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Research Paper

Effects of myricetin, an antioxidant, on the pharmacokinetics of losartan and its active metabolite, EXP-3174, in rats: possible role of cytochrome P450 3A4, cytochrome P450 2C9 and P-glycoprotein inhibition by myricetin

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Abstract

Objectives The effects of myricetin, a natural flavonoid, on the pharmacokinetics of losartan and its active metabolite, EXP-3174, were investigated in rats. Losartan and myricetin interact with cytochrome P450 (CYP) enzymes and P-glycoprotein, and the increase in the use of health supplements may result in myricetin being taken concomitantly with losartan as a combination therapy to treat or prevent cardiovascular diseases.

Methods The pharmacokinetic parameters of losartan and EXP-3174 were determined after oral administration of losartan (9 mg/kg) to rats in the presence or absence of myricetin (0.4, 2 and 8 mg/kg). The effects of myricetin on P-glycoprotein as well as CYP3A4 and CYP2C9 activity were also evaluated.

Key findings Myricetin inhibited CYP3A4 and CYP2C9 enzyme activity with a 50% inhibition concentration of 7.8 and 13.5 μM, respectively. In addition, myricetin significantly enhanced the cellular accumulation of rhodamine 123 in MCF-7/ADR cells overexpressing P-glycoprotein in a concentration-dependent manner. The pharmacokinetic parameters of losartan were significantly altered by myricetin compared with the control. The presence of myricetin (2 or 8 mg/kg) increased the area under the plasma concentration–time curve of losartan by 31.4–61.1% and peak plasma concentration of losartan by 31.8–50.2%. Consequently, the absolute bioavailability of losartan in the presence of myricetin increased significantly ($P < 0.05$, 2 mg/kg; $P < 0.01$, 8 mg/kg) compared with the control. There was no significant change in the time to reach the peak plasma concentration, apparent volume of distribution at steady state or terminal half-life of losartan in the presence of myricetin. Furthermore, concurrent use of myricetin (8 mg/kg) significantly decreased the metabolite–parent area under the plasma concentration–time curve ratio by 20%, implying that myricetin may inhibit the CYP-mediated metabolism of losartan to its active metabolite, EXP-3174.

Conclusions The enhanced bioavailability of losartan may be mainly due to inhibition of the CYP3A4- and CYP2C9-mediated metabolism of losartan in the small intestine or in the liver, and the P-glycoprotein efflux pump in the small intestine by myricetin.

Keywords cytochrome P450 enzymes; EXP-3174; losartan; myricetin; P-glycoprotein

Introduction

Losartan is the prototype of a new class of orally active and long-lasting selective antagonists of angiotensin II receptors used for the treatment of hypertension.[1–3] Following oral administration, losartan is rapidly absorbed, reaching maximum concentrations 1–2 h after dosing, but it has a low and highly variable oral bioavailability (12.1–66.6%).[4] Losartan is metabolized to the active metabolite EXP-3174, which is about 10-fold more potent than its parent drug. Thus, the clinical hypotensive activity is predominantly mediated by the active metabolite EXP-3174, although losartan itself exhibits good efficacy.[5] In addition to metabolism to EXP-3174, losartan undergoes glucuronidation on the hydroxyl and tetrazole groups and shows species differences in the extent of oxidation versus conjugation.[6] Some in-vitro and in-vivo studies have indicated that losartan is metabolized to EXP-3174 mainly by cytochrome P450 (CYP) 2C9 and 3A4 enzymes.[6–10] Furthermore, Soldner *et al.*[11] suggested that losartan is a substrate of P-glycoprotein (P-gp). Considering that losartan is a substrate of both CYP enzymes and P-gp, modulation of CYP and P-gp activities may cause significant

