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RESEARCH ARTICLE
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Effects of Liquorice Juice on the Pharmacokinetics of Esomeprazole

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ABSTRACT

The HPLC-MS technique was tested and verified in this work to quantify esomeprazole in rat plasma samples. A rat investigation demonstrated that co-administration of a single dosage of liquorice juice had no effect on the pharmacokinetic characteristics of esomeprazole, however successive doses of liquorice juice raised the t1/2 and area under the curve of esomeprazole. After introducing liquorice juice into the stomach, the pharmacokinetics of esomeprazole was determined simultaneously by HPLC-MS. The absorption of esomeprazole was rapid; esomeprazole was detected in plasma from the first blood sampling time, and the peak plasma concentration for the esomeprazole-treated group with multiple doses of liquorice was reached one hour after oral administration. At the same time, peak plasma concentration was reached 30 min after oral administration for the esomeprazole-treated group with a single dose of liquorice or distilled water. The plasma concentrations of esomeprazole in the esomeprazole-treated group with single-dose liquorice were comparable to those with single-dose distilled water. The plasma concentrations of esomeprazole were higher in the esomeprazole treated group with multiple doses of liquorice than in the esomeprazole treated group with single-dose distilled water, resulting in a significantly higher AUC, 2.5 times, in the esomeprazole treated group with multiple doses of liquorice. This could be due to decreased metabolism of esomeprazole by multiple doses of liquorice. Since esomeprazole is metabolized in the liver mainly by CYP2C19 and liquorice is a moderate inhibitor of CYP2C19 in humans there was an inhibition of CYP2C19 at multiple doses of liquorice. The inhibited metabolism of esomeprazole by liquorice resulted in a significantly higher Cmax, 1.5 times, and a significantly longer terminal half-life, 1.45 times, than in the control group. Therefore, multiple administration of liquorice could increase the esomeprazole effect since a single dose did not affect esomeprazole metabolism.

Keywords: *esomeprazole; proton pump inhibitors; licorice; pharmacokinetics; drug interactions*

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INTRODUCTION

Esomeprazole (ESMO) is a compound that is intended for the oral route of administration and belongs to a class of medications known as proton pump inhibitors (PPIs) used in the treatment of gastric oesophageal reflux diseases (GERD), H. pylori eradication, peptic ulcer disease, and prevention of gastrointestinal bleeds associated with NSAID administration [1–4]. ESMO works via the inhibition of H+/K+ ATPase enzyme pumps in the gastric lumen, decreasing the amount of gastric acid produced [5]. ESO is metabolized in the body by the cytochrome P450 enzyme system, mostly through CYP2C19, to generate the hydroxy and 5-O-desmethyl metabolites [6].

ESMO, bis(5-methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl] sulfinyl]-1-H-benzimidazole-1-yl) [7] consists only of the optical S-isomer of omeprazole [8]. It has an empirical formula of (C17H19N3O3S) and a molecular weight of 345.4 g/mol (Fig. 1) [9].

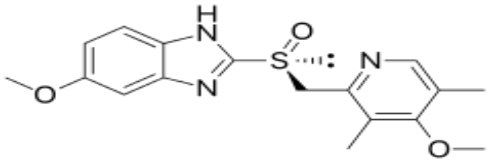

FIGURE 1. Chemical structure of ESMO.

Because of the wide use of PPIs, monitoring the potential interaction of drugs [10] and food [11] with ESMO is essential in evaluating the therapeutic potency and efficacy of ESMO. Altered absorption or metabolism are the two of the primary mechanisms for drug-drug and drug-food interactions [12].

Recently published data have proven that using plant extracts or plant-based beverages with medications has been shown to inhibit biochemical processes in the intestine, leading to altered pharmacokinetics and pharmacodynamics outcomes. [13]

Liquorice (LIQ, Glycyrrhiza glabra of the Leguminosae Family) is a well-known and most widely consumed traditional drink, particularly in the Middle East region [14]. Most of the beneficial effects of LIQ come from its roots and rhizomes, which have been used alone or in combination with other herbs to treat a wide variety of conditions, including those related to the digestive system (such as stomach ulcers, flatulence, hyperdipsia, and colic) and the respiratory system (tonsillitis, asthma, coughs, sore throat, and jaundice) [15–18]. On the other hand, LIQ was discovered to affect the kinetics of some medications, notably thiazides [19]. Bioavailability of cyclosporine was observed to be drastically decreased due to LIQ's interference with P-glycoprotein and CYP3A4 [20].

