FEX, those of RSV phase were increased compared to those of the control phase (Figure 1). The mean AUC of fexofenadine was increased by 76.7% after RSV treatment ( $2520.92 \pm 516.92$  versus  $4454.48 \pm 1238.27$  ng·h/mL,  $P < 0.05$ ) as compared to control phase. In addition, RSV increased the mean  $C_{max}$  value by 65.2% compared to that of the control phase ( $415.08 \pm 67.63$  versus  $685.58 \pm 184.24$  ng/mL,  $P < 0.05$ ). The mean value of CL/F and Vd/F were decreased significantly by 42.6% ( $49.46 \pm 12.27$  versus  $28.37 \pm 7.03$  L/h,  $P < 0.05$ ) and 42.1% ( $591.73 \pm 197.25$

versus  $342.62 \pm 108.56$  L,  $P < 0.05$ ) respectively after RSV treatment as compared to control phase. The AUC and  $C_{max}$  of FEX were increased where as CL/F and Vd/F were decreased in all individuals upon RSV treatment as compared to control phase (Figure 2). However, there was no significant change was observed in  $T_{1/2}$ ,  $T_{max}$  and  $K_{el}$  of FEX between RSV treatment and control phases. The 90% CI for the ratio of geometric means (RSV treatment phase:control phase) for AUC,  $C_{max}$ , CL/F and Vd/F were fell outside the interval (0.8-1.25) but in case  $T_{1/2}$ ,  $T_{max}$  and  $K_{el}$  fell within the interval (Table 2) which indicates the interaction between RSV and FEX, consequently the pharmacokinetics of FEX were altered upon RSV treatment.

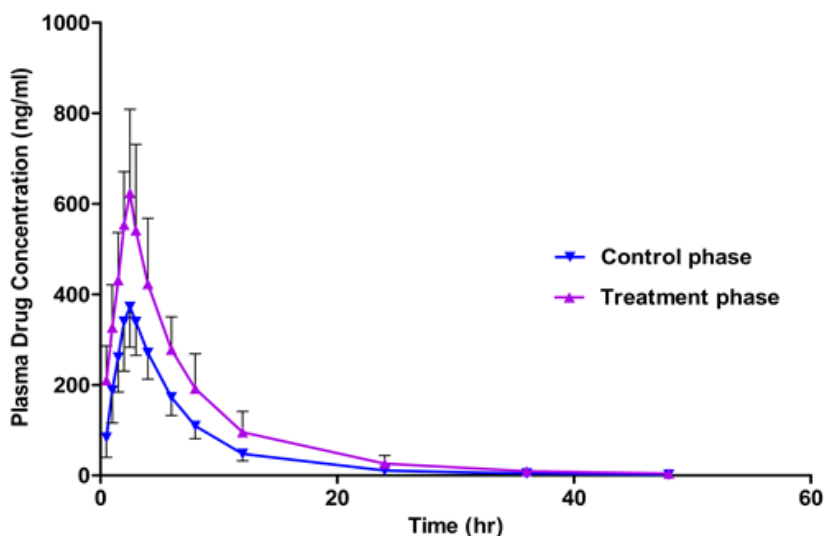
## Discussion

P-gp is an adenosine triphosphate (ATP)-dependent multidrug transporter expressed mainly on the apical membrane of the intestine. P-gp has been reported to promote the elimination of many drugs into the intestinal lumen, thereby limiting their gastrointestinal absorption. P-gp can also reduce the intracellular concentrations of many cytotoxic anti-tumor drugs and is involved in multidrug resistance in tumor cells [16]. Recently inhibition of this transporter protein was implicated as a mechanism underlying certain drug-phytochemical interactions. In the clinical setting, familiarity with known inhibitors of P-gp, together with knowledge of the role of P-gp in determining substrate pharmacokinetics, should increase awareness of potential adverse or desired effects when phytochemicals that interact with P-gp substrates.