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changes in the pharmacokinetic profiles of losartan and its active metabolite EXP-3174. For example, Zaidenstein *et al.*[12] reported that concomitant intake of grapefruit juice significantly altered some of the pharmacokinetic parameters of losartan and its metabolite EXP-3174 in healthy volunteers via inhibition of CYP3A4 metabolism. Kobayashi *et al.*[13] demonstrated that bucolome, a CYP2C9 inhibitor, significantly increased the area under the plasma concentration–time curve (AUC) of losartan but decreased the AUC of EXP-3174. In addition, flavonoids epigallocatechin and hesperidin increased the $AUC_{0-\infty}$ and peak plasma concentration (C_{max}) of verapamil (a substrate of CYP3A4 and P-gp) in rats,[14,15] and morin and hesperidin increased the $AUC_{0-\infty}$ and C_{max} of diltiazem (a substrate of CYP3A4 and P-gp) in rats.[16,17] Such studies strongly suggest that potential drug interactions could occur via the inhibition of CYP-mediated metabolism of losartan.

Flavonoids represent a group of phytochemicals that are produced by various plants in high quantities.[18] Flavonoids have been referred to as 'nature's biological response modifiers' because of strong experimental evidence of their inherent ability to modify the body's reaction to allergens, viruses and carcinogens. It has been reported that flavonoids possess anti-inflammatory, antioxidant, anti-allergic, hepatoprotective, antithrombotic, antiviral and anticarcinogenic activities.[19] In recent years, interest in the effects of flavonoids on the cardiovascular system has been rekindled.[20] Myricetin is a naturally occurring flavonoid found in several foods including onions, berries and grapes, as well as red wine.[21,22] Myricetin has antihaemorrhagic potential,[23] effects in myocardial infarction[24] and antihypertension effects.[20]

Von Moltke *et al.*[25] reported that myricetin inhibits human CYP3A4 and CYP2C9, while Václavíková *et al.*[26] found that myricetin inhibits human CYP3A4 and CYP2C8. Thus, the inhibitory effects of myricetin against human CYP enzymes remain somewhat unclear. Myricetin is an inhibitor of P-gp in the KB/MDR cell line,[27] but the inhibitory effect of myricetin against P-gp is ambiguous elsewhere. We therefore re-evaluated the inhibition of CYP enzyme activity and P-gp activity by myricetin using CYP inhibition assays and rhodamine 123 retention assays in P-gp-overexpressing MCF-7/ADR cells.

Losartan and myricetin interact with CYP enzymes and P-gp, and the increase in the use of health supplements may result in myricetin being taken concomitantly with losartan to treat or prevent cardiovascular diseases. It is important to assess the potential pharmacokinetic interactions after the concurrent use of losartan and myricetin or myricetin-containing dietary supplements in order to ensure the effectiveness and safety of the drug therapy. However, the possible effects of myricetin on the bioavailability and pharmacokinetics of losartan have not been reported *in vivo*. In the present study, we investigated the effects of myricetin on the pharmacokinetics of losartan and its active metabolite, EXP-3174, in rats.

Materials and Methods

Materials

Losartan, its metabolite EXP-3174 and the internal standard L-158.809 were kindly provided by Merck Co. (NJ, USA). Myricetin was purchased from Sigma-Aldrich Co. (St Louis, MO, USA). Acetonitrile, methanol and *tert*-butylmethylether were purchased from Merck Co. (Darmstadt, Germany). All other chemicals were of reagent grade and all solvents were of HPLC grade.

Animal studies

All animal studies were performed in accordance with the Guiding Principles in the Use of Animals in Toxicology adopted by the Society of Toxicology (USA) and the experimental protocols were approved by the Animal Care Committee of Chosun University. Male Sprague-Dawley rats (280–300 g) were purchased from Dae Han Laboratory Animal Research and Co. (Eumsung, Korea), and had free access to normal standard chow diet (Superfeed Company, Wonju, Korea) and tap water. Throughout the experiment, the animals were housed, four or five per cage, in laminar flow cages maintained at 22 ± 2°C, 50–60% relative humidity, under a 12-h light–dark cycle. The animals were kept in these facilities for at least 1 week before the experiments. Rats were fasted for 24 h before beginning the experiments.

