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DETERMINATION OF CARBAMAZEPINE IN RAT PLASMA BY USING HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) IN PRESENCE OF SOME TRADITIONAL BEVERAGES (TAMARIND, MANGO, SUGARCANE, RED BULL) AND ITS PHARMACOKINETIC APPLICATIONS

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ABSTRACT

A simple, rapid and accurate method of High-Performance Liquid Chromatography (HPLC) with UV detector was used for determination of Carbamazepine (CBZ).

The mobile phase was a mixture of 55% of water contains (1 ml triethylamine per 1 liter) and 45% acetonitrile, the pH was adjusted with phosphoric acid, BDS hypersil C18 column (5 µmx150mmx4.6mm) equipped with UV detection at 285 nm with flow rate of 1.0ml/min, using 15µl injection volume and 10°C auto-sampler temperature. Metronidazole benzoate was used as internal standard; the method was precise, and accurate.

Beverages were given in drinking water to the rats before giving CBZ dose (10mg/kg). Plasma level of CBZ alone (group 1) was compared to CBZ with tamarind (group 2), mango (group 3), sugarcane (group 4), and red bull (group 5). Maximum plasma concentrations (Cmax) were

2222.7 ng/ml, 1006.3 ng/ml, 2090.4 ng/ml, 4446.3 ng/ml, and 4523.6 ng/ml respectively for the five groups, group 2 was significantly decreased in Cmax (p-value <0.05) while the others weren't significantly changed and this may due to the low number of rats.

The area under the curve (AUCINF) were not significantly changed (p-value >0.05).

The times for reaching the peak of concentration (Tmax) were significantly increased in all comparison to drug alone (p-value <0.05).

In conclusion, we recommend to be cautious in intake the previous beverages because it will delay the Tmax of the drug and will change the maximum concentration of CBZ in the plasma when pre-administrated, therefore dose adjustment during consumption of these beverages is needed.

Keywords: Carbamazepine; Tamarind; Mango; Sugarcane; Red bull; HPLC

1. INTRODUCTION

Carbamazepine (figure 1) is approved as a mood stabilizer in bipolar disorder with manic and mixed episodes [1], it decreases the neuropathic pain of trigeminal neuralgia [2], it is also used in schizophrenia [3], seizures developed in autism [4], and in the treatment of temporal lobe epilepsy and generalized tonic-clonic seizures. [5]

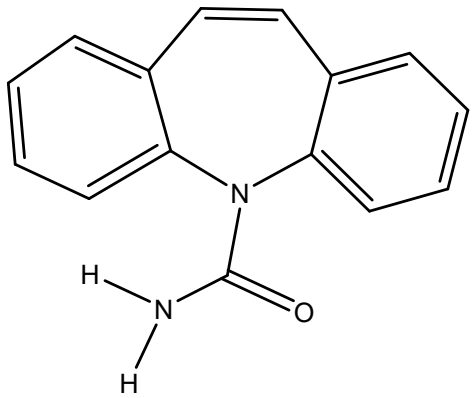

Figure 1: the chemical structure of Carbamazepine

CBZ is erratically and slowly absorbed after oral administration. It binds approximately 75% to plasma proteins. [6]

CBZ is metabolized completely in the liver with only about 5% of the drug being excreted unchanged without metabolism. [7]

The main route of metabolism is the transformation of CBZ to its active metabolite Carbamazepine 10.11-epoxide (CBZ-E) this reaction is catalyzed by the cytochrome p (CYP), CYP3A4 mainly, and CYP3A5, CYP2C8, CYP2E1, CYP2B6, CYP2A6, and CYP1A2 which also play a minor role. On the other hand, its minor metabolic route is ring hydroxylation either by adding hydroxyl group on position 2 or 3 or both, to form 2-hydroxy- carbamazepine (2-OH CBZ), 3-hydroxy carbamazepine (3-OH CBZ) or 2,3 dihydroxy carbamazepine respectively [8].

