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EFFECT OF QUERCETIN ON THE PHARMACOKINETIC PROFILE OF ELETRIPTAN, A CYP3A SUBSTRATE, IN RAT MODEL

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Keywords:

Eletriptan, Quercetin, Bioavailability, Pharmacokinetics, p-glycoprotein

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ABSTRACT: Quercetin is a plant flavonol that is available from both daily diet and nutraceuticals. Various studies report that Quercetin alters the pharmacokinetics of various drugs by mechanisms like p-glycoprotein (p-gp) inhibition or other unknown mechanisms. The study was undertaken to evaluate the effect of Quercetin on the pharmacokinetics of Eletriptan. A single dose *in-vivo* pharmacokinetic study was carried out in rat models. In this study, rats were treated with Quercetin (10 mg/kg) and Eletriptan (2 mg/kg) orally and blood samples were collected at various time points such as 0 (predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 24 h post-treatment. Plasma concentration of Eletriptan was estimated using the HPLC method. AUC (0-24) of Eletriptan has significantly ($p<0.01$) increased in the Eletriptan and Quercetin combination group 1451.98 ± 93.78*** (ng/ml/h) when compared to AUC (0-24) Eletriptan alone treated group 883.94 ± 77.25 (ng/ml/h). AUC0-∞ of Eletriptan has significantly (***$p<0.001$) increased in the combination group (1543.32 ± 182.39*** (ng/ml/h).) in comparison to AUC0-∞ of Eletriptan of Eletriptan - alone treated group (925.59 ± 78.73 (ng/ml/h)). In conclusion, the results obtained herein indicate that Quercetin is enhancing the bioavailability of Eletriptan by augmenting the exposure (AUC) of the Eletriptan when concomitantly administered by the oral route.

INTRODUCTION: Eletriptan, a selective 5-HT agonist is used for the treatment of migraines with or without aura. Eletriptan binds with high affinity to 5-HT 1B, 5-HT 1D and 5-HT 1F receptors, has a modest affinity for 5-HT 1A, 5-HT 1E, 5-HT 2B and 5-HT 7 receptors and little and no affinity for 5-HT 2A, 5-HT 2C, 5-HT 3, 5-HT 4, 5-HT 5A, and 5-HT 6 receptors.

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Two theories have been proposed to explain the efficacy of 5-HT receptor agonists in migraine. One theory suggests that activation of 5-HT 1, receptors located on intracranial blood vessels, including those on arteriovenous anastomoses, leads to vasoconstriction, which is correlated with the relief of migraine headache.

The other hypothesis suggests that activation of 5-HT 1 receptors on sensory nerve endings in the trigeminal system results in the inhibition of pro-inflammatory neuropeptide release [1-6]. Flavonoids abundant in plant products are believed to modify the expression and activity of enzymes and transporters concerned in drug metabolism and excretion [7-9].

The effects of flavonoids on the pharmacokinetic profile of drugs have already been described in humans [10-12]. Quercetin is the most predominant flavonoids in plant products, herbs, beverages and dietary supplements, *e.g.* onions, grapes, berries, apples, broccoli, red wine, tea, St. John's wort and ginkgo. It displays significant properties like anti-inflammatory, anti-oxidant and free radical scavenging effects. It acts by inhibiting drug-metabolizing enzymes, CYP3A4 and drug transporter pump, p-glycoprotein.

The daily dietary intake of quercetin is estimated to be in the range of 4 to 68 mg based on epidemiological studies in the U.S., Europe, and Asia [13-16]. But can be as high as several hundred mg in the dietary supplement and several grams in anticancer therapy [17]. According to recent studies, there is increasing evidence that quercetin interacts with numerous xenobiotics. For instance, quercetin enhances the bioavailability of numerous drugs like rosiglitazone [18], fexofenadine [19] in humans, paclitaxel [20], valsartan [21], tamoxifen [22] in rat models, digoxin [23] in pigs. In contrast, quercetin decreases the bioavailability of simvastatin [24] in pigs and cyclosporine [25] in pigs and rats. Quercetin was established to be a potent P-glycoprotein inhibitor based on experimental studies [7] and epidemiological [14-16] studies. Eletriptan propensity to interact with co-administered products and as a substrate for human P-glycoprotein [26], it is quite reasonable to investigate the effect of Quercetin on the pharmacokinetics of Eletriptan. Thus, a study was designed to observe effects of Quercetin on the pharmacokinetics of Eletriptan in animal models.