Drug administration

Rats were divided into five groups ($n = 6$ in each group) as follows: Group 1: losartan (9 mg/kg p.o.; control); Groups 2–4: losartan (9 mg/kg p.o.) with myricetin (0.4, 2 or 8 mg/kg, given orally at 30 min before losartan administration); and Group 5: losartan (3 mg/kg i.v., control). Blood samples were collected from the femoral artery into heparinized tubes at 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after oral administration of losartan and at 0, 0.1, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h after intravenous administration of losartan. The blood samples were centrifuged at 16 810*g* for 5 min and the plasma samples obtained were stored at –40°C until analysed by HPLC.

HPLC assay

The plasma concentrations of losartan were determined by the HPLC assay reported by Zarghi *et al.*[28] with slight modification. Briefly, 50 μl of L-158.809 (0.2 μg/ml dissolved in methanol; an internal standard) and 0.5 ml of acetonitrile were added to a 0.2-ml plasma sample in a polypropylene microtube. The mixture was then stirred for 5 min and centrifuged at 16 810*g* for 10 min. A 0.5-ml sample of the organic layer was transferred into a clean test tube and evaporated under a gentle stream of nitrogen gas at 35°C. The residue was reconstituted in 150 μl of the mobile phase and centrifuged at 16 810*g* for 5 min and then a 70-μl sample of the supernatant was injected into the HPLC system. The HPLC system comprised two solvent delivery pumps (model LC-10AD; Shimadzu Co., Japan), a UV-Vis detector (model SPD-10A), a system controller (model SCL-10A), a degasser (model DGU-12A) and an autoinjector (SIL-10AD). The UV detector was set at 215 nm. The stationary phase was a Kromasil KR 100-5C_8 column (5 μm, 4.6 × 250 mm; EKA Chemicals, Sweden) and the mobile phase was acetonitrile/0.01 M phosphate buffer (41 : 59 v/v, pH 2.5 adjusted with phosphoric acid). The retention times at a flow rate of 0.8 ml/min were as follows: internal standard 6.7 min, losartan 11.5 min and EXP-3174 17.1 min. The lower limit

of quantification for losartan and EXP-3174 in rat plasma was 10 ng/ml.

CYP3A4 and CYP2C9 inhibition assays

Inhibition assays on human CYP3A4 and 2C9 enzyme activity were performed in a multiwell plate using a CYP inhibition assay kit (GENTEST, Woburn, MA, USA) as described previously.[29] Briefly, human CYP enzymes were obtained from baculovirus-infected insect cells. CYP substrates (7-BFC and 7-MFC for CYP3A4) were incubated with or without test compounds in the enzyme/substrate containing buffer with 1 pmol of P450 enzyme and an NADPH-generating system (1.3 mM NADP, 3.54 mM glucose 6-phosphate, 0.4 U/ml glucose 6-phosphate dehydrogenase and 3.3 mM $MgCl_2$) in a potassium phosphate buffer (pH 7.4). Reactions were terminated by adding a stop solution (0.5 M Tris-buffer mixed with acetonitrile) after incubation for 45 min. Metabolite concentrations were measured by a spectrofluorometer (Molecular Device, Sunnyvale, CA, USA) at an excitation wavelength of 409 nm and an emission wavelength of 530 nm. A positive control (1 μM ketoconazole for CYP3A4) was run on the same plate and produced 99% inhibition. All experiments were done in duplicate and the results are expressed as the percent of inhibition.

