

Original article

Pharmacokinetics of ferulic acid following oral administration ethyl ferulate alone and in combination with piperine in rats

Megha A. Modi, Nitin V. Kale, Jatin H. Patel*, Rasesh D. Varia, Falguni D. Modi and Priti D. Vihol

Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A.H., Navsari Agricultural University, Navsari-396450, Gujarat, India

*Department of Veterinary Pathology, College of Veterinary Science and A.H., Navsari Agricultural University, Navsari-396450, Gujarat, India

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Abstract

The present study was undertaken to evaluate pharmacokinetics of ferulic acid following oral administration of ethyl ferulate alone and in combination with piperine in rats. Following oral administration of ethyl ferulate and in combination with piperine, the mean peak plasma ferulic acid concentration of 18.38 ± 1.38 vs 15.27 ± 1.18 $\mu\text{g/ml}$ was achieved at 0.25 h. Plasma concentration of ferulic acid at 0.5 h differ significantly ($p < 0.05$) and plasma concentration of ferulic acid at 0.08 h, 0.25 h, 0.75 h and 1 h did not differ significantly. All pharmacokinetic parameter of ferulic acid did not differ significantly except volume of distribution (1.25 ± 0.12 vs 2.85 ± 0.57 L/kg) and total body clearance (7.35 ± 0.57 vs 17.19 ± 1.59 L/h/kg). The study indicates rapid absorption and clearance of ferulic acid from body following oral administration of ethyl ferulate alone and in combination with piperine in rats.

Key words: Ethyl ferulate, ferulic acid, piperine, pharmacokinetics, rat

1. Introduction

Plants are rich in a variety of phytochemicals like tannins, terpenoids, alkaloids, saponins, propanoid, flavonoid, *etc.*, which are used widely in Chinese and Indian herbal medicine from ancient times. Ferulic acid (FA, 4-hydroxy-3-methoxycinnamic acid) is a phenolic acid, yellow colour crystalline appearance with molecular formula $\text{C}_{10}\text{H}_{10}\text{O}_4$. Research report shows that absorption of ferulic acid after oral administration is quite rapid but bioavailability and mean residence time of it is low in rats (Rondini *et al.*, 2002). So, in order to improve bioavailability, esterification of ferulic acid is one way (Biasutto *et al.*, 2007) and to decrease *in vivo* metabolism, piperine can be favourable agent as biochaner (Singh *et al.*, 2009; Chauhan *et al.*, 2017; Patel *et al.*, 2018). Ethyl ferulate is (ethyl-3-hydroxy-4-methoxycinnamate) phenyl propanoid, alkyl ester derivative of ferulic acid. Ethyl ferulate has also been widely studied and some recent findings include its anticholinesterase activity, inhibition of nuclear factor-kappa B (NF- κ B), inhibition of inducible nitric oxide synthase (iNOS), inhibition of neurodegenerative disorders and cytoprotective effect (Nazare *et al.*, 2014). In the

backdrop of above facts and available literature, the present study was undertaken to evaluate pharmacokinetics of ferulic acid following oral administration of ethyl ferulate in rats with special attention on effect of piperine co-treatment on pharmacokinetic profile of ferulic acid.

2. Materials and Methods

2.1 Experimental animals

The experiment was conducted in 48 female Wistar rats weighing between 300 to 400 g. Rats were kept under constant observation for two weeks before the commencement of the experiment and subjected to clinical examination to exclude possibility of any disease. The animals were randomly divided into two groups and kept in polypropylene cages. Standard feed and water was provided *ad libitum*. The experimental protocol and use of animals for conducting the study was approved by the Institutional Animal Ethics Committee with protocol numbers 059-VCN-VPT-2018 and 060-VCN-VPT-2018.