MATERIALS AND METHODS:

Drugs and Chemicals: Eletriptan Hydrobromide was obtained as a gift sample from Matrix Laboratories; Hyderabad (India). Quercetin was purchased from Sigma-Aldrich Chemical Co., St. Louis, MO, USA. All HPLC grade solvents (acetonitrile, sodium lauryl sulfate, ortho-phosphoric acid and water) were procured from SD Fine Chemicals, Mumbai, India. All other chemicals used were of analytical grade and purchased from local chemical agencies.

Animals: Albino Wistar rats (National Institute of Nutrition, Hyderabad, India), of either sex, weighing 200–250 g, were selected. Animals were maintained under standard laboratory conditions at 25 ± 2 ºC, relative humidity 50 ± 15%, and normal photoperiod (12 h dark / 12 h light). Commercial pellet diet (Rayon's Biotechnology Pvt. Ltd., India) and water were provided *ad libitum*. The experimental protocol was approved by the Institutional Animal Ethics Committee of Nova College of Pharmacy bearing registration number 1747/PO/Re/S/14/CPCSEA and studies were carried out as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India.

Pharmacokinetic Study in Rats:

Preparation of Drugs: Eletriptan hydrobromide was dissolved in distilled water whereas quercetin (10 mg) was accurately weighed before being triturated in a dry clean mortar with an addition of 30 µL of tween 80 and then, the required volume of 0.9% sodium CMC was added and triturated again to suspend the drug in it. Then, the suspension was transferred to plastic vials. Quercetin suspension was administered concomitantly with Eletriptan Hydrobromide solution to the animals within 10 min of the preparation of the suspension.

Experimental Procedure: Wistar rats were randomly distributed into two groups of six animals in each group. Before doing, all experimental animals fasted for 18 h and but the water was given *ad libitum*. The experimental design was as follows. Group I – Eletriptan (2 mg/kg; p.o.), Group II - Eletriptan (2 mg/kg; p.o.), + (Quercetin (10 mg/kg; p.o.). Blood was collected from orbital sinuses using 2 ml Eppendorf tubes containing sodium citrate as an anticoagulant. Plasma was separated by centrifugation at 5000 RPM/10 min and stored at −20 °C until further analysis. Plasma concentration of Eletriptan was estimated by a sensitive HPLC method.

Blood Sample Collection from Rats: In this study, blood samples were collected at time points 0 (predose), 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 12, 24 hours post-treatment from the retro-orbital sinuses using fine capillary tubes into 2 ml Eppendorf tubes containing sodium citrate as an anticoagulant. Plasma was separated by centri-fugation at 5000 RPM/10 min and stored at −20 °C until further analysis. The plasma concentration of eletriptan was estimated by a sensitive HPLC method.

Estimation of Eletriptan in Plasma by a Sensitive HPLC Method: The HPLC method developed was also used for the estimation of eletriptan in plasma samples using an internal standard method. For this purpose, a calibration curve was constructed by analyzing plasma samples containing different concentrations of eletriptan.

Standard Solutions: The primary stock solution of 1 mg/ml of eletriptan was prepared in methanol. Appropriate dilutions of eletriptan from stock solution were made in the mobile phase to produce working stock solutions of 0.05, 0.10, 0.25, 0.50, 1, 2 and 4 µg/ml. these dilutions were used to spike plasma in the preparation of calibration of the curve. Eletriptan spiked plasma samples were prepared by mixing 1 ml blank plasma with appropriate volumes of the standard eletriptan solutions (100 µL) on the day of the analysis. A blank was also prepared to contain 1 mL of blank plasma.

Extraction Procedure: Plasma was spiked with varying quantities of eletriptan stock solution was prepared, so as to give a series of drug concentrations ranging from 0.05 to 4 µg/ml. 125 µL of spiked plasma was taken and to this 25 µL of internal standard (Topiramate stock solution 10 µg/mL in methanol) was added and then vortexed (Vortex mixer, Genei, Mumbai) for 60 sec. Then 500 µL of methanol was added to precipitate proteins and vortexed for 5 min and centrifuged at 5000 rpm in a microcentrifuge (REMI Scientifics, India) for 10 min. supernatant was taken and dried in a vacuum oven at 40 ºC.

Dried samples were then redispersed in 100 µL methanol and vortexed. The supernatant was transferred into a microcentrifuge tube and from this 20 µL was injected for HPLC analysis.

