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ORIGINAL RESEARCH

Pharmacokinetics of Herb-Drug Interactions of Plumbagin and Tazemetostat in Rats by UPLC-MS/MS

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Objective: A sensitive and rapid UPLC-MS/MS method for determination of tazemetostat in rat plasma was developed, and the pharmacokinetics of herb-drug interactions (HDIs) of plumbagin (PLB) and tazemetostat was investigated.

Methods: After the rat plasma samples were precipitated by acetonitrile, tazemetostat and verubecestat (ISTD) were detected. Gradient elution was performed with 0.1% formic acid and acetonitrile as mobile phases. The multi-reaction monitoring was used with ESI+ source, and the ion pairs for tazemetostat and ISTD were m/z 573.12→135.99 and m/z 410.10→124.00, respectively. 12 SD rats were randomly divided into the control group and the experimental group, 6 rats in each group. The rats in the experimental group were given PLB 100 mg/kg by gavage once a day for 7 consecutive days. The rats in the control group were given the same amount of 0.1% sodium carboxymethyl cellulose solution by gavage once a day for 7 consecutive days. At the seventh day, tazemetostat (80 mg/kg) was given and the blood was collected at different time points. The main parameters of pharmacokinetics were calculated and the herb-drug interactions (HDIs) were evaluated.

Results: In the calibrated range of 1–1000 ng/mL, tazemetostat had a good linearity. The extraction recovery was more than 84%, and the RSD of intra-batch and inter-batch precision were both less than 15%. The C_{max} of tazemetostat in the experimental group was 32.48% higher than that in the control group, and the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of tazemetostat in the experimental group were 46.24% and 46.67% higher than that in the control group, respectively, and the $t_{1/2}$ was prolonged from 10.56 h to 11.73 h.

Conclusion: A simple, rapid and sensitive UPLC-MS/MS method for the determination of tazemetostat in rat plasma was established. PLB can inhibit the metabolism of tazemetostat and increase the plasma exposure of tazemetostat in rats.

Keywords: plumbagin, tazemetostat, UPLC-MS/MS, pharmacokinetics, herb-drug interactions

Introduction

Complementary and alternative drugs (CAM) are commonly used in cancer patients, and the prevalence of using CAM is so high in the cancer population, herb-drug interactions (HDIs) are of great concern, especially since they may interfere with cancer treatment regimens.[1] Due to the potential risk of adverse reactions, HDIs are a major health problem worldwide. Theoretically, many herbs may interfere with anticancer agents through pharmacokinetic and pharmacodynamic interactions, which may result in toxic or sub-therapeutic outcomes associated with adverse clinical outcomes.[1,2]

Plumbago zeylanica L. (family: Plumbaginaceae), also known as Chitrak, is a medicinal plant and mainly distributed around Africa and Asia including India and China.[3] Plumbagin (5-hydroxy-2-methyl-1,4-napthoquinone, PLB), widely distributed in the Plumbaginaceae family, is a naturally occurring naphthoquinone, which is isolated from the roots of the medicinal plant *Plumbago zeylanica L.* PLB has been reported to possess a wide spectrum of biological and pharmacological properties including activities against malaria, leishmania, and trypanosome parasites, as well as against viruses, cancers, and bacteria.[4,5] PLB has anticancer activity via many molecular mechanisms, such as targeting apoptosis, autophagy pathway, cell

cycle arrest, antiangiogenesis pathway, anti-invasion, and antimetastasis pathway, and has been reported to possess anticancer activities on a variety of cancer cells.[5] PLB can inhibit proliferation and induce apoptosis of hepatic cancer through inhibiting the SIVA/mTOR signaling pathway, which indicates that PLB may be a good candidate against liver cancer.[6] PLB displays stronger cytotoxic effects on A375 cells, which exhibit lower respiratory function than SK-MEL-28 cells with higher respiratory function, and triggers cell-specific metabolic changes in accordance with its cytotoxic effects.[7] PLB is cytotoxic for cancer cells due to its ability to trigger reactive oxygen species (ROS) formation and subsequent apoptosis. PLB may inhibit the differentiation of bone resorbing osteoclasts in cancer-related models.[8] PLB may bind to and inhibit the dihydroorotase (a key enzyme in pyrimidine biosynthesis) and exhibit cytotoxicity on the survival, migration, and proliferation of 4T1 cells and induce apoptosis.[9] PLB may be an effective drug in inhibiting the tumor angiogenesis of gastric cancer and the mechanism of anti-tumor may be associated with NF-κB pathway.[10]

