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Measurement of tepotinib by UPLC–MS/MS and its interaction with naringenin in rats

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Abstract

We established a method based on ultra performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS) to quantitatively measure tepotinib, which was validated as acceptable and used in the evaluation of food-drug interactions between tepotinib and naringenin in rats. We used pemigatinib as the internal standard (IS), and acetonitrile and 0.1% formic acid aqueous solution constituted the mobile phase. To extract the target analyte, acetonitrile was used for protein precipitation (PPT). For UPLC–MS/MS, we performed liquid chromatography using a C18 column, and mass spectrometry was performed in positive multiple reaction monitoring (MRM) mode. Excellent linearity was shown in the range of 0.1–500 ng/mL, and the coefficient of correlation was > 0.99. Notably, the lower limit of quantification (LLOQ) for tepotinib was determined to be 0.1 ng/mL. The intra- and inter-day accuracy of tepotinib ranged from − 1.7 to 7.3%, while the precision was ≤ 8.4%, at three concentrations except LLOQ. The recovery of each substance was ≥ 81.2%, and the matrix effects were within 90.5-98.6%. The stabilities of all analytes under different conditions met all requirements for quantitation in plasma samples. The relevant parameters, such as LLOQ, were evaluated in accordance with the principles of the Food and Drug Administration (FDA) biological verification method. Food-drug interaction study had shown that the plasma concentration of tepotinib could be significantly increased, accompanied by a decrease in clearance rate when administered with 50 mg/kg naringenin. The results showed that naringenin could increase the plasma concentration and decrease the clearance rate of tepotinib when naringenin and tepotinib were administered at the same time.

Keywords Tepotinib, Pharmacokinetics, Naringenin, Drug–drug interaction, UPLC–MS/MS

Introduction

Tepotinib (Fig. 1A) is a highly selective MET tyrosine kinase inhibitor that has been approved in Japan and the USA for the treatment of non-small cell lung cancer (NSCLC) [1, 2]. Mutations in the MET proto-oncogene can increase the risk of cell canceration, and the most representative one is the deletion of MET exon 14 transcription, which can drive tumor growth through the phosphoinositide 3-kinase (PI3K) pathways [3, 4]. Similar to many antitumor drugs, the metabolism of tepotinib is also related to the CYP3A4 enzyme and P-glycoprotein [2]. Previous studies have reported the characteristics and properties of tepotinib with a T_{max} of 8 h and a $t_{1/2}$ of 29.9 h [2]. In phase I clinical trials, tepotinib showed

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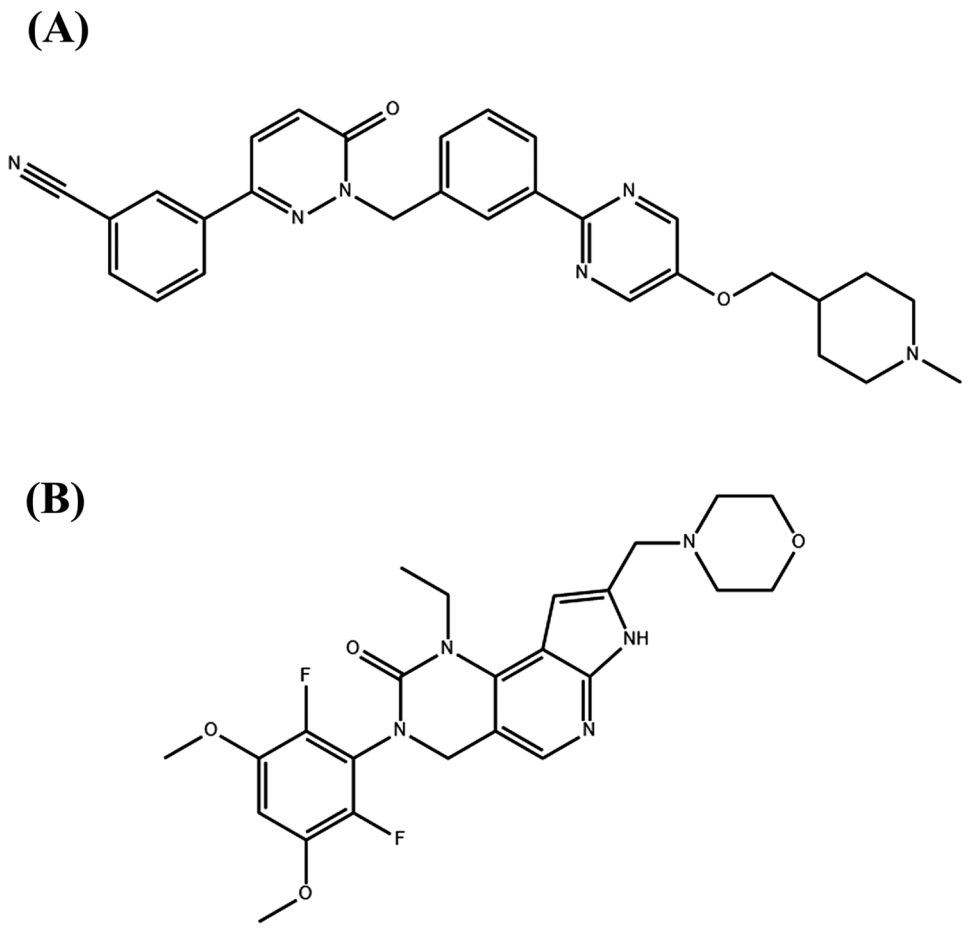

