Comparative pharmacokinetic study of theaflavin in healthy and experimentally induced liver damage rabbits

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Abstract

This current work aimed to study the pharmacokinetics of theaflavin in healthy and hepatotoxic rabbits for comparison. Aspartate aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) were significantly raised ($P<0.05$) after administration of 0.2 mg/kg body weight (BW) Carbone tetrachloride (CCL4) subcutaneously. Pharmacokinetic parameters calculated following administration of theaflavin intravenously and orally at 30 mg/kg and 500 mg/kg respectively to both healthy animals and those with damaged liver. Theaflavin concentration in blood measured by HLPC at various time intervals. Pharmacokinetic results showed that theaflavin concentration when given orally reached its maximum concentration after 5 hours in healthy rabbits. While in hepatotoxic group, theaflavin concentration achieved the highest level in blood after three hours. Theaflavin bioavailability in hepatotoxic animals was significantly high and almost double its bioavailability in healthy animals. Results revealed that the area under curve (AUC) value in rabbits with damaged liver was significantly greater than in healthy group ($P<0.05$). t ½ of theaflavin after intravenous administration was 6.3±0.82 hour in damaged liver group which is significantly higher than that in healthy group ($P<0.05$). Theaflavin mean concentration in hepatotoxic group required more than 3 hours to decline to 352±19.4 ng/ml when compared to its concentration in healthy group which is required only 45 minutes to decrease to 310± 9.5 ng/ml. In conclusion liver has critical impact on the pharmacokinetics of theaflavin especially bioavailability and biotransformation and this research recorded reasonably large differences between healthy and liver damaged groups regarding theaflavin pharmacokinetic parameters which may result in negative influences on its biological efficacy when used in the treatment of various diseases.

Keyword: Pharmacokinetics, Theaflavin, Carbon tetrachloride, Hepatotoxicity, Rabbits.
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دراسة مقارنة الحركة الدوائية للثيفلافين في الأرانب السليمة والمصابة بتلف الكبد المستحدث تجريبياً

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فرع الفسلجة والأدوية، كلية الطب البيطري، جامعة واسط، واسط، العراق

الخلاصة

إن الهدف من هذا العمل هو دراسة خواص حركية الدواء للثيفلافين في الأرانب السليمة والمصابة بتلف الكبد من اجل المقارنة. تلف الكبد استحدث بواسطة رباعي كلوريد الكاربون. حيث أن تركيز أنزيمات الكبد (ألنين امينوتراسفيريز، الاسبارتيت امينوترانفيريز والالكلاين فوسفاتيز) ارتفعت معنوياً بعد إعطاء رباعي كلوريد الكاربون بتركيز ٠,٢ ملغم/كغم من وزن الجسم تحت الجلد. حسبت معايير الحركة الدوائية بعد إعطاء ثيفلافين بتركيز ٣٠ ملغم/كغم من وزن الجسم وريديا وبتركيز ٥٠٠ ملغم/كغم فمويا لكل من مجموعة الأرانب السليمة والمصابة بتلف الكبد. حسب تركيز الثيفلافين في بلازما الدم بواسطة جهاز HPLC وبأوقات مختلفة بعد إعطائه. أظهرت نتائج الحركة الدوائية أن تركيز الثيفلافين بعد التجريع الفموي قد وصل إلى اعلى مستوى له في الدم بعد ٥ ساعات من الإعطاء في الأرانب السليمة. بينما سجلت مجموعة الأرانب المصابة بتلف الكبد ارتفاعا معنويا في تركيز الثيفلافين حيث وصل إلى اعلى مستوى له بعد ٣

ساعات. التوافر الحيوي للثيفلافين في الحيوانات المصابة بتلف الكبد قد سجل ارتفاعا معنويا حيث وصل تقريبا ضعف توافره الحيوي في الحيوانات السليمة. كذلك أظهرت النتائج ان قيمة المساحة تحت المنحني في الأرانب المصابة كانت اعلى من تلك التي سجلت في السليمة. عمر النصف للثيفلافين بعد الإعطاء الوريدي كان ٠,٨٢±٦,٣ ساعة في الأرانب المصابة بتلف الكبد حيث ازداد التركيز معنويا عند المقارنة بعمر النصف في الحيوانات السليمة. معدل تركيز الثيفلافين في الأرانب المصابة قد استغرق أكثر من ٣ ساعات لينخفض إلى ١٩,٤ ± ٣٥٢ نغم/مل عندما تمت مقارنته مع تركيزه في مجموعة الحيوانات السليمة حيث احتاج إلى ٤٥ دقيقة فقط ليقل إلى ٩,٥±٣١٠ نغم/مل. استنتج من الدراسة أن الكبد له دور كبير بالتأثير على معايير الحركة الدوائية للثيفلافين وخاصة التوافر الحيوي والأيض وقد سجل اختلافا كبير نسبيا في معايير الحركة الدوائية للثيفلافين بين الحيوانات السليمة والمصابة والذي بدورة قد يزيد من سمية المادة.