Rhodamine 123 retention assay

MCF-7/ADR cells were seeded in 24-well plates. At 80% confluence, the cells were incubated in fetal bovine serumfree Dulbecco's modified Eagle's medium for 18 h. The culture medium was changed to Hanks' balanced salt solution and the cells were incubated at 37°C for 30 min. After incubation of the cells with 20 μM rhodamine 123 in the presence of myricetin (3, 10, and 30 μM) for 90 min, the medium was completely removed. The cells were then washed three times with ice-cold phosphate buffer (pH 7.0) and lysed in lysis buffer. The rhodamine 123 fluorescence in the cell lysates was measured using excitation and emission wavelengths of 480 and 540 nm, respectively. Fluorescence values were normalized to the total protein content of each sample and presented as the ratio to control.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was performed using WinNonlin software version 5.2.1 (Pharsight Co., Mountain View, CA, USA). The area under the plasma concentration–time curve from time zero to the time of the last measured concentration (AUC_{0-t}; C_{last}) was calculated by the linear trapezoidal rule. The AUC zero to infinity ($AUC_{0-\infty}$) was obtained by the addition of AUC_{0-t} and the extrapolated area determined by C_{last}/K_{el}, the elimination rate constant. The peak plasma concentration (C_{max}) and the time to reach the peak plasma concentration (T_{max}) were observed values from the experimental data. K_{el} was calculated by log-linear regression of losartan or EXP-3174 concentration data during the elimination phase. The terminal half-life ($t_{1/2}$) was calculated by $0.693/K_{el}$. The total body clearance for the intravenous route (CL_t) was calculated from D/AUC, where D is the dose of losartan. The mean residence time (MRT) was calculated by dividing the first moment of AUC ($AUMC_{0-\infty}$) by $AUC_{0-\infty}$. The apparent volume of distribution at steady state (Vd_{ss}) was estimated by the product of $MRT_{i.v.}$ and CL_t after intravenous dosing. The bioavailability of losartan was calculated by $AUC_{oral}/AUC_{i.v.} \times Dose_{i.v.}/Dose_{oral} \times 100$, the relative bioavailability was calculated by $(AUC_{control}/AUC_{with\ myricetin}) \times 100$ and the metabolite–parent ratio (MR) was estimated by $(AUC_{EXP\text{-}3174}/AUC_{losartan}) \times (MW_{losartan}/MW_{EXP\text{-}3174})$.

Statistical analysis

All means were presented with their standard deviations. The pharmacokinetic parameters were compared by one-way analysis of variance, followed by *a posteriori* testing with Dunnett's correction. A value of $P < 0.05$ was considered statistically significant.

Results

Inhibition of CYP3A4 and 2C9

The inhibitory effect of myricetin on CYP3A4 and CYP2C9 activity is shown in Figure 1. Myricetin inhibited CYP3A4 and CYP2C9 enzyme activity and the 50% inhibition concentration (IC50) values of myricetin on CYP3A4 and CYP2C9 activity were determined as 7.8 and 13.5 μM, respectively.

Rhodamine 123 retention assay

As shown in Figure 2, accumulation of rhodamine 123, a P-gp substrate, was reduced in MCF-7/ADR cells over-expressing P-gp compared with that in MCF-7 cells lacking P-gp. The concurrent use of myricetin enhanced the cellular uptake of rhodamine 123 in a concentration-dependent manner and showed a statistically significant ($P < 0.01$) increase over the concentration range of 3–30 μM. This result suggests that myricetin significantly inhibits P-gp activity.

Effects of myricetin on the plasma concentrations after oral administration

The plasma concentration–time profiles of losartan in the presence of myricetin were significantly increased compared with those in the control group in Figure 3. The mean pharmacokinetic parameters of losartan are summarized in Table 1.

As shown in Table 1, the presence of myricetin (2 or 8 mg/kg) significantly altered the pharmacokinetic parameters of losartan compared with those in the control group given losartan alone. Myricetin significantly ($P < 0.05$, 2 mg/kg; $P < 0.01$, 8 mg/kg) increased the $AUC_{0-\infty}$ of losartan by 31.4–61.1% and the C_{max} of losartan by 31.8–50.2%. Consequently, the absolute bioavailability of losartan in the presence of myricetin was significantly ($P < 0.05$, 2 mg/kg; $P < 0.01$, 8 mg/kg) higher than that in the control group. The relative bioavailability of losartan was 1.14- to 1.61-fold greater than that of the control group. However, there was no significant change in T_{max}, Vd_{ss} and $t_{1/2}$ of losartan with myricetin. Given that losartan is a substrate of P-gp, CYP3A4 and CYP2C9, the enhanced bioavailability of losartan may be due to inhibition of the CYP3A- and