Chromatographic Conditions: A quaternary gradient HPLC (Waters Delta prep HPLC system, USA) with a rheodyne manual injector (Rheodyne, Cotati, CA, USA) attached with a 100 µL sample loop was used for loading the sample. A variable wavelength programmable photodiode array (PDA) detector (Waters 2999 PDA, USA) and reversed-phase C-18 column {(250 mm × 4.63 mm ID; particle size 5 µm) (waters associates)} was used. The HPLC system which was equipped with the EMPOWER 2 software (Waters, Milford, MA, USA) was used for data acquisition and processing. The mobile phase consisted of Acetonitrile and phosphate buffer (15 mM) {(50:50, v/v)}. The pH of the mobile phase was adjusted to 3.5 ± 0.1 with orthophosphoric acid. The filtered mobile phase components were pumped from the respective reservoirs at the flow rate of 1ml/min. the column temperature was maintained at room temperature (30 ºC). The eluent was detected by a PDA detector at a wavelength of 236 nm.

Pharmacokinetic Data Analysis: Pharmacokinetic parameters were calculated using the Try-kinetica software trial version 5.0. When "NCA assistant-non-compartmental-extra vascular" page was opened. Units of time points and concentrations were given. Then, various time points and corresponding concentrations (for which PK parameters to be determined) were entered into the page of "NCA assistant-non-compartmental-extra vascular". Once the data was entered, the analyze button was clicked and then a graph appeared. The study button was pressed to see few PK parameters. For getting complete PK parameters, a dose of Eletriptan hydrobromide 2 mg/kg was entered in the dose option.

Then, data were again analyzed by clicking on analyze. Then, two-line graphs appeared. Then, the study option was clicked to see the complete PK parameters of Eletriptan hydrobromide. Each animal data was given and PK parameters were calculated for each animal data. Then, an average of one PK parameter for all the animals of the same group was taken. This data was subjected to statistical analysis.

Statistical Analysis: The results were expressed as mean ± S.D. Comparisons of plasma concentration *vs.* time profiles of eletriptan hydrobromide-alone group and eletriptan hydrobromide with the quercetin combination group were analyzed using two-way ANOVA followed by bonferroni post hoc test whereas comparisons of pharmacokinetic parameters of these two groups were analyzed using unpaired student's t-test. *P<0.05, **P<0.01, ***P<0.001 were considered as statistically significant.

RESULTS:

Calibration Curve: The run time was set at 10 min and eletriptan and internal standard appeared on the chromatogram at 3.109 min and 8.502 respectively as shown in **Fig. 2** to **4**. There was no interference of any other peak with a drug peak. When the same sample containing drug was injected six times, the retention time of the drug was almost the same for all the six injection samples. The mean peak area of eletriptan and its respective peak areas were subjected to regression analysis by the least square method, and the high correlation coefficient was observed (r = 0.994) in the range of 0.05-4 µg/mL. The regression of eletriptan concentration over its peak area was found to be Y = 1.137x + 0.200 with a high correlation coefficient, where Y is peak area and X is the plasma concentration of eletriptan. This regression equation was used to estimate the amount of eletriptan in plasma. Calibration values were shown in **Table 1** and the Linearity graph was shown in **Fig. 1**.

TABLE 1: CALIBRATION OF THE HPLC METHOD FOR THE ESTIMATION OF ELETRIPTAN IN PLASMA BY USING TOPIRAMATE AS INTERNAL STANDARD

S. no.	Plasma concentration of Eletriptan (µg/ml)	Mean peak area of Eletriptan	Mean peak area of internal standard	Mean peak area ratio
1	0.05	69701.45	435212.81	0.160
2	0.10	96378.64	428349.52	0.225
3	0.25	202790.34	429855.78	0.472
4	0.50	367206.29	425007.28	0.864
5	1	584666.07	433728.54	1.348
6	2	1149978.73	428776.56	2.682
7	4	1953184.27	421289.19	4.636