Introduction

Camellia sinensis is a plant family that the traditional tea produces from their leaves. Tea is the most beverage consumed in the world after water (1). Tea was initially utilized as a traditional medicine and later as a daily basis beverage and there are four unique kinds of tea are white, black, green and oolong tea (2). Tea has a complex chemical composition with several components: proteins, polysaccharides, amino acids, organic acids, minerals, chlorophyl, lignins, volatile compounds, polyphenols (proanthocyanidins theaflavins and thearubigins) and also alkaloids such as (caffeine theophylline and theobromiine) (3). Caffeine is the most plentiful alkaloid in tea (4). Theaflavins and thearubigins are the most essential polyphenols in traditional black tea, they are formed from tea leaves fermentation by catechins polymerization and oxidation. Theaflavins and catechins represent 2-6% and 3-10%, respectively while thearubigins represent greater than 20% of the aqueous extract of black tea (5-7). Recently, theaflavins have established wide attentions because of their anti-oxidant, anti-inflammatory, and anti-tumor activities (8,9).

Thearubigins are a very complex polymers with high molecular weight (10,11). While theaflavins are a little simpler structure in different five forms; theaflavin 5, theaflavin-3-O-gallate 6, theaeflavin-3′-Ogallate 7, and theaeflavin-3,3′-O-digalate 8. These different types of theaflavin are the essential components of black tea with a potential bioactive in which associated to beneficial effects on health (12,9). There are many *in-vitro* and *in-vivo* studies reported the activity of theaflavins against pro-inflammatory cytokines like inhibition of interleukins-6 (IL-6), interleukins 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α). In addition, it prevents DNA damage in lymphocytes (13,14). Furthermore, it suppresses the free radicals formation by preserving the activities of antioxidants (15). It has been shown that theaflavin has antihypertensive activity in people who consuming black tea for long time regularly (16), also theaflavin decreases the plasma creative protein and reduce the activation of platelet in healthy people (17). Moreover, some prospective studies demonstrated a relation between black tea intake and the prevalence of different cancers (18-20).

Sarkar and Bhaduri (21) approved that constituents of black tea especially theaflavins are more effective than green tea in abolishing NO and O_2 production in activated macrophages. The main difficulty in examining the relationship of tea consumption with biological activity is the absence of adequate quantitative data. Even in animal studies, understanding the inhibitory mechanism of tea action on different disease is vulnerable by a little and limited information about the pharmacokinetics profile such as bioavailability, biotransformation and clearance of tea constituents (22).

In my opinion the advantages of green tea over black tea in relation to health benefit is basically because of the data of black tea therapeutic effects of black tea on health are insufficient. Therefor information on the absorption, distribution and bioavailability of theaflavin is critical for understanding the biological benefits of black tea. Subsequently, there are few researches have been studied the pharmacokinetics of the black tea (22-25). The objective of this research is to estimate the pharmacokinetic parameters of theaflavin in healthy and hepatotoxic rabbits to understand the role of liver in biotransformation and bioavailability of theaflavin.

Materials and methods

Preparation of Theaflavin stock solution

Theaflavin obtained from (Aktin Chemicals, Inc. India). The solution was prepared by dissolving of 1µg of theaflavin in 1ml of double sterile distilled water.

Experimental Animals

Ninety-six healthy male rabbits (local breed rabbits), their ages and weights ranged between 13-15 weeks and 1.5 - 2 kg, respectively were used in this work. Rabbits were kept in standard cages, located in a special animal house. Rodent diet pellets and water were provided for two weeks for adaption before experiments, then animals were kept in fasting state prior to starting any experiment started. Housing conditions were maintained at 20-25 ^{o}C in controlled room condition, the air of the room was changed continuously by using ventilation vacuum. Cages were cleaned daily. All experiments were done according to

research protocols established by the animal care committee of the Veterinary Medicine College, Wasit University.