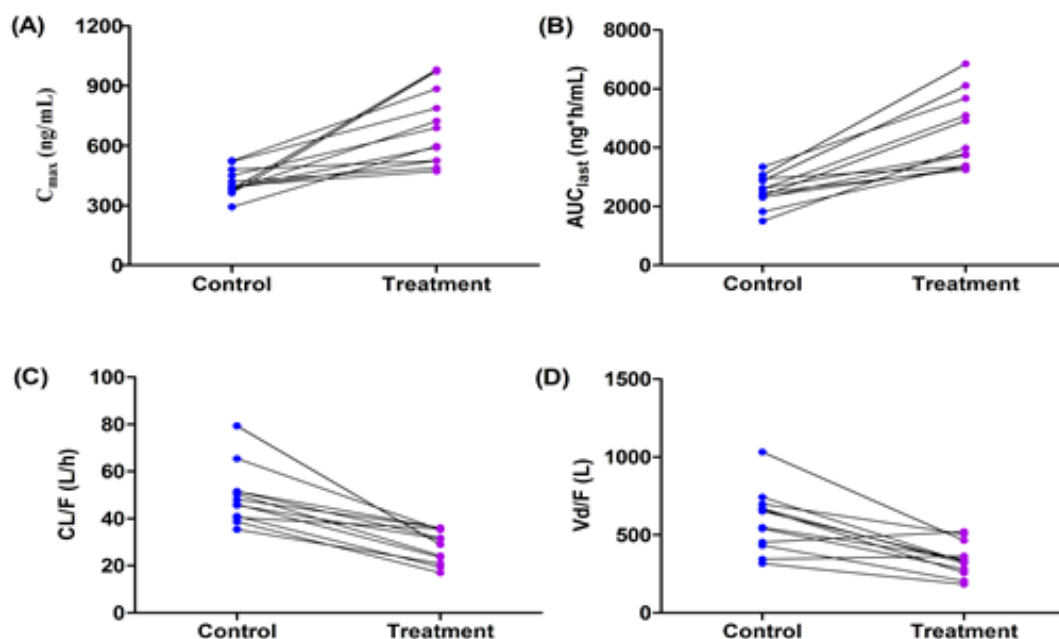
Pharmacokinetic parameters	Control phase	Treatment phase	Geometric mean ratio	90% CI
$C_{max}$ (ng/mL)	415.08 ± 67.63	685.58 ± 184.24*	1.61	1.38-1.88
$T_{max}$ (h)	2.37 ± 0.37	2.41 ± 0.36	1.02	0.94-1.10
$K_{el}$ (h <sup>-1</sup> )	0.088 ± 0.02	0.087 ± 0.02	0.99	0.87-1.12
$T_{1/2}$ (h)	8.27 ± 1.82	8.48 ± 2.15	1.01	0.91-1.14
AUC <sub>last</sub> (ng·h/mL)	2520.92 ± 516.92	4454.48 ± 1238.27*	1.74	1.53-1.98
AUC <sub>inf</sub> (ng·h/mL)	2541.65 ± 527.18	4512.33 ± 1265.17*	1.75	1.54-1.99
CL/F (L/h)	49.46 ± 12.27	28.37 ± 7.03*	0.56	0.50-0.64
Vd/F (L)	591.73 ± 197.25	342.62 ± 108.56*	0.58	0.48-0.69

Pharmacokinetic data are expressed as mean ± SD. \* $P < 0.05$ , compared with the control phase.

**Table 2:** Pharmacokinetic parameters of fexofenadine after a single-dose administration of 120 mg fexofenadine hydrochloride in 12 healthy subjects, after 500 mg resveratrol once daily for 10 days.



**Figure 1:** Mean plasma concentrations of fexofenadine in 12 healthy volunteers after a single 120 mg oral dose of fexofenadine hydrochloride, following a 10-day treatment with resveratrol 500 mg once daily. Values are shown as shown as the mean ± SD.



