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Original Article

Dynamic Interplay of Age and Protein Malnutrition on the Pharmacokinetic Profile of Acetaminophen in Wistar Rats

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Abstract

Objectives Age and protein malnutrition (PMN) are well-known determinants of drug pharmacokinetics. The combined influence of age and nutrition on the pharmacokinetics of acetaminophen (APAP) remains insufficiently explored; therefore, this study investigates the role of age and PMN on APAP pharmacokinetics.

Materials and Methods Wistar rat weanlings were divided into four groups. Groups ND-5 ($n = 6$) and ND-18 ($n = 6$) were fed with normal diet (ND, 18% protein) and groups LPD-5 ($n = 6$) and LPD-18 ($n = 6$) were fed with low-protein diet (LPD, 10%) for 5 and 18 months, respectively. Blood samples were collected at different time intervals (0, 0.5, 1, 3, 6, 24, 36, and 48 hours), and plasma was separated and analyzed for APAP using high-performance liquid chromatography. Pharmacokinetic data was analyzed by the noncompartmental model using Phoenix WinNonlin 8.3 software.

Results The pharmacokinetic parameters of APAP were elevated in both LPD groups compared with their age-matched controls. The average area under the curve was increased by approximately 131% (LPD-5) and 17.57% (LPD-18), and the average maximum plasma concentrations (C_{max}) was increased by 33.5% (LPD-5) and 26.3% (LPD-18) compared with their respective age-matched controls. The average mean retention time was approximately 114% (LPD-5) and 17.4% (LPD-18) higher than their respective age-matched controls, whereas the clearance rate (Cl/F) and volume distribution (Vz/F) of the drug were significantly lower. Consequently, there was a 68.5% (ND-5) and 4.73% (ND-18) prolongation in the mean half-life of APAP.

Conclusion The altered pharmacokinetics may arise from the intricate interplay of dietary and age influences on physiology, protein binding, and cytochrome P450enzyme activity/expression. However, the exact reason requires further investigation for a better understanding of vulnerable populations.

Keywords
- acetaminophen
- age
- noncompartmental model
- protein malnutrition
- pharmacokinetics
- rats

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Introduction

Acetaminophen (APAP) is one of the well-known analgesic and antipyretic medications sold over the counter. During the coronavirus disease 2019 pandemic, the demand for APAP increased, and self-medication and overdose enhanced the risk of hepatotoxicity.[1] APAP poisoning has been considered the most common cause of acute liver failure in recent decades.[2] Ingesting higher amounts, whether unintentionally or on purpose, results in severe hepatotoxicity.

Pharmacokinetic studies are essential for providing critical information regarding the ADME profile of the drug and understanding the cause of severe hepatotoxicity due to APAP exposure. Although the pharmacokinetic profile of APAP has been widely studied, very few studies have been conducted on the influence of age[3] and nutrition[4,5] individually, and no study has been reported on the interaction or combination of these factors.

Age influences drug biotransformation, thereby hindering its therapeutic efficacy and safety. Physiological changes during the aging process increase interindividual variation in old age. APAP is the most commonly used analgesic by older people to treat musculoskeletal or lower back pain.[6] The most significant causes of pharmacokinetic change in aging are due to decreased hepatic mass, decreased hepatic blood flow, and reduced renal function, which impairs the clearance of many drugs and their metabolites.[7]

Malnutrition is a potential risk factor for APAP-induced hepatotoxicity. The liver protects the body from toxins and is a "nutritional guardian." The liver is susceptible to low dietary protein and calorie intake. Therefore, it is crucial to consider hepatic changes in malnutrition that can alter xenobiotic metabolism.[8] Poor nutritional status and malnutrition in the elderly are essential concerns.[9] The relationship between nutrition and drug metabolism is fascinating and has gained momentum in recent years. Nutritional influences in vivo and in vitro have recently drawn considerable attention. Early-life nutritional insults can program metabolic dysfunctions later in life, significantly impacting world health.[10]

Clinicians do not seriously consider age and nutrition when prescribing drugs. APAP is both popular and widely available without a prescription. This message emphasizes how age and diet affect pharmacokinetic profiles, which should have an impact on clinical practice and prescribing guidelines.

Materials and Methodology

Chemicals

A free sample of paracetamol was provided by Ce-Chem Pharmaceuticals Pvt. Ltd. 4th phase, #336, 9th Cross Rd, Ganapathy Nagar, Phase 3, Peenya, Bengaluru, Karnataka – 560,058.Ethyl acetate (RANKEM - Cat # LTR/RANK30200) and methanol (HIMEDIA - Cat # AS061).