2.2 Drugs and chemicals

Ethyl ferulate, ferulic acid and piperine were obtained from Sigma-Aldrich, St. Louis, USA. Tween 80 and 1-methyl-2 Pyrrolidone acetonitrile, glacial acetic acid and ortho-phosphoric acid were purchased from Merck Specialties Private Limited, Mumbai. Arachis oil was purchase from local pharmacy.

Author for correspondence: Dr. Jatin H. Patel

Department of Veterinary Pharmacology and Toxicology, College of Veterinary Science and A.H., Navsari Agricultural University, Navsari-396450, Gujarat, India

E-mail: drjatinvet@yahoo.co.in

Tel.: +91-9428489543

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2.3 Experimental design for pharmacokinetic study

Pharmacokinetic of ferulic acid was evaluated following oral administration of ethyl ferulate alone (150 mg/kg) as well as along with piperine (40 mg/kg), following oral administration in rats (n=48). Ethyl ferulate and piperine were dissolved in arachis oil, tween 80 and 1-methyl-2 pyrrolidone in equal ratio. Multiple numbers of rats were used for serial collection of blood samples at alternating time points. Blood samples were collected in K3EDTA vials, at different time interval, *i.e.*, 0.083, 0.25 0.5, 1, 1.5, 2, 4, 6, 8 and 12 h from retro orbital plexus. Plasma was collected by the centrifugation (3000 rpm for 10 min) and stored at -20°C in cryovials. Samples were analyzed within 24 h for determination of ferulic acid concentration through high performance liquid chromatography (HPLC).

2.4 HPLC analysis of ferulic acid from plasma samples

For the precipitation of the plasma protein, acetonitrile and glacial acetic acid mixture (9:1 ratio) was added in plasma as 1:1 ratio and was mixed in a clean microcentrifuge tube on a vortex mixer for 1 min. It was followed by centrifugation for 10 min at 10000 rpm. The clean supernatant was transferred into inserts of automatic sampler vial, from which 20 µl of supernatant was injected into high performance liquid chromatography (HPLC) system.

Plasma samples were analyzed to quantify ferulic acid using HPLC system by using procedure as described by Adam *et al.* (2002), Cheng *et al.* (2012^{ab}) and Patel *et al.* (2018) with minor modifications. In brief, the HPLC apparatus of Shimadzu (Japan) comprised of binary gradient delivery pump (model LC 20AP), diode array detector (model SPD M20A), auto sampler (model SIL 20A) and reverse phase C18 column (250×4.6 mm ID). Mobile phase consisted of Solvent A (5% orthophosphoric acid in lab grade water) and Solvent B (100 % acetonitrile). Mobile phase solvents were filtered by 0.2 µ size filter (Axiva N₆₆) and degassed by ultra-sonication. The mobile phase was pumped into column at a flow rate of 1.5 ml/min at ambient temperature in gradient flow as follows: 0-5 min (30% solvent B) and 5.01-10 min (50% solvent B). The effluent was monitored at 322 nm wavelength.

For validation of HPLC method, initial stock solution of ferulic acid was prepared by dissolving 2 mg ferulic acid in 2 ml drug free plasma. Final standards were prepared in drug-free plasma of rat. Quantification of ferulic acid in plasma samples was done by reference to the resultant standard curve (Figure 1). The calibration curves showed good linearity over the concentration ranges 0.09 to 25 µg/ml with a mean correlation coefficient (R²) was 0.99. Representative chromatograms of blank plasma of rat, ferulic acid standard (25 µg/ml) in plasma, 15 min post oral administration of ethyl ferulate in rat, 1 h post oral administration of ethyl ferulate in rat, 15 min post oral administration of ethyl ferulate and in combination with piperine in rat and 1 h post oral administration of ethyl ferulate and in combination with piperine in rat are depicted in Figure 2. The precision and accuracy of the assay were assessed using samples at concentration of 25, 12.50, 1.56, 0.39 and 0.09 µg/ml. At all concentrations, the C.V. was less than 9.23 %. The lower limit of detection and limits of quantification of the drug was 0.09 and 0.19 µg/ml, respectively.