Various methods such as Liquid chromatography tandem-mass spectrometry (LC-MS/MS), High-performance liquid chromatography (HPLC), Gas chromatography (GC), High-performance thin-layer chromatography (HPTLC), and Ultrafast liquid chromatography(UFLC) have been used in the laboratories for the CBZ quantitative and qualitative analysis during all the phases of quality control and clinical research. [9]

The HPLC method is specific, rapid, and sensitive [10] so it is employed usually as a routine technique for CBZ determination and it is the best method for the monitoring of CBZ and its metabolites in plasma or serum samples. [11]

A drug interaction happens when the pharmacological activity of a drug could be altered by the presence of another drug, food, herbal medicine, or drink. Whenever the drug are concurrently taken with something else there is an opportunity of an interaction between them, this interaction may lead to decrease or increase in the adverse reactions or effectiveness of the drug. [12-19]

CBZ is associated with drug [20], food and juice interactions. [21]

A simple and accurate HPLC method had already been developed and validated for determination of CBZ in rat plasma. [14]

A partial validation for the method was done to determine the rat plasma level of CBZ alone and in combination with beverages such as Tamarind, Mango, Sugarcane, and Red bull and study the effect of these beverages on the pharmacokinetic profile of CBZ.

2. MATERIALS AND METHOD

2.1 Materials

Carbamazepine was taken from Dar Al Dawaa, Metronidazole benzoate was obtained from Jordanian Pharmaceutical Manufacturing Company (Amman, Jordan), Orthophosphoric acid 85% and Triethylaminewere obtained from Tedia (CA, USA). Deionized water (Nanopur™), Acetonitrile (chromanorm®) and Methanol of HPLC were purchased from Fisher Scientific Ltd (Loughborough, UK).

2.2 Chromatographic conditions

Reverse-phase high pressure liquid chromatography was used to separate samples for analysis[14] using Finnigan surveyor system (Thermo Electron Corporation, San Jose , CA, USA) on BDS HYPERSIL™ C18 column with particle size of 5 µm and dimensions of 150mmx4.6mm equipped with ultraviolet detection at 285 nm (UV-VIs Plus Detector) to quantify the samples. The chromatographic data analysis was performed with a computer system (Win-

dows XP, SP3) with ChromQuest software 4.2.34, chromatographic conditions briefly shown in (table 1).

Table 1: Summary of chromatographic conditions

Mobile phase composition	
The mobile phase consisting of 55% of Water contains (1 ml Triethylamine per 1 liter) and 45% of Acetonitrile, the pH 6.0 adjusted by phosphoric acid	
Column type	
HYPERSIL™ Thermo Electron Corporation, BDS C18 (150mm x 4.6mm, 5 µm)	
HPLC conditions	
Wave length	**285 nm**
Pump flow rate	**1.0 ml/min**
Auto-sampler injection volume	**15 µl**
Auto-sampler temperature	**10 °C**
Column oven temperature	**25 °C**
Expected retention times (minutes)	
Carbamazepine	**2.6-3.00**
Metronidazole benzoate (IS)	**3.5-3.9**

2.3 Preparation of stock and working solutions

2.3.1 Preparation of stock and working solutions of Metronidazole benzoate

A stock solution of the internal standard (IS) was prepared by dissolving 10 mg of Metronidazole benzoate in 10 ml acetonitrile the final concentration 1 mg/ml.

Working solutions of IS with a concentration of 8µg/ml was prepared by taking 0.8 ml of the stock solutions and diluted to 100ml of the acetonitrile.

2.3.2 Preparation of stock and working solutions of carbamazepine

The stock solution of CBZ is a solution containing 200µg/ml was prepared by dissolving 10.0 mg CBZ in 50ml methanol. Then, the stock solution was stored at -20°C. This solution was diluted in methanol to give working solutions (3.2, 6.4, 12.8, 32.0, 64.0, 128.0, 192.0, 9.6, 96.0 and 160.0µg/ml).

2.3.3 Preparation of calibration curve and quality control (QC) samples in plasma

In order to get the seven spiked levels (calibration curve) in plasma, 25 µl volumes were taken from each working solution to be spiked in 975 µl of plasma to reach a final volume of 1ml. The obtained calibration curve concentrations were (80, 160, 320, 800, 1600, 3200 and 4800 ng/ml) in plasma, while the QC concentrations were (240, 2400 and 4000 ng/ml).

2.4 Preclinical study

2.4.1 Preparation of carbamazepine

Dose of 125mg which equivalent to the human dose 700 mg was dissolved in 50 ml of distilled water with 0.5% Carboxymethyl cellulose (CMC) to get concentration 10 mg/kg suspension of CBZ, each rat took 2.5mg/ml/rat.

2.4.2 Preparation of beverages

The preparation of tamarind was done according to the traditional way, 225g of tamarind was soaked in 1.5 L of water with no additives for 2 hours then filtration was done.