Animals

Female Wistar rats after weaning (15–18 g) were housed at the NUCARE animal house facility in Deralakatte, Mangalore, India. Standard laboratory conditions (12 hours light/dark cycle; temperature 22°C; relative humidity 60%) were maintained, with free access to their assigned diets (normal diet [ND] and low-protein diet [LPD]) and filtered drinking water. With approval number NGSMIPS/Dec-2020/2022, all animal experiments were conducted in compliance with the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) standards.

Study Design

Female Wistar rats were employed to simulate various clinical scenarios involving different nutritional conditions. The rats were exposed to APAP at the onset and conclusion of their reproductive age. Two groups of weaned Wistar rats were allocated to either a ND consisting of 18% protein (sourced from Amruth Feeds, Pune, Maharashtra, India) or a LPD containing 10% protein prepared in the laboratory. One group received a single excessive dose of APAP (1,000 mg/kg p.o. [per os]) in saline at 5 months of age, while the other group received the same dose at 18 months of age.

Blood Sampling

Blood (0.5 mL) was collected from multiple sites using isoflurane anesthesia at selected time intervals (0, 0.5, 1, 3, 6, 24, 36, and 48 hours postadministration) using ethylenediaminetetraacetic acid -coated tubes. After centrifugation at 3,000 rpm for 5 minutes, the samples were subjected to separation, and the plasma was isolated and stored at −20°C for subsequent pharmacokinetic analysis.

Pharmacokinetic Study

The pharmacokinetics of APAP were analyzed by extracting APAP from plasma samples at 0, 0.5, 1, 3, 6, 24, 36, and 48 hours postadministration.

APAP Extraction from Plasma Samples

APAP was extracted using the liquid–liquid extraction method from plasma samples.[11,12] Before use, the frozen plasma sample was thawed. Ethyl acetate (1.5 mL) was added to plasma (50 µL), vortexed for 5 minutes with a Remi rotor, and then centrifuged at 3,000 rpm for 5 minutes. Separated supernatant was vacuum-dried, and the mobile phase (200 µL) was added to the dry residue and vortexed. The high-performance liquid chromatography (HPLC) system was then injected with the mobile phase (10 µL) mixture for analysis.

Sample Analysis Using HPLC Method

The analysis of the samples was performed utilizing a Waters RP-HPLC system, consisting of a Model-1525 separation module and a Model-2998 photodiode array detector. A C18 column (Waters SPHERISORB, 5 µm, ODS 1, 4.6 * 150 mm) was employed, following the methodology described in literature reference.[11] The mobile phase consisted of a methanol: water solution (60:40, v/v), which was filtered using a 0.45 µm nylon syringe membrane filter. An injection volume of 10 µL was used, and the effluent was monitored at a flow rate of 1 mL/min using an ultraviolet (UV) detector at 254 nm. The standard retention time for APAP was observed

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Table 1 Characterization of protein malnutrition in different aged groups using biometric and biochemical parameters ($n = 6$)

			5 months		18 months	
Sl. no.	Parameter	Unit	ND-5	LPD-5	ND-18	LPD-18
1.	Body wt.	g	169.37 ± 7.03	90.68 ± 3.15[a]	250.96 ± 14.32	172.69 ± 6.64[a]
2.	BMI	g/cm^2	0.44 ± 0.013	0.29 ± 0.016[a]	0.55 ± 0.03	0.43 ± 0.021[b]
3.	Liver wt.	g	6.65 ± 0.68	4.15 ± 0.43	8.47 ± 0.48	6.31 ± 0.36
4.	Relative liver wt.		0.041 ± 0.004	0.052 ± 0.003	0.036 ± 0.002	0.038 ± 0.001
5.	Albumin	g/dL	3.22 ± 0.18	1.93 ± 0.26[a]	3.60 ± 0.16	2.50 ± 0.14[a]
6.	Total protein	g/dL	8.02 ± 0.45	6.10 ± 0.07[a]	7.66 ± 0.13	6.56 ± 0.17[a]
7.	Triglyceride	mg/dL	180.68 ± 14.08	127.07 ± 19.36	180.57 ± 29.03	83.03 ± 8.44[b]
8.	AST	U/L	208.53 ± 13.88	202.90 ± 14.37	149.66 ± 5.55	161.23 ± 11.75
9.	ALT	U/L	74.18 ± 5.75	89.10 ± 5.23	57.57 ± 2.52	55.42 ± 5.04
10.	ALP	U/L	279.20 ± 29.21	576.33 ± 93.00[a]	198.13 ± 19.89	254.50 ± 42.71

Abbreviations: ;ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, Aspartate aminotransferase; BMI, body mass index; LPD, low-protein diet; ND, normal diet; SEM, standard error of mean.
Parameters values are expressed as mean ± SEM.
[a] $p < 0.001$.
[b] $p < 0.01$ when compared with the ND of their respective age groups using *t*-test.

at 3.407 minutes. The quantity of APAP was determined by calculating the UV area of the standard curve.