2.5 Calculation of pharmacokinetic parameters

Pharmacokinetic parameters were calculated as per standard methods (Baggot, 1977; Gibaldi and Perrier, 1982). Absorption rate constant (α) and elimination rate constant (β) were calculated by least square regression analysis method. Absorption half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) were calculated from $0.693/\alpha$ and $0.693/\beta$, respectively. Maximum drug concentration in plasma (C_{max}) and time of maximum observed concentration in plasma (T_{max}) were obtained from actual plasma concentrations of each rat. Area under curve ($AUC_{(0-\infty)}$) and area under the first moment of curve (AUMC) were calculated by linear trapezoidal rule. Apparent volume of distribution ($Vd_{(area)/F}$) was calculated from $(Dose \times F)/(\beta \times AUC)$. The value of total body clearance ($Cl_{(B)}$) was obtained using formula $\beta \times Vd$ (area). Mean residence time (MRT) was obtained by dividing the value of AUMC by AUC.

2.6 Statistical analysis

All data obtained for pharmacokinetic parameters of ferulic acid was presented as mean \pm SE. The data for plasma ferulic acid concentration suitably tabulated and analyzed by 't' test. The *p* values <0.05, <0.01 and <0.01 were considered as statistically significant or highly significant, respectively.

3. Results

Ferulic acid levels in plasma as a function of time schedule after oral administration of ethyl ferulate (150 mg/kg) and its combination with piperine (40 mg/kg) in rats are presented in Table 1, while semilogarithmic plots of the same have been presented in Figure 3. Pharmacokinetic parameters of ferulic acid following oral administration of ethyl ferulate (150 mg/kg) and its combination with piperine (40 mg/kg) in rats are shown in Table 2.

Following oral administration of ethyl ferulate alone or in combination with piperine, the plasma drug (ferulic acid) concentration of 7.67 ± 0.77 vs 9.97 ± 0.70 µg/ml were observed at 0.08 h. The mean peak plasma drug concentration of 18.38 ± 1.38 vs 15.27 ± 1.18 µg/ml was achieved at 0.25 h which declined rapidly to 4.60 ± 0.65 vs 3.92 ± 0.35 µg/ml at 0.75 h. The drug concentration of 0.83 ± 0.04 vs 0.87 ± 0.05 µg/ml in plasma was detected at 1 h and beyond then the drug was not detected in plasma.

4. Discussion

As shown in Figure 2, ferulic acid peaks were well separated from endogenous substances in the blank plasma. These results imply that the bioanalytical method developed herein may provide acceptable selectivity without endogenous interferences occurring at the appearance of ferulic acid peaks. The calibration curves for ferulic acid in plasma were observed to be linear from 0.09 to 25 µg/ml. A representative equation for the calibration curves is as follows: $y = 27215x - 1182.9$. The correlation coefficients (r^2) is 0.99, indicating an acceptable linearity of our method. The intra- and inter-day accuracy and precision were determined for ferulic acid at four quality control (QC) levels, *i.e.*, 25, 12.50, 1.56, 0.39 and 0.09 µg/ml. The mean precision of the method was determined to be 9.2%, and its mean accuracy was 91.99%. These values are within the acceptable range, indicating that the present method is reproducible,

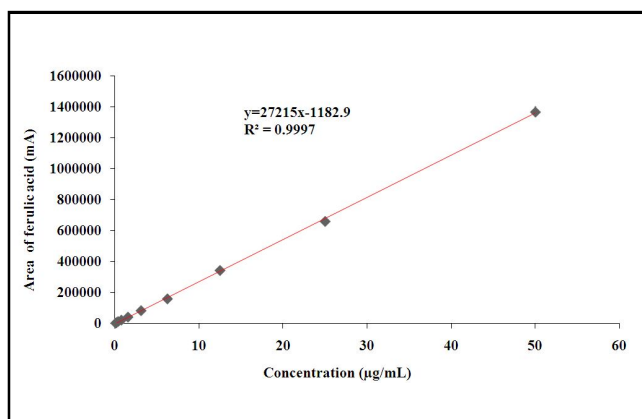


Figure 1: Standard curve of ferulic acid in drug-free plasma of rats.