The preparation of mango juice was done by mixing 5 ripe mango fruit with 1.5 L of water in the mixer.

Sugarcane of 1.5 L was obtained fresh from the down town.

6 cans of Red bull beverage (250 for each) were bought from the market which equivalent to 1.5L.

2.4.3 Animal handling and study protocol

The study protocol was approved by ethical committee of the High Research Council in (8/2017), Faculty of Pharmacy and Medical Science, University of Petra Amman, Jordan. Adult male and female Wistar albino laboratory rats were supplied by the animal house of Applied Science University with the average weight of 250g. They were placed in air-conditioned environment 20-25°C and exposed to a photoperiod cycle (12 hours light / 12 hours dark) daily.

All rats were marked on the tail for the identification, weighed and randomized into groups. Five groups of approximately 8 rats; control (group1), tamarind (group2), mango (group3), sugarcane (group4), and red bull (group5). CBZ 2.5 mg/ml/rat was given for all groups. Combination of tamarind, mango, sugarcane, and redbull with the drug were administrated to the second group, third group, fourth group, and fifth group respectively.

Pre administered of the beverages was performed for 2 days before the experimental in approximately 15ml per day for each rat and left them overnight instead of drinking water and then the juices were administered before 15 minutes of CBZ administration in the experimental day in a constant amount (5 ml for each rat).

2.4.4 Sample collection and processing

The blood samples were taken from the optical vein of the rats at the following time points (zero, 0.25, 0.5, 1, 2.0, 3.5, 4.5, 6.5 and 24.0 hours). Blood samples were drawn into an Ethylenediaminetetraacetic acid (EDTA) containing micro-tubes. Blood samples were immediately centrifuged at 5,000 RPM for 10 minutes; plasma was

obtained and placed into labeled eppendorf tubes and stored at -30°C till analysis.

In order to perform the sample extraction, the following experimental procedure was followed; Calibrator 100 µl of each test sample (blank, zero, standards, QC low (QCL), QC mid (QCM), QC high (QCH)). 100 µl of Internal standard (8.0 µg/ml of metronidazole benzoate was prepared in acetonitrile) was added to previous samples. Samples were vortex vigorously for 1.0 minute, and then samples were centrifuged at 14000 rpm for 15 minutes. The clear supernatant was transfer to a flat bottom insert and 15 µlwas injected into the HPLC column.

3. RESULTS AND DISCUSION

3.1 Partial validation results

Calibration curves of the four days of analysis were done (table 2), the accuracy ranges of (85-107%), (100-113%), (99-119%) and (95-102%) for the four calibrations curves were reported, respectively. The accuracy ranges of QC low, mid and high for the four days were (89-101%), (95-107%), (93-98%) and (96-105%), respectively (table 3). The accuracy values were within the required range when compared with EMEA (European Medicines Agency) guidelines which should be within 80-120%. Moreover, precision values (CV %) was also within the range which is 15%. These results indicated that the method was precise and accurate.

3.2.1 Results of administration of Carbamazepine with Tamarind

When this combination was given, CBZ reached its maximum plasma concentration (1006.33 ng/ml) after 1.6 hr of administration (figure 2), and then it is gradually decreased to reach its minimum concentration of (229.9 ng/ml) after 24 hours. AUC last was (11675.59 ng*hr/ml), while AUCINF was (16676.82 ng*hr/ml), Kel and half life were found (0.13hr−1 and 11.22 hr) respectively (Table 4).

3.2.2 Discussion the results of the administration of Carbamazepine with Tamarind

The Tmax of control alone was 0.35 hr while Tmax with tamarind was 1.6 hr which is significantly changed with P-value 0.043 and with ratio parameter 301.5.The Cmax decreased from 2222.78 ng/mL to 1006.33 ng/mL with significant change in P-value 0.013 and ratio parameter 37.04.These two results may due to delay in gastric emptying or decrease in dissolution of the particles or maybe due to the carotenoid constituent of tamarind which may cause CYP-450 induction[22], the other parameters were significantly unchanged.

3.3.1 Results of administration of Carbamazepine with Mango

When this combination was given, CBZ reached its maximum plasma concentration (2090.42 ng/ml) after 1.5 hr of administration (figure 3), and then it is gradually decreased to reach its minimum concentration of (251.73 ng/ml) after 24 hours. AUC last was (16981.27 ng*hr/ml), while AUC INF was (28136.61 ng*hr/ml), Kel and half life were found (0.20 hr−1 and 7.78 hr) respectively (table 5).