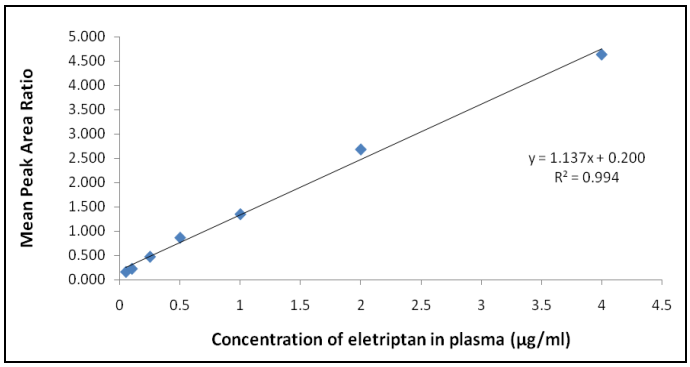


FIG. 1: CALIBRATION CURVE FOR THE ESTIMATION OF ELETRIPTAN IN PLASMA

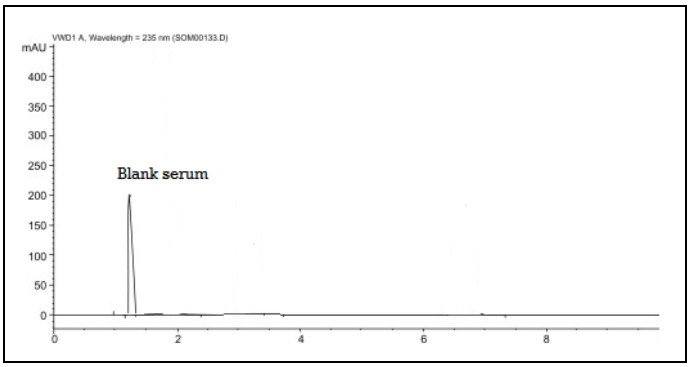


FIG. 2: HPLC CHROMATOGRAM OF BLANK PLASMA

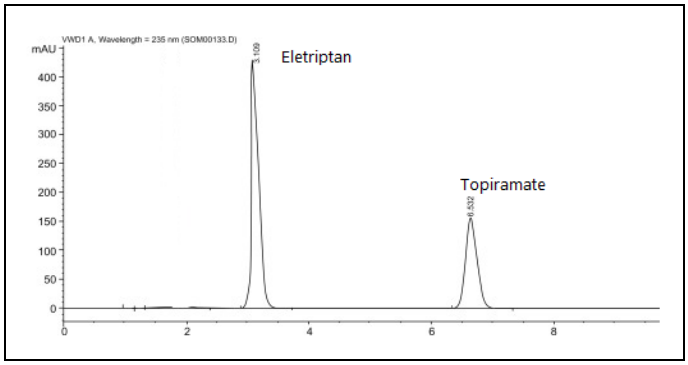


FIG. 3: HPLC CHROMATOGRAM OF BLANK PLASMA WITH INTERNAL STANDARD (TOPIRAMATE)

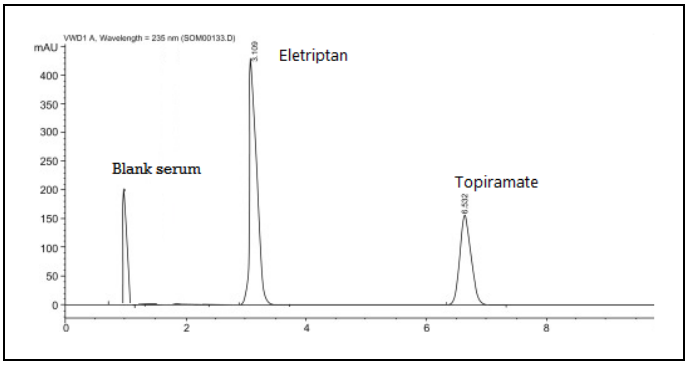


FIG. 4: HPLC CHROMATOGRAM OF SPIKED PLASMA WITH ELETRIPTAN

Effect of Quercetin on Plasma Concentration Time Profiles of Eletriptan: The plasma concentration *vs.* time profiles of Eletriptan in rats following oral treatment of Eletriptan Hydrobromide with and without Quercetin were shown in **Table 2** and **Fig. 5**. From the comparison of plasma concentration profiles of Eletriptan in the absence and presence of Quercetin, it is clear that

there was a significant increase in the plasma drug exposure of Eletriptan in the combination group at following time points 0.5 h (nsP > 0.05), 1.0 h (nsP > 0.05), 1.5 h (nsP > 0.05), 2.0 h (**P<0.01), 2.5 h (***P<0.001), 3.0 h (***P<0.001), 3.5 h (***P <0.001), 4 h (nsP>0.05), 6.0 h (nsP>0.05), 8.0 h (nsP>0.05), 12.0 h (**P<0.01) and 24.0 h (nsP>0.05).