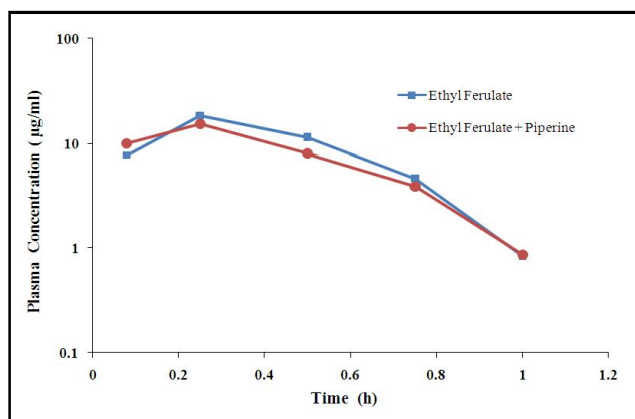


Figure 3: Semi logarithmic plot of comparison of ferulic acid concentration in plasma versus time following oral administration of ethyl ferulate (150 mg/kg) alone and along with piperine (40 mg/kg) in rats. Each points represents mean \pm SE.

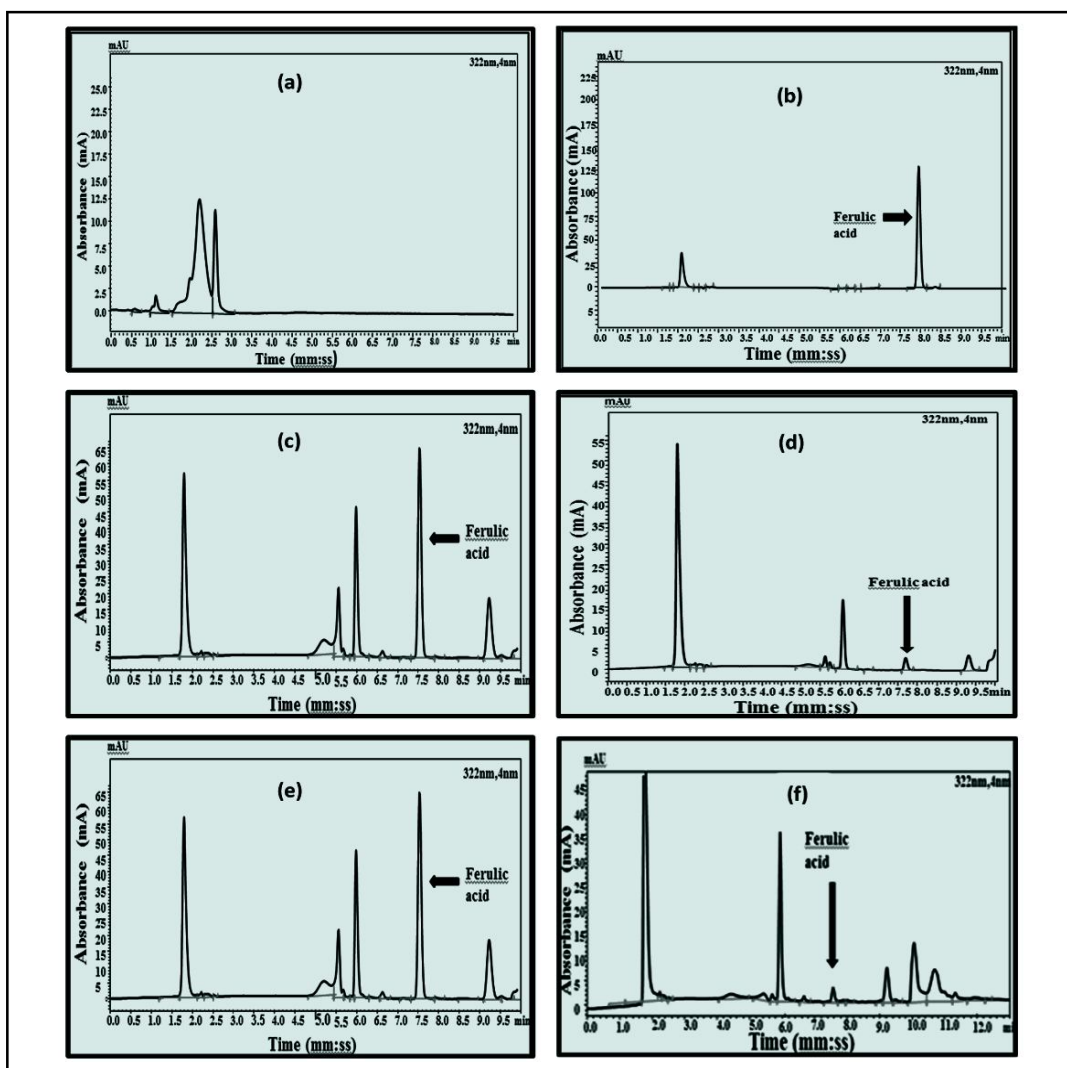


Figure 2: Representative chromatograms of a) blank plasma of rat, b) ferulic acid standard (25 µg/ml) in plasma, c) 15 min post oral administration of ethyl ferulate in rat, d) 1 h post oral administration of ethyl ferulate in rat, e) 15 min post oral administration of ethyl ferulate and in combination with piperine in rat and f) 1 h post oral administration of ethyl ferulate and in combination with piperine in rat.

Table 1: Plasma concentrations ($\mu\text{g/ml}$) of ferulic acid following oral administration of ethyl ferulate alone (150 mg/kg) and along with piperine (40 mg/kg) in rats (n=6)

Time after drug administration (h)	Plasma concentration of ferulic acid	
	Ethyl ferulate alone (150 mg/kg) (Mean \pm S.E)	Ethyl ferulate (150 mg/kg) with piperine (40 mg/kg) (Mean \pm S.E)