Tazemetostat (EPZ-6438, Figure 1A), a first-in-class small molecule enhancer of zeste homolog 2 (EZH2) inhibitor, is developed by Epizyme in collaboration with Eisai, and it is the first therapy to be approved specifically for the treatment of epithelioid sarcoma.[11] Tazemetostat was another important supplement for the treatment of patients with relapsed or refractory follicular lymphoma (R/R FL), it likely helps improve the development trajectory of the disease.[12] Tazemetostat significantly increased the expression of CC chemokine ligand 17 (CCL17)/thymus and activation-regulated chemokine (TARC) in B-cell lymphoma and enhances T-cell recruitment,[13] and tazemetostat has shown acceptable safety and clinically significant efficacy in some patients, such as: patients with relapsed or refractory B-cell non-Hodgkin-type lymphoma (B-NHL), patients with R/R FL with EZH2 mutation, patients with FL and diffuse large B-cell lymphoma (DLBCL).[14,15]

The recommended dose of tazemetostat was 800 mg twice a day, and the pharmacokinetics of tazemetostat was not affected by gender, age, weight, race, renal damage (including end-stage renal disease) and mild liver damage, and food also had no substantial effect on plasma exposure.[11] As an oral drug, tazemetostat had 33% bioavailability, and was metabolized by CYP3A in the liver to form two main inactive metabolites M5 (EPZ-6930) and M3 (EPZ006931), while M5 was further metabolized by CYP3A, which could account for the drug-drug interaction with tazemetostat.[16] Tazemetostat was rapidly absorbed after a single oral dose of 800 mg, and the median T_{max} of tazemetostat and EPZ-6930 was about 2 hours, and the mean $t_{1/2}$ values of tazemetostat was 7.59 hours, the mean $t_{1/2}$ values of EPZ-6930 was 8.83 hours.[14]

In recent years, the antitumor effect of PLB had been further confirmed, and it had been widely used in the treatment of breast cancer, hepatoma, leukemia, melanoma, prostate cancer, brain tumor, tongue squamous cell carcinoma, esophageal cancer, oral squamous cell carcinoma, lung cancer, kidney adenocarcinoma, cholangiocarcinoma, gastric
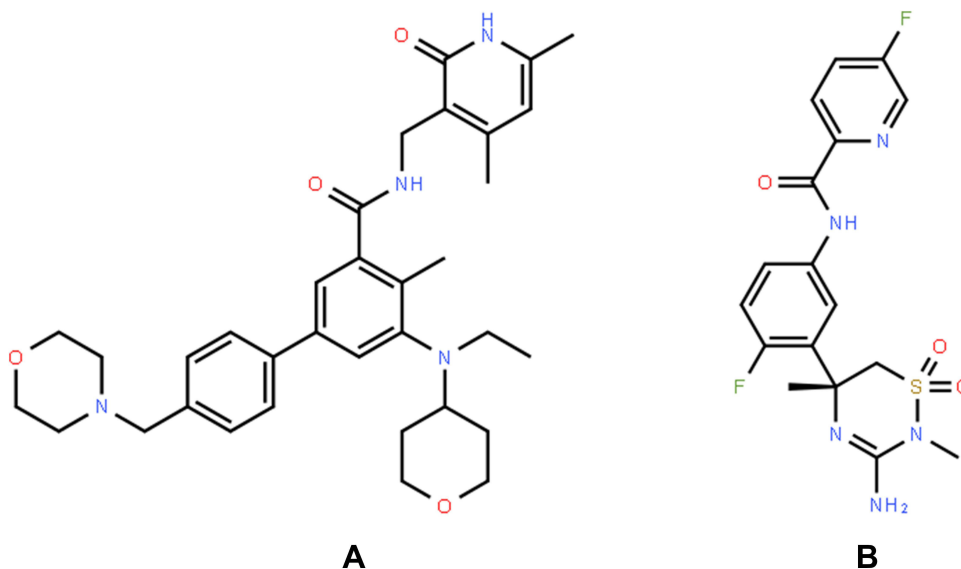

Figure I The chemical structure of tazemetostat (**A**) and ISTD (**B**) in the present research.

cancer, lymphocyte carcinoma, osteosarcoma, and canine cancer.[5] Studies had shown that PLB could inhibit the activities of CYP 450 in both human and rat liver with non-time-dependent mode. PLB was not only a mixed inhibitor of CYP2B6, CYP2C9, CYP2D6, CYP2E1 and CYP3A4, but also a non-competitive inhibitor of CYP1A2.[3] So it might cause the HDIs based on CYP450.

