

## EFFECT OF LICORICE AND GRAPEFRUIT JUICE ON PARACETAMOL PHARMACOKINETICS IN HUMAN SALIVA

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### ABSTRACT

The effect of grapefruit juice and licorice juice on salivary pharmacokinetics of paracetamol (acetaminophen, APAP) in 8 healthy subjects (4 males and 4 females) was investigated. Paracetamol tablet (500 mg) was administered to the volunteers with either 240 mL grapefruit juice, licorice juice or water followed by saliva samples collection at different time intervals in a sequential study design with washout period of 3 days. Results have shown unexpected significant decrease in salivary  $C_{max}$  and AUC of paracetamol due to grapefruit consumption with delay in  $T_{max}$  ( $p < 0.05$ ), while licorice consumption did not produce any significant changes in all tested parameters. However, a notable increase in the  $C_{max}$  and AUC in females receiving licorice juice, but not in males, was revealed when compared to female control group. Therefore, in order to remove the confounding results of gender effect, the pharmacokinetic parameters of paracetamol following ingestion of grapefruit and licorice juice were analyzed for each sex separately and showed no differences within each gender when compared to the water control group. In addition, smoking had shown essentially no effect on paracetamol pharmacokinetics except a shift in  $T_{max}$  when licorice juice was consumed. In conclusion, consuming grapefruit juice and licorice juice along with paracetamol could cause differences in the salivary pharmacokinetics of paracetamol and should be avoided until further clinical studies establish the safety of such interactions in both males and females.

**Keywords:** Paracetamol; Pharmacokinetic; Grapefruit; Licorice; Metabolism; Saliva; Human, Drug-food interactions.

### INTRODUCTION

Some dietary substances, particularly fruit juices, have been shown to inhibit biochemical processes in the intestine, leading to altered pharmacokinetic and pharmacodynamic outcomes. Cytochrome P450 (CYP450) enzymes constitute the major catalysts of phase I drug biotransformation<sup>1</sup>. The CYP3A subfamily is the most abundantly expressed in the intestine, representing, on average, approximately 80% of total immunoquantified CYP450 protein<sup>2</sup>. Inhibition of intestinal CYP3A mediated metabolism is the major mechanism by which fruit juices enhances systemic exposure of many drugs<sup>3</sup>. Amongst the most consumed juices especially by the elderly people are grapefruit juice and licorice juice. Elderly patients are particularly at risk because more than 30% of all the prescription drugs are taken by this population. Failure to identify and properly manage drug interactions can lead to serious consequences<sup>4</sup>.

The grapefruit (*Citrus paradisi*), particularly as juice, is one of the most extensively studied dietary substances shown to interact with an array of medications<sup>5</sup>. It is believed that class of compounds namely; furanocoumarins was established as a major mediator of the grapefruit effect in human subjects<sup>6</sup>. It has been reported that grapefruit juice can enhance systemic exposure of some drugs by inhibiting CYP3A-mediated presystemic (first-pass) metabolism in the intestine<sup>7</sup>. However, other minimally metabolized substrates, including the antihistamine fexofenadine and some  $\beta$ -blockers showed contradictory results when significant decreases in the amounts of these drugs in human blood were detected when grapefruit was consumed concomitantly<sup>8,9</sup>.

The licorice plant (*Glycyrrhiza glabra*), on the other hand, has long been used in both Eastern and Western cultures. Glycyrrhizin is the major triterpenoid saponin in licorice root, and glycyrrhetic acid is its predominant metabolite and a pharmacologically active form of glycyrrhizin<sup>10</sup>. Several studies suggest the likelihood of an interaction between licorice root components and CYP3A-metabolised drugs and indicate that licorice root should be used with caution when taken concomitantly with other drugs that interact with CYP3A<sup>10-12</sup>.

