ORIGINAL ARTICLE

Quercetin declines plasma exposure of metoprolol tartrate in the rat model

Siva R. Challa,
Venkatesh R. Challa[1],
Satheesh K. Ragam[1]

Department of Pharmacology, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, [1]Department of Pharmacology, AMR Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India

J. Adv. Pharm. Technol. Res.

ABSTRACT

The study was undertaken to evaluate the effect of quercetin on the pharmacokinetics of Metoprolol tartrate. A single dose *in vivo* pharmacokinetic study was carried out in rat models. In this study, rats were treated with quercetin (10 mg/kg) and metoprolol tartrate (20 mg/kg) orally and blood samples were collected 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8, 12 h post treatment. Plasma concentration of metoprolol tartrate was estimated using reverse phase-high-performance liquid chromatography method. Area under the plasma concentration-time curve (AUC_{0-12}) of metoprolol has significantly ($P < 0.001$) decreased by 9.8 times in the metoprolol and quercetin combination group (9434.65 ± 3525.02) when compared with AUC_{0-12} metoprolol of metoprolol-alone treated group (962.17 ± 242.81). $AUC_{0-\infty}$ of metoprolol has significantly ($P < 0.001$) decreased by 14.9 times in the combination group (16670.79 ± 12129.06) in comparison to $AUC_{0-\infty}$ of metoprolol of metoprolol-alone treated group (1113.68 ± 441.83). the results obtained herein indicate that quercetin remarkably declines the plasma exposure of metoprolol when concomitantly administered by oral route.

Key words: Bioavailability, metoprolol tartrate, organic cation transporter-2, p-glycoprotein, pharmacokinetics, quercetin

INTRODUCTION

Metoprolol, a selective β1-adrenergic receptor antagonist, is widely used for the treatment of hypertension, angina pectoris, myocardial infarction, and arrhythmia.[1] It is marketed as a racemate, but the pharmacologic effect resides in the (S)-enantiomer.[2] Metoprolol is extensively metabolized in the liver through *O*-demethylation, α-hydroxylation, and *N*-dealkylation. Metoprolol *O*-demethylation accounts for about 65% of the dose whereas α-hydroxylation and *N*-dealkylation each account for 10%.[3] *In vitro* studies with human liver, microsomes have indicated that metoprolol α-hydroxylation is almost completely mediated by CYP2D6 and that *O*-demethylation is partially mediated by CYP2D6.[4] About 70% of metoprolol metabolism is estimated to be mediated by CYP2D6 *in vivo*.[5] In extensive metabolizers for CYP2D6, the metabolism of metoprolol is stereoselective, with the area under the plasma concentration–time curve extrapolated to infinity (AUC) of the (*S*)-metoprolol being significantly higher than that of (*R*)-metoprolol.[6]

Flavonoids are believed to alter the expression and activity of enzymes and transporters implicated in drug metabolism and excretion.[7-9] Effects of flavonoids on the pharmacokinetics of drugs have already been described in humans.[10-12] Quercetin is the most predominant flavonoid in plant foods, herbs, beverages and dietary supplements, e.g. onions, grapes, berries, apples, red wine, tea, St. John's wort and ginkgo. The daily dietary intake of quercetin is estimated to be in the range of 4-68 mg based on epidemiological studies in the US, Europe, and Asia,[13-16] but can be as high as several 100 mg in the dietary supplement and several grams in anticancer therapy.[17]

According recent studies, there is an increasing evidence that quercetin interacts with numerous xenobiotics. For instance, quercetin enhances the bioavailability of numerous drugs

Address for correspondence:
Dr. Siva Reddy Challa,
Department of Pharmacology, KVSR Siddhartha College of Pharmaceutical Sciences, Pinnamaneni Poly Clinic Road, Siddhartha Nagar, Vijayawada - 520 010, Andhra Pradesh, India.
E-mail: sivareddypharma@gmail.com

Access this article online	
Quick Response Code:	Website: www.japtr.org
	DOI: 10.4103/2231-4040.143038

like rosiglitazone,[18] fexofenadine[19] in humans, paclitaxel,[20] valsartan,[21] tamoxifen[22] in rat models, digoxin[23] in pigs. In contrast, quercetin decreases the bioavailability of simvastatin[24] in pigs and cyclosporine[25] in pigs and rats.