TABLE 2: COMPARISON OF MEAN CONCENTRATIONS OF ELETRIPTAN TREATED GROUP AND ELETRIPTAN WITH QUERCETIN TREATED GROUP – SINGLE DOSE STUDY

Time Points	Eletriptan (2mg/kg)			Eletriptan (2 mg/kg) + Quercetin (10 mg/kg)		
(h)	Mean	S.D	S.E.M	Mean	S.D	S.E.M
0	0.00	0.00	0	0.00	0.00	0
0.5	43.01	21.89	8.94	32.30	11.44	4.67
1	76.29	23.41	9.56	85.58	25.93	10.59
1.5	134.37	19.26	7.86	140.50	23.02	9.40
2	134.13	19.78	8.08	169.80	23.74	9.69
2.5	123.18	14.27	5.83	180.84	22.12	9.03
3	110.25	11.69	4.77	173.15	36.31	14.82
3.5	101.47	14.59	5.96	143.71	14.45	5.90
4	95.05	18.80	7.68	110.58	18.41	7.52
6	74.22	15.17	6.19	89.62	11.91	4.86
8	44.53	15.32	6.26	68.45	11.55	4.72
12	19.06	8.95	3.65	55.63	15.70	6.41
24	4.90	2.20	0.90	7.58	3.89	1.59

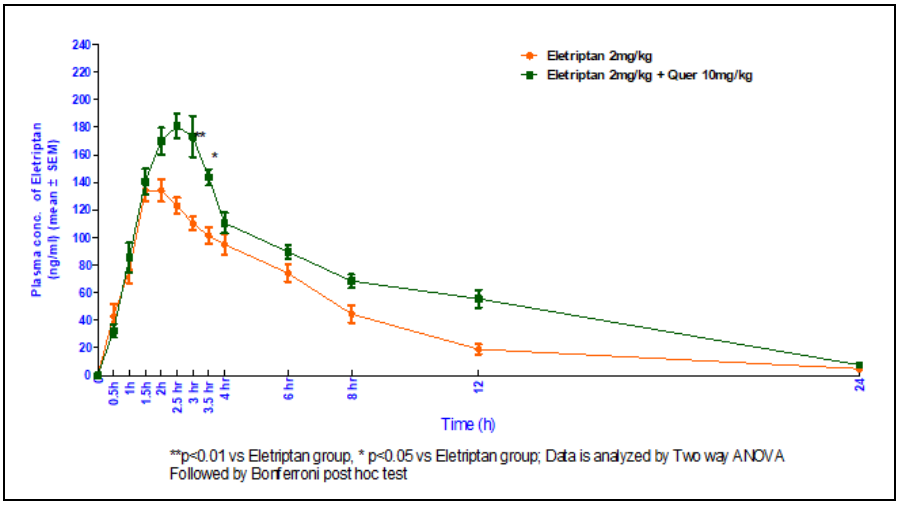
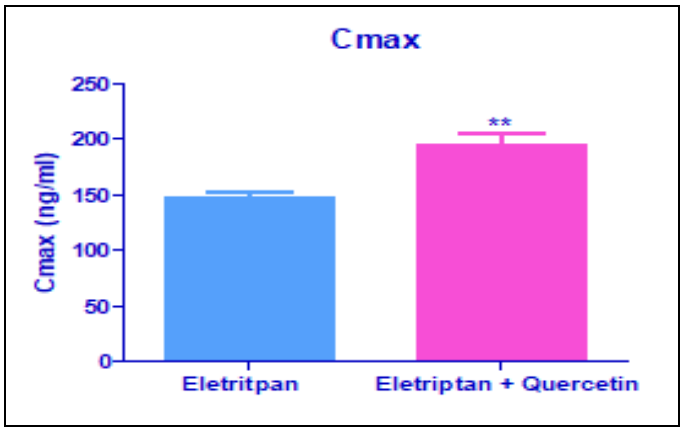


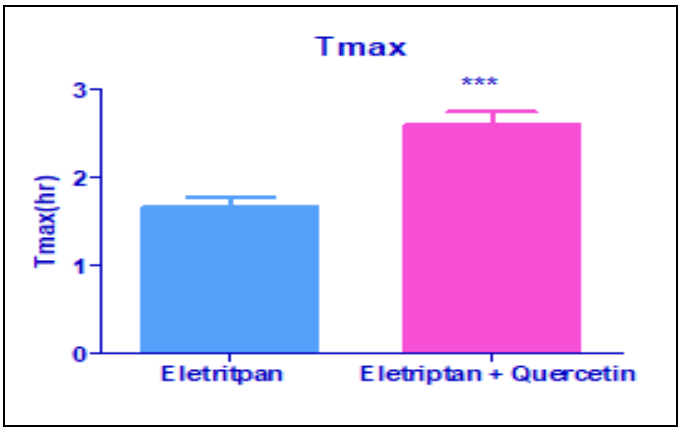
FIG. 5: COMPARISON OF MEAN PLASMA CONCENTRATIONS OF ELETRIPTAN TREATED GROUP AND ELETRIPTAN WITH QUERCETIN TREATED GROUP – SINGLE DOSE STUDY