Salivary excretion of some drugs has been reported previously as a good indicator for drug bioavailability, therapeutic drug monitoring, pharmacokinetics and also drug abuse. Furthermore, saliva sampling offers simple, non-invasive and cheap method as

compared with plasma sampling with no contamination risk<sup>13,14</sup>. Paracetamol (acetaminophen, APAP) is a widely used over the counter medication. Nonetheless, by causing acute liver injury, paracetamol toxicity is one of the most common causes of poisoning worldwide<sup>15</sup>. Although paracetamol is extensively reported to be well absorbed throughout small intestine in human and most animals and mainly metabolized in the liver<sup>16</sup>, its presystemic intestinal metabolism is not fully revealed, and therefore, this accounts as another factor for choosing paracetamol as a drug model in the current study.

The objective of this pilot study is to investigate the effect of grapefruit juice and licorice juices consumption on the salivary pharmacokinetics of paracetamol in humans. According to our knowledge, such drug interactions have not been reported previously in humans.

### MATERIALS AND METHODS

#### Drugs and Chemicals:

Paracetamol (Panadol® 500 mg tablets, batch number: 090308 C, GSK, UK) was purchased from a local drug store. Paracetamol and cefadroxil raw materials were purchased from Merck Chemicals, Germany. Potassium dihydrogen phosphate, perchloric acid, 85% phosphoric acid, triacetone nitrile and methanol were obtained from Acros Organics, USA. All the chemicals used were of HPLC grade. Analyte-free saliva used for the preparation of calibration standards and quality control samples were obtained from volunteers and screened for interfering peaks prior to use.

#### Licorice and Grapefruit Juice Preparation:

The traditional way in preparing licorice drink was followed in this study. Initially, 300 g of pulverized ground licorice root obtained from a local herb shop was soaked in 150 mL clean water for 1 hour. The wet licorice paste was then wrapped in a clean white cloth without being squeezed and tied on a drinking water tap. Finally, four liters of cold water were allowed to drizzle over the tied licorice cushion in a period of 2 hours. The prepared licorice juice was stored at 4 °C and consumed within 48 hours.

Grapefruit juice, on the other hand, was freshly hand squeezed at the day of experimentation without any further treatment or additives and kept refrigerated at 4 °C until used.

### Study Population

Eight healthy volunteers enrolled in this study (4 males and 4 females). All volunteers gave written informed consent before random assignment to treatments. On admission, a full drug history, blood pressure, body temperature, body mass index (BMI) and coffee and tobacco consumption were recorded for all volunteers (Table 1).

Volunteers were also trained on the method of saliva collection before starting the study. This study was performed according to all national laws and regulations governing the conduct of Clinical Trials. The study protocol was revised by the Independent Review Board (IRB) of the Jordanian Pharmaceutical Research Center (JPRC, Amman, Jordan). It conformed to the revised declaration of Helsinki, and to Good Clinical Practice.

**Table 1: Demographics of the participated human volunteers**

Code name	A- Female	B- Female	C- Female	D- Female	E- Male	F- Male	G- Male	H- Male
Height (cm)	1.67	1.54	1.66	1.65	1.68	1.78	1.62	1.67
Weight (kg)	50	44	47	59	90	64	65	60
Body Mass Index (BMI)	17.9	18.6	17.1	21.7	31.9	20.2	24.8	21.5
Temperature (°C)	37.5	37	37.1	36.7	36.9	36.9	37.3	37
Pulse (bpm)	88	66	72	70	70	80	68	74
Blood pressure (mmHg)	110/65	100/70	120/80	110/70	110/70	115/75	120/80	120/80
Smoking (cig./day)	No	No	No	No	No	No	20	10
Cups of coffee/day	1	1	1	1	1	1	2	1

### Study Design and Saliva Sampling

The sequential study design was divided into three periods. Each period was separated by three days washout to allow complete elimination of paracetamol. Volunteers were fasted 10 hours before paracetamol administration in each period. In the first period, all volunteers were administered one tablet containing 500 mg paracetamol with 240 mL drinking water. In the second period, the paracetamol tablet was ingested with 240 mL of licorice juice. In the third period, paracetamol was ingested with 240 mL of grapefruit juice.