Quercetin was found to be cardio-protective based on experimental[26,27] and epidemiological[14-16] studies. Since metoprolol is cardioprotective in case of cardiovascular disorders like myocardial infarction, it is quite logical to investigate the effect of quercetin on the pharmacokinetics of metoprolol. Hence, the study was designed to see if there is any effect of quercetin on the pharmacokinetics of metoprolol in animal models.

MATERIALS AND METHODS

Drugs and chemicals

Metoprolol tartrate was obtained as a gift sample from Matrix Laboratories; Hyderabad (India). Quercetin was purchased from Sigma-Aldrich Chemical Co., St. Louis, MO, USA. All high-performance liquid chromatography (HPLC) grade solvents (acetonitrile, Sodium Lauryl Sulfate, Ortho Phospharic Acid, and water) were procured from SD Fine chemicals, Mumbai, India. All other chemicals used were of analytical grade and purchased from local chemical agencies.

Equipments

High-performance liquid chromatography (Waters 2695 [isocratic system]) with Gelman science vacuum pump and Lab India Ultraviolet (UV 3000+) UV-visible Spectrophotometer. Zodiac C8, 150 × 4.6 mm, 5 µm was used. The system was equipped with Empower-2 Software. Sonicator (Hwashin Technology, Seoul, Korea), Biofuge (Hearus instrument, Hanau, Germany), micropipettes, tubes (Tarsons Products Pvt. Ltd, Kolkata, India) were used.

Animals

Albino Wistar rats (National Institute of Nutrition, Hyderabad, India), of either sex, weighing 200-250 g, were selected. Animals were maintained under standard laboratory conditions at 25°C ± 2°C, relative humidity 50% ± 15% and normal photoperiod (12 h dark/12 h light). Commercial pellet diet (Rayon's Biotechnology Pvt Ltd, India) and water were provided *ad libitum*. The experimental protocol was approved by the Institutional Animal Ethics Committee of KVSR Siddhartha College of Pharmaceutical Sciences and studies were carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, India. IAEC Clearance number of the article was IAEC/11/03/2014/008.

Pharmacokinetic study in rats

Experimental procedure

Wistar rats were randomly distributed into two groups of six animals in each group. Before doing, all experimental animals were fasted for 18 h and but water was given *ad libitum*. Experimental design was as follows. Group I: Metoprolol tartrate (20 mg/kg; p.o.), Group II: Metoprolol tartrate (20 mg/kg; p.o.) + (quercetin (10 mg/kg; p.o.). Blood was collected from orbital sinuses using 2 ml Eppendorf tubes containing sodium citrate as an anticoagulant. Plasma was separated by centrifugation at 5000 RPM/10 min and stored at −20°C until further analysis. Plasma concentration of metoprolol was estimated by a sensitive reverse phase-HPLC (RP-HPLC) method.

Preparation of drugs

Metoprolol tartrate was dissolved in distilled water whereas quercetin (10 mg) was accurately weighed before being triturated in a dry clean mortar with the addition of 30 µL of tween 80 and then, required a volume of 0.9% sodium CMC was added and triturated again to suspend the drug in it. Then, suspension was transferred to plastic vials. Quercetin suspension was administered concomitantly with metoprolol tartrate solution.

Blood sample collection from rats

In this study, blood samples were collected at time points 0, 0.25,0.5, 0.75, 1, 1.5, 2, 4, 8, 12 h post treatment from the retro-orbital sinuses using fine capillary tubes into 2 ml Eppendorf tubes containing sodium citrate as an anticoagulant. Plasma was separated by centrifugation at 5000 RPM/10 min and stored at −20°C until further analysis. Plasma concentration of metoprolol was estimated by a sensitive RP-HPLC method.

Estimation of metoprolol by a sensitive reverse phase-high-performance liquid chromatography method

Chromatographic conditions

The mobile phase consisted of a buffer (1.3 g of Sodium Lauryl Sulfate and 1 ml Ortho Phosphoric acid transfer into 1litre water and it was made to dissolve and adjust pH-2.0 with orthophosphoric acid) and acetonitrile in the ratio of (50:50). The injection volume was 20 µL. The mobile phase was delivered at 1.0 ml/min. The mobile phase was filtered through 0.22 µm membrane filter. The flow rate was adjusted to 1.5 ml/min, and the effluent was monitored at 224 nm. The total run time of the method was set at 6 min. Retention time was obtained at 4-5 min.