**Figure 2:** Individual peak plasma concentration ( $C_{max}$ ) (A), area under the concentration (AUC) (B), apparent oral clearance (CL/F) (C) and apparent volume of distribution (Vd/F) (D) of fexofenadine in 12 healthy volunteers after a single 120 mg oral dose of fexofenadine hydrochloride, following a 10-day treatment with resveratrol 500 mg once daily.

In this study, we assessed the effect of RSV on the pharmacokinetics of FEX, a substrate of P-gp in humans and found that RSV affected the pharmacokinetics of FEX and increased its bioavailability. To assess the inhibitory effect of RSV on P-gp in humans, we used FEX as a P-gp substrate [17]. RSV treatment significantly increased the  $C_{max}$  and AUC of FEX to 65.2% and 76.6% respectively as compared to control phase. On the other hand, CL/F and Vd/F of FEX were significantly decreased to 42.6% and 42.1% respectively as compared to control phase. However, there was no significant change observed in  $T_{1/2}$ ,  $T_{max}$  and  $K_{el}$  of FEX upon RSV treatment when compared to control phase. The interaction between RSV and FEX was also assessed by geometric mean ratios and 90% CI. The 90% CI for the ratio of geometric means for AUC,  $C_{max}$ , CL/F and Vd/F were fell outside the interval (0.8-1.25) which indicates the significant difference in mean values of AUC,  $C_{max}$ , CL/F and Vd/F between control and treatment phases. On the other hand, 90% CI for the ratio of geometric means for  $T_{1/2}$ ,  $T_{max}$  and  $K_{el}$  fell within the interval (0.8-1.25) which indicates the insignificant difference in mean values of  $T_{1/2}$ ,  $T_{max}$  and  $K_{el}$  between control and treatment phases. These findings provide *in vivo* evidence that RSV might increase the bioavailability of FEX via the inhibition of P-gp mediated drug efflux during the absorption phase in the intestine. Likewise, other P-gp inhibitors such as itraconazole [18-20], ritonavir [21] exhibited similar inhibitory effects on the pharmacokinetics of FEX, namely an increase in  $C_{max}$  and AUC, decrease in CL/F and Vd/F. On the other hand, in the case of P-gp inducers such as St. John's wort [22], rifampin [23] and carbamazepine [24], the CL/F and Vd/F of FEX were reported to have been increased while the  $C_{max}$  and AUC were decreased. Furthermore, it has been reported that P-gp was the main transport protein responsible for FEX transport and the *in vitro* FEX transport was inhibited by various P-gp inhibitors such as ketoconazole, verapamil, erythromycin and ritonavir in the Caco-2 cell model [25,26]. Considering that  $T_{1/2}$  and  $T_{max}$  were not changed significantly by RSV, the results of the present study suggest that RSV

affects P-gp expressed in the small intestine instead of the kidney and liver.

In this study we assessed whether RSV could act as an inhibitor of P-gp mediated drug efflux. Previously it has been reported that RSV exerted an inhibitory effect on P-gp mediated efflux *in vitro* resulted in increased intracellular accumulation of daunorubicin [5]. In addition, an *in vitro* study has demonstrated that RSV enhanced the chemosensitivity of doxorubicin by increasing the cellular influx of doxorubicin [7]. Additionally, RSV has been found to potentiate the cytotoxic activity of docetaxel and doxorubicin due to enhanced intracellular levels by inhibition of P-gp [8]. Further, *in vivo* studies in rats demonstrated that RSV was able to increase the bioavailability of P-gp substrates through the inhibition of P-gp mediated drug efflux [9,10]. It has been reported that RSV exerted an inhibitory effect on drug metabolizing enzyme CYP3A4 *in vitro* [27], similarly RSV exhibited inhibitory effect on drug metabolizing enzymes including CYP3A4, CYP2D6, and CYP2C9 *in vivo* in human volunteers [28]. Therefore, it is possible a priori to assume that the interaction between RSV and FEX might result from the inhibition of RSV on the metabolism of FEX. However, to our knowledge, FEX is not a substrate of these enzymes and it has been revealed that FEX itself is not further metabolized [29,12]. It has been previously reported that verapamil (a standard P-gp inhibitor) enhanced the bioavailability of FEX through P-gp inhibition [30]. Moreover, our results were comparable to previous work where quercetin substantially enhanced the bioavailability of FEX in healthy volunteers by inhibiting P-gp mediated drug efflux in the intestine [13]. Based on these findings, we suggest that RSV acts as an inhibitor of P-gp mediated efflux of FEX in humans.

