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Effect of myricetin on cytochrome P450 isoforms CYP1A2, CYP2C9 and CYP3A4 in rats

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Myricetin is one of the main ingredients of Chinese bayberry, which is used as a traditional medicine. The purpose of this study was to find out whether myricetin influences the rat cytochrome P450 (CYP) enzymes (CYP1A2, CYP2C9 and CYP3A4) by using cocktail probe drugs *in vivo*. A cocktail solution at a dose of 5 mL/kg, which contained phenacetin (20 mg/kg), tolbutamide (5 mg/kg) and midazolam (10 mg/kg), was orally administered to rats treated for 14 days with myricetin. Blood samples were collected at a series of time-points and the concentrations of probe drugs in plasma were determined by HPLC-MS/MS. The corresponding pharmacokinetic parameters were calculated by the software of DAS 2.0. Our study showed that treatment with multiple doses of myricetin had no effects on rat CYP1A2. However, CYP2C9 and CYP3A4 enzyme activities were inhibited after multiple doses of myricetin. Therefore, caution is needed when myricetin is co-administered with CYP2C9 or CYP3A4 substrates, which may result in herb-drug interactions.

1. Introduction

Chinese bayberry (*Myrica rubra* Sieb. et Zucc.), the economically most important plant in the *Myricaceae* family, is a plant with high health-promoting value. It is a subtropical plant native to China that has been cultured for thousands of years in Asian countries (Chen et al. 2008). Chinese bayberry fruit is quite popular due to its delicious taste and attractive color. There are about 200,000 ha of commercially cultivated bayberry in China. The fruits ripen from May through June and early July in the main Chinese production areas such as Zhejiang, Jiangsu, and Fujian provinces, earlier than the majority of other domestically-grown fruits. Therefore, bayberry provides an extended dietary source of fresh fruit for Chinese consumers and a high economic return to producers due to the lack of competition within this market niche. Besides its attractive fruit, bayberry is also a plant with high medicinal value as different organs of the bayberry tree have been used as traditional Chinese medicines for more than 2000 years (Sun et al. 2013). Bayberry extracts have been used as an astringent and an antidote, or for the treatment of diarrhea, digestive problems, headache, burns and skin diseases in Chinese or Japanese folk medicine.

Myricetin (3,5,7,3′,4′,5′-hexahydroxyflavone), a naturally occurring flavonol, is commonly found in tea, berries, fruits, and Chinese bayberry (*Myrica rubra* Sieb. et Zucc.). Phytochemical investigations showed that myricetin is one of the main ingredients of Chinese bayberry, which is used as a folk medicine. Myricetin has been shown to possess antioxidative and cytoprotective properties (Ko et al. 2005; Ong and Khoo 1997). A therapeutic effect of myricetin in patients with cardiovascular diseases associated with diabetes mellitus has also been reported (Ong and Khoo 1997). Myricetin has also demonstrated the ability to improve glucose utilization, lowering plasma-glucose levels in a type 1 diabetes-like animal model (Liu et al. 2006). Furthermore, myricetin displays the characteristics of antiobesity and antihyperlipidaemic effects (Chang et al. 2012). There are some reports that myricetin inhibits human cytochrome P450 (CYP) enzymes and myricetin is an inhibitor of P-gp in the KB/MDR cell line (Kitagawa et al. 2005; Vaclavikova et al. 2003; von Moltke et al. 2004), but the effects of myricetin against human CYP enzymes are ambiguous. Therefore, we re-evaluated the effects of myricetin on CYP activities in rats.

Because herbal compounds have been considered to be better bioavailable than synthesis-based drugs, attempts to develop new drugs originating from natural products have largely been made worldwide (Kim et al. 2008; Zhou et al. 2004). However, following an increase in consumption of natural compounds for use as herbal medicines, potential risks related to pharmacokinetic interactions have been reported. For example, herb-drug interactions through modulation of CYP, a primary cause of drug-drug or herb-drug interactions, have been reported for St. John's wort and *Ginkgo biloba* (Guengerich 1997; Markowitz et al. 2000, 2003).

The CYP family is involved in 95% of drug-drug interaction cases associated with a modulation of drug metabolism by inductive or inhibitive effects of active components derived from herbs or drugs. In addition, inhibition of CYP has been reported as the cause of 70% of drug interactions (Iwata et al. 2005). Therefore, the possibility of herb-drug interactions, particularly through the inhibitory effects of pharmacological components on CYP enzymes should be considered in the process of drug development.