In all tested periods, saliva samples (1.0 to 1.5 mL) were collected in labeled plastic tubes before paracetamol administration and after 0.16, 0.33, 0.50, 0.66, 1.0, 1.25, 1.50, 2.0, 2.5, 3.0, 4.0 hours post administration. The collected saliva samples were stored immediately in a freezer at -20 °C until analysis.

### Saliva Samples Analysis

#### Chromatographic Conditions

Saliva samples were analyzed using a Merck-Hitachi high performance liquid chromatography (HPLC) system (Merck-Hitachi, Japan) consisted of L-7100 LaChrom pump, L-7400 Lachrom UV detector set at wavelength of 245 nm, an L-7200 Lachrom autosampler and a D-7000 Interface.

A mobile phase consisting of water/acetonitrile/triethylamine (91:9:1, v/v) adjusted to pH 2.75 with phosphoric acid was circulated through a Hypersil BDS C18 analytical column (Thermo Scientific, USA) with dimensions of 150 × 4.6 mm and a particle size of 5 µm at a flow rate of 1 mL/min. Typical retention times were 3.20 and 3.70 min for paracetamol and the internal standard cefadroxil, respectively.

#### Preparation of Standard and Quality Control Samples

A stock solution of paracetamol was prepared by dissolving 50 mg of paracetamol raw material in 50 mL of distilled water (1000 µg/mL). Then, appropriate dilutions in freshly collected drug-free saliva were prepared to construct calibration standards containing paracetamol concentrations of 0.25, 1.0, 3.0, 5.0, 10.0 and 20.0 µg/mL. Three quality control samples containing paracetamol were prepared in the same manner at concentrations of 0.75, 8.0 and 16.0 µg/mL.

#### Preparation of Test Samples

Saliva samples were collected in labeled plain tubes and frozen at -20 °C until analyzed. Saliva samples were thawed at room temperature and 200 µL of 5 % perchloric acid containing 50 µg/mL cefadroxil (internal standard) was added to 100 µL of each saliva sample to precipitate salivary proteins. The samples were vortexed for and centrifuged at 1800 g for 5 min. The supernatant was transferred to the HPLC system by injecting 20 µL of each sample into the column.

### Validation of the Saliva Assay

Each analytical run consisted of the six calibration standards, duplicate quality control samples at each of the three levels, a drug-free saliva sample and test samples. Standards and quality control samples were randomly positioned throughout each analytical run.

#### Data Analysis

Pharmacokinetic parameters for the measured salivary paracetamol concentrations were calculated by non-compartmental analysis (NCA) using Kinetica TM 2000 software. The pharmacokinetics were characterized by maximum concentration in plasma ( $C_{max}$ ), time to maximum plasma concentration ( $T_{max}$ ) and AUC between time zero and 4 hours after dosing ( $AUC_{0-4}$ ) and presented as Mean (CV%). Plasma paracetamol profiles are expressed as Mean ± SEM. Results were analyzed by a two-tailed Student's *t*-test. The acceptable level of significance was established at  $p < 0.05$ .

### RESULTS AND DISCUSSION

It is well documented that CYP450 isoenzymes are key enzymes in food-drug interactions<sup>17</sup>. For example, CYP3A4-related interaction by food components may be related to the high level of expression of CYP3A4 in the small intestine, as well as its broad substrate specificity, as CYP3A4 is responsible for the metabolism of more than 50% of clinical pharmaceuticals<sup>18</sup>. Therefore, most food-drug interaction studies suggested the requirement of dosage adjustment to maintain drug concentrations within their therapeutic windows.