Recently, it has been reported that in addition to P-gp, FEX is also a substrate of drug uptake transporters, such as organic anion transporter (OAT-3) and organic anion-transporting polypeptides (OATP)-A (OATP1A2) and OATP-B (OATP2B1) [12,17,31,32]. Dresser et al. [33] reported that grapefruit and apple juices reduce FEX

bioavailability through the inhibition of OATP1A2 which resulted in delay in  $T_{max}$ . However, the inhibition of uptake transporters leads to a delay in  $T_{max}$ , but no significant difference was observed in  $T_{max}$  between the RSV treatment and control phases. Furthermore, even though the disposition of FEX may be affected by OATP, there were no reports available regarding the RSV having the inhibitory effect on OATP-mediated efflux. Therefore, the role of OATP in the interaction between RSV and FEX may be minor compared to that of P-gp.

RSV could be used as a P-gp inhibitor like verapamil, itraconazole and ritonavir and it is having the potential to increase the bioavailability of P-gp substrates like digoxin, talinolol including FEX. In addition, the intake of dietary supplements containing RSV may increase the absorption or oral bioavailability of FEX and can be useful to reduce the dose of FEX and possibly helpful in reducing the side effects of FEX. However, further studies should be carried out in patients to explore the RSV mediated P-gp interactions and the potential clinical application of dietary phytochemicals as potent P-gp modulators.

## Conclusions

The results of the present study showed that multiple use of RSV substantially enhanced the bioavailability of FEX, probably by the inhibition of P-gp mediated drug efflux in humans. The inhibition of P-gp by dietary phytochemicals containing RSV may provide a novel approach for improving the absorption and exposure of low bioavailable drugs like anti-viral and anti-cancer drugs. Accordingly, much effort is currently being expanded toward identifying natural compounds from plant origins that inhibit P-gp and developing as P-gp modulators.

## Acknowledgements

PN had support from University Grants Commission, New Delhi, India (F.36-130/2009.SR) and start-up research funds of University College of Pharmaceutical Sciences at Kakatiya University, Warangal, AP, India, for the submitted work. SY was partly supported by FAMRI-062558 and RO1CA143128.