Calculation of Pharmacokinetic Parameters

The plasma concentration-time data was analyzed using Phoenix WinNonlin 8.3 software through noncompartmental analysis. Individual plasma concentration-time curves were utilized to determine the maximum plasma concentrations (C_{max}) and the corresponding times to reach maximum plasma concentrations (t_{max}). The areas under the plasma concentration-time curves (area under the curve $[AUC]_{0–48}$ and $AUC_{0-\infty}$) were also assessed. Furthermore, additional parameters such as the elimination half-life ($t_{1/2}$), apparent whole-body clearance or oral clearance (CL/F), volume of distribution (V_Z/F), terminal rate constant (Lambda_z), and mean residence time (MRT) were calculated and interpreted.

Statistics

The data was expressed as mean ± SEM. Statistical analysis to assess the differences between groups was performed using a one-way analysis of variance followed by Tukey's test, using GraphPad Prism 8.0.1 software.

Results

Protein deprivation (10% protein) for 5 and 18 months after weaning significantly decreased body weight gain in both LPD age groups. Protein malnutrition (PMN) was further confirmed by biochemical markers such as albumin, total protein (TP), triglyceride (TG), and alkaline phosphatase (ALP) in both age groups. Hypoalbuminemia occurs in the majority of malnourished individuals, the degree depending on the duration, and severity of under nutrition. This may be due to a decrease in the turnover rate of albumin with a reduction in both synthesis and catabolism. The rate of albumin synthesis is directly related to the level of protein intake and amino acid supply.[13] TP and albumin, clinically relevant markers of PMN, fell significantly in the LPD groups owing to prolonged low protein intake. Serum ALP levels were significantly higher in the LPD group. Impairment of bone development and liver function raises ALP levels. Elevated ALP in PMN has already been reported.[14] In contrast, PMN remarkably depressed plasma TG levels, possibly due to lipid accumulation in the liver. These biometric and biochemical parameters in the LPD group confirmed the development of protein malnutrition in the rat model compared with age-matched controls (►**Table 1**).

APAP disposition differed considerably in groups fed diets with different percentages of proteins. The mean plasma APAP concentrations after APAP dose (1,000 mg/kg p.o.) in ND and LPD rats are shown in ►**Fig. 1**. Since APAP disposition is concentration- and time-dependent, total body clearance estimations are time-averaged values.[3]

The pharmacokinetic parameters based on the noncompartmental model of the concentration versus time data are presented in ►**Table 2**. The average MRT was approximately 114% (LPD-5) and 17.4% (LPD-18) higher in the LPD group than in their respective age controls, whereas Cl/F and Vz/F were significantly lower. As a result, there was 68.5% (LPD-5) and 4.73% (LPD-18) prolongation in the half-life of APAP, which increased from 4.49 to 7.57 hours (LPD-5) and 5.70 to 5.97 hours (LPD-18), respectively. The systemic exposure parameters (C_{max} and AUC) were higher in both LPD groups than in age-matched controls. The average AUC was approximately 131% (LPD-5) and 17.57% (LPD-18) higher in the LPD group compared with controls. Likewise, the average C_{max} was 33.5% (LPD-5) and 26.3% (LPD-18) higher in the LPD groups than the respective controls.

Discussion

The PK profile of APAP depends on the differences in absorption and metabolism in the context of nutritional status. Among