0.08	7.67 \pm 0.77	9.97 \pm 0.70
0.25	18.38 \pm 1.38	15.27 \pm 1.18
0.5	11.49 \pm 1.17 ^a	8.04 \pm 0.73 ^b
0.75	4.60 \pm 0.65	3.92 \pm 0.35
1	0.83 \pm 0.04	0.87 \pm 0.05

Means bearing different superscripts within rows differ significantly ($p < 0.05$).

Table 2: Pharmacokinetic parameters of ferulic acid following oral administration of ethyl ferulate alone (150 mg/kg) and along with piperine (40 mg/kg) in rats (n=6)

Pharmacokinetic parameters	Unit	Ethyl ferulate alone (Mean \pm S.E)	Ethyl ferulate with piperine (Mean \pm S.E)
K_a	h^{-1}	7.87 \pm 0.47	7.44 \pm 0.30
β	h^{-1}	6.66 \pm 0.70	5.98 \pm 0.25
$t_{1/2K_a}$	h	0.09 \pm 0.01	0.09 \pm 0.00
$t_{1/2\beta}$	h	0.11 \pm 0.01	0.12 \pm 0.01
C_{max}	$\mu\text{g/ml}$	18.38 \pm 1.38	15.27 \pm 1.18
T_{max}	h	0.25 \pm 0.00	0.25 \pm 0.00
$\text{AUC}_{(0-\infty)}$	$\mu\text{g}\cdot\text{h/ml}$	8.95 \pm 0.76	7.55 \pm 0.52
AUMC	$\mu\text{g}\cdot\text{h}^2/\text{ml}$	3.61 \pm 0.29	2.92 \pm 0.19
$V_d(\text{area})$	L/kg	2.85 \pm 0.57	1.25 \pm 0.12*
$Cl_{(B)}$	L/h/kg	17.19 \pm 1.59	7.35 \pm 0.57***
MRT	h	0.40 \pm 0.00	0.38 \pm 0.00*