Preparation for the calibration curve of metoprolol tartrate for *in vivo* samples

Preparation of linearity solution

Linearity solutions of various concentrations were prepared ranging from 0.2 µg to 1.2 µg/mL of Metoprolol tartrate. To 250 µL of sample, 250 µL of the mobile phase was added and was mixed well. Further, 500 µL of acetonitrile was added to precipitate all the proteins and mixed in vortex cyclomixture. Then, these were centrifuged at 4000 RPM for 15-20 min and supernatant solution was collected in HPLC vial and was injected into HPLC and chromatogram

was recorded.

Construction of calibration curve

A stock solution representing 100 µg/ml of metoprolol tartrate was prepared in a dilution (Water and acetonitrile were mixed in the ratio of 70:30) and this solution was stored at 2-8°C until use. Six different concentration levels (0.20, 0.30, 0.40, 0.80, 1.00 and 1.20 µg/ml) were prepared from each stock solution and diluted with above diluents. Each concentration solution was prepared in triplicate. A linear relationship was obtained between the peak area and the corresponding concentrations. The slope of the plot determined by the method of least-square regression analysis was used to calculate the metoprolol tartrate concentration in an unknown sample. A linear calibration curve in the range of 0.20 μg^{-1} 20 µg was established ($r^2 = 0.999$). Retention time was obtained at 4-5 min.

Preparation of plasma sample

Plasma samples were labeled accordingly to their time intervals and then, centrifuged. To 250 µL of sample, 250 µL of the mobile phase was added and mixed well. Further, 500 µL of acetonitrile was added to precipitate all the proteins and mixed in vortex cyclomixture. Then, it was again centrifuged at 4000 RPM for 15-20 min and supernatant solution was collected in HPLC vial and was injected into HPLC and chromatogram was recorded.

Pharmacokinetic data analysis

The plasma concentrations versus time data obtained from each individual rat were submitted to a non-compartmental pharmacokinetic analysis using Kinetica Software (Version 5.1, Thermo Electron Corporation, and USA). The maximum plasma concentrations (C_{max}) and times to achieve maximum plasma concentrations (T_{max}) were obtained directly from the individual plasma concentration-time curves. AUC_{0-12} was calculated by the linear trapezoidal rule, and $AUC_{0-\infty}$ was determined by the following formula:

$$AUC_{0-\infty} = C_{last}/K_{el} + AUC_{0-12}$$

Where C_{last} is the last quantifiable concentration. The apparent total body clearance or oral clearance (CL/F) was calculated as follows:

$$CL/F = dose/AUC_{0-\infty}$$

The elimination rate constant (K_{el}) was obtained by linear regression of the terminal phase, and the elimination half-life ($t_{1/2}$) was calculated as $0.693/K_{el}$.

Statistical analysis

The results were expressed as mean ± standard deviation. Comparisons of plasma concentration versus time profiles of metoprolol tartrate-alone group and metoprolol tartrate with the quercetin combination group were analyzed using two-way ANOVA followed by Bonferroni *post hoc* test, whereas comparisons of pharmacokinetic parameters of these two groups were analyzed using unpaired Student's *t*-test. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ were considered to be statistically significant.

RESULTS

Calibration curve

Linear relationship was obtained between the peak area and the corresponding concentrations. The equations of linear regression were performed using the least-square method. Retention time was obtained at 5 min. Chromatogram was shown in Figure 1 and Linearity graph was shown in Figure 2.

Effect of quercetin on plasma concentration time profiles of metoprolol

The plasma concentration versus time profiles of metoprolol in rats following oral treatment of metoprolol tartrate with and without quercetin was shown in Figure 3. From the comparison of plasma concentration profiles of metoprolol in the absence and presence of quercetin, it is clear that there was a significant reduction in the plasma drug exposure of metoprolol in the combination group at following time points 0.25 h ($P < 0.001$), 0.5 h ($P < 0.001$), 0.75 h ($P < 0.001$), 1st h ($P < 0.001$), 1.5th h ($P < 0.001$), 2nd h ($P < 0.001$) and 4th h ($P < 0.05$). It is quite interesting to find that the metoprolol concentrations in metoprolol and quercetin combination group are almost negligible at 4th h, whereas in the metoprolol alone group; metoprolol concentrations were even slightly present at 12th h.