Recently, several studies have reported the effect of consuming grapefruit juice and licorice juice on metabolism of many drugs catalyzed by liver oxidative enzymes including CYP450 isoenzymes<sup>19,20</sup>. Since most of published studies used the oral route of administration, it is expected that such drug interactions was caused by either inhibition of intestinal pre-systemic drug first-pass (Phase I) metabolism or by inhibition of the apical efflux/uptake processes in the intestine that can alter the pharmacokinetic of drugs<sup>3,21</sup>.

The metabolic pathway of paracetamol has been identified in human; however, some differences were reported when compared to other species<sup>22,23</sup>. Generally, a therapeutic dose of paracetamol in human is metabolized in the liver by conjugation with glucuronic acid and sulfate while a small fraction of paracetamol is metabolized by CYP450 oxidation to produce a toxic reactive metabolite namely; N-acetyl-p-benzoquinone imine (NAPQI) which detoxified by conjugation with glutathione<sup>24</sup>. Although previous studies explored the drug-food interaction between paracetamol and grapefruit juice and licorice juice, clinical studies of such interactions is still lacking.

The current pilot clinical study utilized a validated human saliva sampling and analysis protocols for determining changes in paracetamol pharmacokinetic parameters following grapefruit juice and licorice juice administrations. Mean salivary paracetamol concentrations calculated for all volunteers are presented in Fig 1.

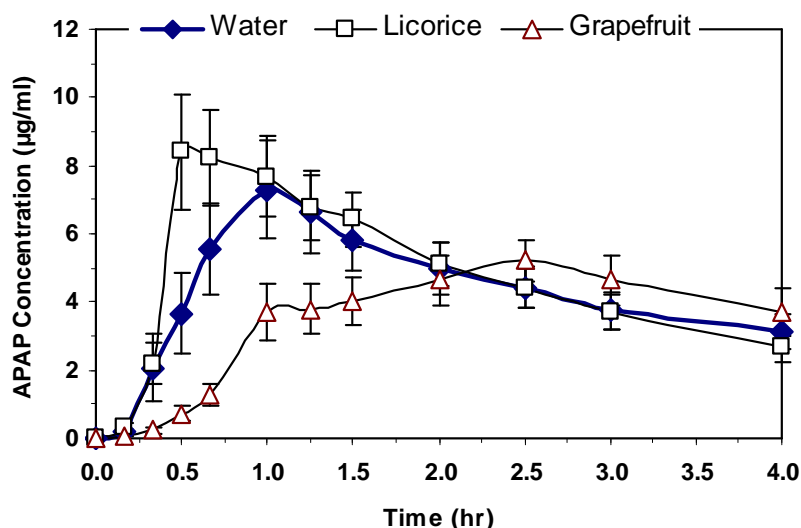


Fig. 1: Paracetamol saliva concentration vs. time following oral administration of a single 500 mg dose of paracetamol consumed either with water, licorice juice or grapefruit juice by both males and females ( $n = 8$ ). Each data point represents Mean  $\pm$  SEM.

The pharmacokinetic analysis of these profiles indicates a statistical decrease in salivary  $C_{max}$  and AUC of paracetamol due to grapefruit consumption with delay in  $T_{max}$  ( $p < 0.05$ ). However, licorice juice consumption prior to paracetamol administration showed no statistically

significant effects on paracetamol pharmacokinetics (Table 2). Our results on licorice are inline with what was previously reported, although in vitro, that presence of licorice with conventional medicines showed only a weak interaction potential with drug metabolizing enzymes<sup>25</sup>.

Table 2: Pharmacokinetic parameters of paracetamol in human saliva following oral administration of a single 500 mg dose of paracetamol consumed either with water, licorice juice or grapefruit juice by both males and females ( $n = 8$ ). Each data point represents Mean (CV%). \*  $p < 0.05$ .