Induction of hepatic injury

The chemical agent used for inducing hepatic injury was "CCl_4" (Sigma Chemicals, USA). It was given subcutaneously to 48 rabbits every alternate day for 3 weeks with a dose of 0.2 ml/kg (26).

Liver enzyme estimation

Biomeruix kit, (France) was used to measure "Alanine aminotransferase (ALT) Aspartate aminotransferase (AST), and Alkaline phosphatase (ALP)" according to standard laboratory methods.

Pharmacokinetics study of theaflavin in healthy animals

A 24 rabbits were given 500mg/kg of theaflavin as single oral dose. Blood samples were collected at various times; 10min, 30min, 1hr, 3hr, 5hr, 8hr, 12hr and 24hrs. Likewise 24 rabbits given 30mg/kg of theaflavin as a single intravenous dose. Blood samples were collected at various times; 5min, 15min, 45min, 3hrs, 5hrs, 8hrs, 12hrs and 24hrs (27). Three animals used for each withdrawal time.

Study the pharmacokinetics of theaflavin in damaged liver animals

A 24 rabbits administrated single oral (500 mg/kg) dose of theaflavin. Similarly, 24 rabbits administrated a single intravenous (30mg/kg) dose of theaflavin similar to procedure in healthy animals. Three animals used for each withdrawal time. Animals were anesthetized by intramuscular injection of Xylazine 2% (VMD, Belgium) 4 mg/kg and Ketamine 10% (Fabrique par: KEPRO, Netherland) 50 mg/kg (28). Four ml of blood sample was withdrawn from the heart of each rabbits (each time interval for all animals), then blood samples were centrifuged at 2000g for ten minutes. One ml of plasma mixed thoroughly with 20 ml of ascorbic-EDTA solution [0.1% EDTA (pH 3.6) and 0.4 M NaH_2PO_4 buffer containing 20% ascorbic acid], then stored at -80 °C until analyzed (29).

Pharmacokinetic parameters

Elimination rate constant (Ke hr^{-1}) Absorption rate constant (Ka hr^{-1}), concentrations of theaflavin at time zero ng/ml, volume of distribution (vd) (L/Kg), t1/2a (hr), t1/2e (hr), area under concentration curve (AUC) ng/ml.hr, Tmax, Cmax clearance (CL) L/Kg/hr and Bioavailability F % were calculated to estimate the pharmacokinetics parameters.

Quantitative determination of theaflavin

Determination of theaflavin in plasma was conducted by using HPLC, procedure described by Lee (29) with slight alteration. "The HPLC system consisted of an ESA two-pump solvent delivery system, and a supelcosil C18 reversed-phase column (150 × 4.6 mm; particle size, 5 µm) and an ESA model 540 refrigerated autosampler. Buffer A consisted of 30 mm NaH_2PO_4, acetonitrile, and tetrahydrofuran in a ratio of 98.13:1.75:0.12 (pH 3.35). Buffer B consisted of 15 mm NaH_2PO_4, acetonitrile, and tetrahydrofuran in a ratio of 41.5:58.5:12.5 (pH 3.45)". The flow rate was maintained at 1 ml/min. fifty microliter of the sample were injected onto the HPLC (29).

Standard Curves and Calculation

Standard curve in figure 1 was accomplished by spike plasma samples with known concentrations of stander theaflavin 32, 64, 128, 256, 512, 1024, and 2048 ng/ml. The peak heights were plotted against the sample concentration. Analytes concentrations were attained by comparing the peak heights of the sample to standard.

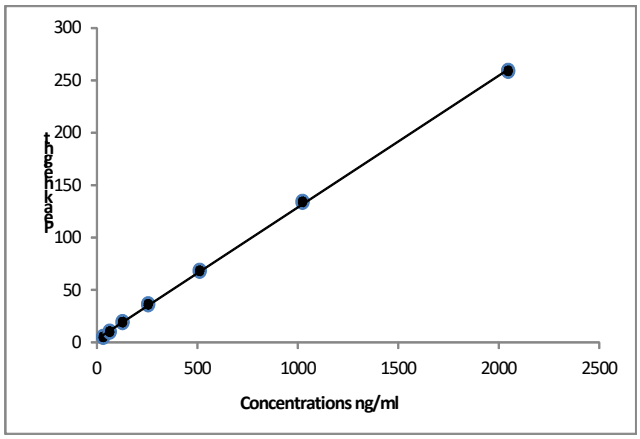

Figure 1: Standard curve of theaflavin in plasma.