Several methods have been developed to estimate ESMO in pharmaceutical preparations, including UV-visible-[21,22] and HPLC [23,24] methods. In biological fluids, ESO was determined by LC-MS/MS [25–27] and the desorption electrospray mass spectrometry (DESI-MS) method [28].

Drinks made from herbs have become more popular in recent years. The current study proposes a new HPLC-MS method for simultaneous ESMO determination in the presence of LIQ to investigate the potential pharmacokinetic interactions between them when taken together in experimental rats.

Experimental

Chemicals and reagents

Deionized Water, Nano-pure (Fisher Scientific), Methanol (Fisher Scientific), HPLC grade acetonitrile, and ethanol were from Merck Company (Darmstadt- Germany), Formic acid (Acros), 12 M of Hydrochloric acid (Fisher Scientific). ESMO raw material (purity 98.5%) was a kind gift from Pharma International Company - Amman. Azithromycin (internal standard (IS), purity > 98.5%) was a kind gift from Hikma Pharma -Amman. LIQ was purchased from the local market. All other chemicals were of analytical grade

Apparatus and chromatographic conditions

An Agilent 1200 Series liquid chromatograph (Agilent Technologies, Waldbronn, Germany) with an autosampler, quaternary pump, degasser, and thermostatted column compartment was used for all analyses, as well as an AB Sciex 3200-AB API triple quad mass spectrometer (Darmstadt, Germany) with electrospray ionization (ESI).

Using chromatographic separation at 45°C, a 500 mm × 2.1 mm ACE5-C18 column with 5 m particle size was employed. Mobile phase A (0.1 percent formic acid) and mobile phase B (water) were used in a gradient elution procedure for chromatographic separation (methanol). Quantification was performed using the peak-area technique, and the flow rate was maintained at 0.1 mL/min. A search for the intended ions was conducted in SIM mode.

With ESMO, we saw a retention duration of 3.4 minutes, and with the IS, we saw a retention time of 2.4 minutes. The whole 4.5-minute LC-MS/MS process took place.

Preparation of stock solutions

Primary stock solutions of ESMO (4 mg/mL) and the Azithromycin IS (1 mg/mL) were produced in methanol and kept at -20 °C until use. We used methanol to dilute the stock solutions to the appropriate concentrations for our normal working solutions.

Quality control (QC) samples were made at concentrations of 0.9, 9, and 15 g/mL ESMO and 2 g/mL IS, respectively. There was a uniform temperature of 4 degrees Celsius for storing all functioning solutions.

Analytical Method Validation

Table 1 displays the results of tests performed to ensure that the analytical procedure complies with ICH standards for linearity, accuracy, extraction recovery, precision, and specificity.

TABLE 1. Percentage drug recovery, linearity, calibration curve, precision, and accuracy for the analytical method.

% drug recovery	Linearity and calibration curve	accuracy	precision
96.0-102.0 %	in the range of 0.3–18 μg/mL plasma, $y = 0.0018x - 0.0063$	All standard points met the accuracy and precision criteria of ±20% for the lowest and ±15% for all (0.3, 0.6, 1.2, 2.4, 6.0, 12.0, and 18.0 μg/mL) of the calibration curve.	intra- and inter-day precision were within 91.4% - 113.2% of the nominal values

Linearity

By adding known amounts of ESMO and IS to blank rat plasma (0.3, 0.6, 1.2, 2.4, 6.0, 12.0, and 18.0 μg/mL, respectively) and measuring the resulting concentrations using an LC-MS, we were able to establish the linearity of the approach. After that, calibration curves were constructed by plotting response ratios (ratios of ESMO peak areas to IS peak areas) against the appropriate spiking concentration of calibration standards. Slope (a), intercept (b), and correlation coefficient (r) were calculated using linear regression.