	Water	Licorice	Grapefruit
$C_{max}$ ( $\mu\text{g/ml}$ )	8.12 (38)	9.67 (39)	*6.17 (21)
$T_{max}$ (hr)	1.38 (49)	0.85 (50)	*2.06 (37)
$AUC_{0-4}$ ( $\mu\text{g/ml*hr}$ )	17.42 (42)	19.11(34)	*14.29 (30)

Conversely, and through reviewing the literature, it was expected that grapefruit would increase the salivary concentrations of paracetamol by inhibiting its intestinal metabolism, however, the pharmacokinetic outcomes in the current study showed reduction in the systemic exposure of paracetamol. These outcomes suggest that inhibition of the active uptake of paracetamol might have occurred due to the presence of grapefruit. A similar conclusion was previously reported when a clinical study investigated the interactions between pomelo juice, which is botanically close to grapefruit, and sildenafil. While increase in the systemic exposure of sildenafil was expected due to the presence

of furanocoumarins in the juice, a decrease in the mean AUC and  $C_{max}$  of sildenafil were obtained. The authors speculated that the underlying mechanism of such interactions was either related to a physicochemical interaction between sildenafil and the components of the juice or through inhibition of an intestinal uptake process<sup>26</sup>.

Although an increase in  $C_{max}$  was observed in the current study following licorice juice administration compared to the control group (water administered group), it was found that this increase was influenced by the gender; mainly due to females (Fig 2 and 3).

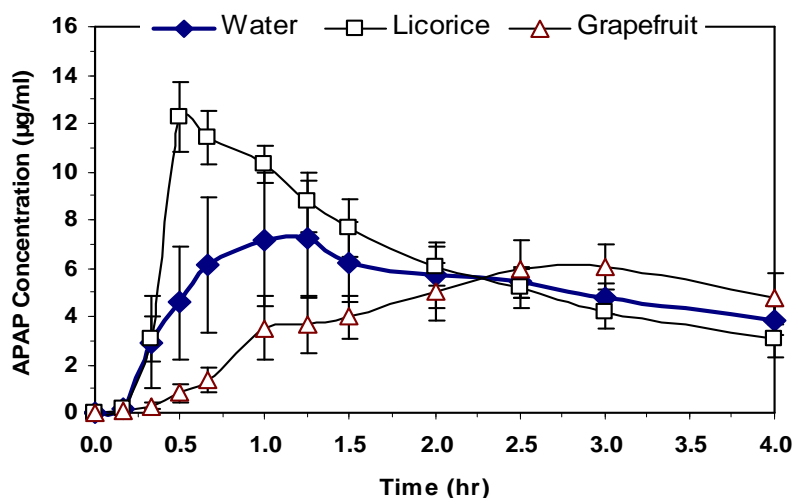


Fig. 2: Paracetamol saliva concentration vs. time following oral administration of a single 500 mg dose of paracetamol consumed either with water, licorice juice or grapefruit juice by females ( $n = 4$ ). Each data point represents Mean  $\pm$  SEM.