Effect of quercetin on pharmacokinetic parameters of metoprolol

The calculated pharmacokinetic parameters of metoprolol tartrate in rats were shown in Table 1. AUC_{0-12} of metoprolol has significantly ($P < 0.001$) decreased in the combination

Table 1: Comparison of pharmacokinetic parameters of metoprolol in rats before and after treatment with quercetin

Parameters	Metoprolol	Metoprolol and quercetin
C_{max} (ng/ml)	5757.24±1010.69	1411.03±275.62***
T_{max} (h)	0.5±0.0	0.5±0.0
AUC_{0-12} (ng/h/ml)	9434.65±3525.02	962.17±242.81***
$AUC_{0-\infty}$ (ng/h/ml)	16670.79±12129.06	1113.68±441.83***
$t_{1/2}$ (h)	5.91±2.20	2.35±1.25
Clearance (L/h)	0.002016±0.001536	0.019936±0.006477***
Volume of distribution (V_d) (L/h)	0.00794±0.004347	0.023878±0.011763*

The data are represented as mean±SD; $n=6$, ***$P<0.001$, *$P<0.05$ compared to metoprolol group analyzed by unpaired Student's *t*-test. SD: Standard deviation, AUC: Area under the plasma concentration-time curve

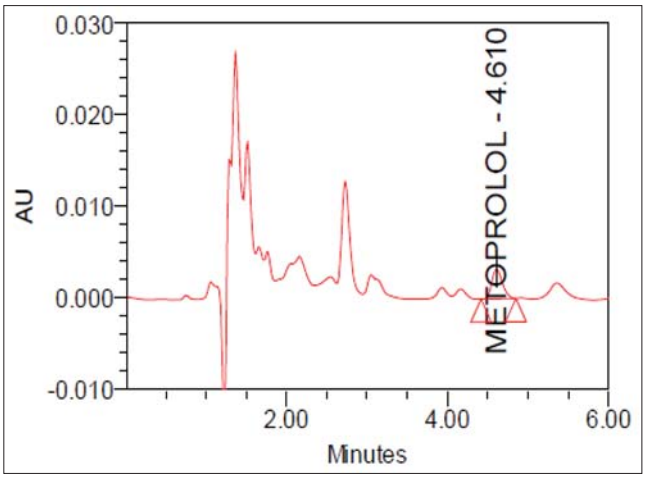

Figure 1: Metoprolol chromatogram in plasma spiked with metoprolol tartrate

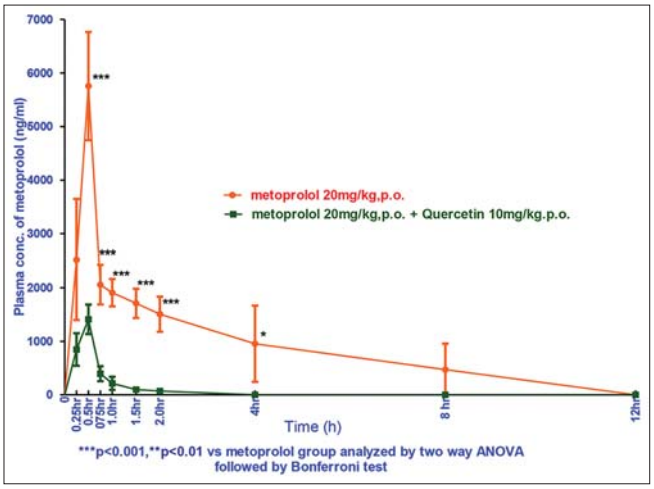

Figure 3: Time versus plasma concentration profile of metoprolol in metoprolol alone treatment group and metoprolol and quercetin combination group

group (9434.65 ± 3525.02) than AUC_{0-12} of metoprolol of metoprolol-alone treated group (962.17 ± 242.81) [Figure 4]. This decrease is almost 9.8 times. $AUC_{0-\infty}$ metoprolol has significantly ($P < 0.001$) decreased in the combination group (16670.79 ± 12129.06) than $AUC_{0-\infty}$ of metoprolol of metoprolol alone treated group (1113.68 ± 441.83). This decrease is 14.9 times. In a similar manner, the C_{max} of metoprolol has significantly ($P < 0.001$) decreased in the combination group (1411.03 ± 275.62) than C_{max} of metoprolol of metoprolol alone treated group (962.17 ± 242.81). This decrease is almost 4 times. These parameters were altered without significant alteration in the t_{max} of metoprolol. V_d and CL of metoprolol has significantly ($P < 0.01$ and $P < 0.001$) decreased in the combination group, respectively.