Accuracy, Extraction Recovery, and Precision

Percentage of recovery was used to calculate the method's efficacy. Rat plasma was spiked with ESMO at 0, 9, and 15 g/mL while maintaining a fixed IS concentration. In addition, a second set of concentration-matched standard mixes was made in the mobile phase. The plasma was collected and injected three times into the LC-MS apparatus in a manner similar to that described in 2.4.1. Linearity above. The following formula was used to determine ESMO's percentage of recovery:

$$Recovery = A/B * 100$$

Where:

A = the response ratio of the ESMO concerning the IS in plasma samples

B = the response ratio of the ESMO concerning the IS in standard mixtures.

Injecting (n=6) plasma samples spiked at three distinct concentration levels (0.9, 9, and 15 g/mL), while holding the IS concentration constant, into LC-MS for three consecutive days yielded results represented as %RSD.

Specificity/Selectivity

The specificity/selectivity of the LC-MS method was confirmed by injecting spiked blank rat plasma with 300 µg/mL ESMO and 2.0 µg/mL IS (n=6), treating actual rat plasma samples without ESMO and IS, and only blank mobile phase. It is required that there must be no interference from endogenous or exogenous substances over the peak shape as well as the retention times of ESMO and IS.

Effects of LIQ on ESMO PK

The animal experiments were done in compliance with ICH guidelines, and the Scientific Research and Ethics Committee approved the study protocol at the Faculty of Pharmacy, Mutah University, Al-Karak 61710, Jordan, approval number SREC 3-2022/12 / Feb.3, 2022

Eight-week-old (250±30 g) male Sprague Dawley (SD) rats were given by the Animal House (Applied Sciences University, Amman, Jordan). These rats were kept in an air-conditioned environment (25 °C) with a 12-hour light-dark cycle and had unrestricted access to their usual feed and water.

Effects of a single dosage of LIQ on ESMO PK

16 SD rats (250±30 g) fasting for 12 hours were split evenly between the control and experimental groups. In the experimental group, participants received LIQ at a dosage of 25 mg/kg orally, whereas those in the control group received water. Rats in the two groups received 0.5714 mg/kg of ESMO through stainless steel oral gavage needle 30 minutes after LIQ treatment (Table 2).

TABLE 2. Animal groups used in the study to study effect of LIQ on ESMO PK.

Groups of animal	Time of dosing	Time of plasma withdrawn
Sixteen rats divided into control and test grups	30 min after administration of LIQ, rats adminstered 0.5714 mg/kg of ESMO	1.2 mL blood samples withdrawn at 0.33, 0.66, 1.0, 2.0, 4.0, 8.0, 24.0, 36.0, 48.0, 72.0, and 96.0 hours

Blood samples of 1.2 mL from each group were obtained through the tail vein (at time points intervals 0.33, 0.66, 1.0, 2.0, 4.0, 8.0, 24.0, 36.0, 48.0, 72.0, and 96.0 hours) and collected into heparinized 1.5 mL polythene tubes after the administration of the ESMO. The samples were immediately centrifuged at 2,000 x g for 10 min, and then 100-125 µL plasma was transferred to another tube and stored at -30 ◦C [29].

Effects of multiple dosages of LIQ on ESMO PK

In this procedure, eight SD rats (250 ±30 g) of 12 hours fasted-rats were selected for 7-day oral administration of LIQ (25 mg/kg, twice daily). The dosage of the ESMO was the same as for the single dose of LIQ was administered orally on day number eight of the experiment.

Preparation of ESMO solution and LIQ juices

ESMO solution was freshly prepared on the day of the experiment. The ESMO dose of 0.5714 mg/kg was chosen based on the average human dose. A stock solution of 0.022 mg/ml was prepared by dissolving ESMO in distilled water followed by solution filtration. The administered dose of ESMO solution to the rats was calculated using the following formula:

$$Dose\ of\ ESMO\ solution\ (ml)\ = \frac{weight\ of\ the\ rat\ (kg) * Average\ human\ dose\ (mg/kg)}{ESMO\ solution\ Concentration\ (mg/ml)}$$

The root of LIQ was milled using a sterilized grinding stone resulting in a yellow powder stored in airtight containers for future use. LIQ root extracts (LREs) were prepared by suspending 20 gm of the yellow powder plant material in Ethanol: water mixture (1:1) in an Erlenmeyer flask to produce a 250 mg/mL extract solution. The solution was refrigerated at 4±1 °C and administered to the rats without further treatment [30].