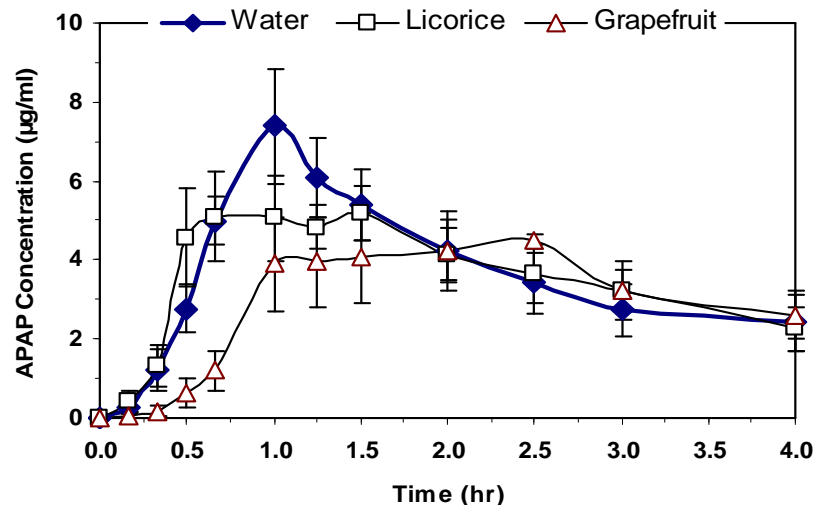


Fig. 3: Paracetamol saliva concentration vs. time following oral administration of a single 500 mg dose of paracetamol consumed either with water, licorice juice or grapefruit juice by males ( $n = 4$ ). Each data point represents Mean  $\pm$  SEM.

By comparing paracetamol pharmacokinetic outcomes in males versus females, the gender difference affected significantly ( $p < 0.05$ ) the  $C_{max}$  and the AUC in the case of licorice consumption (Table 3). Such differences might be attributed to differences in CYP450 expressions between male and females<sup>27</sup>. For example, CYP3A4 was found to be more expressed in females than in males<sup>28</sup>. On the other hand, when

analyzing the pharmacokinetic parameters of paracetamol presented in Table 4 in each sex separately, none significant differences in all parameters compared to control were observed in both licorice and grapefruit treated groups ( $p > 0.05$ ). These results made the effect of gender on the pharmacokinetics of paracetamol also questionable with grapefruit consumption.

Table 3: The effect of gender (males vs. females) on the statistical significance of the calculated pharmacokinetic parameters of paracetamol when consumed with different dosing media. Data are expressed as  $p$  values. \*  $p < 0.05$ , \*\*  $p < 0.01$ .

	Water	Licorice	Grapefruit
$C_{max}$ ( $\mu\text{g/ml}$ )	0.57	**0.002	*0.046
$T_{max}$ (hr)	0.217	0.247	0.537
$AUC_{0-4}$ ( $\mu\text{g/ml*hr}$ )	0.38	*0.027	0.246

Table 4: Pharmacokinetic parameters of paracetamol in human saliva following oral administration of a single 500 mg dose of paracetamol consumed with licorice juice or grapefruit juice. The parameters were calculated for each gender alone and compared to control group. Each data point represents Mean (CV%). None significant differences were seen in all comparisons with  $p$  values  $> 0.05$ .

	Females		Males	
	Licorice	Grapefruit	Licorice	Grapefruit
$C_{max}$ ( $\mu\text{g/ml}$ )	12.82 (17.2)	7.06 (16.5)	6.51 (20.9)	5.29 (15.9)
$T_{max}$ (hr)	0.67 (35.5)	2.25 (38.5)	1.04 (51.5)	1.88 (40)
$AUC_{0-4}$ ( $\mu\text{g/ml*hr}$ )	23.8 (23.5)	16.4 (27.4)	14.41 (23.6)	12.2 (30.1)

In addition, smoking had shown no statistical differences as shown in Table 5, except a significant increase in  $T_{max}$  in the licorice administered group ( $p < 0.01$ ). The effect of smoking on paracetamol has been variable, depending on the extent of smoking, and does not appear to be of clinical significance<sup>29</sup>. However, it was found that smoking tobacco was an independent risk factor of severe

hepatotoxicity, acute liver failure and death following paracetamol overdose that could be related to the presence of a number of substances that are potent inducers of CYP450<sup>30</sup>. Since prolonged use of licorice has been reported to induce CYP450 related metabolism<sup>11</sup>, adding the effects of smoking could explain the shift in  $T_{max}$  values of smokers in the current study.