Fig. 1 Chemical structures of tepotinib (**A**) and pemigatinib (IS, **B**)

good pharmacokinetic stability [5], while there are studies showing that there is a drug–drug interaction between tepotinib and P-glycoprotein substrate drugs [6].

As we know, there is only one published study available for the determination of the tepotinib metabolic intermediate in vitro based on ultra performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS), without description of the detailed information of the establishment of the detection method [7]. In other words, there is no published analytical or bioanalytical method available for tepotinib determination in biological fluids. Therefore, it is necessary to establish a sensitive quantitative detection method for tepotinib in biological fluids to provide a basis for subsequent pharmaceutical research.

Naringenin is a natural flavonoid [8] that is rich in our daily diet and has been proven to have many clinical values, such as protecting against smoke-induced lung damage [9], antifibrosis [10], and reducing tumor cell metastasis [11]. The clinical value of naringenin is achieved through the regulation of a variety of cell signal transduction pathways, enzymes and cytokines [12], including CYP3A4 enzyme and P-glycoprotein. A previous study showed that naringenin can inhibit cell proliferation and induce cell apoptosis in prostate cancer by inhibiting PI3K/AKT pathway, which also plays an important role in NSCLC [3, 4, 13]. Naringenin also inhibits cancer progression through a variety of mechanisms, such as apoptosis induction, cell cycle blockade, angiogenesis hindrance, and modification of various signaling pathways, including the Wnt/β-linker protein and TGF-β pathways [8]. Moreover, naringenin is a natural product that has the potential to treat different types of cancer when used alone or in combination with other drugs [8]. Based on the fact that both tepotinib and naringenin can have an effect on PI3K pathway, it is possible that patients using tepotinib may also be able to enhance the effect on the PI3K pathway with the combination of naringenin. The effect of naringenin on the metabolism of other antitumor drugs has been reported [14, 15], but the food-drug interactions between naringenin and tepotinib remain unknown. Therefore, studies on the interaction between naringenin and tepotinib are necessary, and our study will provide a basis for dose adjustment when naringenin and tepotinib are used in combination.

Therefore, the present aim of our research was to use a rat model to establish a stable, hypersensitive and quantitative UPLC–MS/MS assay to measure the tepotinib concentration in biological fluids. In addition, we verified the accuracy of this method and successfully applied it to the study of the pharmacokinetic characteristics of tepotinib and the exploration of potential drug–drug interactions between naringenin and tepotinib.

Experiment

Chemical materials and reagents

The analytical grade formic acid and standard reagents with purity > 98.0% used in this study, including tepotinib, naringenin, and pemigatinib (Fig. 1B, internal standard, IS), were all provided by Beijing Sunflower Technology Development CO., LTD (Beijing, China). Other chemicals, such as acetonitrile and methanol, were all LC grade and purchased from Merck Company (Darmstadt, Germany). Ultrapure water in this experiment was acquired from the Milli-Q water purification system (Millipore, Bedford, USA).

Animal experiments

All our animal experiments were approved by the Animal Protection and Use Committee of The First Affiliated Hospital of Wenzhou Medical University before starting. The 12 male Sprague–Dawley rats used in the experiments were provided by the Laboratory Animal Center of The First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China) and were kept under laboratory conditions for 14 days to adapt to the environment. Except for a 12-h fast before the start of the experiment, we did not restrict the food and water of the experimental animals and kept their weight in the range of 200 ± 20 g. Environmental conditions, such as temperature and humidity, were properly set to ensure the welfare of the experimental animals.