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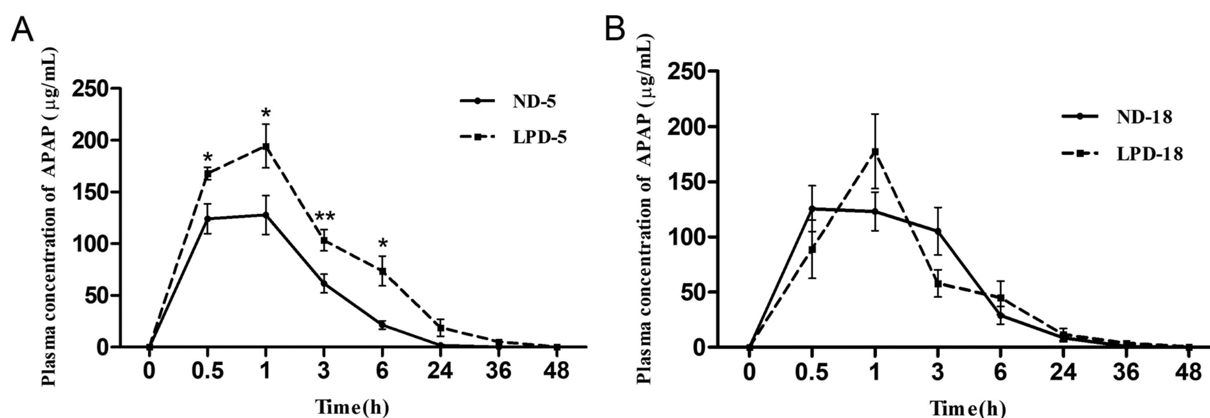

Fig. 1 Mean plasma concentration-time profiles of acetaminophen (APAP) (1,000 mg/kg; oral) single dose administration in normal diet (ND) and low-protein diet (LPD) receiving Wistar rats. Mean plasma concentration–time profiles of APAP following an oral administration of APAP to rats ($n = 6$). All values are mean ± standard error of mean. Bars represent the standard error. $p < 0.05^{*}$, $p < 0.001^{**}$ when compared with the normal diet group.

young rats (5 months old), PMN significantly increased APAP absorption, t½ and MRT when compared with age-matched controls. This could be due to the reduced CYP450 enzyme expression[15] or its activity in PMN rats, as reported earlier.[15] APAP metabolizes into N-acetyl-p-benzo-quinone imine (NAPQI) through CYP450-mediated biotransformation. It is possible that PMN significantly reduces CYP450 enzyme expression and activity, leading to delayed metabolism and elimination in PMN rats compared with normal rats. In contrast, in PMN rats, the higher concentration of APAP during terminal elimination could be due to the lower rate of metabolism and consequent delay in clearance at 48 hours.[16,17]

Nutritional effects on drug-metabolizing enzymes influence both endogenous chemicals (hormones) and xenobiotics (pharmaceuticals), which are metabolized by the same or similar enzymes.[18] Nutrition can affect drug bioavailability, receptor binding, metabolism, and clearance in different ways[19] and thereby influence pharmacological action. Significant individual variations made comparisons more difficult in 18-month-old rats. On the whole, absorption is less affected by age than metabolism (►**Fig. 1**). The pattern and extent of APAP absorption in both ND and LPD-aged rats (18 months) were similar to younger rats of respective nutritional regimens. However, the difference is in the metabolism pattern, which is rapid in normal young rats as against PMN rats, as shown by the clearance data. On the other hand, aged PMN rats showed a different pattern of metabolism compared with young (normal and PMN) rats. These observations confirm the impact of age and nutrition on APAP metabolism. This could be due to altered CYP450 enzyme

Table 2 Plasma pharmacokinetic parameters of APAP (1,000 mg/kg; oral) in ND and LPD receiving Wistar rats ($n = 6$) in different aged groups

			5 months		18 months	
Sl. no.	Parameter	Unit	ND-5	LPD-5	ND-18	LPD-18
1.	Lambda_z	1/h	0.16 ± 0.01^{d}	0.10 ± 0.02^{d}	0.13 ± 0.01	0.12 ± 0.01
2.	$t_{1/2}$	h	4.49 ± 0.26^{d}	7.57 ± 1.05^{d}	5.70 ± 0.62	5.97 ± 0.44
3.	T_{max}	h	0.83 ± 0.11	0.75 ± 0.11	1.10 ± 0.48	1.00 ± 0.00
4.	C_{max}	μg/mL	144.50 ± 20.39	192.93 ± 17.26	140.38 ± 5.58	177.44 ± 33.83
5.	AUC_{0-48}	h*μg/mL	661.22 ± 91.53^{b}	1484.67 ± 166.98^{b}	977.70 ± 172.39	1134.32 ± 287.49
6.	$AUC_{0-\infty}$	h*μg/mL	674.82 ± 93.03^{b}	1564.73 ± 175.44^{b}	986.48 ± 173.42	1149.75 ± 285.68
7.	MRT	h	4.33 ± 0.28^{d}	9.27 ± 1.67^{d}	6.82 ± 0.76	8.01 ± 1.01
8.	Vz/F	(mL)	1784.35 ± 242.09^{bd}	646.48 ± 77.03^{bc}	2477.46 ± 755.34^{d}	1531.38 ± 277.87^{c}
9.	Cl/F	(mL)/h	274.87 ± 34.41^{a}	61.20 ± 6.05^{ab}	291.01 ± 59.97^{b}	181.0 ± 34.93

