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

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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 4544.48 ng.h/mL) and 65.2% (415.08 versus 685.58 ng/mL) respectively when compared to control phase. On other hand, apparent oral 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 T1/2, Ka 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 µM [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 doxetaxel 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 [14C] 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
Blood samples were collected in heparinized vacutainers and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24, 36 and 48h after FEX administration. Blood samples were drawn immediately before as well as after administration of FEX. Standardized meals were given at 4 and 10 h after dosing. Subjects were instructed to abstain from alcohol, caffeine-containing beverages, tea and fruit juices during the study period. All the subjects were nonsmokers, ate a normal diet and were not taking any herbal dietary supplements. The subjects were instructed to abstain from alcohol, caffeine-containing beverages, tea and fruit juices during the study period.

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 (Banglore, 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 ± 1.59 (range 26-31) years, weight of 68.3 ± 7.95 (range 52-82) kg, height of 173.2 ± 7.33 (range 165-188) cm and body mass index (BMI) of 22.76 ± 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, Banglore, 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 condition 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 48h after FEX administration. Blood samples were collected in heparinized vacutainers and centrifuged at 4,000 rpm for 15 min and the separated plasma samples were stored at -70°C until the assays were 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 μL) were added to 200 μL 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 μL of supernatant, then 5 μL 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 × 4.6 mm, i.d. 3.5 μm) 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 302.3 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 (Cmax) and the time taken to reach Cmax (Tmax) were estimated directly from the observed plasma concentration-time data. The elimination rate constant (Kel) was determined by linear regression analysis of logarithmic part of the plasma concentration-time curve. The half-life of FEX was calculated using the linear trapezoidal rule. The AUCfrom 0 to infinity (AUCinf) was calculated as AUC = Cmax × Tm/Kel, where Tm was the last plasma concentration measured. The half-life (T1/2) of FEX was calculated using T1/2 = ln2/Kel. The apparent oral clearance (CL/F) of FEX was calculated as CL/F = dose/AUC0-∞ and the apparent volume of distribution (Vd/F) was calculated using Vd/F = CL/F × T1/2.

Statistical analysis

The results are expressed as the mean ± SD. The pharmacokinetics of FEX between the control and treatment phases were compared to each other using a paired t-test (twotailed) and the Wilcoxon signed-rank test.
rank sum test after normality test using Kolmogorov-Smirnov test. All the data obtained were analyzed using GraphPad 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 ± 516.92 versus 4454.48 ± 1238.27 ng·h/mL, P < 0.05) as compared to control phase. In addition, RSV increased the mean Cmax value by 65.2% compared to that of the control phase (415.08 ± 67.63 versus 685.58 ± 184.24 ng/mL, P < 0.05). The mean value of CL/F and Vd/F were decreased significantly by 42.6% (49.46 ± 12.27 versus 28.37 ± 7.03 L/h, P < 0.05) and 42.1% (591.73 ± 197.25 versus 342.62 ± 108.56 L, P < 0.05) respectively after RSV treatment as compared to control phase. The AUC and Cmax 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 T1/2, Tmax and Kd of FEX between RSV treatment and control phases. The 90% CI for the ratio of geometric means (RSV treatment phase: control phase) for AUC, Cmax, CL/F and Vd/F were fell outside the interval (0.8–1.25) but in case T1/2, Tmax and Kd 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.

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](image1.png)

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 mean ± SD.
The insignificant difference in mean values of T1/2, Tmax and Kel between P-gp substrate [17]. RSV treatment significantly increased the Cmax and the inhibitory effect of RSV on P-gp in humans, we used FEX as a pharmacokinetics of FEX and increased its bioavailability. To assess of FEX, a substrate of P-gp in humans and found that RSV affected the values of AUC, Cmax, CL/F and Vd/F between control and treatment interval (0.8-1.25) which indicates the significant difference in mean phases. On the other hand, 90% CI for the ratio of geometric means for T1/2, Tmax and Kel fell within the interval (0.8-1.25) which indicates the significant difference in mean values of AUC, Cmax, CL/F and Vd/F between control and treatment phases. On the other hand, 90% CI for the ratio of geometric means for T1/2, Tmax and Kel fell within the interval (0.8-1.25) which indicates the significant difference in mean values of AUC, Cmax, CL/F and Vd/F 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 Cmax 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 Cmax 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 T1/2 and Tmax 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 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 Cmax 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 was observed in T1/2, Tmax and Kel 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, Cmax, CL/F and Vd/F were fell outside the interval (0.8-1.25) which indicates the significant difference in mean values of AUC, Cmax, CL/F and Vd/F between control and treatment phases. The 90% CI for the ratio of geometric means for T1/2, Tmax and Kel fell within the interval (0.8-1.25) which indicates the significant difference in mean values of T1/2, Tmax and Kel 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 Cmax 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 Cmax 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 T1/2 and Tmax 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 drug 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 drugmetabolizingenzymeCYP3A4 in vitro [27], similarly RSV exhibited inhibitory effect on drugmetabolizingenzymes 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-gpmediated 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 organicanion-transporting polypeptides (OATP)-A (OATP1A2) and OATP-B (OATP2B1) [12,17,31,32]. Dresser et al. [33] reported that grapefruit and apple juices increase FEX
bioavailability through the inhibition of OATP1A2 which resulted in delay in $T_{\text{max}}$. However, the inhibition of uptake transporters leads to a delay in $T_{\text{max}}$, but no significant difference was observed in $T_{\text{max}}$ 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, iraconazole and ritonavir and it is having the potential increase the bioavailability of P-gp substrates like digoxin, talinolol including FEX. In addition, the intake of dietary supplements containing RSV may increase the bioavailability of P-gp substrates like digoxin, talinolol including FEX. In addition, 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.

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