Recently, a high-throughput screening approach using a cocktail of specific drug-probe substrates and high performance liquid

Table 1: Main pharmacokinetic parameters of phenacetin in rats (n = 6, Mean ± SD)

Parameter	CG	TG
$t_{1/2}$ (h)	3.863 ± 0.221	4.213 ± 0.278
T_{max}(h)	0.247 ± 0.005	0.245 ± 0.005
C_{max} (ng/mL)	3698.978 ± 231.772	3709.360 ± 247.562
$AUC_{(0-\infty)}$(μg·h/L)	15475.691 ± 329.547	17794.913 ± 355.949
$MRT_{(0-\infty)}$(h)	5.267 ± 0.047	6.244 ± 0.218
CL (L/h/kg)	1.292 ± 0.011	1.124 ± 0.022

*Significantly different from control, $P < 0.05$;** Significantly different from control, $P < 0.01$.

chromatography mass spectrometry (HPLC-MS) is used. This approach allows a rapid and simultaneous assay of several CYP enzyme activities, with increased throughput, reduced costs and labor (Kozakai et al. 2012; Youdim and Saunders 2010). This has been made possible due to advances in chromatographic methods and mass-spectrometry sensitivity and the establishment of specific probes for each clinically relevant CYP isoform (Bu et al. 2001a, b, c, d; Gao et al. 2002).

In this study, phenacetin, tolbutamide and midazolam were selected to evaluate the potential inductive or inhibitory effects of myricetin on CYP1A2, CYP2C9 and CYP3A4 by a cocktail method in rats.

2. Investigations and results

2.1. Validation of the cocktail approach

Under the conditions described in the experimental section, a validated HPLC-MS/MS method was used to determine the levels of the three probe drugs (phenacetin for CYP1A2, tolbutamide for CYP2C9, and midazolam for CYP3A4) in rat plasma after oral administration of myricetin for 14 days. Standard curves of each probe drug in rat plasma were established over the concentration range 5.0–1000 ng/mL. The calibration curves were: $y = 0.00335c + 0.027775$ for phenacetin; $y = 0.00395c + 0.06663$ for tolbutamide; $y = 0.033575c + 0.035475$ for midazolam (c = concentration of each probe drug; y = peak area ratio of each probe drug versus internal standard). The results of linear regression analysis showed that the correlation coefficients of the calibration curves for all sample types were above 0.996. The detection limits of the assays for phenacetin, tolbutamide and midazolam were all found to be 5.0 ng/mL. The precision and accuracy of intra-day and inter-day of all the probe drugs for the low-, medium- and high-quality control samples were below 15%. The result of the chromatographic validation showed that the assay methods were suitable for this study.

2.2. Effect of myricetin on the activity of CYP1A2 in rats

CYP1A2 activity was evaluated by comparing pharmacokinetic behaviors of phenacetin between the control group (CG) and the treatment group (TG). The pharmacokinetic profiles of phenacetin before and after oral administration of myricetin for fourteen days are shown in Table 1 and Fig. 1. Compared with CG, the pharmacokinetic parameters ($t_{1/2}$, T_{max}, C_{max}, $AUC_{(0-\infty)}$, $MRT_{(0-\infty)}$ and CL) of phenacetin showed no significant change. Our results indicated that myricetin has no inductive or inhibitory effect on the activity of CYP1A2 after multiple oral administration in rats.

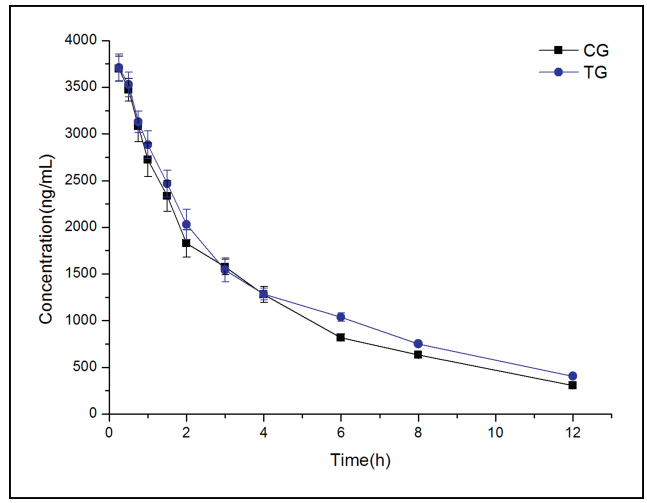

Fig. 1: Mean plasma concentration-time curves of phenacetin in rats.