Table 5: The effect of smoking on the statistical significance of the calculated pharmacokinetic parameters of paracetamol when consumed with different dosing media. Data are expressed as  $p$  values. \*\*  $p < 0.01$

	Water	Licorice	Grapefruit
$C_{max}$ ( $\mu\text{g/ml}$ )	0.768	0.192	0.933
$T_{max}$ (hr)	0.423	**0.007	0.808
$AUC_{0-4}$ ( $\mu\text{g/ml*hr}$ )	0.387	0.61	0.461

## CONCLUSIONS

There are many reports of herb-drug interactions that could alter the normal metabolism of drugs leading to serious clinical consequences<sup>31</sup>. Consuming grapefruit juice and licorice juice along with paracetamol could cause differences in the salivary pharmacokinetics of paracetamol and should be avoided until further clinical studies establish the safety of such interactions. The presented results indicate that paracetamol pharmacokinetics was affected by the tested gender

when consumed with licorice and grapefruit. Future studies are expected to aim for higher sample size, increasing sampling time, correlating plasma with salivary pharmacokinetics of paracetamol while focusing more on gender and smoking effects on paracetamol interactions with grapefruit juice and licorice juice.

## Conflict of Interest

The authors declare no conflict of interest.

## REFERENCES

- Lin JH, Lu AY. Interindividual variability in inhibition and induction of cytochrome p450 enzymes. *Annu Rev Pharmacol Toxicol* 2001; 41: 535-567.
- Paine MF, Hart HL, Ludington SS, Haining RL, Rettie AE, Zeldin DC. The human intestinal cytochrome p450 "Pie". *Drug Metab Dispos* 2006; 34: 880-886.
- Won CS, Oberlies NH, Paine MF. Influence of dietary substances on intestinal drug metabolism and transport. *Curr Drug Metab* 2010; 11: 778-792.
- Genser D. Food and drug interaction: Consequences for the nutrition/health status. *Ann Nutr Metab* 2008; 52 Suppl 1: 29-32.
- Gertz M, Davis JD, Harrison A, Houston JB, Galetin A. Grapefruit juice-drug interaction studies as a method to assess the extent of intestinal availability: Utility and limitations. *Curr Drug Metab* 2008; 9: 785-795.
- Paine MF, Widmer WW, Hart HL, Pusek SN, Beavers KL, Criss AB et al. A furanocoumarin-free grapefruit juice establishes furanocoumarins as the mediators of the grapefruit juice-felodipine interaction. *Am J Clin Nutr* 2006; 83: 1097-1105.
- Huang SM, Lesko LJ. Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions: What have we learned? *J Clin Pharmacol* 2004; 44: 559-569.
- Dresser GK, Bailey DG, Leake BF, Schwarz UI, Dawson PA, Freeman DJ et al. Fruit juices inhibit organic anion transporting polypeptide-mediated drug uptake to decrease the oral availability of fexofenadine. *Clin Pharmacol Ther* 2002; 71: 11-20.
- Schwarz UI, Seemann D, Oertel R, Miehlik S, Kuhlisch E, Fromm MF et al. Grapefruit juice ingestion significantly reduces talinolol bioavailability. *Clin Pharmacol Ther* 2005; 77: 291-301.
- Li HY, Xu W, Su J, Zhang X, Hu LW, Zhang WD. In vitro and in vivo inhibitory effects of glycyrrhetic acid on cytochrome p450 3a activity. *Pharmacology* 2010; 86: 287-292.
- Paolini M, Pozzetti L, Sapone A, Cantelli-Forti G. Effect of licorice and glycyrrhizin on murine liver cyp-dependent monooxygenases. *Life Sci* 1998; 62: 571-582.
- Al-Deeb ID, Arafat TA, Irshaid YM. The effect of licorice drink on the systemic exposure of verapamil in rabbits. *Drug Metab Lett* 2010; 4: 173-179.