Although there are reports on the pharmacokinetics of tazemetostat in clinical studies,[14,16] the detection method of tazemetostat in biological samples has not been reported in clinical studies. Therefore, in this study, a method for determination of tazemetostat in rat plasma by UPLC-MS/MS was developed and performed using verubecestat as the internal standard (ISTD, Figure 1B), and the pharmacokinetics of HDIs of PLB and tazemetostat in rats were investigated.

Materials and Methods

Reagents and Chemicals

Acetonitrile and methanol were purchased from Merck (Darmstadt, Germany), and both acetonitrile and methanol were HPLC grades. Tazemetostat (standard, purity >98%) and verubecestat (internal standard, IS, purity >98%), both were purchased from Beijing Sunflower Technology Development Co., Ltd. PLB (purity >98%, MB5765) were purchased from Dalian Meilun Biotechnology Co., Ltd. Purified water was produced by utilizing a Milli-Q academic reagent grade water purification system (Millipore, Bedford, USA).

Solutions Ready

10 mg of tazemetostat standard was accurately weighed into a 10 mL volumetric flask and dissolved with methanol to make the volume to 10 mL, and the tazemetostat standard stock solution with the concentration of 1 mg/mL was obtained. The tazemetostat standard stock solution was diluted with methanol for preparation of the standard application solution with the concentrations of 100 μg/mL, 10 μg/mL and 1 μg/mL in sequence. Similarly, ISTD working solution was obtained using the same operation, and the concentration was 5 μg/mL. The above solution samples were stored at 4°C.

Different volumes of standard application solution were added to different volumes of blank rat plasma to obtain the calibration standards with concentrations of 1, 5, 10, 50, 100, 250, 500, 1000 ng/mL, respectively. Quality control (QC) samples were prepared using the same way at three different concentration levels including the low quality control (LQC, 2.5 ng/mL), middle quality control (MQC, 100 ng/mL), and high quality control (HQC, 750 ng/mL).

UPLC-MS/MS Conditions

The chromatographic column used for separation was the Acquity UPLC BEH C18 (2.1 mm×50 mm, 1.7 μm) chromatographic column, the temperature of the column oven was controlled at 45°C. The mobile phase was 0.1% formic acid (phase A) and acetonitrile (phase B), and the gradient elution procedure was as follows: 0–0.5 min, 90% phase A; 0.5–1.0 min, 90%→10% phase A; 1.0–2.0 min, 10% phase A; 2.0–2.1 min, 10%→90% phase A; and maintained 10% phase A until 3.0 min.

By adopting the electrospray ionization (ESI) interface, in the positive ion and multiple reaction monitoring (MRM) mode, the mass spectrometer had realized data measurement. The parent ions and daughter ions used for quantification were as follows: m/z 573.12→135.99 for tazemetostat, m/z 410.10→124.00 for ISTD, respectively. The cone voltage of tazemetostat and IS were 30 V and 10 V, and the collision energy of tazemetostat and IS were 30 V and 20 V, respectively. The dwell time was 79 ms. The control of the experimental instrument and the collection of data were completed by MassLynx4.1 software (Waters Corp).

Sample Preparation

Rat plasma samples were prepared using the protein precipitation method. Generally speaking, 50 μL of rat plasma was put into a 1.5 mL Eppendorf tube, then 5 μL of ISTD working solution (5 μg/mL) was added and mixed. 150 μL of acetonitrile was added and mixed for 1 min, then centrifuged at 6743 g for 15 min. Finally the supernatant was transferred to the sample bottle, and 2 μL of the supernatant was injected directly into the LC-MS/MS system for analysis.

Method Verification

In this experiment, the basic parameters that must be examined for method validation include: specificity, linearity, precision, accuracy, matrix effect, extraction recovery, stability, dilution reliability, and carry-over. The validation of this method was carried out in accordance with the guidelines of the determination of biological samples.[17,18]

Specificity

The analytical method should be able to distinguish tazemetostat from ISTD and the endogenous components of the matrix or other components in the sample. Blank rat plasma samples from six different rats were used to demonstrate selectivity, which is generally acceptable when the response of the interfering component is less than 20% of the response to the LLOQ of tazemetostat.