2.3. Effect of myricetin on the activity of CYP2C9 in rats

Pharmacokinetic profiles of tolbutamide after myricetin treatment were used to describe the activity of CYP2C9. The effects of myricetin on pharmacokinetic parameters of tolbutamide in rats are presented in Table 2. Mean plasma concentration-time curves of tolbutamide in different groups are presented in Fig. 2. Compared with CG, the $t_{1/2}$ of tolbutamide became 8.050 h from 6.717 h, the T_{max} became 2.545 h from 2.147 h, the C_{max} increased to 1.153 times of CG, the $AUC_{(0-\infty)}$ significantly increased (1.412 times of CG), and the CL significantly decreased. There data show that CYP2C9 activity was significantly inhibited by myricetin after multiple oral administration in rats.

2.4. Effect of myricetin on the activity of CYP3A4 in rats

As shown in Table 3 and Fig. 3, compared with pre-administration, the $t_{1/2}$ of midazolam extended, T_{max} changed a little, the C_{max}, $AUC_{(0-\infty)}$ and $MRT_{(0-\infty)}$ increased, CL decreased. These results suggested that CYP3A4 activity was significantly inhibited by myricetin after multiple oral administration in rats.

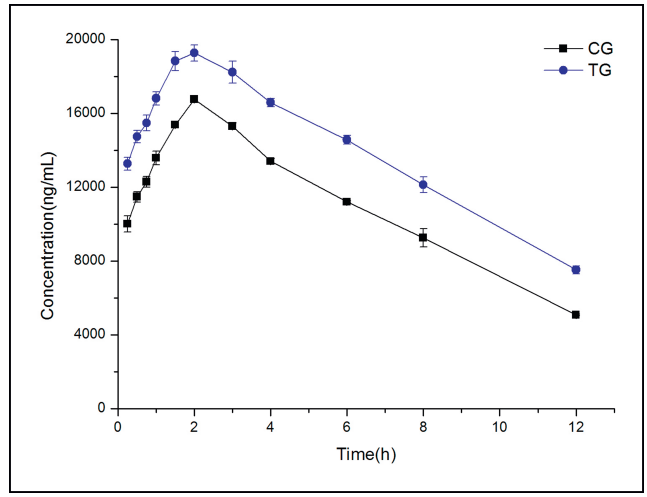

Fig. 2: Mean plasma concentration-time curves of tolbutamide in rats.

Table 2: Main pharmacokinetic parameters of tolbutamide in rats (n = 6, Mean ± SD)

Parameter	CG	TG
$t_{1/2}$ (h)	6.717 ± 1.081	8.050 ± 1.495*
T_{max}(h)	2.147 ± 0.231	2.545 ± 0.355*
C_{max} (ng/mL)	16758.209 ± 106.251	19323.430 ± 248.996*
$AUC_{(0-\infty)}$(μg·h/L)	187618.832 ± 17984.636	264952.114 ± 27274.814**
$MRT_{(0-\infty)}$(h)	10.180 ± 1.450	12.176 ± 2.000*
CL(L/h/kg)	0.027 ± 0.003	0.019 ± 0.002**

*Significantly different from control, $P < 0.05$;** Significantly different from control, $P < 0.01$.

3. Discussion

CYP, an important factor in drug metabolism, is clinically involved in the drug-drug/herb interactions by CYPs inhibition and/or CYPs induction. Among these CYP subtypes, CYP1A, 2C and 3A, are the main subtypes that contribute to the metabolism of drugs (Nebert and Dalton 2006). In this study, we focused on the influence of myricetin on the activities of the three major CYP isozymes.

Many methods are available to measure the enzyme activity of CYPs. The probe substrate approach can be used as a general screening tool to characterize CYPs' inhibition and induction effects for a drug (Bjornsson et al. 2003). It cannot only detect the activity of a variety of drug-metabolizing enzymes, but also reveal inductive or inhibitory effects. The cocktail approach has been, in general, proposed as a screening tool for potential *in vivo* drug-drug interactions. As compared with the individual administration of specific probes, the cocktail approach has several distinct advantages.

Thus, in our study, a probe substrate approach by HPLC-MS/MS was established and validated to evaluate the inductive or inhibitory effects of myricetin on CYP1A2, CYP2C9 and CYP3A4 by determination of the pharmacokinetic parameters of three representative substrate drugs phenacetin, tolbutamide and midazolam. The CYP gene families CYP1, CYP2, and CYP3 appear to be responsible for the majority of drug metabolism.