- Navarro M, Pichini S, Farre M, Ortuno J, Roset PN, Segura J et al. Usefulness of saliva for measurement of 3,4-methylenedioxymethamphetamine and its metabolites: Correlation with plasma drug concentrations and effect of salivary pH. *Clin Chem* 2001; 47: 1788-1795.
- Soderstrom JH, Fatovich DM, Mandelt C, Vasikaran S, McCoubrie DL, Daly FF et al. Correlation of paired toxic plasma and saliva paracetamol concentrations following deliberate self-poisoning with paracetamol. *Br J Clin Pharmacol* 2011, doi: 10.1111/j.1365-2125.2011.04157.x. [Epub ahead of print]
- Sabate M, Ibanez L, Perez E, Vidal X, Buti M, Xiol X et al. Paracetamol in therapeutic dosages and acute liver injury: Causality assessment in a prospective case series. *BMC Gastroenterol* 2011; 11: 80.
- Ward B, Alexander-Williams JM. Paracetamol revisited: A review of the pharmacokinetics and pharmacodynamics. *Acute Pain* 1999; 2: 139-149.
- Rodriguez-Fragoso L, Martinez-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: R112-R124.
- Fujita K. Food-drug interactions via human cytochrome p450 3a (cyp3a). *Drug Metabol Drug Interact*. 2004; 20: 195-217.
- Bailey DG, Malcolm J, Arnold O, Spence JD. Grapefruit juice-drug interactions. *Br J Clin Pharmacol* 1998; 46: 101-110.
- Ploeger B, Mensinga T, Sips A, Seinen W, Meulenbelt J, DeJongh J. The pharmacokinetics of glycyrrhizic acid evaluated by physiologically based pharmacokinetic modeling. *Drug Metab Rev* 2001; 33: 125-147.
- Dresser GK, Bailey DG. The effects of fruit juices on drug disposition: A new model for drug interactions. *Eur J Clin Invest* 2003; 33 Suppl 2: 10-16.
- Jennitz K, Veres Z, Monostory K, Kobori L, Vereczkey L. Interspecies differences in acetaminophen sensitivity of human, rat, and mouse primary hepatocytes. *Toxicol In Vitro* 2008; 22: 961-967.
- Pal A, Banerjee B, Banerjee T, Masih M, Pal K. Hepatoprotective activity of *chenopodium album linn.* plant against paracetamol induced hepatic injury in rats. *Int J Pharm Pharm Sci* 2011; 3 suppl 3: 55-57.
- Kaushal R, Dave KR, Katyare SS. Paracetamol hepatotoxicity and microsomal function. *Environ Toxicol Pharmacol* 1999; 7: 67-74.
- Pandit S, Ponnusankar S, Bandyopadhyay A, Ota S, Mukherjee PK. Exploring the possible metabolism mediated interaction of glycyrrhiza glabra extract with cyp3a4 and cyp2d6. *Phytother Res* 2011; 25: 1429-1434.
- Al-Ghazawi MA, Tutunji MS, AbuRuz SM. The effects of pummelo juice on pharmacokinetics of sildenafil in healthy adult male Jordanian volunteers. *Eur J Clin Pharmacol* 2010; 66: 159-163.
- Marino M, Masella R, Bulzomi P, Campesi I, Malorni W, Franconi F. Nutrition and human health from a sex-gender perspective. *Mol Aspects Med* 2011; 32: 1-70.
- Franconi F, Brunelleschi S, Steardo L, Cuomo V. Gender differences in drug responses. *Pharmacol Res* 2007; 55: 81-95.
- Miller LG. Recent developments in the study of the effects of cigarette smoking on clinical pharmacokinetics and clinical pharmacodynamics. *Clin Pharmacokinet* 1989; 17: 90-108.
- Schmidt LE, Dalhoff K. The impact of current tobacco use on the outcome of paracetamol poisoning. *Aliment Pharmacol Ther* 2003; 18: 979-985.
- Purwantiningsih, Hussin AH, Chan KL. Phase I drug metabolism study of the standardised extract of *eurycoma longifolia* (taf273) in rat hepatocytes. *Int J Pharm Pharm Sci* 2010; 2 suppl 3: 147-152.