Linearity

The response of the instrument to tazemetostat should be evaluated to obtain the standard curve within the specified concentration range 1–1000 ng/mL (1, 5, 10, 50, 100, 250, 500, 1000 ng/mL). Taking the peak area ratio of tazemetostat to ISTD as ordinate (y) and theoretical concentration of tazemetostat as abscissa (x), the standard curve was drawn with least square method, and the weight factor was $1/x^2$. The LLOQ was regarded as the minimum value of the calibration curve.

Accuracy and Precision

Six LLOQ, LQC, MQC, and HQC in the same analytical batch were prepared to obtain the intra-batch accuracy and precision. Six LLOQ, LQC, MQC, and HQC of three analytical batches (at least 2 days) were prepared to obtain the inter-batch precision and accuracy. The accuracy was expressed in terms of relative error (RE %), precision was expressed by the relative standard deviation (RSD %).

Matrix Effect and Extraction Recovery

For matrix effect, the ratio of peak area in the presence of matrix (measured by adding tazemetostat and ISTD after extraction from blank rat matrix) to corresponding peak area without matrix (pure solution of tazemetostat and ISTD) should be calculated. The extraction recovery was calculated by ratio of the response after treatment of tazemetostat added in the blank rat plasma to the response of the same tazemetostat added in the treated blank rat plasma. The extraction recovery as well as the matrix effect were determined in six replicates at LQC, MQC, and HQC.

Stability

The stability of QC samples were studied under four different conditions: room temperature for 12 h, three freeze-thaw cycles, stored at −20°C for 4 weeks, and 4°C for 4 h in automatic sampler. In this study, the stability of tazemetostat was evaluated by analyzing six LQC, MQC, and HQC samples.

Carry-Over

Carry-over should be examined and minimized in the establishment of the method. The carry-over should be estimated by injecting a blank sample after injecting a high concentration sample or a calibration standard sample. The carry-over test was performed by injecting a blank plasma sample spiked with tazemetostat (1000 ng/mL) and ISTD (500 ng/mL) followed by injecting a blank sample. In this blank sample, the carry-over should be less than 20% of the LLOQ.

Animals

12 healthy male SD rats, weighing 280 ± 20 g, were obtained from the Huaxing experimental animal farm (Zhengzhou). The animal production license number was SCXK(Henan) 2019–0002. The rats were fed with standard food and water for 1 week before the experiment. The experimental plan was approved by the ethics committee of the animal laboratory of Henan University of science and technology, and strictly followed the "Experimental Animals-Welfare Ethical Review Guidelines" (GB/T 35892-2018).

Experiment Design

Dose conversion was performed according to the equivalent dose between animals and humans in pharmacological experiments. The recommended dose of tazemetosat was 800 mg, twice a day, taken orally with or without food.[11] The dose to rats is 6 times that to humans, so the dose of tazemetostat was 80 mg/kg. According to the literature, the dosage of PLB was 100 mg/kg.[4]

12 SD rats were randomly divided into the control group and the experimental group, 6 rats in each group. The rats in the experimental group were given PLB 100 mg/kg (PLB was dissolved with 0.1% sodium carboxymethyl cellulose solution at a concentration of 20 mg/mL) by gavage once a day for 7 consecutive days. The rats in control group were given the same amount of 0.1% sodium carboxymethyl cellulose solution by gavage once a day for 7 consecutive days. At the seventh day, tazemetostat (80 mg/kg) was given to both groups 30 min after intragastric administration of 0.1% sodium carboxymethyl cellulose solution or PLB, and the blood was collected at different time points such as 0.33, 0.67, 1, 1.5, 2, 3, 4, 6, 9, 12, 24, and 48 h. The blood samples were collected into polyethylene tubes containing heparin, the plasma was taken and frozen at −20°C until analysis.

Plasma Sample Detection

The established UPLC-MS/MS method was used to detect the concentration of tazemetostat in rat plasma by batch processing method. Each analytical batch included the standard curve, QC samples, and rat plasma samples to be tested.