Pharmacokinetic analysis

Phoenix Win-01-Nonlin version 7.01 (Pharsight®, Princeton, NJ, USA) was used to calculate pharmacokinetic parameters for ESMO. Using the concentration-time profiles, we were able to determine the maximum plasma concentrations (Cmax). The linear trapezoidal rule was used to determine area under the curve (AUC) values. The terminal log-linear slope of the plasma concentration-time profile was used to determine the elimination rate constant (ke), and t0.5 was then computed using the formula $t_{0.5} = \frac{Ln2}{ke}$.

Statistical analysis

We used one-way ANOVA and Tukey's multiple comparison test for our statistical study. Using the Statistical Package for the Social Sciences (SPSS) version 18, non-parametric analysis was done using the Mann-Whitney test (IBM Corporation, Armonk, NY, USA). We accept as significant a value of P less than 0.05.

RESULTS AND DISCUSSION

Method validation

In order to evaluate the validity of the method, we referred to the ICH recommendations. For this validation, we utilized QC samples from the complete calibration range, including the LLOQ, the medium QC sample (around the center of the calibration range), and the high QC sample, as specified by the ICH recommendations (near the upper limit of the calibration range). Specificity, linearity, lower limits of quantitation, extraction recovery, accuracy, and precision were all verified, among others.

Linearity of the calibration curve

The peak area ratios obtained for ESMO to that of IS were linearly connected to the corresponding ESMO spiking concentrations in the range of 0.3-18 µg/mL plasma using the least-squares approach. A 3-day calibration curve was used in the study. Thus, y=0.0018x-0.0063 was found to be the ESMO regression equation. The high value of the correlation coefficient (r = 0.9999) and the modest intercept demonstrated the high degree of linearity of the approach.

As a result, an LLOQ of 0.3 µg/mL was sufficient for ESMO analysis. The study was performed using a 3-day calibration curve, and it was correlated with the mean calibration's equation of y=0.0018x-0.0063, with a coefficient of determination R2 = 0.9999.

The calibration curve's standard points (0.3, 0.6, 1.2, 2.4, 6.0, 12.0, and 18.0 µg/mL) were all within the required accuracy and precision ranges of ± 20% for the lowest and ±15% for all.

Specificity and selectivity

The ESMO and the IS were examined using an AB Sciex 3200-AB mass spectrometer (electrospray ionization) in Darmstadt, Germany (ESI). There was no interference peak in the ESMO pure drug chromatograms and mass spectra of six distinct plasma samples when compared to those of plasma samples coeluted with the ESMO and IS (Fig 2). Retention durations of 3.8 and 2.4 minutes for the spiked sample of 300 µg/mL ESMO and 2 µg/mL IS in rat blank plasma were observed during the short 4.5 minute run period (Fig 2). That there is a high level of technique specificity may be inferred from this.