A 0.5% CMC-Na solution was used for tepotinib and naringenin preparation. According to the experimental needs, the rats were randomly divided into two groups (n = 6): a blank group (Group A) and a naringenin group (Group B). Based on a previous study, the dose of tepotinib administered was selected to be 50 mg/kg [16]. The rats in the two groups were fed 0.5% carboxymethyl cellulose sodium (CMC-Na) and naringenin at a dose of 50 mg/kg. Thirty minutes after oral administration, the two groups of rats were orally administered tepotinib at the same dose of 50 mg/kg.

The obtained samples used were 0.3 mL of rat tail vein blood collected into 1.5 mL heparinized polythene tubes, and the time points of continuous blood sampling were set to 0.333, 0.667, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h after administration. The sample processing procedure was to centrifuge at 4000 × g for 10 min at room temperature, then take 100 µL of plasma, and finally freeze it at -80 °C for subsequent analysis.

Table 1 Specific mass spectrometric parameters and retention times (RTs) for tepotinib and IS, including cone voltage (CV) and collision energy (CE)

Analyte	Precursor ion	Product ion	CV (V)	CE (eV)	RT (min)
Tepotinib	493.03	112.03	30	20	1.24
IS	488.01	400.98	30	15	1.19

Euthanasia

According to the AVMA Guidelines, Euthanasia of experimental animals was performed using the anesthesia method with intravenous pentobarbital (150 mg/kg). After ensuring that the animals were free of life pointers, they were packaged and cremated.

Instrumentations and analytical conditions

The system used for the experiment consisted of a Waters Xevo TQ-S triple quadrupole tandem mass spectrometer (Milford, MA, USA) and a Waters ACQUITY UPLC I-Class system (Milford, MA, USA). The supporting software used for data analysis was the Quanlynx program with Masslynx 4.1 software (Milford, MA, USA). The chromatograph in this system was equipped with a C18 column of Acquity UPLC BEH (Milford, MA, USA, 2.1 mm × 50 mm, 1.7 µm).

Liquid chromatography was used to separate tepotinib and pemigatinib (IS). Acetonitrile (solution A) and 0.1% formic acid aqueous solution (solution B) constituted the mobile phase. The single injection volume was 2.0 µL, and the flow rate was 0.40 mL/min. The temperature of the autosampler was 10 °C, and that of the column was 40 °C. Linear gradient with a total running time of 2.0 min: Solution A maintained the initial 10% in the first 0.5 min, increased from the initial 10–90% in the next 0.5 min, then maintained 90% for 0.4 min, and then dropped back to 10% in the following 0.1 min, keeping it at 10% in the last 0.5 min.

The fixed parameters of the mass spectrometer were as follows: desolvation gas was 1000 L/h, desolvation temperature 600 °C, cone gas 150 L/h, capillary voltage 2.0 kV, and collision gas 0.20 mL/min. Measurements in the positive ion mode were performed using multiple reaction monitoring (MRM), which has an electrospray ionization source (ESI). Table 1 summarizes the parameters for the MS, and the ion transitions for tepotinib and pemigatinib (IS) were m/z 493.03 → 112.03 and m/z 488.01 → 400.98, respectively.

Calibration curve and quality control (QC) samples

1.00 mg/mL stock solutions of tepotinib and IS, quality control (QC) samples and calibration curve of tepotinib

with the corresponding concentration, and 200 ng/mL IS working solution were all prepared with methanol and stored at -80 °C. The sample was prepared by adding 10 μL of the corresponding working solution to 90 μL of blank plasma. The concentration levels of the calibration curve standards of tepotinib were set to eight concentrations between 0.1 and 500 ng/mL, and those of the QC samples of tepotinib were set to 0.1, 0.2 (LQC), 40 (MQC), and 400 (HQC) ng/mL.

Sample processing

Protein precipitation was used to prepare the test samples. 300 μL acetonitrile (protein precipitant) and 20 μL IS working solution were added to 100 μL of plasma in sequence, and then was vortexed for 2.0 min to mix. The mixture was centrifuged for 10 min at 13,000 rpm at 4 °C. After centrifugation, 100 μL of supernatant was drawn into the sample vial. The sample was then placed in an autosampler and 2.0 μL of the supernatant was aspirated for analysis.