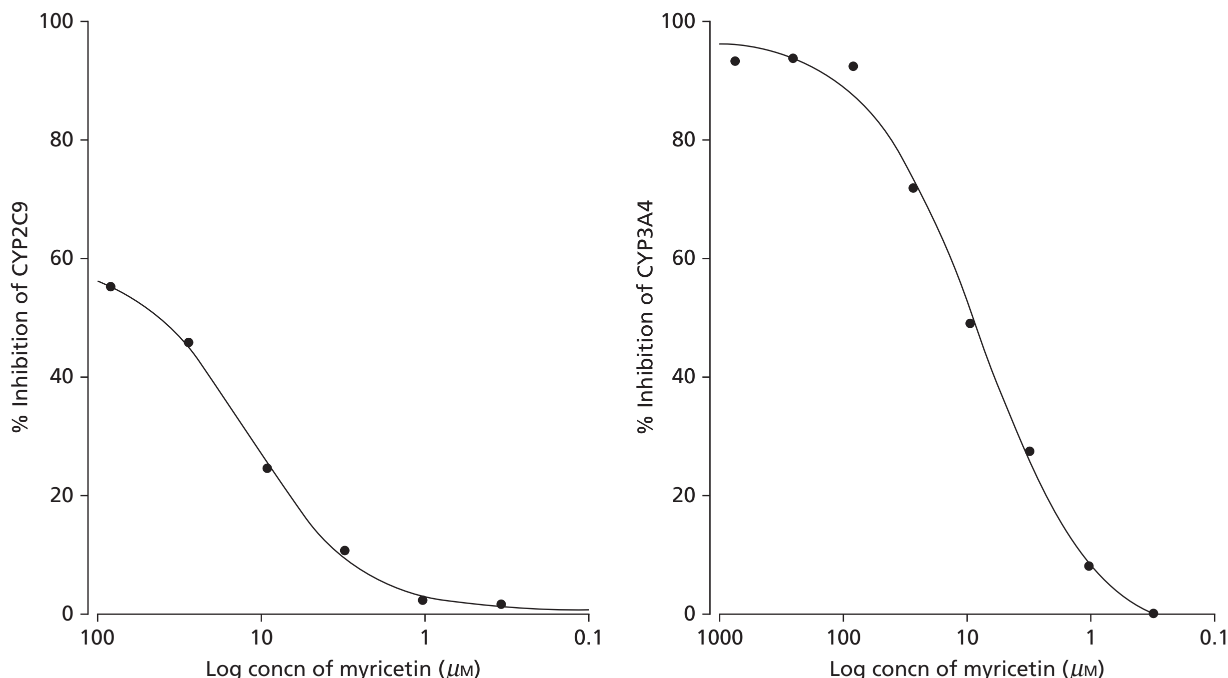

Figure 1 Inhibitory effect of myricetin on CYP3A4 and CYP2C9 activity. All experiments were done in duplicate and results are expressed as the percent of inhibition. The IC50 values of myricetin on CYP3A4 and CYP2C9 activity were 7.81 and 13.5 μM, respectively.

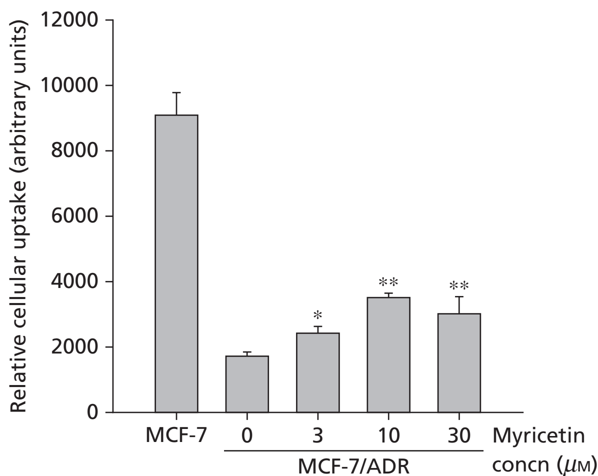

Figure 2 Rhodamine 123 retention. MCF-7/ADR cells were preincubated with myricetin for 24 h. After incubation of MCF-7/ADR cells with 20 μM rhodamine 123 for 90 min, fluorescence values in cell lysates were measured. The values were divided by the total protein content in each sample. Data represents mean ± s.d. of six separate samples. *$P < 0.05$, **$P < 0.01$, significant difference compared with control MCF-7 cells.