Data Analysis

Using the DAS 2.0 program, the main pharmacokinetic parameters of tazemetostat in the control group and the experimental group were obtained using a non-compartmental model, and the differences of pharmacokinetic parameters between the experimental group and the control group were compared. The peak concentration (C_{max}) and peak time (T_{max}) were the measured values, and the data were expressed as mean ± standard deviation (SD).

t-test of nonparametric two independent samples was used to compare the differences between the control group and the experimental group by SPSS 16.0 software, and a *P* value of less than 0.05 between groups was considered a statistical difference, and a *P* value of less than 0.01 was considered a statistically significant difference.

Results and Discussion

Method Validation and Improvement

UPLC-MS/MS has the advantages of high sensitivity, strong specificity, short analysis time, and good reproducibility. Therefore, it is often used in the detection of biological samples and the study of pharmacokinetics and HDI.[19,20]

In order to better determine the compounds to be tested, different mobile phase systems were investigated in this experiment, such as methanol-water system, methanol-0.1% formic acid aqueous solution system, acetonitrile-water system, acetonitrile-0.1% formic acid aqueous solution system, etc. The results showed that the components to be tested had a strong response under the gradient elution system of acetonitrile-0.1% formic acid aqueous solution, and the endogenous components in plasma did not interfere with the determination of tazemetostat and ISTD, the chromatographic peaks were good, so acetonitrile-0.1% formic acid aqueous solution was finally selected as the mobile phase.

In order to select the appropriate ion pair for each substance to be measured, the mass spectrometry parameters were optimized in this experiment. The responses of the substance to be measured in positive and negative ion modes were investigated. The results showed that the substance to be measured in positive ion mode had a higher response, so the experiment was carried out in positive ion mode. At the same time, the conditions such as spray voltage, air curtain gas, atomization gas, auxiliary heating gas, and auxiliary gas temperature are optimized. Under the final detection conditions, the response value of tazemetostat and ISTD were strong and the peak area was the largest. The mass spectra of tazemetostat and ISTD are shown in Figure 2.