Method validation

A series of confirmatory experiments, including lower limit of quantification (LLOQ), selectivity, calibration curve, precision and accuracy, recovery rate, stability and matrix effect, were carried out in accordance with the principles of FDA bioanalytical testing and verification [17–19].

Statistical analysis

In this study, the mean plasma concentration-time curves of tepotinib were obtained using GraphPad version 9.0 software (GraphPad Software, Inc., USA). The noncompartmental pharmacokinetic analysis of tepotinib was calculated with DAS software (Drug and Statistics, Version 2.0, Shanghai University of Traditional Chinese Medicine, China). Unpaired *t*-test was performed by Statistical Package for the Social Sciences (version 17.0; SPSS Inc., Chicago, IL, USA) to compare the pharmacokinetic parameters between groups, which suggested that the difference between groups was statistically significant.

Results and discussion

Assay establishment and optimization

In previous experiments, acetonitrile and water were mostly used as mobile phases. In this study, we also tried this option, but the peak shape and sensitivity obtained in the experiment did not meet the detection requirements. To obtain the maximum sensitivity, we optimized the UPLC settings for the analytes. By using acetonitrile (mobile phase A) and 0.1% formic acid aqueous solution (mobile phase B) as the mobile phase, we obtained higher sensitivity and symmetrical peaks, and the ionization of the analyte was also improved. The protein precipitation (PPT) method used in this study, as a fast and simple method for protein extraction, has been widely used for sample preparation of various analytes [20–24]. As a commonly used PPT, acetonitrile shows a good recovery rate and almost no matrix effect in comparison with other PPTs, such as methanol. Through the verification and screening of the preliminary experiment, we chose acetonitrile as the PPT and obtained a satisfactory recovery rate.

Method validation

Selectivity

In the determination of tepotinib, this assay was demonstrated to be selective and specific. Representative chromatograms of tepotinib and IS in rat plasma are shown in Fig. 2: (A) blank plasma; (B) blank plasma spiked with standard solution at LLOQ (0.1 ng/mL) and IS; (C) sample obtained from a rat at 1.0 h after oral administration of 50 mg/kg tepotinib. The retention times of tepotinib and IS in blank plasma were 1.24 and 1.19 min, respectively, with no detectable endogenous interference.

Standard curve and LLOQ

For tepotinib, a standard curve was drawn based on the ratio of the peak area ratio (analyte/IS) to the nominal plasma concentration of the analyte, and the coefficient of determination was represented by r^2. Perfect linearity was shown in the plasma concentration range of 0.1–500 ng/mL with $r^2 > 0.99$ in all validations, and the LLOQ of this experiment was 0.1 ng/mL.

Accuracy and precision

Relative error (RE) is defined as accuracy, and relative standard deviation (RSD) is defined as precision. Three samples of four different QC concentrations were used to quantify the interday and intraday precision on three separate days ($n=6$). Table 2 shows data about the precision and accuracy of tepotinib in rat plasma ($n=6$). Both the RE and RSD meet our expectations and FDA standards, indicating that this method has good precision, accuracy and repeatability.

Matrix effect and extraction recovery

The recovery is defined as the peak area ratio of the analytes in the blank matrix before and after extraction. The matrix effect is defined as the peak area ratio of the analyte added to the blank matrix and the pure analyte solution after extraction. This method has good extraction recovery and almost no matrix effect in rat plasma. In the QC samples at different concentrations, the recovery rate of tepotinib ranged from 81.2 to 86.9%, and the matrix effect ranged from 90.5 to 98.6%. Table 3 exhibits the