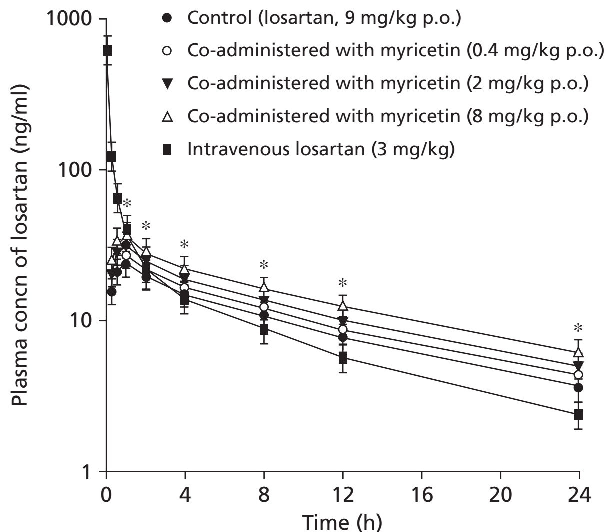

Figure 3 Plasma concentration–time profiles of losartan after intravenous or oral administration of losartan in the presence and absence of myricetin. Data are the means ± s.d., $n = 6$. *$P < 0.05$, significant difference compared with the control group given losartan alone.

CYP2C9-mediated metabolism of losartan in the liver and the P-gp efflux pump in the small intestine by myricetin.

Effects of myricetin on the plasma concentrations of EXP-3174

The plasma concentration–time profiles of EXP-3174, an active metabolite, in the presence of myricetin were significantly increased compared with those in the control group as seen in Figure 4. As shown in Table 2, myricetin significantly ($P < 0.05$, 8 mg/kg) increased the $AUC_{0-\infty}$ of losartan by 29.6% and the C_{max} of losartan by 31.2%. The metabolite–parent AUC ratio decreased by 20% in the presence of myricetin compared with that in the control group, indicating that myricetin may inhibit the CYP-mediated metabolism of losartan. However, there was no significant change in T_{max}, Vd_{ss} and $t_{1/2}$ of EXP-3174 with myricetin.

Table 1 Pharmacokinetic parameters of losartan after oral administration in the presence and absence of myricetin

Parameter	Losartan (9 mg/kg p.o.; control)	Losartan co-administered with myricetin			Losartan (3 mg/kg i.v.)
		0.4 mg/kg p.o.	2 mg/kg p.o.	8 mg/kg p.o.	
$AUC_{0-\infty}$ (ng h/ml)	283 ± 57.4	323 ± 65.9	372 ± 74.5*	456 ± 88.1**	296 ± 59.6
C_{max} (ng/ml)	23.9 ± 4.7	27.0 ± 5.4	31.5 ± 6.3*	35.9 ± 6.8**	ND
T_{max} (h)	0.92 ± 0.21	0.92 ± 0.21	1.17 ± 0.41	1.17 ± 0.41	ND
Vd_{ss}(l/kg)	7.1 ± 2.4	6.7 ± 2.0	6.0 ± 1.9	5.3 ± 1.8	ND
$t_{1/2}$ (h)	10.5 ± 2.8	10.9 ± 2.9	11.2 ± 3.2	11.6 ± 3.3	8.7 ± 2.5
Absolute bioavailability (%)	28.7 ± 6.5	32.8 ± 7.1	37.7 ± 8.2*	46.1 ± 9.8**	100
Relative bioavailability (%)	100	114	131	161	ND

Data are the means ± s.d., $n = 6$. $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 h to infinity; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; Vd_{ss}, volume of distribution; $t_{1/2}$, terminal half-life; ND, not determined. *$P < 0.05$, **$P < 0.01$, significant difference compared with the control group given oral losartan alone.