Specificity

Regarding the specificity of this chromatographic analysis method, three sets of samples were selected for testing and analysis: blank rat plasma, blank plasma containing tazemetostat and internal standard, and plasma sample collected 1 hour after oral administration of tazemetostat. Figure 3 showed the chromatogram, and it could be seen that the retention time of tazemetostat was 1.15 min, and the retention time of ISTD was 1.21 min. The chromatographic peak of tazemetostat and ISTD in rat plasma were well separated and were not interfered by endogenous substances.
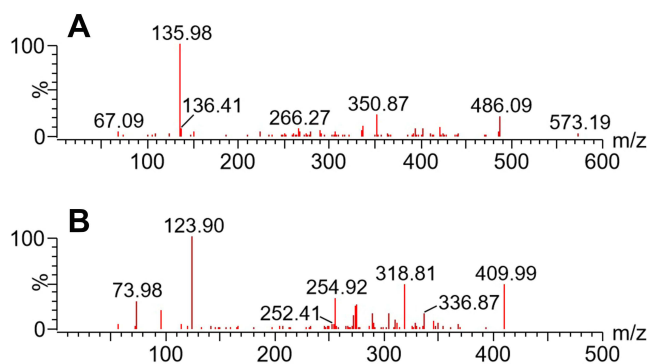
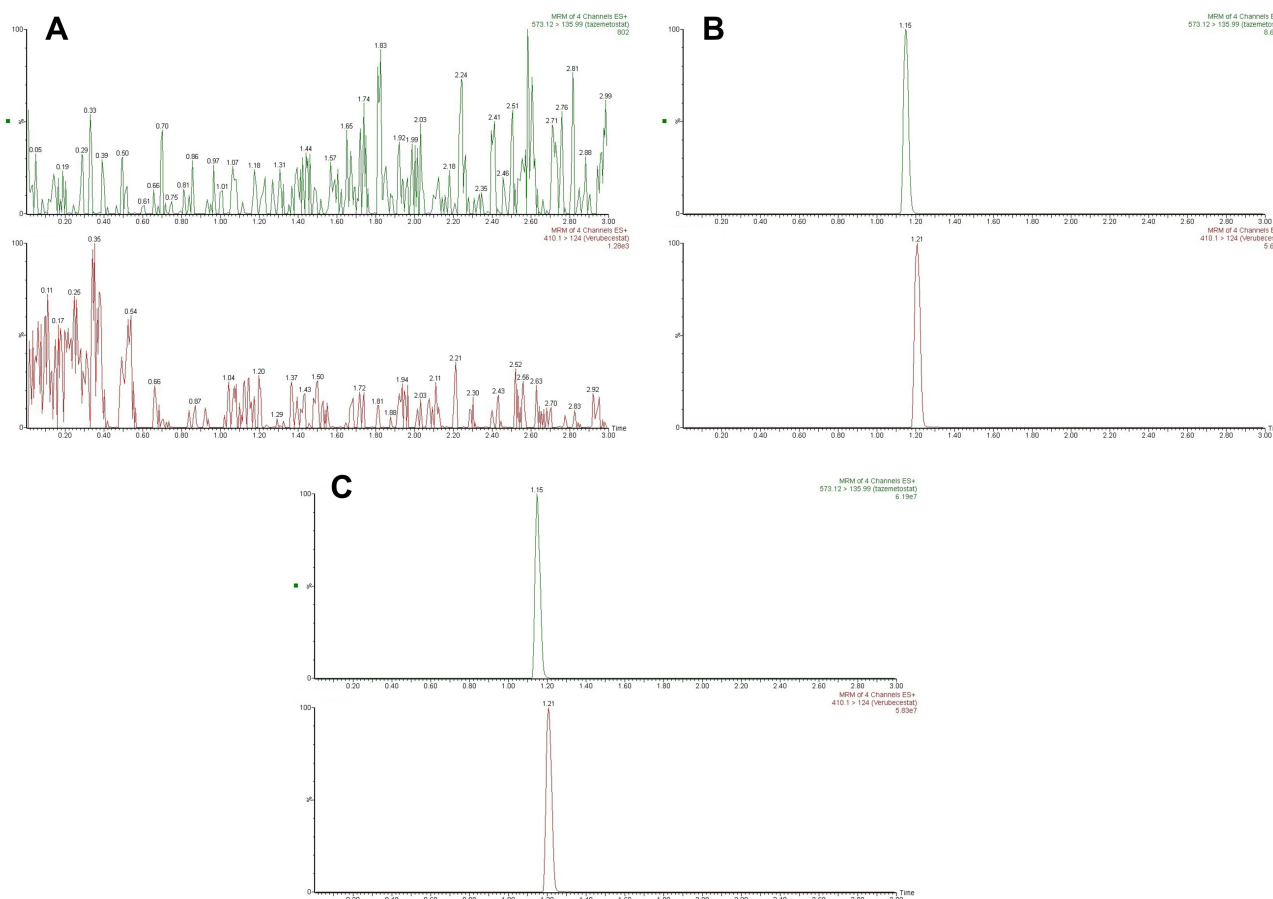**Figure 2** The mass spectra of tazemetostat (**A**) and ISTD (**B**).

Figure 3 Representative chromatograms of tazemetostat. (**A**) a blank rat plasma sample; (**B**) a blank rat plasma sample containing tazemetostat and ISTD; (**C**) a rat plasma sample collected 1 hour after oral administration of 80 mg/kg tazemetostat.

Linearity

The standard curve regression equation of tazemetostat was as follows: $y = 0.0127\,x + 0.0150$, r=0.9991, with the range of 1.0–1000 ng/mL. The LLOQ for tazemetostat was the lowest concentration point of standard curve (1.0 ng/mL).

Precision and Accuracy

The precision and accuracy results of intra-batch and inter-batch are shown in Table 1. From Table 1, it can be seen that RSD were all less than 9.23%, and RE were between −1.89% and 2.96%, meeting the requirements of methodological validation.

Table 1 Precision and Accuracy of Tazemetostat in Rat Plasma (n = 6)

Added (ng/mL)	Intra-Batch			Inter-Batch		
	Found (ng/mL)	RSD (%)	RE (%)	Found (ng/mL)	RSD (%)	RE (%)
1	0.99 ± 0.09	9.23	−1.50	1.01 ± 0.09	8.56	0.61
2.5	2.53 ± 0.14	5.46	1.20	2.45 ± 0.08	3.21	−1.89
100	102.96 ± 2.20	5.05	2.96	101.00 ± 0.83	0.82	1.00
750	747.19 ± 14.73	1.97	−0.37	736.03 ± 3.88	0.53	−1.86

Extraction Recovery and Matrix Effect

The extraction recoveries of tazemetostat in rat plasma at LQC, MQC, and HQC were (84.38 ± 6.12)%, (87.54 ± 3.40)%, and (90.75 ± 2.66)%, respectively. The matrix effect was around 100%, which proved that the matrix effect did not affect the detection of tazemetostat and ISTD.