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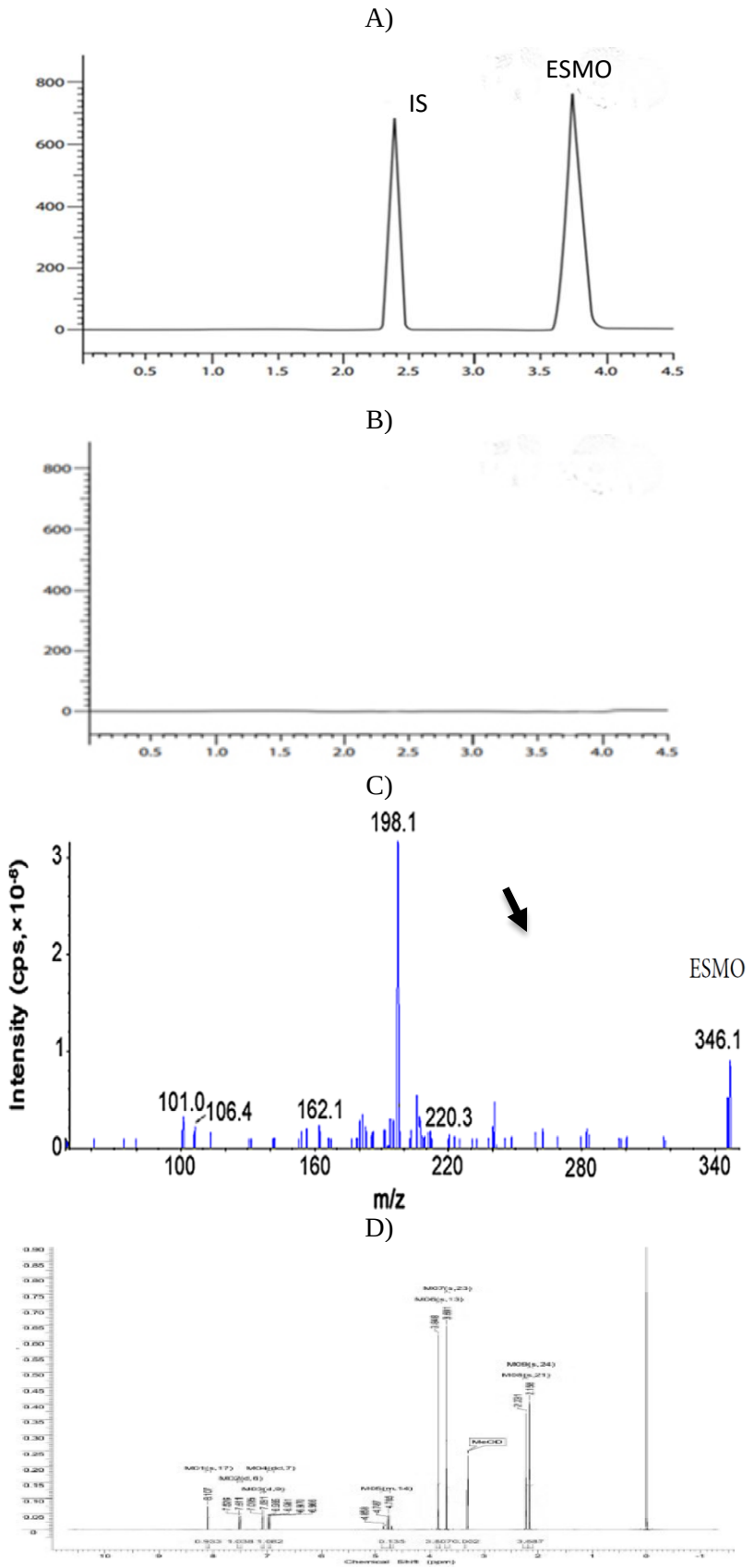

FIGURE 2. A) Representative chromatogram of ESMO (300.0 µg/mL) and IS (2.0 µg/mL) at retention time (Rt) of 3.8 and 2.4min, respectively. B) The blank. C) Mass spectra of ESMO D) LIQ. The pooled blank rat plasma (n = 6) showed no interference signal.

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Accuracy and precision

Analysis of replicates (n = 6) of QCL, QCM, and QCH concentrations of 0.9, 9, and 15 µg/mL, respectively, allowed for the determination of intra- and inter-day accuracy and precision. Precision ranged from 91.4 to 113.2% of the nominal values both within and between days. The intra- and inter-day tests for QCL, QCM, and QCH met or exceeded the ICH guideline's acceptance requirements for accuracy and precision.

Extraction recovery

By comparing the peak responses of the Pre- and Post-extraction samples, we were able to determine the mean extraction recovery of six duplicate QC ESMO and the IS samples. QCL, QCM, and QCH all had mean extraction recovery values of 96.0-102.0 percent for ESMO. The results show that ESMO and the IS were reliable in their extraction effectiveness.