DISCUSSION

The results of the study revealed that there is a significant decrease in the bioavailability of metoprolol administered

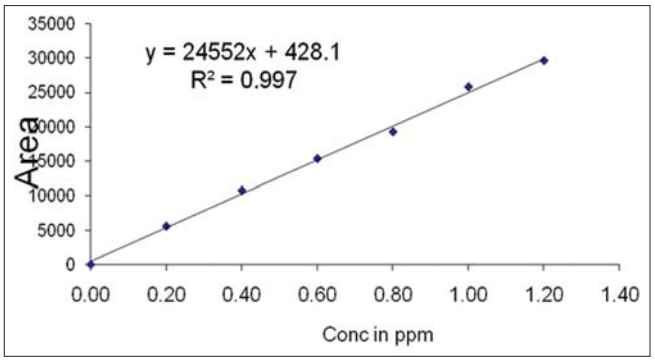

Figure 2: Metoprolol linearity graph plotted with plasma spiked with Metoprolol tartrate

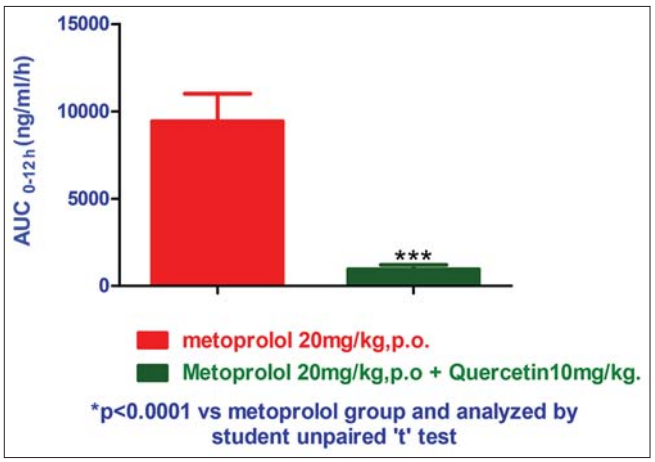

Figure 4: Comparison of area under the plasma concentration-time curve from time 0 to 12 h of Metoprolol in Metoprolol alone treatment group and Metoprolol and quercetin combination group

concomitantly with quercetin, and that was evidenced clearly by significant ($P < 0.001$) decrease in the AUC_{0-12} and $AUC_{0-\infty}$. Mechanisms underlying the interaction between these two drugs are uncertain. However, the various possibilities of interaction are discussed. There was evidence that propranolol, beta-blocker, stimulated four to six-fold increase in MDR1 mRNA and P-glycoprotein (p-gp) protein expression measured by quantitative real-time polymerase chain reaction and immunoblotting, respectively. These changes were accompanied by an induction in transporter activity measured by rhodamine 123 efflux. In contrast, metoprolol, a compound with similar permeability but no affinity for PGP had no effect on PGP expression.[28] According to this study, it is clearly evident that metoprolol has no ability to increase the expression of p-gp, while other β-blocker like propranolol able to do so. Hence, the decreased bioavailability of metoprolol probably not attributed to the increased expression of p-gp.

Until date, there are no reports stating that metoprolol is a p-gp substrate though other beta-blocker, carvedilol is a known p-gp substrate.[29] Hence, it is very unlikely

that metoprolol and quercetin interact at p-gp because metoprolol is not reportedly a p-gp substrate though quercetin is a known p-gp inhibitor.[30] This rule out the possibility of decreased bioavailability due to p-gp mediated interaction between these two drugs. It is presumed that these two drugs are likely to interact at other transporters.