3.3.2 Discussion the results of the administration of Carbamazepine with Mango

The Tmax of control alone was 0.35 hr while Tmax with mango was 1.5 hr which is significantly changed with P-value 0.018 and with ratio parameter 303.14; this may due to delay in gastric emptying or decrease in dissolution of the particles or may due to the main constituent of mango, mangiferin, which has weak solubility, weak bioavailability, and weak membrane permeability. [23] The Cmax decrease from 2222.78 ng/mL to 2090.42 ng/mL but this change wasn't significant according to P-value, the other pharmacokinetics weren't changed.

3.4.1 Results of administration of Carbamazepine with Sugarcane

When this combination was given, CBZ reached its maximum plasma concentration (4446.31 ng/ml) after 1.7 hr of administration (figure 4), and then it is gradually decreased to reach its minimum concentration of (22.6 ng/ml) after 24 hours. AUC last was (23040.11 ng*hr/ml), while AUC inf was (35067.94 ng*hr/ml), Kel and half life were found (0.26 hr−1 and 5.04 hr) respectively (table 6).

3.4.2 Discussion the results of the administration of Carbamazepine with Sugarcane

The Tmax of control alone was 0.35 hr while Tmax with sugarcane was 1.7 hr which is significantly changed with P-value 0.042 and with ratio parameter 381.26; this may due to delay in gastric emptying or decrease in dissolution of the particles. The Cmax increased from 2222.78 ng/mL to 4446.31 ng/mL which means it becomes the double this may be due to flavonoids constituent of sugarcane which inhibit the p-glycoprotien and inhibit the CYP450 of other drugs which may lead to increase in the concentration of the CBZ in combination with sugarcane [24]but this change wasn't significant according to P-value due to the low rats number which may lead to high variation. The volume was decreased significantly from 2194.3 ml to 885.24 ml with P-value 0.0319

and ratio parameter 37.05 this may due to increase in Kel from 0.12 hr-1 to 0.26 hr-1 and no change in clearance this may lead to decrease in the volume (Cl = V * Kel).

3.5.1 Results of administration of Carbamazepine with Red Bull

When this combination was given, CBZ reached its maximum plasma concentration (4523.67 ng/ml) after one hour of administration(figure 5), and then it is gradually decreased to reach its minimum concentration of (293.9 ng/ml) after 24 hours. AUC last was (29646.32 ng*hr/ml), while AUC INF was (34129.14 ng*hr/ml), Kel and half life were found (0.236 hr−1 and 6.42 hr) respectively (table 7).

3.5.2 Discussion the results of the administration of Carbamazepine with Red Bull

The Tmax of control alone was 0.35 hr while Tmax with red bull was 1.05 hr which is significantly changed with P-value 0.026 and with ratio parameter 277.98; this may due to delay in gastric emptying or decrease in dissolution of the particles. The Cmax increased from 2222.78 ng/mL to 4523.67 ng/mL which means it becomes the double this may due to inhibition of CYP1A2 by caffeine constituent of red bull which is same isoenzyme of CBZ [25] but this change wasn't significant according to P-value due to the low rats number which may lead to high variation. The AUC increased from 14730.56 ng*hr/ml to 29646.32 ng*hr/ml but this change wasn't significant according to P-value. The volume was decreased from 2194.3 ml to 912.19 ml with P-value 0.054 which wasn't significant according to P-value this change may due to increase in Kel from 0.12 hr-1 to 0.23 hr-1 and decrease in clearance from 196.9 ml/hr to 150.8 ml/hr this may lead to decrease in the volume (Cl = V * Kel) and increase in AUC (Cl=Dose/AUC).

Table 2: The average of Accuracy % based on the concentration of each standard point in the four days

Concentration for each Standard Point (ng/ml)	Accuracy values of the calibration curve						
	Day 1	Day 2	Day 3	Day 4	SD	CV%	Average Percent Recovery
80.000	91.13	110.88	102.98	96.78	8.47	8.43	100.44
160.000	85.28	106.55	100.72	96.65	8.98	9.23	97.30
320.000	91.68	113.04	119.27	98.95	12.65	11.96	105.74
800.000	88.82	103.69	102.53	102.07	7.00	7.05	99.28
1600.000	97.21	103.1	99.1	94.82	3.49	3.54	98.56
3200.000	107.34	99.6	100.9	102.39	3.38	3.29	102.56
4800.000	96.59	96.59	99.19	99.19	1.49	1.53	97.89