It is well known that a major contributing factor of drug-drug interactions is the inhibition of CYP enzyme-mediated activities, of which human CYP1A2 accounts for about 13% of the total CYP content in human liver (Shimada et al. 1994). CYP1A2 is involved in the metabolism of several endogenous compounds and some widely used drugs, also it could activate procarcinogens such as aflatoxin B1, a commonly recognized hepatocarcinogen (Zhou et al. 2009). In this study, we found that there was no significant difference of the pharmacokinetic parameters of the CYP1A2 substrate phenacetin before and after administration of myricetin. This suggests that myricetin has no inductive or inhibitory effect on the activity of CYP1A2 after multiple oral administration in rats.

Table 3: Main pharmacokinetic parameters of midazolam in rats (n = 6, Mean ± SD)

Parameter	CG	TG
$t_{1/2}$ (h)	3.734 ± 0.104	4.212 ± 0.151*
T_{max}(h)	0.227 ± 0.015	0.245 ± 0.022
C_{max} (ng/mL)	4042.788 ± 72.783	4715.429 ± 51.374*
$AUC_{(0-\infty)}$(μg·h/L)	9879.381 ± 102.725	17319.061 ± 103.572**
$MRT_{(0-\infty)}$(h)	3.680 ± 0.100	5.228 ± 0.193**
CL (L/h/kg)	1.012 ± 0.011	0.578 ± 0.017**

*Significantly different from control, $P < 0.05$;** Significantly different from control, $P < 0.01$.

CYP2C9 is one of the most abundant CYP enzymes in the human liver, forming 20% of the total hepatic CYP content and metabolizing about 15% of clinical drugs (Zhou et al. 2009). Therefore, the induction or inhibition of CYP2C9 activity may lead to some undesirable effects. According to our results, CYP2C9 activity could be significantly inhibited by myricetin after multiple oral administration in rats. This result appeares to be consistent with the findings of other studies (Choi et al. 2010; von Moltke et al. 2004). Therefore, those studies in conjunction with our present findings suggest that the combination of myricetin and CYP2C9 substrate drugs may result in a significant pharmacokinetic drug interaction.

CYP3A4 is known as the rate-limiting step in the metabolism and clearance of a large variety of clinical medications, including many pediatric drugs (Lu et al. 2003). In the present study, we investigated the activity of CYP3A4 by midazolam as probe substrate. According to Table 3 and Fig. 3, CYP3A4 activity was significantly inhibited by myricetin after multiple oral administration in rats. These results show that when myricetin is used in combination with other drugs metabolized by CYP3A4, herb-drug interactions may occur. This result also shows to be consistent with the findings of another study (Vaclavikova et al. 2003).

In conclusion, the inconspicuous effects of myricetin on CYP1A2 suggest that there are no clinically relevant herb-drug interactions between the drugs metabolized by these enzymes and myricetin when they are used concomitantly. In addition, from our present results, we cannot exclude that comedication of myricetin with drugs metabolized by CYP2C9 and CYP3A4 may inhibit metabolism and increase plasma concentrations of these drugs, which will result in herb-drug interactions. Further clinical studies are required to fully assess the safety of myricetin in terms of CYP.

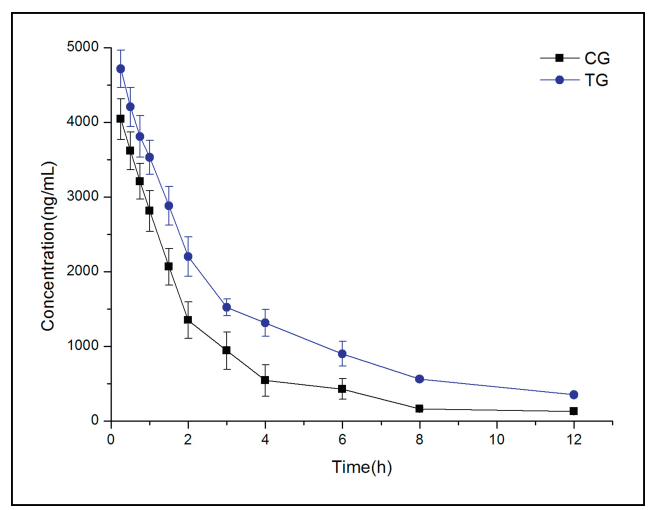

Fig. 3: Mean plasma concentration-time curves of midazolam in rats.