Substantial evidence shows that these drugs interact at organic cation transporter (OCT-2) which is one of transporter accounts for the secretion of beta-blockers in the basolateral membrane of the intestine. In support of this idea, the previous study investigated the affect of selected flavonoids (quercetin, isoquercitrin, spiraeoside, rutin, kaempferol, naringenin, naringin and kempferol) on the transport of the P-gp substrate [3H] talinolol (beta-blocker) across Caco-2 cell monolayers. In addition, Researchers attempted to explore the mechanism behind the interaction observed in this system. The results revealed that six of the investigated flavonoids reduced the secretory flux of talinolol across Caco-2 cells. However, none of the selected flavonoids was able to replace [3H] talinolol from its binding to P-gp. However, the investigated flavonoids did show potency to inhibit OCT-mediated transport. Thus, previous *in vitro* results demonstrate that flavonoids bear the ability to interfere with secretory intestinal transport processes. This might be due to the interaction with P-gp, but apparently not via competition at the talinolol binding site of P-gp. Another mode of interaction may be the inhibition of members of the OCT-family, which is located at the basolateral membrane of intestinal epithelial cells.[9] Thus, metoprolol might be interacting at OCT-2 at intestine, and this interaction could be one possibility for the decreased bioavailability of metoprolol.

In addition, our results also revealed that there is significant ($P < 0.001$) decrease in the C_{max} of metoprolol by quercetin co-administration. This reduction might be attributed to the significant enhancement of volume of distribution of metoprolol by quercetin. At the same time, clearance of the metoprolol was also significantly increased along with quercetin. It is unclear as to how and which mechanism is contributing to the increased clearance of the drug. Quercetin is believed to be a CYP3A4 inhibitor, whereas metoprolol is CYP2D6 substrate. Hence, it is very unlikely to have the interaction mediating CYP metabolic enzymes. It is imperative to identify the mechanisms to further clarify our result.

CONCLUSION

Our results reveal that quercetin reduced plasma exposure of metoprolol in rat models. However, mechanism of interaction is unclear. This interaction could be of clinical significance. However, further clinical studies are needed to confirm this interaction.

ACKNOWLEDGMENTS

The authors are grateful to Matrix Laboratories, Hyderabad for providing the gift sample of metoprolol tartrate and Principal and management of KVSR Siddhartha College of Pharmaceutical Sciences (i.e. Siddhartha Academy of General and Technical Education) for providing facilities to carrying out this research work.

REFERENCES

1. Ha HR, Follath F. Metabolism of antiarrhythmics. Curr Drug Metab 2004;5:543-71.
2. Lennard MS, Tucker GT, Woods HF. The polymorphic oxidation of beta-adrenoceptor antagonists. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1986;11:1-17.
3. Borg KO, Carlsson E, Hoffmann KJ, Jönsson TE, Thorin H, Wallin B. Metabolism of metoprolol-(3-h) in man, the dog and the rat. Acta Pharmacol Toxicol (Copenh) 1975;36:125-35.
4. Otton SV, Crewe HK, Lennard MS, Tucker GT, Woods HF. Use of quinidine inhibition to define the role of the sparteine/debrisoquine cytochrome P450 in metoprolol oxidation by human liver microsomes. J Pharmacol Exp Ther 1988;247:242-7.
5. Johnson JA, Burlew BS. Metoprolol metabolism via cytochrome P4502D6 in ethnic populations. Drug Metab Dispos 1996;24:350-5.
6. Lennard MS, Tucker GT, Silas JH, Freestone S, Ramsay LE, Woods HF. Differential stereoselective metabolism of metoprolol in extensive and poor debrisoquin metabolizers. Clin Pharmacol Ther 1983;34:732-7.
7. Cermak R, Wolffram S. The potential of flavonoids to influence drug metabolism and pharmacokinetics by local gastrointestinal mechanisms. Curr Drug Metab 2006;7:729-44.
8. Morris ME, Zhang S. Flavonoid-drug interactions: Effects of flavonoids on ABC transporters. Life Sci 2006;78:2116-30.
9. Ofer M, Wolffram S, Koggel A, Spahn-Langguth H, Langguth P. Modulation of drug transport by selected flavonoids: Involvement of P-gp and OCT? Eur J Pharm Sci 2005;25:263-71.
10. Alemdaroglu NC, Dietz U, Wolffram S, Spahn-Langguth H, Langguth P. Influence of green and black tea on folic acid pharmacokinetics in healthy volunteers: Potential risk of diminished folic acid bioavailability. Biopharm Drug Dispos 2008;29:335-48.
11. Bailey DG, Dresser GK, Leake BF, Kim RB. Naringin is a major and selective clinical inhibitor of organic anion-transporting polypeptide 1A2 (OATP1A2) in grapefruit juice. Clin Pharmacol Ther 2007;81:495-502.
12. Rajnarayana K, Reddy MS, Krishna DR. Diosmin pretreatment affects bioavailability of metronidazole. Eur J Clin Pharmacol 2003;58:803-7.
13. Knekt P, Järvinen R, Seppänen R, Hellövaara M, Teppo L, Pukkala E, *et al.* Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. Am J Epidemiol 1997;146:223-30.
14. Hertog MG, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, *et al.* Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. Arch Intern Med 1995;155:381-6.
15. Hertog MG, Feskens EJ, Hollman PC, Katan MB, Kromhout D. Dietary antioxidant flavonoids and risk of coronary heart disease: The Zutphen Elderly Study. Lancet 1993;342:1007-11.
16. Rimm EB, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of flavonoids and risk for coronary heart disease in male health professionals. Ann Intern Med 1996;125:384-9.
17. Lamson DW, Brignall MS. Antioxidants and cancer, part 3: Quercetin. Altern Med Rev 2000;5:196-208.