Abbreviations: ANOVA, analysis of variance; APAP, acetaminophen; $AUC_{0-\infty}$, area under the drug concentration-time curve from time zero to infinity; AUC_{0-48}, area under the drug concentration-time curve from time zero to the time of the last measurable concentration; C_{max}, maximum plasma concentration; Lambda_z, individual estimation of the terminal rate constant; LPD, low-protein diet; MRT, mean residence time; ND, normal diet; t_{max}, times to achieve maximum plasma concentrations; $t_{1/2}$, the elimination half-life period of the drug; Cl/F, the apparent total body clearance or oral clearance & V_Z/F volume of distribution; SEM, standard error of mean.
Mean ± SEM with same superscript letters in the same row are significant at $^{a}p < 0.001$, $^{b,c}p < 0.01$, & $^{d}p < 0.05$ using one way ANOVA followed by Tukey's test.

expression or activity in older age. The pattern of metabolism in aged PMN rats is not affected, but there may be impaired or reduced CYP450 enzyme activity.[13,20]

Aging is characterized by structural and functional changes that affect all organ systems, resulting in reduced homeostasis. Changes in the composition of the body, as well as hepatic and renal functions, are also accountable for increased volume of distribution (V_Z/F) of lipid-soluble medications and decreased clearance of lipid-soluble and water-soluble pharmaceuticals. All of these modifications result in an extended plasma elimination half-life ($t_{1/2}$). Also, as per the literature, the total hepatic CYP450 levels decrease with advancing age, and the expression of CYP2E1.Total hepatic CYP450 levels decline with advancing age, while CYP2E1 and 3A4 protein expression is inversely related to age. Each of these proteins' content decreased by 5% (CYP2El) and 8% (CYP3A) for each decade of life, demonstrating that age has a quantitative impact.[7] This might be the reason for the increased plasma concentration of APAP in old rats (18 months) on ND compared with young rats (5 months), whereas the results are contrary in LPD groups, attributed to altered metabolism due to early nutritional stress.

The interplay of age and nutrition on the pharmacokinetics of APAP is demonstrated using a rat model in this study. To address the age factor, the young (5 months) and aged (18 months) rats were used with different nutritional exposure. While addressing the nutritional factors, though the study incorporates a validated marasmic-kwashiorkor PMN rat model,[21] it is limited by not explaining the results in different types of protein malnutrition. This limitation turns out to be the scope of the study for future research. Considering the 3 R's of animal ethics, the study was conducted using a minimum number of rats and that was sufficient to conclude the study. The study focused on both young and aged rats, giving a baseline understanding of the role of age and nutritional state on the pharmacokinetic profile of APAP. In long-term nutritional studies, changes in immediate consecutive weeks are mostly negligible.[21] Therefore, it is reasonable to believe that this study addresses the role of nutrition among different age groups with clarity. In such studies, major limitations include an adaptation of rats to the diet that may interfere with the PMN category. Further, it is essential to study the role of age and protein malnutrition on CYP450 enzyme expression and its activity.

Conclusion

Both physiology and nutrition can modify pharmacokinetics, insofar as the rat model reflects the human situation. The pharmacokinetic changes could be attributable to the complex interplay of nutrition, physiology, protein binding, and CYP enzyme expression/activity. Additional investigation is needed to better understand the underlying mechanisms in vulnerable populations. This study emphasizes the need to consider age and nutrition when analyzing drug pharmacokinetics, which should be incorporated into clinical practice and prescribing guidelines.

Ethics Committee Approval
Ethics Committee Approval: All the animal experiments were conducted as per the guidelines of the CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) with approval number: **NGSMIPS/Dec-2020/2022.**
Approval date: 29th December 2020
Institution name: NGSM Institute of Pharmaceutical Sciences

Authors' Contributions
M.B. and V.A. conceptualized and designed the study. V.A., V.D., M.R.J. were involved in data collection and writing of the manuscript. V.A., M.B.S., and V.K. contributed to analysis or interpretation. V.A. and V.D. helped in literature search.

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Conflict of Interest
None declared.