Table 3: The average Accuracy% based on the concentration mean for each QC (low, mid and high) for the four days

QC/Day	Day 1	Day 2	Day 3	Day 4	SD	CV%	Average Accuracy%
QCL	89.43	94.82	92.86	96.14	2.91	3.12	93.31
QCM	100.60	107.40	97.90	102.44	4.00	3.92	102.09
QCH	95.44	104.13	93.83	104.64	5.66	5.69	99.51

Table 4: Comparison between Carbamazepine (10mg/kg) alone ±SEM (n=7) and in combination with Tamarind ±SEM (n=8) according to pharmacokinetic parameters, P value, and ratio parameter

Content	Control	Tamarind	P value	Ratio parameter
Kel (1/hr)	0.12±0.03	0.13±0.04	0.47	69.35
Half life (hr)	7.69±1.77	11.22±3.13	0.47	144.19
Tmax(hr)	0.35±0.05	1.6±0.56	0.043*	302.54
Cmax(ng/ml)	2222.78±380.87	1006.375±265.88	0.013*	37.04
AUClast((ng/ml)*hr)	14730.56±4702.02	11675.59±4850.13	0.22	49.90
AUCINF((ng/ml)*hr)	18048.10±5440.1	16676.82±6804.96	0.25	45.16
Vz (ml)	2194.36±707.01	5092.89±1418.35	0.074	231.45
Cl (ml/hr)	196.98±38.26	730.45±302.22	0.26	193.99
AUMCINF((ng/ml)*hr^2)	209081.58±81864.3	330466.11±141854.5	0.55	57.17
MRTINF(hr)	11.72±3.08	15.40±4.23	0.81	110.92

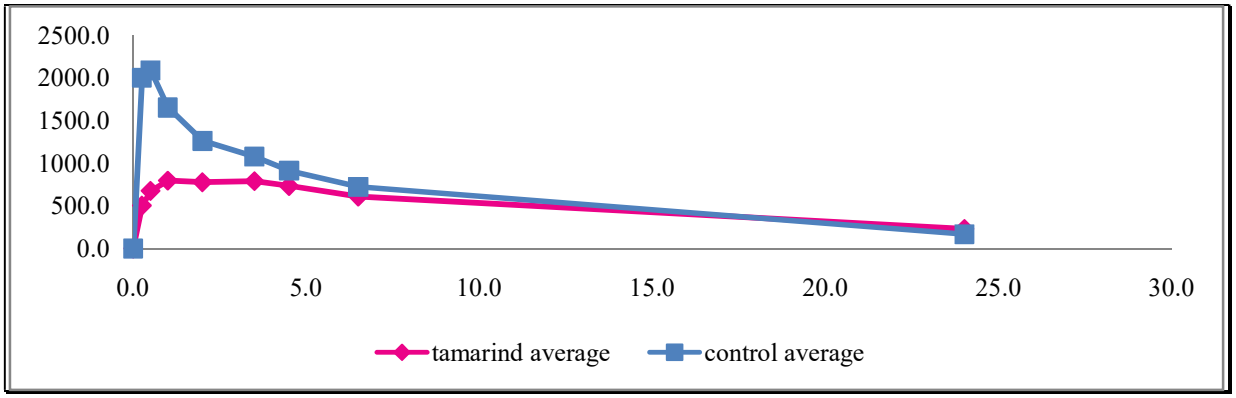

Figure 2: Carbamazepine alone and in combination with Tamarind juice (concentration –time) plasma profile after 10 mg/kg oral dose of Carbamazepine

Table 5: Comparison between Carbamazepine (10mg/kg) alone ±SEM (n=7) and in combination with Mango ±SEM (n=8) according to pharmacokinetic parameters, P value, and ratio parameter

Content	Control	Mango	P value	Ratio parameter
Kel (1/hr)	0.12±0.03	0.20±0.04	0.74	118.03
Half life (hr)	7.69±1.77	7.78±4.11	0.74	84.72
Tmax(hr)	0.35±0.05	1.5±0.37	0.018*	303.14
Cmax(ng/ml)	2222.78±380.87	2090.42±586.42	0.43	73.28
AUClast((ng/ml)*hr)	14730.56±4702.02	16981.27±7323.62	0.75	83.35
AUCINF((ng/ml)*hr)	18048.10±5440.1	28136.61±15283.99	0.66	73.83
Vz (ml)	2194.36±707.01	1637.07±348.52	0.65	81.45
Cl (ml/hr)	196.98±38.26	348.31±124.89	0.73	122.04
AUMCINF((ng/ml)*hr2)	209081.58±81864.3	884362.81±801478.6	0.55	57.1
MRTINF(hr)	11.72±3.08	11.28±5.71	0.41	69.68