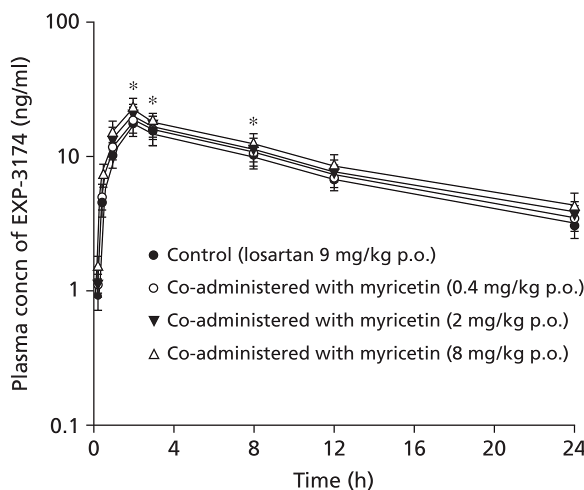

Figure 4 Plasma concentration–time profiles of EXP-3174 after oral administration of losartan in the presence and absence of myricetin. Data are the means ± s.d., $n = 6$. *$P < 0.05$, significant difference compared with the control group given losartan alone.

Discussion

Some in-vitro and in-vivo studies have indicated that losartan is metabolized to EXP-3174 mainly by CYP2C9 and 3A4 enzymes.[6–10] Furthermore, Soldner *et al*.[1] suggested that losartan is a substrate of P-glycoprotein (P-gp). Considering that losartan is a substrate of both CYP enzymes and P-gp, the modulation of CYP and P-gp activities may cause the significant changes in the pharmacokinetic profiles of losartan and its active metabolite, EXP-3174.

P-gp is co-localized with CYP3A4 in the apical membrane of the intestine,[30,31] and they act synergistically in regulating the first-pass metabolism and bioavailability of many oral drugs. The inhibitory effect of myricetin against CYP3A4-mediated metabolism was confirmed by the use of a recombinant CYP3A4 enzyme. As shown in Figure 1, myricetin exhibited an inhibitory effect against CYP3A4-mediated metabolism, with an IC50 of 1.8 μм. Furthermore, the cell-based assay using rhodamine 123 indicated that myricetin (30 μм) significantly ($P < 0.01$) inhibited P-gp-mediated drug efflux (Figure 2). These results appeared to be consistent with the findings of some previous studies.[25,27]

The results suggest that myricetin may improve the bioavailability of losartan, a substrate of CYP3A4 and P-gp. Therefore, the pharmacokinetic characteristics of losartan were evaluated in the absence and the presence of myricetin in rats. As CYP3A9 expressed in rats corresponds to the ortholog of CYP3A4 in humans,[32] rats were selected as the animal model in this study to evaluate the potential pharmacokinetic interactions mediated by CYP3A4, although there should be some extent of difference in enzyme activity between rats and human.[33]

As summarized in Table 1,myricetin significantly increased the $AUC_{0-\infty}$ of losartan by 31.4–61.1% and the C_{max} of losartan by 31.8–50.2%. The absolute bioavailability of losartan in the presence of myricetin was significantly ($P < 0.05$) higher than that in the control group. Myricetin inhibited CYP3A and CYP2C9 isozymes and P-gp activity in the present study. Our results appeared to be consistent with the findings of some previous studies,[14–17] in which epigallocatechin and hesperidin increased the bioavailability of verapamil (a substrate of CYP3A4 and P-gp) in rats, and in which morin and hesperidin increased the $AUC_{0-\infty}$ and C_{max} of diltiazem (a substrate of CYP3A4 and P-gp) in rats. Piao *et al*.[34] reported that morin, a flavonoid, significantly enhanced the bioavailability of nicardipine because of possible nicardipine inhibition of P-gp and intestinal metabolism by morin.