In vivo Pharmacokinetic studies

After introducing LIQ juice into the stomach, the pharmacokinetics of ESMO was determined simultaneously by HPLC-MS. The mean plasma concentration-time profiles of esomeprazole for three groups are shown in Fig 3, and the relevant pharmacokinetic parameters are listed in Table 1. The absorption of esomeprazole was rapid; esomeprazole was detected in plasma from the first blood sampling time, and the peak plasma concentration (Cmax) for the esomeprazole-treated group with multiple doses of LIQ was reached one hour after oral administration. While peak plasma concentration (Cmax) reached 30 min after oral administration for esomeprazole treated group with a single dose of LIQ or DW (Fig 3). The plasma concentrations of esomeprazole in the esomeprazole-treated group with single-dose LIQ were comparable to those with single-dose DW.

The plasma concentrations of esomeprazole were higher in the esomeprazole treated group with multiple doses of LIQ than in the esomeprazole treated group with single-dose DW (Fig 3), resulting in a significantly higher AUC, 2.5 times, in the esomeprazole treated group with multiple doses of LIQ (Table 1). This could be due to decreased metabolism of esomeprazole by multiple doses of LIQ. Since esomeprazole is metabolized in the liver mainly by CYP2C19 and LIQ is a moderate inhibitor of CYP2C19 in humans [31,32], there was an inhibition of CYP2C19 at multiple doses of LIQ. The inhibited metabolism of esomeprazole by LIQ resulted in a significantly higher Cmax, 1.5 times, and a significantly longer terminal half-life, 1.45 times, than that in the control group (Table 1). Therefore, multiple administration of LIQ could increase the esomeprazole effect since a single dose did not affect esomeprazole metabolism.

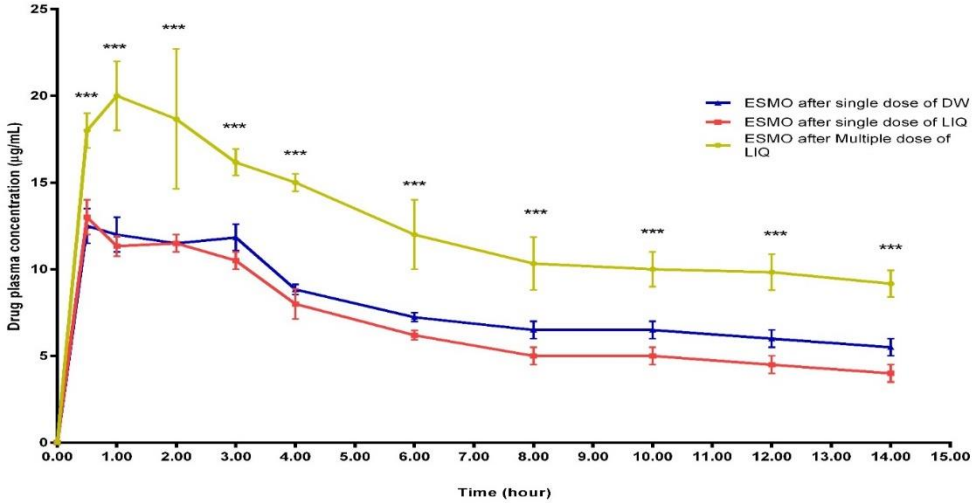

FIG. 3. Time concentration curves of ESMO after single and multiple-dose of LIQ juice.

TABLE 1: Effects of LIQ juice on pharmacokinetic parameters of ESMO

Parameter	Control	Single-dose	Multiple-dose
C-max (µglmL)	12.35 ± 0.35	13.62 ± 0.30	20.15± 0.60
T-max (hr)	0.5	0.5 ± 0.15	1.00±0.35
AUC(0→∞) (µglmL*hr)	94.13±6.04	86.73 ± 1.09	218.68±12.07
T½ (hr)	4.47	3.91	5.68 +1.20*
Ke (hr-1)	0.16	0.18	0.12

CONCLUSIONS

As part of this research, the HPLC -MS technique for determining ESMO levels in rat plasma was investigated and verified. The authors of this study are the first to look at how LIQ juice affects the PK of ESMO when the two are given together. Multiple doses of LIQ juice increased the t1/2 and area under the curve ESMO, but co-administration of a single dosage of LIQ did not substantially modify the PK characteristics of ESMO in rats. Nonetheless, further clinical research is needed.

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