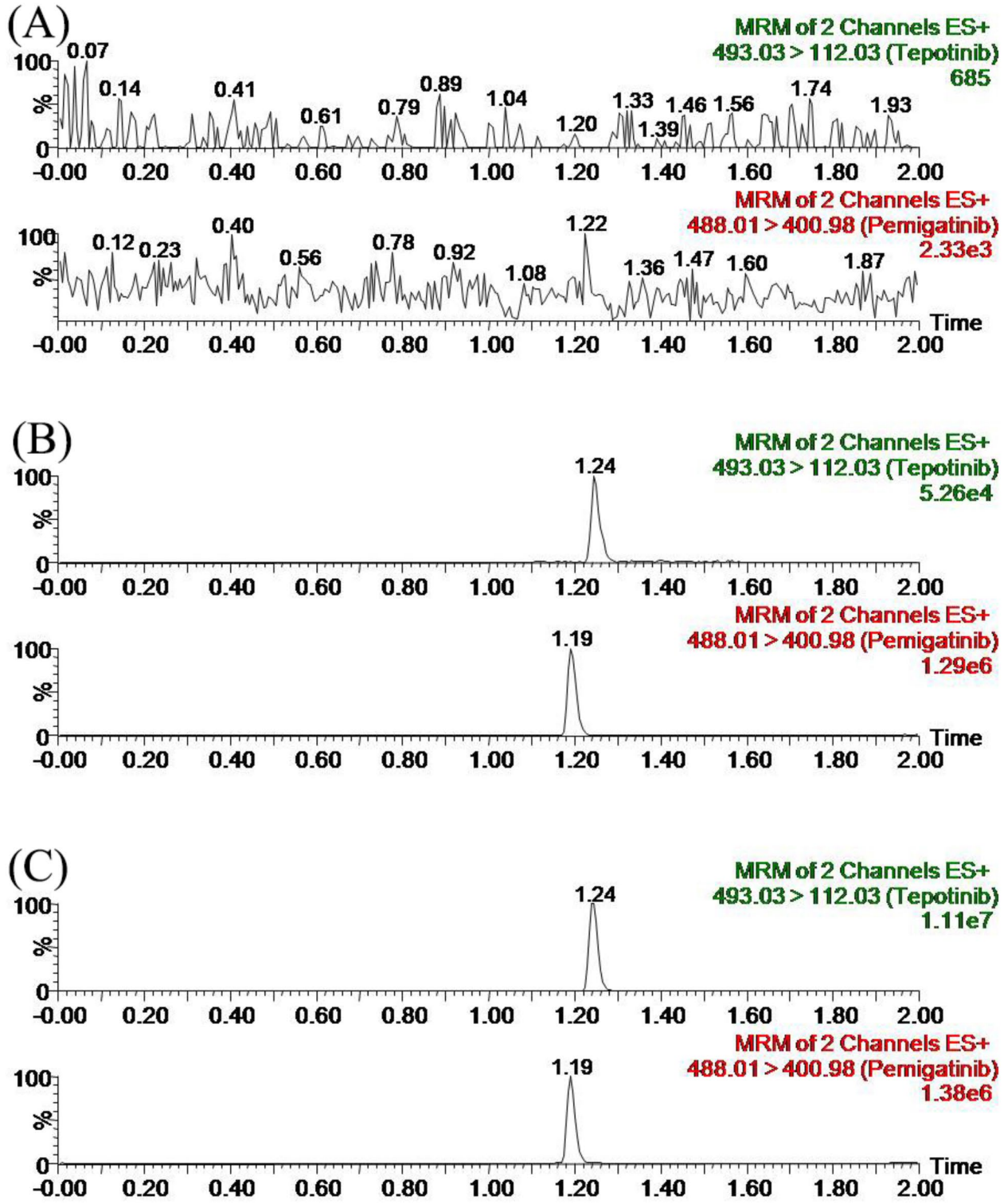

Fig. 2 Representative chromatograms of tepotinib and IS in rat plasma: (**A**) blank plasma; (**B**) blank plasma spiked with standard solution at LLOQ (0.1 ng/mL) and IS; (**C**) sample obtained from a rat at 1.0 h after oral administration of 50 mg/kg tepotinib

Table 2 The precision and accuracy of tepotinib in rat plasma ($n=6$)

Analyte	Concentration (ng/mL)	Intraday		Interday	
		RSD%	RE%	RSD%	RE%
Tepotinib	0.1	12.5	5.4	11.1	0.8
	0.2	8.4	-1.7	7.1	0.3
	40	4.9	1.5	3.7	6.2
	400	4.6	3.2	3.4	7.3

Table 3 Recovery and matrix effect of tepotinib in rat plasma ($n=6$)

Analyte	Concentration (ng/mL)	Recovery (%)		Matrix effect (%)	
		Mean ± SD	RSD (%)	Mean ± SD	RSD (%)
Tepotinib	0.2	81.2 ± 10.2	12.6	98.6 ± 12.8	13.0
	40	85.2 ± 10.5	12.4	90.5 ± 10.3	11.4
	400	86.9 ± 11.4	13.2	96.3 ± 2.9	3.0