Statistical analysis

The data was collected and reported as mean ± SE. SPSS software (30) used to find out the significant result. Continuous and numerical values were analyzed by student t-test. P-value <0.05 were considered as significant difference between groups or periods.

Results

Liver enzyme analysis

The results in table 1 revealed severe liver damage in rabbits injected with 0.2 ml/kg CCL4 in alternate days for 3 weeks when compared to rabbits before injection. This was evidenced by a mark increased of serum enzymes level (ALT, AST and ALP) in rabbits treated with CCl_4.

Pharmacokinetics analysis

Theaflavin was analyzed in blood samples of all animals before experiments begun to assure that animals clean from

theaflavin by using HPLC (method mention previously). Theaflavin was not found in plasma samples from all experimental animals.

Results of the theaflavin concentrations in plasma versus time after intravenous administration in both healthy and damaged liver rabbits displayed bi-exponential elimination that obey first order kinetics, two compartment model (according to Plasma concentration-time curve).

Theaflavin mean concentration in blood plasma of healthy rabbits after IV administration of 30mg/kg was 640±22.4 ng/ml after 5 minutes then, after 24hr, the concentration decreased to 3±0.3 ng/ml. While its concentration in hepatotoxic rabbits after IV administration was 730±20.3 ng/ml after 5 minutes, whereas after 24hr the concentration was decrease to 166±12.7 ng/ml as shown in table 2, figures 2 and 3, respectively.

The highest level that theaflavin concentration reached after 5 hours of oral dosing of 500mg/kg was 143±6.2 ng/ml in healthy animals. Then, theaflavin concentration reduced to 8±1.2 ng/ml after 24hr, whereas in hepatotoxic group its concentration required only 3hrs following administration to achieved peak level 172±3.7 ng/ml. Then the concentration declined after 24hrs to 102±3.3 ng/ml, as shown in table 3, figures 4 and 5.

Table 1: Serum liver enzymes in experimentally liver damaged group

Liver enzymes	Group (n=30)	
	Before treated with CCl_4	After treated with CCl_4
ALT (U/I)	44.3 ± 3.11 A	134.7 ± 7.12 B
AST (U/I)	36.7 ± 5.32 A	210.8 ± 10.83 B
ALP (U/L)	112.3 ± 6.55 A	243.6 ± 8.33 B

Values are expressed as mean ± standard error, Different capital letters mean significant (P≤0.05) results between periods. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase.

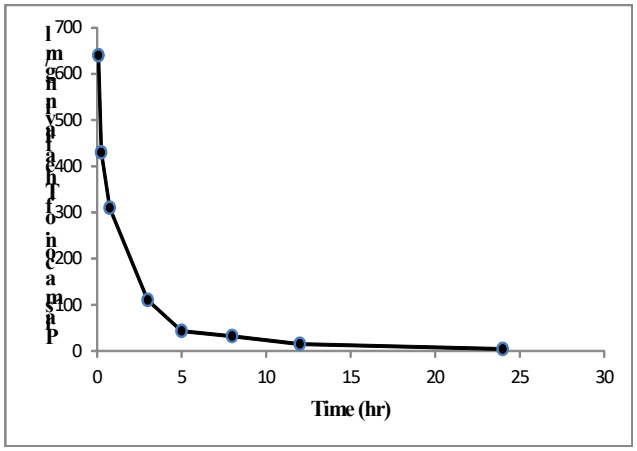

Figure 2: Plasma concentrations of Theaflavin versus time profile after a single IV (30 mg/kg) administration in healthy animals.