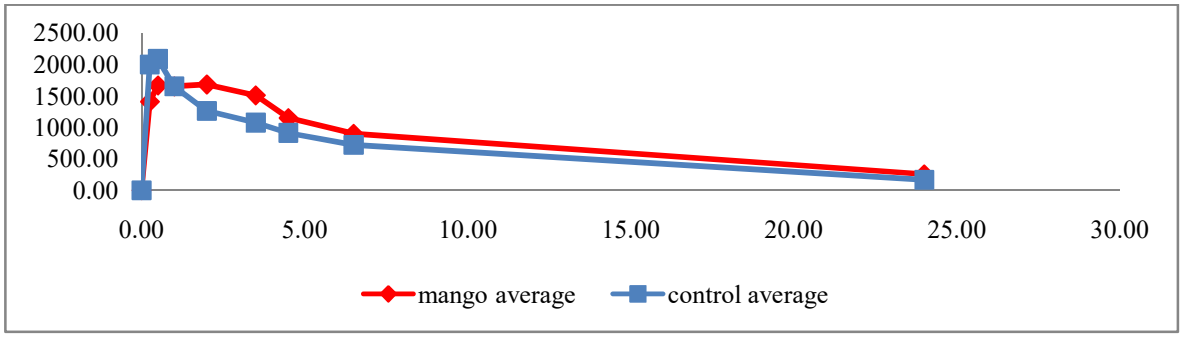

Figure 3: Carbamazepine alone and in combination with Mango juice (concentration –time) plasma profile after 10 mg/kg oral dose of Carbamazepine

Table 6: Comparison between Carbamazepine (10mg/kg)alone±SEM (n=7) and in combination with Sugarcane ±SEM (n=9) according to pharmacokinetic parameters, P value, and ratio parameter

Content	Control	Sugarcane	P value	Ratio parameter
Kel (1/hr)	0.12±0.03	0.26±0.08	0.36	157.22
Half life (hr)	7.69±1.77	5.04±1.74	0.36	63.60
Tmax(hr)	0.35±0.05	1.72±0.47	0.042*	381.26
Cmax(ng/ml)	2222.78±380.87	4446.31±873.38	0.203	161.91
AUClast((ng/ml)*hr)	14730.56±4702.02	23040.11±8868.5	0.65	128.18
AUCINF((ng/ml)*hr)	18048.10±5440.1	35067.94±9880.2	0.74	124.43
Vz (ml)	2194.36±707.01	885.24±267.7	0.031*	37.05
Cl (ml/hr)	196.98±38.26	200.36±72.43	0.54	70.40
AUMCINF((ng/ml)*hr^2)	209081.58±81864.3	341682.4±137545.8	0.73	73.79
MRTINF(hr)	11.72±3.08	7.6±2.56	0.13	51.95

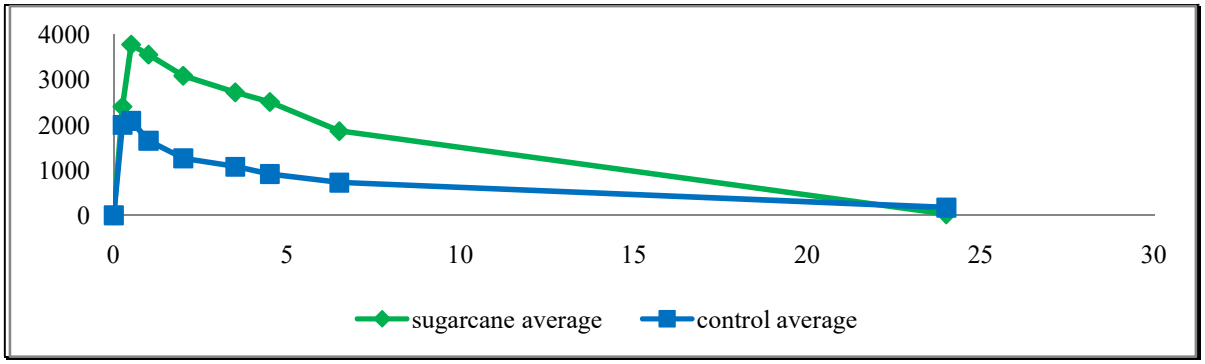

Figure4: Carbamazepine alone and in combination with Sugarcane (concentration –time) plasma profile after 10 mg/kg oral dose of Carbamazepine