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References

1 Romano S, Galante H, Figueira D, Mendes Z, Rodrigues AT. Time-trend analysis of medicine sales and shortages during COVID-19 outbreak: data from community pharmacies. Res Social Adm Pharm 2021;17(01):1876–1881
2 Ghanem CI, Ruiz ML, Villanueva SS, et al. Effect of repeated administration with subtoxic doses of acetaminophen to rats on enterohepatic recirculation of a subsequent toxic dose. Biochem Pharmacol 2009;77(10):1621–1628
3 Galinsky RE, Corcoran GB. Influence of advanced age on the formation and elimination of acetaminophen metabolites by male rats. Pharmacology 1986;32(06):313–320
4 Jung D. Disposition of acetaminophen in protein-calorie malnutrition. J Pharmacol Exp Ther 1985;232(01):178–182
5 Souza VD, Shetty M, Badanthadka M, Mamatha BS, Vijayanarayana K. The effect of nutritional status on the pharmacokinetic profile of acetaminophen. Toxicol Appl Pharmacol 2022; 438:115888
6 Marcum ZA, Duncan NA, Makris UE. Pharmacotherapies in geriatric chronic pain management. Clin Geriatr Med 2016;32(04): 705–724
7 George J, Byth K, Farrell GC. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. Biochem Pharmacol 1995;50(05):727–730
8 Krishnaswamy K. Drug metabolism and pharmacokinetics in malnutrition. Clin Pharmacokinet 1978;3(03):216–240
9 Evans C. Malnutrition in the elderly: a multifactorial failure to thrive. Perm J 2005;9(03):38–41

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10 de Oliveira JC, de Moura EG, Miranda RA, et al. Low-protein diet in puberty impairs testosterone output and energy metabolism in male rats. J Endocrinol 2018;237(03):243–254
11 Pingili RB, Pawar AK, Challa SR. Systemic exposure of paracetamol (acetaminophen) was enhanced by quercetin and chrysin co-administration in Wistar rats and in vitro model: risk of liver toxicity. Drug Dev Ind Pharm 2015;41(11):1793–1800
12 Liao Q, Xie Z, Pan B, et al. LC-MS-MS simultaneous determination of paracetamol, pseudoephedrine, and chlorpheniramine in human plasma: application to a pharmacokinetic study. Chromatographia 2008;67:687–694
13 Waterlow JC, Garlick PJ. Metabolic Adaptations to Protein Deficiency. In: Rothschild MA, Oratz M, Schreiber SS. , eds. Alcohol and Abnormal Protein Biosynthesis. New York: Pergamon Press; 1975:67–94
14 Freiman I, Pettifor JM, Moodley GM. Serum phosphorus in protein energy malnutrition. J Pediatr Gastroenterol Nutr 1982;1(04): 547–550
15 Lee JH, Suh OK, Lee MG. Pharmacokinetic changes in drugs during protein-calorie malnutrition: correlation between drug metabolism and hepatic microsomal cytochrome P450 isozymes. Arch Pharm Res 2004;27(07):693–712
16 Bidlack WR, Brown RC, Mohan C. Nutritional parameters that alter hepatic drug metabolism, conjugation, and toxicity. Fed Proc 1986;45(02):142–148
17 Kim YG, Kim SK, Kwon JW, et al. Effects of cysteine on amino acid concentrations and transsulfuration enzyme activities in rat liver with protein-calorie malnutrition. Life Sci 2003;72(10):1171–1181
18 Rodríguez-Fragoso L, Martínez-Arismendi JL, Orozco-Bustos D, Reyes-Esparza J, Torres E, Burchiel SW. Potential risks resulting from fruit/vegetable-drug interactions: effects on drug-metabolizing enzymes and drug transporters. J Food Sci 2011;76(04): R112–R124
19 Raiten DJ. Nutrition and pharmacology: general principles and implications for HIV. Am J Clin Nutr 2011;94(06):1697S–1702S
20 Da Costa NM, Visoni SB, Dos Santos IL, Barja-Fidalgo TC, Ribeiro-Pinto LF. Maternal protein restriction during lactation modulated the expression and activity of rat offspring hepatic CYP1A1, CYP1A2, CYP2B1, CYP2B2, and CYP2E1 during development. Braz J Med Biol Res 2016;49(11):e5238
21 Varsha A, Badanthdka M, Madhura RJ, Dsouza V, Kumar M, Shetty V. Longitudinal evaluation of developmental protein malnutrition resembling marasmic-kwashiorkor condition in wistar rats. Turk J Pharm Sci 2024

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