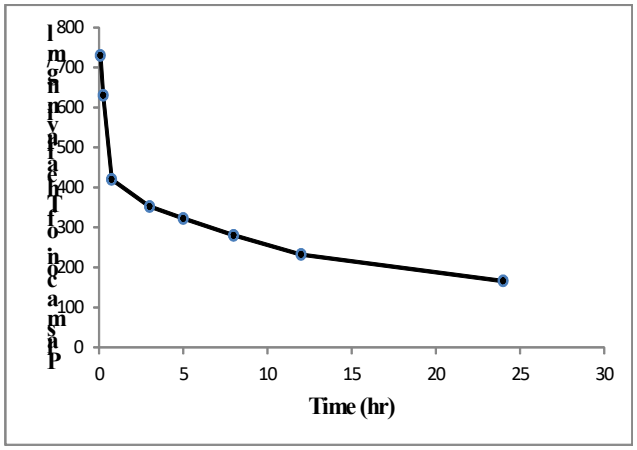

Figure 3: Plasma concentrations of Theaflavin versus time profile after a single IV (30 mg/kg) administration in liver damaged animals.

Table 2: Plasma concentrations of theaflavin at different times interval after single IV (30 mg/kg) administration in healthy and hepatotoxic animals

Single IV (30 mg/kg) in healthy group (n=24)								
Times	5min	15min	45 min	3hr	5hr	8hr	12hr	24hr
Concentrations (ng/ml)	640±22.4 a	430±21.9 b	310±9.5 b	110±6.5 b	41±2.3 b	31±1.5 b	15±0.8 b	3±0.3 b
Single IV (30 mg/kg) in hepatotoxic group (n=24)								
Times	5min	15min	45 min	3hr	5hr	8hr	12hr	24hr
Concentrations (ng/ml)	730±20.3 a	630±26.9 a	420±23.2 a	352±19.4 a	322±18.1 a	280±20.2 a	232±10.6 a	166±12.7 a

Values are expressed as mean ± standard error, Group no = 24, three animals used for each withdrawal time. Different small letters mean significant (p<0.05) results between groups.

Table 3: Plasma concentrations of theaflavin at different times interval after single oral (500 mg/kg) administration in healthy and hepatotoxic groups

Single oral (500 mg/kg) in healthy group (n=24)								
Times	10min	30min	1hr	3hr	5hr	8hr	12hr	24hr
Concentrations (ng/ml)	12±1.7 a	43±2.8 a	83±2.3 a	110±5.3 b	143±6.2 b	118±3.1 b	62±4.1 b	8±1.2 b
Single oral (500 mg/kg) in hepatotoxic group (n=24)								
Times	10min	30min	1hr	3hr	5hr	8hr	12hr	24hr
Concentrations (ng/ml)	23±1.08 a	45±2.3 a	86±2.7 a	172±3.7 a	168±3.2 a	150±3.1 a	143±2.4 a	102±3.3 a

Values are expressed as mean ± standard error, Group no = 24, three animals used for each withdrawal time. Different small letters mean significant ($p<0.05$) results between groups.

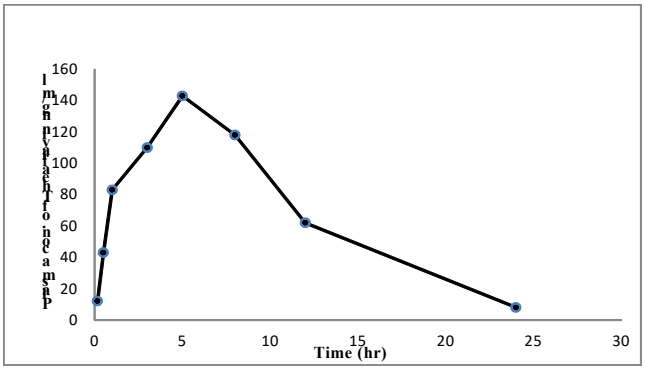

Figure 4: Plasma concentrations of Theaflavin versus time profile after a single oral (500 mg/kg) administration in healthy animals.

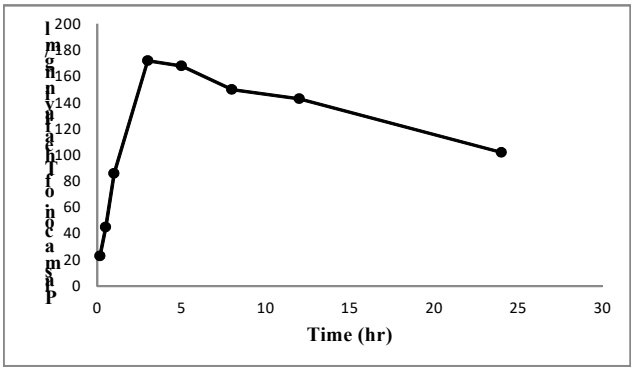

Figure 5: Plasma concentrations of Theaflavin versus time profile after a single oral (500 mg/kg) administration in liver damaged liver animals.