Stability

Table 2 shows the results of stability, and the RE values were all between −5.80~2.47% which means it could be concluded that tazemetostat was stable under the above four test conditions.

Carry-Over

The results of the carry-over test showed that tazemetostat or ISTD were not detected in the next blank sample after injecting a high concentration sample. In the UPLC-MS/MS analysis, carry-over did not affect the determination of tazemetostat.

The Effect of PLB on the Pharmacikinetics of Tazemetostat

The rats in the experimental group and the control group were given 80 mg/kg tazemetostat, the mean plasma concentration-time curve of tazemetostat is shown in Figure 4, and the main pharmacokinetic parameters of tazemetostat are shown in Table 3. The C_{max} of tazemetostat in the experimental group was 32.48% higher than that in the control group, and the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$ of tazemetostat in the experimental group were 46.24% and 46.67% higher than that in the control group, respectively, and the $t_{1/2}$ was prolonged from 10.56 h in the control group to 11.73 h in the experimental group. The clearance rate (CL) and apparent volume of distribution (Vd) of tazemetostat in the experimental group were smaller than that of the control group. The results showed that after PLB 100 mg/kg was given to rats for one week, tazemetostat was given again. The metabolism of tazemetostat in rats was slowed down and the plasma concentration of tazemetostat increased, which indicated that PLB could inhibit the metabolism of tazemetostat and increase the plasma exposure of tazemetostat in rats.

HDIs

A large number of cancer patients worldwide use herbal supplements during their oncological treatments and the number is reported to increase.[21] Medicinal plants are often used in combination with drugs, which has raised concerns about HDIs, because a large number of clinically significant adverse reactions have been observed.[22] HDIs can occur on both a

Table 2 The Stability of Tazemetostat in Rat Plasma (n = 6)

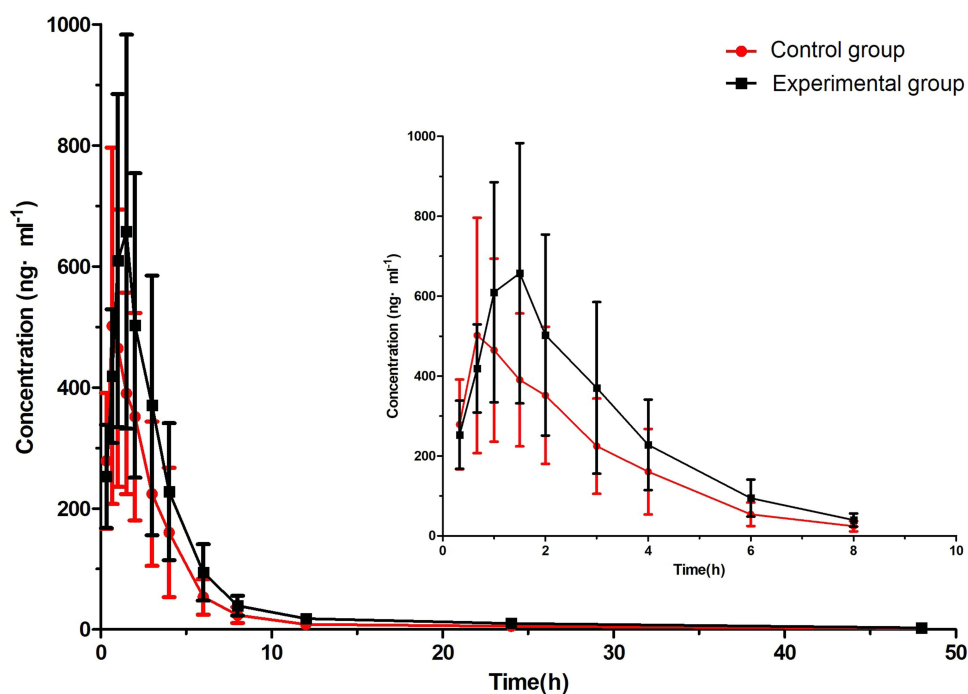| Added (ng/mL)	Room Temperature, 12 h		Three Freeze-Thaw		−20°C, 4 Weeks		Autosampler 4°C, 4 h	
	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)	RSD (%)	RE (%)
2.5	5.18	2.47	7.49	−4.60	6.84	−5.80	5.12	1.40
100	2.68	1.32	4.69	2.00	2.32	2.65	3.69	−1.55
750	2.06	−1.04	4.81	−2.19	3.21	−4.09	2.70	2.45