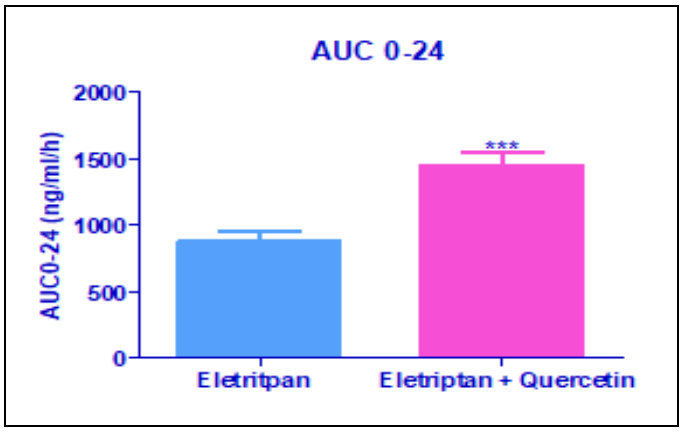
Effect of Quercetin on Pharmacokinetic Parameters of Eletriptan: The calculated pharmacokinetic parameters of eletriptan Hydro-bromide in rats were shown in **Table 3**. AUC0-24 of eletriptan has significantly (p<0.001) increased in the combination group (1451.98 ± 93.78) than AUC0-24 of eletriptan of eletriptan alone treated group (883.94 ± 77.25***). This increase is almost 1.8 times. In a similar manner, the C_{max} of eletriptan has significantly (p<0.01) increased in the combination group (194.72 ± 9.58**) than C_{max} of eletriptan of eletriptan alone treated group (146.51 ± 6.05). This increase is almost 1.47 times. Compared with the eletriptan alone group, the AUMC, MRT, t1/2 and V_d significantly (p<0.001) increased when eletriptan combined with quercetin (combination group). In contrast, the clearance of combined group (0.0010 ± 0.0001***) significantly (p<0.001) decreased when compared with eletriptan alone group (0.0021 ± 0.0001). The t_{max} of the alone group and treated group not significantly altered. The pharmacokinetic parameters were represented in **Table 3** and expressed in **Histogram 1**.

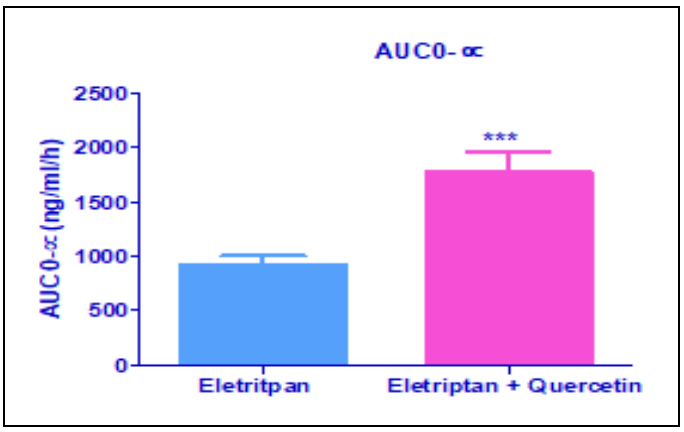
TABLE 3: COMPARISON OF PHARMACOKINETIC PARAMETERS OF ELETRIPTAN ALONE GROUP AND ELETRIPTAN WITH QUERCETIN COMBINATION GROUP – SINGLE DOSE STUDY