Table 4 The main pharmacokinetic parameters of tepotinib in different treatment groups of rats. Group A: the control group (0.5% CMC-Na); Group B: 50 mg/kg naringenin. ($n=5$, mean ± SD)

Parameters	Group A	Group B
$AUC_{0\to t}$ (ng/mL•h)	4596.47 ± 458.17	5802.37 ± 895.75*
$AUC_{0\to\infty}$ (ng/mL•h)	4630.42 ± 453.80	5995.51 ± 937.05*
$MRT_{0\to t}$ (h)	18.93 ± 1.21	18.56 ± 3.16
$MRT_{0\to\infty}$ (h)	19.43 ± 1.36	18.96 ± 3.45
$t_{1/2}$ (h)	9.40 ± 2.35	12.49 ± 4.52
T_{max} (h)	8.80 ± 3.03	10.40 ± 2.19
CLz/F (L/h)	10.88 ± 1.04	8.52 ± 1.46*
C_{max} (ng/mL)	180.28 ± 38.25	267.69 ± 95.87

Compared with Group A, *$P<0.05$

specific data of the extraction recovery rate and matrix effect of tepotinib.

Stability

Using QC plasma samples at 3 concentrations for stability experiments, the environmental conditions were set at ambient temperature, autosampler (10 ℃), -80 ℃ and three complete freeze–thaw processes (-80 ℃ to ambient temperature). The results showed that the stability of tepotinib can be maintained for 3 h at ambient temperature (short-term stability), 6 h in an autosampler, 4 weeks (long-term stability) in a -80 ℃ refrigerator, and 3 freeze–thaw cycles under these four different environmental conditions.

Pharmacokinetics

Using the quantitative method of the determination of tepotinib in this study, we successfully measured the pharmacokinetic parameters of tepotinib in a noncompartmental model in rats. The specific data are summarized in Table 4. Figure 3 shows the mean plasma concentration-time curves of a single oral administration of 50 mg/kg tepotinib in the two groups of rats.

A previous study had reported that gender had no relevant effect on the PK of tepotinib [25], thus, we used only male rats for our experiment. According to the results of our experiment, tepotinib rapidly reached its maximum concentration (C_{max}) after oral administration of 50 mg/kg. The peak time (T_{max}) and C_{max} of tepotinib were 8.80±3.03 h and 180.28±38.25 ng/mL, respectively. The $AUC_{0\to t}$ (ng/mL•h) and $AUC_{0\to\infty}$ (ng/mL•h) of tepotinib were 4596.47±458.17 and 4630.42±453.80, respectively. In addition, the half-life ($t_{1/2}$) and the CLz/F are 9.40±2.35 h and 10.88±1.04 L/h, respectively. Only T_{max} in the above data is similar to the previous study, which is 9 h [5], and all other parameters are very different from previous studies. The reason for this difference may be the species difference between humans and rats. When combined with naringenin, we found that the $t_{1/2}$, T_{max} and C_{max} of tepotinib, which were 12.49±4.52, 10.40±2.19, and 267.69±95.87, respectively, were not significantly affected by naringenin. The $AUC_{0\to t}$ (ng/mL•h) and $AUC_{0\to\infty}$ (ng/mL•h) of tepotinib were significantly increased to 5802.37±895.75 and 5995.51±937.05, respectively, accompanied by a decrease in CLz/F ($P<0.05$).

As a CYP3A4 inhibitor, naringenin is widely present in our daily diet and has been proven to have a positive impact on the recovery of many respiratory diseases [9, 26] and is often combined with antitumor drugs [14, 15]. Previous studies have shown that, similar to many antitumor drugs, the metabolism of tepotinib is also related to CYP3A4 [2]. Therefore, we speculate that naringenin reduces the metabolism of tepotinib in rats, which may be related to its role as a CYP3A4 inhibitor. Our study suggested that naringenin may cause elevated exposure to tepotinib and increase the likelihood of adverse reactions. Therefore, clinicians may need to make dosage adjustments of tepotinib when the combination of tepotinib and naringenin is unavoidable.

Conclusions

In summary, we developed and validated a rapid, sensitive, and reliable UPLC-MS/MS method for the determination of the concentration of tepotinib in rat plasma, which fulfilled the need for validating a method for the detection of tepotinib. The assay was demonstrated in a food-herb interaction study between tepotinib and naringenin in rats, where it was found that naringenin significantly increased the plasma exposure and decreased the clearance of tepotinib. Therefore, dosage adjustments of tepotinib may be necessary for patients who need to use a combination of tepotinib and naringenin.