4. Experimental

4.1. Chemicals and reagents

Myricetin (purity > 98.0%) was purchased from Sigma-Aldrich Company (St. Louis, USA). Phenacetin (purity > 98.0%), tolbutamide (purity > 98.0%), midazolam (purity > 98.0%) and the internal standard carbamazepine (IS, purity > 98.0%) were also purchased from Sigma-Aldrich Company (St. Louis, USA). HPLC grade acetonitrile and methanol were from Merck Company (Darmstadt, Germany). All other chemicals were of analytical grade and used without further purification. Ultra-pure water (resistance > 18.2 mΩ) prepared by a Millipore Milli-Q purification system (Bedford, USA).

4.2. Apparatus

All analyses were performed with a 1200 Series liquid chromatograph (Agilent Technologies, Waldbronn, Germany) equipped with a quaternary pump, a degasser, an autosampler, a thermostatted column compartment, and a Bruker Esquire HCT mass spectrometer (Bruker Technologies, Bremen, Germany) equipped with an electrospray ion source and controlled by ChemStation software.

4.3. Animals

Male Sprague-Dawley rats with body weights of 220 ± 30 g were provided by the Animal Care and Use Committee of Wenzhou Medical College. They were housed in house cages at 23–25 °C and had free access to regular rodent diet and water. After an 1-week acclimatization period, the rats were used for experiments and all efforts were made to minimize any animal suffering. All experimental procedures and protocols were reviewed and approved by the Animal Care and Use Committee of Wenzhou Medical College and were in accordance with the Guide for the Care and Use of Laboratory Animals.

4.4. Drug administration and sampling

Twelve male Sprague-Dawley rats were randomly divided into two groups (n = 6): control group (CG) and test group (TG, 2.0 mg/kg), which were given multiple doses of vehicle or myricetin (dissolved in 0.5% CMC-Na solution). After oral administration for consective 14 days, a cocktail solution at a dose of 5 mL/kg, which contained phenacetin (20 mg/kg), tolbutamide (5 mg/kg) and midazolam (10 mg/kg) in CMC-Na solution, was administered orally to all rats in each group. Blood samples of each rat were collected pre-dose (0 h) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12 h after probe drugs administration and immediately separated by centrifugation at 13,000 rpm for 10 min to obtain plasma. From the 7th blood collection, the rats were treated orally with normal saline of the same blood collection volume in order to restore blood capacity quickly. Plasma samples (100 μL) were transferred to another tube and stored frozen at -80 °C until analyzed.

4.5. Sample preparation

In a 1.5 mL centrifuge tube, an aliquot of 0.2 mL acetonitrile with carbamazepine (500 ng/mL) as the internal standard was added to 0.1 mL of collected plasma sample. After the tube was vortex-mixed for 1.0 min, the sample was centrifuged at 13,000 rmp for 10 min. Next, the supernatant (10 μL) was injected into the HPLC-MS/MS system for analysis.

4.6. Chromatographic conditions

Chromatographic separation was achieved on an Agilent Zorbax SB-C18 column (150 mm × 2.1 mm, 3.5 μm) with the column temperature set at 30 °C. The mobile phase consisted of (A) acetonitrile and (B) 0.1% formic acid in water, and a gradient elution of 10–85% A at 0–1.5 min, 85–85% A at 1.5–6.0 min, 85–10% A at 6.0–7.0 min and 10–10% A at 7.0–10.0 min was employed. The flow rate was 0.4 mL/min. The injection volume was 10 μL.

The quantification was performed by the peak-area method. The determination of target ions were performed in SIM mode (m/z 180 for phenacetin, m/z 271 for tolbutamide, m/z 326 for midazolam and m/z 237 for IS) and positive ion electrospray ionization interface. Drying gas flow was set to 6 L/min and temperature to 350 °C. Nebuliser pressure and capillary voltage of the system were adjusted to 20 psi and 3,500 V, respectively.

4.7. Statistical analysis

The concentration-time profile of each probe drug was analyzed by DAS software (Version 3.0, Wenzhou Medical College, China) and statistic analyses were tested by t-test using SPSS (Version 13.0, Wenzhou Medical College, China). A value of $P < 0.05$ was considered to be statistically significant.

Conflict of interest: The Authors declare that they have no conflict of interests.

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