Means bearing different superscripts within rows differ significantly $p < 0.05^*$, $p < 0.01^{**}$, $p < 0.001^{***}$

accurate, and precise. Notably, our present method with a simple protein deproteinization procedure achieved an equivalent LLOQ (0.19 $\mu\text{g/ml}$) in a previous study involving liquid-liquid extraction (Zhang *et al.*, 2005).

The elimination half-life ($t_{1/2\beta}$) of ferulic acid following oral administration of ethyl ferulate in the present study was 0.11 \pm 0.01 h. In accordance to present study, Shin *et al.* (2016) observed elimination half-life of 0.08 h at 2 mg/kg and 0.11 h at 10 mg/kg following intravenous administration of ferulic acid in rats and Cheng *et al.* (2012a) observed the elimination half-life of 0.35 h in rats following oral administration of *Portulaca oleracea* L. extract. However, Qi *et al.* (2007) observed the higher value of elimination half-life (3.45 h), following oral administration of *Ligusticum chuanxiong* (*Rhizoma chuanxiong*) and *Carthamus tinctorius* (Carthami Flos) in rats and Ge *et al.* (2015) observed higher value of terminal half-life (5.55 h) after oral administration of ferulic acid puerarinastragaloside combination preparation in cerebral ischemic injury in rats.

Mean apparent volume of distribution ($V_d(\text{area})$) of ferulic acid following oral administration of ethyl ferulate was 2.85 \pm 0.57 L/kg in rats. It is in agreement with value of volume of distribution (12.4 L/kg) observed following oral administration of ferulic acid puerarin astragaloside combination in rats (Ge *et al.*, 2015). Whereas, lower values of volume of distribution were reported by Cheng *et al.*

(2012b) (0.07 L/kg) and Shin *et al.* (2016) (0.21 \pm 0.019 L/kg and 0.23 \pm 0.028 L/kg), following intravenous administration of *P. oleracea* extract in rats and intravenous administration of ferulic acid in rats, respectively. Following oral administration of ethyl ferulate observed AUC was 8.95 \pm 0.76 $\mu\text{g}\cdot\text{h/ml}$. In agreement to our findings, comparable AUC values were observed by Ge *et al.* (2015) (12.93 $\mu\text{g}\cdot\text{h/ml}$) and Zhao *et al.* (2003) (15.58 $\mu\text{g}\cdot\text{h/ml}$), following oral administration of ferulic acid puerarin astragaloside combination (250 mg/kg) preparation in rats and oral administration of ferulic acid (14 mg/kg) in rats, respectively. Whereas, lower values of AUC, *i.e.*, 2.36 $\mu\text{g}\cdot\text{h/ml}$ and 0.69 $\mu\text{g}\cdot\text{h/ml}$ were reported after the oral administration of *L. chuanxiong* (*R. chuanxiong*) and *C. tinctorius* (Carthami Flos) (2 mg/ml) in rats (Qi *et al.*, 2007) and following oral administration of *P. oleracea* extract in rats, respectively (Cheng *et al.*, 2012a).

The total body clearance of ferulic acid was observed to be 17.1 \pm 1.59 L/h/kg, following oral administration (150 mg/kg) of ethyl ferulate in rats. In contrast to our observations, lower values of clearance were reported by Ge *et al.* (2015) (0.0004 L/h/kg), Shin *et al.* (2016) (3.27 \pm 1.97 L/h/kg at 2 mg/kg and 2.17 \pm 4.01 L/h/kg at 10 mg/kg) and Cheng *et al.* (2012a), following oral administration of ferulic acid puerarin astragaloside combination (250 mg/kg), intravenous administration of ferulic acid in rats and oral administration of *P. oleracea* extract in rats, respectively. The MRT value calculated, following oral administration of ferulic acid in present study was 0.40 h. In accordance with present study, Shin *et al.* (2016) also observed similar MRT values (0.067 h at 2 mg/kg and 0.10 h at 10 mg/kg), following intravenous administration of ferulic acid in rats. However, higher value of MRT (1.35 h) was reported, following intravenous administration of *P. oleracea* extract in rats (Cheng *et al.*, 2012b).