The results also appeared to be consistent with the findings of other studies.[12,13] For example, Zaidenstein *et al*.[12] reported a significant difference in some of the pharmacokinetic parameters of losartan and its metabolite EXP-3174 as a result of concomitant intake of grapefruit juice, a CYP3A4 inhibitor.

As summarized in Table 2, myricetin significantly decreased metabolite–parent AUC ratios (MR). This result appears to be consistent with the findings of previous studies reporting that the MR, a characteristic of the magnitude of metabolic conversion, was significantly changed, indicating the inhibition of CYP3A4-mediated metabolism of losartan

Table 2 Pharmacokinetic parameters of EXP-3174 after oral administration of losartan in the presence and absence of myricetin

Parameter	Losartan (9 mg/kg p.o.; control)	Losartan co-administered with myricetin		
		0.4 mg/kg p.o.	2 mg/kg p.o.	8 mg/kg p.o.
$AUC_{0-\infty}$ (ng h/ml)	230 ± 43.3	245 ± 49.2	269 ± 53.6	298 ± 60.4*
C_{max} (ng/ml)	17.3 ± 3.5	18.5 ± 3.8	20.6 ± 4.4	22.7 ± 4.8*
T_{max} (h)	1.67 ± 0.52	1.67 ± 0.52	1.83 ± 0.41	2.17 ± 0.41
Vd_{ss} (l/kg)	9.1 ± 2.7	8.5 ± 2.4	8.0 ± 2.3	7.6 ± 2.1
$t_{1/2}$ (h)	9.6 ± 2.6	9.7 ± 2.8	10.1 ± 3.0	10.4 ± 3.0
MR (%)	0.81 ± 0.18	0.76 ± 0.17	0.72 ± 0.14	0.65 ± 0.13*

Data are the means ± s.d., $n = 6$. $AUC_{0-\infty}$, area under the plasma concentration–time curve from 0 h to infinity; C_{max}, peak plasma concentration; T_{max}, time to reach C_{max}; MR, metabolite–parent ratio ($AUC_{EXP-3174}/AUC_{losartan}$) ($MW_{losartan}/MW_{EXP-3174}$). *$P < 0.05$, significant difference compared with the control group given losartan alone.

after co-administration of grapefruit juice, and concurrent use of bucolome, a CYP2C9 inhibitor, significantly increased the AUC of losartan by the inhibition of metabolic conversion of losartan to EXP-3174.[12,13] Also epigallocatechin and morin significantly decreased MR of verapamil and diltiazem, respectively.[14,16] Those studies in conjunction with our present findings suggest that the combination of losartan and CYP (CYP2C9, CYP3A4) inhibitors may result in a significant pharmacokinetic drug interaction.

Although the intestine contains CYP enzymes, there is no evidence of significant oxidation of losartan by the enterocytes using either in-vitro or in-situ absorption models.[35] In contrast, some previous studies have suggested that the active metabolite EXP-3174 detected in rats is most likely of hepatic origin.[35,36] In the present study, the decrease in the metabolite–parent AUC ratios may be mainly due to the inhibitory effect of myricetin on hepatic metabolism rather than intestinal metabolism of losartan. Therefore, the enhanced bioavailability of losartan may be mainly due to inhibition of the CYP3A and CYP2C9-mediated metabolism of losartan in the liver and the P-gp efflux pump in the small intestine by myricetin. Although potentially an adverse effect, this interaction may provide a therapeutic benefit whereby it enhances bioavailability and lowers the dose administered. The present study raises awareness about potential drug interactions with concomitant use of myricetin and losartan, and further evaluation in clinical studies is necessary.

Conclusions

Myricetin significantly enhanced the oral bioavailability of losartan in rats. The enhanced bioavailability of losartan may be due to inhibition of the CYP3A- and CYP2C9-mediated metabolism of losartan in the liver and the P-gp efflux pump in the small intestine by myricetin. The clinical significance of these findings should be further investigated in clinical trials. Concomitant use of myricetin with losartan may require close monitoring for potential drug interactions.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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