The average pharmacokinetic parameter of theaflavin following oral dosing and IV administration in healthy and hepatotoxic animals shown in tables 4 and 5. Theaflavin concentrations following IV administration at time zero in healthy rabbits' group in α and β phases were 61.94±4.65 and 86.24±4.14 ng/ml, respectively. While in hepatotoxic rabbits group the average concentration found to be 231±7.82 and 413±10.31 ng/ml, respectively. Results confirmed that the concentrations at time zero in both phases for hepatotoxic group were significantly ($P<0.05$) greater than what were recorded in healthy group. While following oral dosing there was no significant differences in mean concentrations at time zero between the two groups.

The apparent volume of distribution (Vd) of theaflavin in hepatotoxic group following IV administration was significantly ($P<0.05$) higher than that recorded in healthy group. Also, it was recorded that the t ½ of theaflavin in healthy group after iv administration was 4.95 hr. Whereas it was increased to 6.3hr in hepatotoxic group. While after oral dosing the t ½ increased from 4.62 hrs in healthy group to 5.8hrs in hepatotoxic group.

There were noticeable significant differences ($P<0.05$) in clearance of theaflavin between the healthy rabbits and those with damaged liver either after IV or oral administration. Additionally, results showed that clearance significantly decreased in hepatotoxic group.

Discussion

CCL_4 is a very familiar toxicant agent which causes liver damage and it converts to trichloromethyl free radicals a highly reactive metabolites by the action of liver cytochrome P-450 enzymes (31). These free radicals may again react with oxygen to form trichloromethyl peroxyl radicals, which may attack lipids on the membrane of endoplasmic reticulum to elicit lipid peroxidation, finally resulting in cell necrosis and consequent cell death (31,32). In the present study, all animals that dosed with CCL_4 demonstrated significant liver damage which was reflected through a considerable rise in the serum enzymes "AST and ALT and ALP". Serum aminotransferases considered as sensitive indicator of hepatic injury. Results in agreement with Alaraj and Qiblawi whose recorded elevation of serum enzymes after treatment of rabbits with CCL_4(33).

Table 4: Pharmacokinetic parameters for Teaflavin after IV (30 mg/kg) administration in healthy and hepatotoxic rabbits

Pharmacokinetics parameters	Mean±SE	
	Healthy group	Hepatotoxic group
Distribution rate constant (α) hr^{-1}	0.73 ± 0.12 A	0.62 ± 0.05 A
Elimination rate constant (β) hr^{-1}	0.14 ± 0.01 A	0.03 ± 0.01 B
Concentration ng/ml in α phase at time zero (A)	61.94 ± 4.65 B	231 ± 7.82 A
Concentration ng/ml in β phase at time zero (B)	86.24 ± 4.14 B	413 ±10.31 A
t 1/2 α hr	0.94 ± 0.07 A	1.11 ± 0.52 A
t 1/2 β hr	4.95 ± 1.02 B	6.3 ±0.82 A
Volume of distribution Vd (L/kg)	1.26 ± 0.43 B	2.5 ±0.14 A
Area under curve AUC (ng/ml*hr)	65 ± 0.83 A	75 ± 1.58 A
Clearance CL (L/kg/hr)	0.17 ± 0.02 B	0.07 ± 0.007 A

Values represent mean±SE, Group no = 24,three animals used for each withdrawal time.
Different capital letters mean significant ($p<0.05$) results between groups.

Table 5: Pharmacokinetic parameters for Teaflavin after oral (500 mg/kg) administration in healthy and hepatotoxic rabbits