## References

- Kalantari H, Das DK (2010) Physiological effects of resveratrol. *Biofactors* 36: 401-406.
- Soleas GJ, Diamandis EP, Golberg DM (1997) Resveratrol: a molecule whose time has come? and gone? *Clin Biochem* 30: 91-113.
- Bertelli AA, Giovanni L, Stradi R, Urien S, Tillement JP, et al. (1996) Kinetics of trans- and cis-resveratrol (3,4,5-trihydroxystilbene) after red wine oral administration in rats. *Int J Clin Pharmacol Res* 26: 77-81.
- Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, et al. (1997) Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 275: 218-220.
- Nabekura T, Kamiyama S, Kitagawa S (2005) Effects of dietary chemopreventive phytochemicals on P-glycoprotein function. *Biochem Biophys Res Commun* 327: 866-870.
- Quan F, Pan C, Ma Q, Zhang S, Yan L (2008) Reversal effect of resveratrol on multidrug resistance in KBV200 cell line. *Biomed Pharmacother* 62: 622-629.
- Kim TH, Shin YJ, Won AJ, Lee BM, Choi WS, et al. (2014) Resveratrol enhances chemosensitivity of doxorubicin in multidrug-resistant human breast cancer cells via increased cellular influx of doxorubicin. *Biochim Biophys Acta* 1840: 615-625.
- Al-AbdAM, Mahmoud AM, El-Sherbiny GA, El-Moselhy MA, Nofal SM, et al. (2011) Resveratrol enhances the cytotoxic profile of docetaxel and doxorubicin in solid tumour cell lines in vitro. *Cell Prolif* 44: 591-601.
- Choi JS, Choi BC, Kang KW (2009) Effect of resveratrol on the pharmacokinetics of oral and intravenous nicardipine in rats: possible role of P-glycoprotein inhibition by resveratrol. *Pharmazie* 64: 49-52.
- Hong SP, Choi DH, Choi JS (2008) Effects of resveratrol on the pharmacokinetics of diltiazem and its major metabolite, desacetyldiltiazem, in rats. *Cardiovasc Ther* 26: 269-275.
- Simpson K, Jarvis B (2000) Fexofenadine: a review of its use in the management of seasonal allergic rhinitis and chronic idiopathic urticaria. *Drugs* 59: 301-321.
- Tahara H, Kusuhara H, Maeda K, Koepsell H, Fuse E, et al. (2006) Inhibition of oat3-mediated renal uptake as a mechanism for drug-drug interaction between fexofenadine and probenecid. *Drug Metab Dispos* 34: 743-747.
- Kim KA, Park PW, Park JY (2009) Short-term effect of quercetin on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein, in healthy volunteers. *Eur J Clin Pharmacol* 65: 609-614.
- Drescher S, Schaeffeler E, Hitzl M, Hofmann U, Schwab M, et al. (2002) MDR1 gene polymorphisms and disposition of the P-glycoprotein substrate fexofenadine. *Br J Clin Pharmacol* 53: 526-534.
- Guo D, Zou J, Zhu Y, Lou S, Fan H, et al. (2010) Measurement of fexofenadine concentration in micro-sample human plasma by a rapid and sensitive LC-MS/MS employing protein precipitation: application to a clinical pharmacokinetic study. *Biomed Chromatogr* 24: 335-341.
- Matheny CJ, Lamb MW, Brouwer KR, Pollack GM (2001) Pharmacokinetic and pharmacodynamic implications of P-glycoprotein modulation. *Pharmacotherapy* 21: 778-796.
- Cvetkovic M, Leake B, Fromm MF, Wilkinson GR, Kim RB (1999) OATP and P-glycoprotein transporters mediate the cellular uptake and excretion of fexofenadine. *Drug Metab Dispos* 27: 866-871.
- Shon JH, Yoon YR, Hong WS, Nguyen PM, Lee SS, et al. (2005) Effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in relation to the MDR1 genetic polymorphism. *Clin Pharmacol Ther* 78: 191-201.
- Uno T, Shimizu M, Sugawara K, Tateishi T (2006) Lack of dose dependent effects of itraconazole on the pharmacokinetic interaction with fexofenadine. *Drug Metab Dispos* 34: 1875-1879.
- Shimizu M, Uno T, Sugawara K, Tateishi T (2006) Effects of itraconazole and diltiazem on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein. *Br J Clin Pharmacol* 61: 538-544.
- van Heeswijk RP, Bourbeau M, Campbell P, Seguin I, Chauhan BM, et al. (2006) Time-dependent interaction between lopinavir/ritonavir and fexofenadine. *J Clin Pharmacol* 46: 758-767.
- Wang Z, Hamman MA, Huang SM, Lesko LJ, Hall SD (2002) Effect of St John's wort on the pharmacokinetics of fexofenadine. *Clin Pharmacol Ther* 71: 414-420.
- Hamman MA, Bruce MA, Haehner-Daniels BD, Hall SD (2001) The effect of rifampin administration on the disposition of fexofenadine. *Clin Pharmacol Ther* 69: 114-121.
- Yamada S, Yasui-Furukori N, Akamine Y, Kaneko S, Uno T (2009) Effects of the P-glycoprotein inducer carbamazepine on fexofenadine pharmacokinetics. *Ther Drug Monit* 31: 764-768.
- Perloff MD, von Moltke LL, Greenblatt DJ (2002) Fexofenadine transport in Caco-2 cells: inhibition with verapamil and ritonavir. *J Clin Pharmacol* 42: 1269-1274.
- Petri N, Tannergren C, Rungstad D, Lennernas H (2004) Transport characteristics of fexofenadine in the Caco-2 cell model. *Pharm Res* 21: 1398-1404.
- Chan WK, Delucchi AB (2000) Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4. *Life Sci* 67: 3103-3112.
- Chow HH, Garland LL, Hsu CH, Vining DR, Chew WM, et al. (2010) Resveratrol modulates drug- and carcinogen-metabolizing enzymes in a healthy volunteer study. *Cancer Prev Res* 3: 1168-1175.
- Ling KH, Leeson GA, Burmaster SD, Hook RH, Reith MK, et al. (1995) Metabolism of terfenadine associated with CYP3A (4) activity in human hepatic microsomes. *Drug Metab Dispos* 23: 631-636.
- Yasui-Furukori N, Uno T, Sugawara K, Tateishi T (2005) Different effects of three transporting inhibitors, verapamil, cimetidine, and probenecid, on fexofenadine pharmacokinetics. *Clin Pharmacol Ther* 77: 17-23.
- Nozawa T, Imai K, Nezu J, Tsuji A, Tamai I (2004) Functional characterization of pH-sensitive organic anion transporting polypeptide OATP-B in human. *J Pharmacol Exp Ther* 308: 438-445.