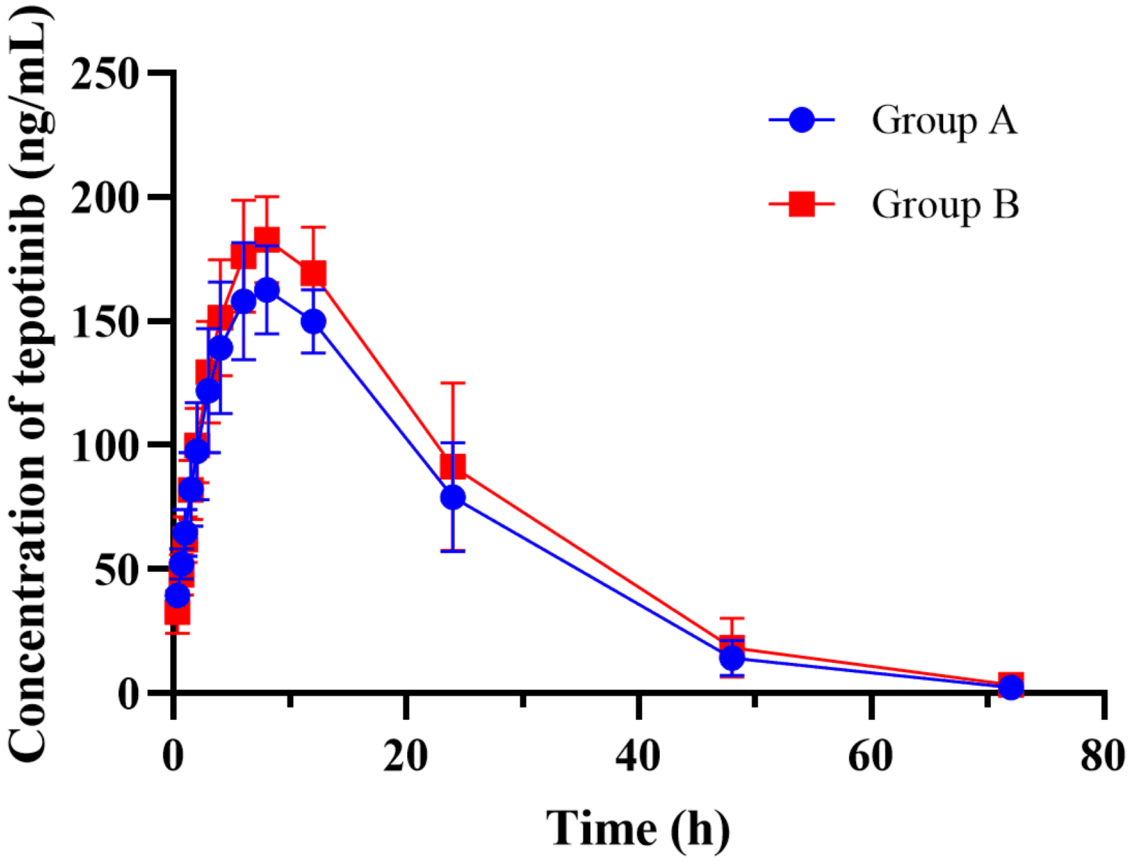

Fig. 3 Mean plasma concentration-time curves of tepotinib in different treatment groups of rats. Group **A**: the blank group (0.5% CMC-Na); Group **B**: 50 mg/kg naringenin with tepotinib (50 mg/kg). ($n = 6$, mean ± SD)

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Author contributions
Shunbin Luo contributed to the conception and design of the study. Zhe Chen and Chaojie Chen obtained the data. Shunbin Luo performed the statistical analysis. Zhe Chen wrote the first draft of the manuscript. Zhe Chen, Chaojie Chen, Ya-nan Liu, and Xinhao Xu wrote sections of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

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Data availability
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Animal experiments were demonstrated to be ethically acceptable and were carried out according to the Guidelines of the Experimental Animal Care and Use of Laboratory Animals of The First Affiliated Hospital of Wenzhou Medical University. All animal procedures and experimental protocols were approved by the Laboratory Animal Ethics Committee of The First Affiliated Hospital of Wenzhou Medical University (Ethics approval number: WYYY-IACUC-AEC-2023-045).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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