Pharmacokinetic analysis of ferulic acid indicates faster absorption and clearance of drug from the body following oral administration of ethyl ferulate in rat. This result is supported by observations of Zhao *et al.* (2003), *i.e.*, 74 % of the administered ferulic acid disappeared from the stomach after 25 min incubation of ferulic acid in rat. Later, the ferulic acid was recovered in the gastric mucosa, portal vein plasma, celiac arterial plasma, bile, and even in the urine. This indicated that ferulic acid could be absorbed from the stomach with a high absorption rate, almost completely absorbed in the rat foregut. In addition to this, *in vitro* results indicated that ferulic acid might diffuse quite freely across the stomach mucosa (Zhoa *et al.*, 2003; Zhoa *et al.*, 2004). Moreover, the orally administered ferulic acid was quickly recovered in rat plasma at a high concentration, whereas the ferulic acid could not be maintained in the plasma at a detectable concentration for longer time. Moreover, the metabolism of ferulic acid in liver is the primary cause for decreasing the proportion of free ferulic and at the same time for increasing the proportion of conjugated ferulic acid to total ferulic acid in plasma. Most of ferulic acid was finally excreted through kidney mainly as conjugated ferulic acid (Zhoa *et al.*, 2003; Zhoa *et al.*, 2004). It is observe that phytochemicals relatively cleared very fast form the body and interaction with standard drug and other phytochemical are observed (Modi *et al.*, 2018; Gondaliya *et al.* 2017^{ab})

All pharmacokinetic parameter of ferulic did not differ significantly except volume of distribution (1.25 \pm 0.12 vs 2.85 \pm 0.57 L/kg), total body clearance (7.35 \pm 0.57 vs 17.19 \pm 1.59 L/h/kg) and mean residence time (0.38 \pm 0.00 vs 0.40 \pm 0.00 h), following

co-administration of piperine in comparison to those following administration of ethyl ferulate alone in rats.

Alteration in pharmacokinetic parameter of ferulic acid following co-administration of piperine with ethyl ferulate after single oral administration in rats might be due to interaction of piperine with enzymes that participate in drug metabolism, such as mixed function oxidases found in the liver and intestinal cells or may be due to inhibition of hepatic and non-hepatic drug metabolizing enzymes (Rondini *et al.*, 2002; Poquet *et al.*, 2008; Singh *et al.*, 2009; Patel *et al.*, 2019; Chauhan *et al.*, 2017). Moreover, ferulic acid primarily metabolise in liver for decreasing the proportion of free ferulic and at the same time for increasing the proportion of conjugated ferulic acid to total ferulic acid in plasma (Zhoa *et al.*, 2004). Above reasons support finding of our study as total body clearance significantly decreased in rats which were administered ethyl ferulate with piperine in comparison to administration of ethyl ferulate alone in rats (7.35 ± 0.57 vs 17.19 ± 1.59 L/h/kg), respectively.

5. Conclusion

In conclusion, following oral administration of ethyl ferulate alone and along with piperine in rats, therapeutic effective concentrations were maintained up to 1 h post drug administration. In rats, ferulic acid remains for a shorter time after oral administration in rats due to rapid clearance from the body. Oral administration of piperine did not affect overall pharmacokinetic profile of ethyl ferulic acid except total body clearance in rats.

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Conflict of interest

The authors declare that there are no conflicts of interest in the course of conducting the research. All the authors had final decision regarding the manuscript and decision to submit the findings for publication.

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