Table 7: Comparison between Carbamazepine (10mg/kg) alone ±SEM (n=7) and in combination with Red bull ±SEM (n=9) according to pharmacokinetic parameters, P value, and ratio parameter

Content	Control	Red bull	P value	Ratio parameter
Kel (1/hr)	0.12±0.03	0.23±0.07	0.47	143.82
Half life (hr)	7.69±1.77	6.42±1.66	0.47	69.52
Tmax(hr)	0.35±0.05	1.055±0.19	0.026*	277.98
Cmax(ng/ml)	2222.78±380.87	4523.67±785.6	0.07	200.76
AUClast((ng/ml)*hr)	14730.56±4702.02	29646.32±7103.6	0.25	190.61
AUCINF((ng/ml)*hr)	18048.10±5440.1	34129.14±8197.6	0.55	150.36
Vz (ml)	2194.36±707.01	912.19±336.9	0.054	41.25
Cl (ml/hr)	196.98±38.26	150.83±45.2	0.40	61.89
AUMCINF((ng/ml)*hr^2)	209081.58±81864.3	345804.37±109907.2	0.97	102.89
MRTINF(hr)	11.72±3.08	8.7±2.3	0.29	63.68

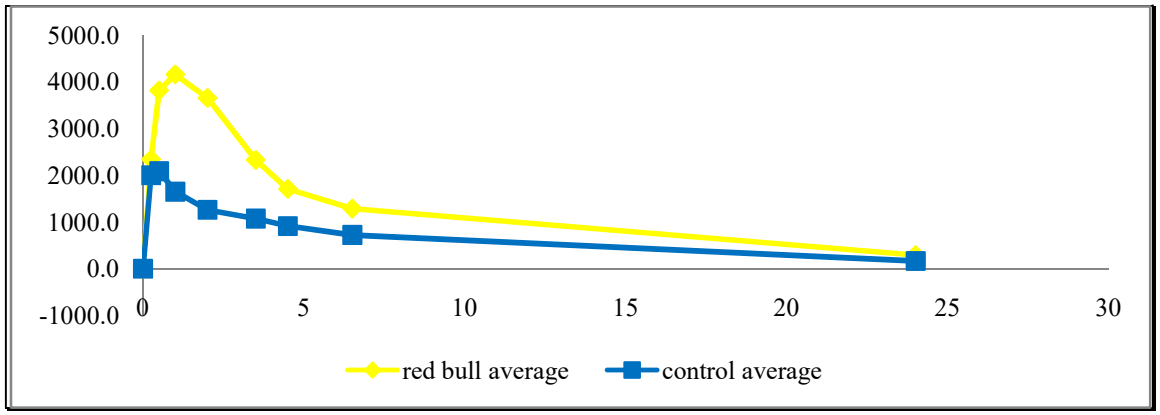

Figure 5: Carbamazepine alone and in combination with Red Bull juice (concentration –time) plasma profile after 10 mg/kg oral dose of Carbamazepine

4. CONCLUSION

A simple, rapid and accurate method of High-Performance Liquid Chromatography with UV detector was used for determination of CBZ in rat plasma. Plasma CBZ level was affected by the administration of beverages such as tamarind, mango, sugarcane, and red bull. The reduction in plasma CBZ level significantly appeared in combination with tamarind while the other beverages were insignificantly affected by the plasma concentration of CBZ. The decrease in the plasma level of CBZ by tamarind juice may be due to the induction of CYP3A4 activity since CBZ is metabolized primarily by CYP3A4.The Tmax of CBZ was significantly delayed by the administration of all beverages this may be due to the low dissolution of the particles or due to delay in gastric emptying. The volume was significantly decreased in combination with sugarcane; this may due to increasing in Kel while the clearance not changed. Future studies are needed to examine the possibility of interactions on the CYP450 in vitro. In addition, further investigations in humans are necessary to examine our important findings since it may have serious consequences on patient health either in losing the efficacy or increasing the toxicity of the drug.

5. ACKNOWLEDGMENT

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