Figure 4 Plasma mean concentration-time curve of tazemetostat in the control group and the experimental group.

pharmacodynamic and pharmacokinetic basis. Pharmacokinetic interaction involves the modulation of absorption, distribution, metabolism, and excretion of drugs by affecting drug transporters and CYP450 enzymes,[23] and the majority of potential HDIs occur on a pharmacokinetic level.[21]

The results of our previous HDI study showed that Danzhi Xiaoyao pills could reduce the plasma exposure of venlafaxine and increase the plasma concentration of its metabolite ODV (the major active metabolite of venlafaxine) and NDV (the minor metabolite of venlafaxine) in beagle dogs.[19] Xiao-Ai-Ping injection could inhibit the metabolism of enasidenib and increase the concentration of enasidenib in rats.[24] Sijunzi pills could inhibit the metabolism of omeprazole and increase the concentration of omeprazole in beagle dogs.[25]

Tazemetostat is a first-in-class small molecule enhancer of EZH2 inhibitor.[11] The most common treatment-related adverse events (AEs) were asthenia, anemia, anorexia, muscle spasms, nausea, and emesis, which were mostly grade 1 or 2 in severity.[12] Tazemetostat is metabolized by CYP3A in the liver,[16] and PLB could inhibit the activity of CYP3A4.[3] So it might cause the HDIs based on CYP450. The results of this study showed that when tazemetostat was used in combination with PLB, the C_{max} of tazemetostat was 32.48% higher than that of it alone, and the $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$

Table 3 The Main Pharmacokinetic Parameters of Tazemetostat in the Control Group and the Experimental Group (n=6, Mean ± SD)

Parameters	Control Group	Experimental Group
$t_{1/2}$ (h)	10.56 ± 2.28	11.73 ± 2.33
T_{max} (h)	0.78 ± 0.17	1.33 ± 0.26 **
C_{max} (ng/mL)	523.43 ± 287.73	693.42 ± 294.00 *
CL_z/F (L/h/kg)	52.27 ± 23.69	34.63 ± 13.13
V_z/F (L/h)	808.83 ± 470.76	603.28 ± 287.01
$AUC_{(0-t)}$ (ng·h/mL)	1753.38 ± 684.97	2564.10 ± 1002.43 *
$AUC_{(0-\infty)}$ (ng·h/mL)	1779.99 ± 690.59	2610.77 ± 999.24 *

Notes: *Compared with the control group, the difference was statistically significant ($P<0.05$). **Compared with the control group, the difference was statistically significant ($P<0.01$).

of tazemetostat were also increased by 46.24% and 46.67%, respectively, and the $t_{1/2}$ was prolonged from 10.56 h to 11.73 h. The CL and Vd of tazemetostat in the experimental group was smaller than that of the control group. The results showed that PLB could slow down the metabolism of tazemetostat and increase the plasma exposure of tazemetostat in rats. Therefore, when PLB and tazemetostat are combined clinically, the dosage of tazemetostat should be adjusted to ensure the efficacy to avoid adverse reactions.

The study of HDIs should have two aspects, including not only the effect of the herb on Western medicine, but also the effect of Western medicine on the active pharmaceutical ingredients (APIs) of the herb. In this study, the effects of PLB on tazemetostat were studied from the aspect of pharmacokinetics. In future studies, we will focus on the interaction of the APIs and Western medicine.

Conclusions

A simple, fast, and sensitive UPLC-MS/MS method for the determination of tazemetostat in rat plasma was established. PLB can inhibit the metabolism of tazemetostat and increase the plasma exposure of tazemetostat in rats. It is suggested that when PLB is combined with tazemetostat, the HDI and adverse reactions should be paid attention to, and the dosage of tazemetostat should be adjusted if necessary.

Data Sharing Statement

The data used to support the findings of this study are included within the article. Data are available from the corresponding author (lyxiangjun@126.com).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors state that there is no conflict of interest in the publication of this paper.

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