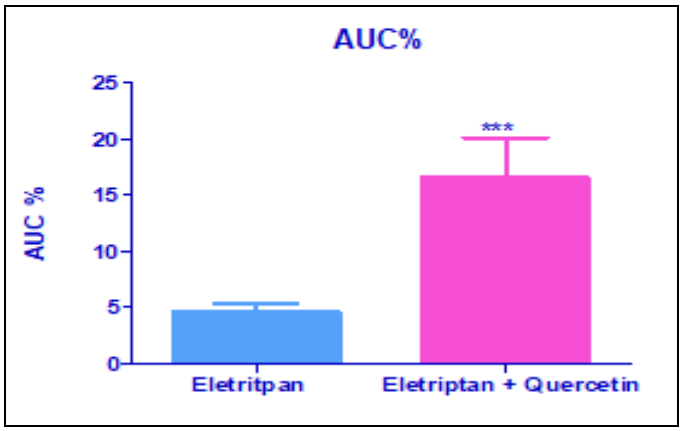
P.K PARAMETERS	Eletriptan alone	Eletriptan with Quercetin
C_{max} (ng/mL)	146.51 ± 6.05	194.72 ± 9.58**
T_{max} (hr)	1.67 ± 0.11	2.58 ± 0.15***
AUC_{0-24} (ng.hr/ml)	883.94 ± 77.25	1451.98 ± 93.78***
$AUC_{0-\infty}$ (ng.hr/ml)	925.59 ± 78.73	1543.32 ± 182.39**
AUC%	4.59 ± 0.74	16.61 ± 3.55**
$AUMC_{0-24}$ (ng/ml/h*h)	5270.15 ± 822.92	12076.90 ± 1129.36***
$AUMC_{0-\infty}$ (ng/ml/h*h)	6321.92 ± 974.66	24941.15 ± 5541.42**
$t_{1/2}$ (h)	3.89 ± 0.48	9.03 ± 1.33$^{n.s}$
MRT_{0-24} (hr)	5.80 ± 0.47	8.25 ± 0.32**
$MRT_{0-\infty}$ (hr)	6.66 ± 0.55	13.31 ± 1.60**
Clearance (L/h)	0.0021 ± 0.0001	0.0012 ± 0.0001***
Volume of distribution (V_d) (L)	0.0121 ± 0.0012	0.0145 ± 0.0011$^{n.s}$