Pharmacokinetics parameters	Mean±SE	
	Healthy group	Hepatotoxic group
Absorption rate constant (Ka) hr^{-1}	1.4 ± 0.09 B	2.4 ± 0.23 A
Elimination rate constant (Ke) hr^{-1}	0.15 ± 0.01 A	0.04 ± 0.01 B
Conentration (ng/ml) in absorption phase at time zero (CP^a)	210 ± 9.87 A	234 ± 21.19 A
Concentration (ng/ml) in elimination phase at time zero (CP^e)	368 ± 11.15 A	420 ± 11.32 A
t 1/2a hr	0.32 ± 0.04 B	1.6 ± 0.15 A
t 1/2e hr	4.62 ± 1.11 A	5.8 ± 0.17 A
Volume of distribution Vd (L/kg)	2.3 ± 0.12 A	1.6 ± 0.13 A
Area under curve AUC (ng/ml*hr)	20 ± 0.14 B	45 ± 4.46 A
Clearance CL (L/kg/hr)	0.18 ± 0.03 A	0.04 ± 0.02 B
Bioavailability F %	30 ± 2.23 B	60 ± 3.88 A
C_{max} (ng/ml)	143 ± 5.42 B	172 ± 8.52 A
T_{max}(hr)	5 ± 1.3 A	3 ± 0.29 B

Values represent mean±SE, Group no = 24,three animals used for each withdrawal time.
Different capital letters mean significant ($p<0.05$) results between groups.

In this study theaflavin concentration following oral dosing reached the Cmax after 5hrs in healthy rabbits. While in hepatotoxic group, theaflavin concentration achieved highest concentration in blood after 3hrs. This delay in absorption and reaching the maximum plasma concentration may be attributed to the use of pure theaflavin rather than black tea extract. This may clarify why in other study (34) the polyphenols in black tea reached the Cmax faster than what has been obtained in this study.

However, there were little information and limited studies focused on the absorption, metabolism and intestinal flora catabolism of black tea derived polyphenols. The bioavailability of theaeflavin in hepatotoxic animals was significantly high and almost double the bioavailability in healthy animals. Also, the results revealed that the AUC in damaged liver rabbits were considerably greater than those recorded in healthy group. A study reported when increase in in the pre-systemic elimination and the catabolism within the gut may contribute more significantly to decreases the oral bioavailability (35).

Sherry Chow and his colleagues reported that following oral dosing, the tea polyphenols are likely to be eliminated pre-systemically (23). Small changes in the pre-systemic elimination of green tea could have a significant impact on the systemic bioavailability of these compounds. This study verified increasing in the bioavailability and AUC in hepatotoxic rabbits and this is because of the damage occurred in liver which affects negatively the metabolic mechanism of theaflavin (23).

Major metabolites of theaeflavin 3,3'- digallate after biotransformation of theaflavins and thearubigines are theaeflavin 3- gallate, theaeflavin 3'-gallate, methylated theaflavin 3,3'-digallate, and gallic acid were found in mouse fecal sample. Neither glucuronidated nor sulfated metabolites were detectable. Gut microflora or "Cattechol-

O-methyltransferasee (COMT)" metabolize the theaeflavin 3,3'-digallatte to form gallic acid, theaflavin and theaeflavin mono-gallate (36).

Tea polyphenols biotransformation occur mainly in Phase II metabolism by glucuronidation and glucosidation. *In-vitro* and *in-vivo* studies constantly show rapid conjugation, particularly conjugation with glucuronic acid in the liver and intestine (37,38), Glucuronidation along with factors like stability and solubility are predominantly accountable for the poor bioavailability of phenolics. Glucuronidation is mediated by UDP glucuronosyltransferases (UGTs) while sulfation is mediated by sulfotransferases (SULT) and along with cytochrome P450 enzymes, which represent more than eighteen percent of the metabolic pathways (39,40). Also, the colonic microflora largely responsible for the metabolism of theaflavin in both human and mice (41,36).

Relative rabid clearance of theaflavin after IV administration may have occurred as a result of its significant accumulation by the kidney and slightly by the spleen and liver as demonstrated by tissue distribution (22). Same study reported after 30 minutes, 36% of theaflavin administration was recovered in the kidney, whereas 12% in the liver and 7.5% in the spleen.

Sulfotransferase and UDP-glucuronyl transferase are the essential enzymes for biotransformation of tea polyphenols in liver (41). Therefore, in this research liver toxicity caused by CCl_4 may led to decrease in the activity of these two enzymes which contributed more in decreasing the theaflavin metabolism in the liver. This might be explaining the increased the t ½ and the decreased clearance in comparison with healthy rabbits. In conclusion, results of this study established that the liver has critical impact on the pharmacokinetics properties of theaflavin especially bioavailability and biotransformation. Additionally, the difference in pharmacokinetic parameters of theaflavin between the two studied groups may influence its therapeutic efficacy when used in various diseases

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