**Citation:** Bedada SK, Yakkanti SA, Neerati P (2014) Resveratrol Enhances the Bioavailability of Fexofenadine in Healthy Human Male Volunteers: Involvement of P-Glycoprotein Inhibition. *J Bioequiv Availab* 6: 158-163. doi:[10.4172/jbb.1000198](https://doi.org/10.4172/jbb.1000198)

32. Niemi M, Kivisto KT, Hofmann U, Schwab M, Eichelbaum M, et al. (2005) Fexofenadine pharmacokinetics are associated with a polymorphism of the SLCO1B1 gene (encoding OATP1B1). *Br J Clin Pharmacol* 59: 602–604.

33. Dresser GK, Kim RB, Bailey DG (2005) Effect of grapefruit juice volume on the reduction of fexofenadine bioavailability: possible role of organic anion transporting polypeptides. *Clin Pharmacol Ther* 77: 170–177.

**Citation:** Bedada SK, Yakkanti SA, Neerati P (2014) Resveratrol Enhances the Bioavailability of Fexofenadine in Healthy Human Male Volunteers: Involvement of P-Glycoprotein Inhibition. *J Bioequiv Availab* 6: 158-163. doi:[10.4172/jbb.1000198](https://doi.org/10.4172/jbb.1000198)

### Submit your next manuscript and get advantages of OMICS Group submissions

#### Unique features:

- User friendly/feasible website-translation of your paper to 50 world's leading languages
- Audio Version of published paper
- Digital articles to share and explore

#### Special features:

- 350 Open Access Journals
- 30,000 editorial team
- 21 days rapid review process
- Quality and quick editorial, review and publication processing
- Indexing at PubMed (partial), Scopus, EBSCO, Index Copernicus and Google Scholar etc
- Sharing Option: Social Networking Enabled
- Authors, Reviewers and Editors rewarded with online Scientific Credits
- Better discount for your subsequent articles

Submit your manuscript at: <http://www.editorialmanager.com/jbiobio>