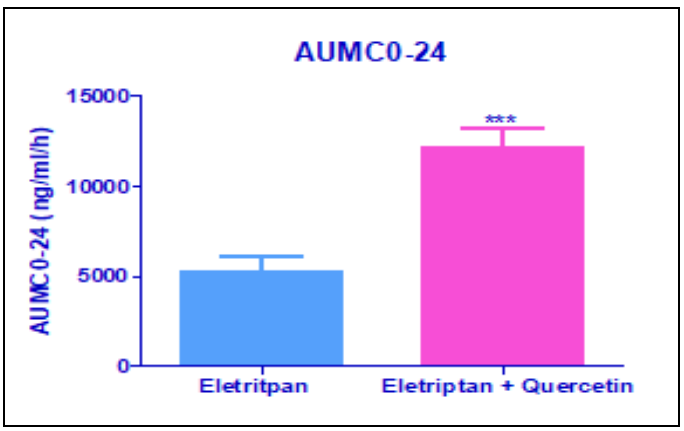


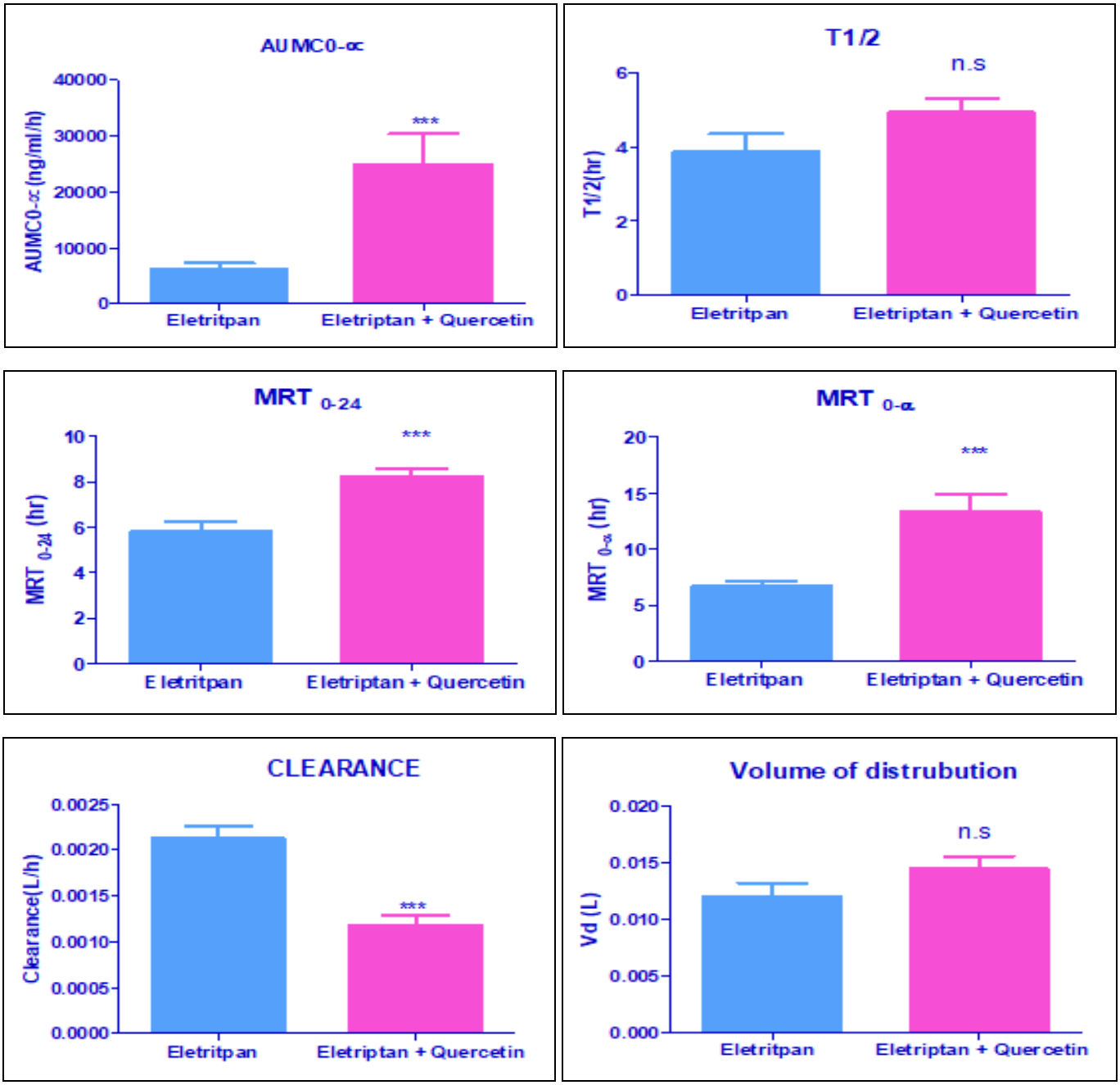












HISTOGRAM 1: COMPARISON OF PHARMACOKINETIC PARAMETERS OF ELETRIPTAN ALONE GROUP AND ELETRIPTAN WITH QUERCETIN COMBINATION GROUP – SINGLE DOSE STUDY

DISCUSSION: The results of the study revealed that there is a significant increase in the bioavailability of Eletriptan administered concomitantly with quercetin and that was evidenced clearly by significant ($p<0.001$) increase in the AUC0-24. Mechanisms underlying the interaction between these two drugs are uncertain. However, the various possibilities of interaction are discussed. There was evidence that Eletriptan, is predominantly metabolized by cytochrome P4503A4 isoenzymes and it is a high-affinity substrate of P-glycoprotein. Data suggest that potent inhibition of this enzyme results in increased systemic exposure and reduced clearance of Eletriptan.

Certain excipients or drugs increase the oral absorption of that drug by inhibiting metabolism in the gut wall and liver and / or by inhibiting the P-gp / MDR efflux pumps found in the intestinal wall and other tissues. Experimental results suggest administration eletriptan with P-gp inhibitor increase the rate of onset of migraine abortion without altering systemic clearance [28].

According to this study, it is clearly evident that Eletriptan bioavailability is augmented when co-dosed with a well known P-gp inhibitor, Quercetin. Human clinical studies [29, 30] investigating the importance of CYP3A and P-glycoprotein through inhibition or inductions of these proteins have provided further evidence of this interaction. These studies reveal that the role of P-glycoprotein in the intestine extends beyond simply limiting parent drug absorption but also includes increasing the access of drugs to metabolism by CYP3A through repeated cycles of absorption and efflux. Thus, previous *in-vitro* results demonstrate that flavonoids (like Quercetin) have the ability to interfere with intestinal endothelial cells and brain endothelial cell membrane pump proteins which expel the drug from those cells.

In addition, our results also revealed that there is a significant increase in the C_{max} of Eletriptan by Quercetin co-administration. Thus an increase in C_{max} can be attributed to decreased metabolism and decreased efflux of Eletriptan. At the same time clearance of Eletriptan significantly decreased by Quercetin. It is unclear as to how and which mechanism is contributing to the decreased clearance of the drug. Quercetin CYP3A inhibitor and Eletriptan CYP3A substrate, it is likely to have an interaction mediating CYP metabolic enzymes. Thus, it is of vital importance to identify the mechanisms to further clarify our results.

CONCLUSION: Our results reveal that Quercetin augments plasma exposure of Eletriptan in rat models. However, the mechanism of interaction is unclear.

This interaction could be of clinical significance. However, further clinical studies are needed to confirm this interaction.

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CONFLICTS OF INTEREST: The authors declare that they have no conflicts of interest to disclose.

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