18. Kim KA, Park PW, Kim HK, Ha JM, Park JY. Effect of quercetin on the pharmacokinetics of rosiglitazone, a CYP2C8 substrate, in healthy subjects. J Clin Pharmacol 2005;45:941-6.
19. Kim KA, Park PW, Park JY. Short-term effect of quercetin on the pharmacokinetics of fexofenadine, a substrate of P-glycoprotein, in healthy volunteers. Eur J Clin Pharmacol 2009;65:609-14.
20. Choi JS, Jo BW, Kim YC. Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin. Eur J Pharm Biopharm 2004;57:313-8.
21. Challa VR, Babu PR, Challa SR, Johnson B, Maheswari C. Pharmacokinetic interaction study between quercetin and valsartan in rats and *in vitro* models. Drug Dev Ind Pharm 2013;39:865-72.
22. Shin SC, Choi JS, Li X. Enhanced bioavailability of tamoxifen after oral administration of tamoxifen with quercetin in rats. Int J Pharm 2006;313:144-9.
23. Wang YH, Chao PD, Hsiu SL, Wen KC, Hou YC. Lethal quercetin-digoxin interaction in pigs. Life Sci 2004;74:1191-7.
24. Cermak R, Wein S, Wolffram S, Langguth P. Effects of the flavonol quercetin on the bioavailability of simvastatin in pigs. Eur J Pharm Sci 2009;38:519-24.
25. Hsiu SL, Hou YC, Wang YH, Tsao CW, Su SF, Chao PD. Quercetin significantly decreased cyclosporin oral bioavailability in pigs and rats. Life Sci 2002;72:227-35.
26. Annapurna A, Reddy CS, Akondi RB, Rao SR. Cardioprotective actions of two bioflavonoids, quercetin and rutin, in experimental myocardial infarction in both normal and streptozotocin-induced type I diabetic rats. J Pharm Pharmacol 2009;61:1365-74.
27. Panda S, Kar A, Banerjee T, Sharma N. Combined effects of quercetin and atenolol in reducing isoproterenol-induced cardiotoxicity in rats: Possible mediation through scavenging free radicals. Cardiovasc Toxicol 2012;12:235-42.
28. Collett A, Tanianis-Hughes J, Warhurst G. Rapid induction of P-glycoprotein expression by high permeability compounds in colonic cells *in vitro*: A possible source of transporter mediated drug interactions? Biochem Pharmacol 2004;68:783-90.
29. Bart J, Dijkers EC, Wegman TD, de Vries EG, van der Graaf WT, Groen HJ, *et al.* New positron emission tomography tracer [(11) C] carvedilol reveals P-glycoprotein modulation kinetics. Br J Pharmacol 2005;145:1045-51.
30. Sarkar MA. Quercetin not only inhibits P-glycoprotein efflux activity but also inhibits CYP3A isozymes. Cancer Chemother Pharmacol 1995;36:448-50.

How to cite this article: Challa SR, Challa VR, Ragam SK. Quercetin declines plasma exposure of metoprolol tartrate in the rat model. J Adv Pharm Technol Res 2014;5:185-90.

Source of Support: Nil, **Conflict of Interest:** Nil.