Flavoured water consumption alters pharmacokinetic parameters and increases exposure of erlotinib and gefitinib in a preclinical study using Wistar rats

Aliyah Almomen[1], Hadir M. Maher[2], Nourah Z. Alzoman[1], Shereen M. Shehata[1] and Amal Alsubaie[3]

[1] Department of Pharmaceutical Chemistry, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia
[2] Faculty of Pharmacy, Department of Pharmaceutical Analytical Chemistry, Alexandria University, Alexandria, Egypt
[3] Biological Products Evaluation Directorate, Saudi Food and Drug Authority, Riyadh, Saudi Arabia

Corresponding author
Aliyah Almomen,
alalmomen@ksu.edu.sa

ABSTRACT

Background. Erlotinib (ERL) and gefitinib (GEF) are considered first line therapy for the management of non-small cell lung carcinoma (NSCLC). Like other tyrosine kinase inhibitors (TKIs), ERL and GEF are mainly metabolized by the cytochrome P450 (CYP450) CYP3A4 isoform and are substrates for transporter proteins with marked inter-/intra-individual pharmacokinetic (PK) variability. Therefore, ERL and GEF are candidates for drug-drug and food-drug interactions with a consequent effect on drug exposure and/or drug-related toxicities. In recent years, the consumption of flavoured water (FW) has gained in popularity. Among multiple ingredients, fruit extracts, which might constitute bioactive flavonoids, can possess an inhibitory effect on the CYP450 enzymes or transporter proteins. Therefore, in this study we investigated the effects of different types of FW on the PK parameters of ERL and GEF in Wistar rats.

Methods. ERL and GEF PK parameters in different groups of rats after four weeks consumption of different flavours of FW, namely berry, peach, lime, and pineapple, were determined from plasma drug concentrations using ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS).

Results. Data indicated that tested FWs altered the PK parameters of both ERL and GEF differently. Lime water had the highest impact on most of ERL and GEF PK parameters, with a significant increase in C_{max} (95% for ERL, 58% for GEF), AUC_{0-48} (111% for ERL, 203% for GEF), and $AUC_{0-\infty}$ (200% for ERL, 203% for GEF), along with a significant decrease in the apparent oral clearance of both drugs (65% for ERL, 67% for GEF). The order by which FW affected the PK parameters for ERL and GEF was as follows: lime > pineapple > berry > peach.

Conclusion. The present study indicates that drinking FW could be of significance in rats receiving ERL or GEF. Our results indicate that the alteration in PKs was mostly recorded with lime, resulting in an enhanced bioavailability, and reduced apparent oral clearance of the drugs. Peach FW had a minimum effect on the PK parameters of ERL and no significant effect on GEF PKs. Accordingly, it might be of clinical importance

to evaluate the PK parameters of ERL and GEF in human subjects who consume FW while receiving therapy.

INTRODUCTION

Lung cancer is one of the leading causes of death among men and women worldwide, with the difficult to treat non-small cell lung carcinoma (NSCLC) accounting for up to 75% of lung cancer cases (*Torre, Siegel & Jemal, 2016*; *Bethune et al., 2010*). Since the discovery of the activating mutation in the epidermal growth factor receptors (EGFR) kinase domain in a subset of patients with NSCLC, accounting for 17% of cases in North America and Europe and 50% of cases in Asia, EGFR tyrosine kinase inhibitors (TKIs) were perceived as an attractive treatment intervention with a 65–90% response rate (*Brehmer et al., 2005*; *Ladanyi & Pao, 2008*). When compared to standard chemotherapeutic platinum-based treatments of advanced NSCLC, first generation TKIs, erlotinib (ERL) and gefitinib (GEF), showed superior response rates and progression-free survival rates (*Sullivan & Planchard, 2016*).

ERL and GEF, so called adenosine triphosphate (ATP)-competitive EGFR TKIs, are orally administered TKIs that act by competing with ATP on the EGFR intracellular ATP binding pockets resulting in an inhibition of cell proliferation, angiogenesis, and metastatic potential (*Brehmer et al., 2005*; *Bronte et al., 2014*). After oral administration, ERL is rapidly absorbed from the gastrointestinal system with a time to reach maximum concentration (t_{max}) of 1.4 h in healthy subjects and a mean bioavailability (F) of 59% (*Scheffler et al., 2011*). In cancer patients, ERL's t_{max} and F are 3 h and 76%, respectively (*Scheffler et al., 2011*). On the other hand, GEF is moderately absorbed after oral administration with t_{max} of 3 h and median F of 57% in healthy subjects (*Scheffler et al., 2011*). In cancer patients, however, GEF's t_{max} is about 7 h and median F is around 59% (*Scheffler et al., 2011*). ERL and GEF each undergo extensive tissue distribution with relatively long half-lives ($t_{1/2}$). The $t_{1/2}$ of ERL is about 24.4 h in healthy patients and up to 40.9 h in cancer patients, while GEF's $t_{1/2}$ is about 41 h in healthy patients and 48 h in cancer patients (*Scheffler et al., 2011*; *Lu et al., 2006*).

ERL and GEF are substrates of the ATP-binding cassette (ABC) transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion-transporting polypeptides (OATPs), particularly the OATP2B1 (*Scheffler et al., 2011*; *Johnston et al., 2014*; *Marchetti et al., 2008*; *Agarwal et al., 2010*; *Bauer et al., 2018*; *Chen et al., 2011*). Factors that affect the expression or action of these transporters can have PK implications on drugs that are substrates to these transporters (*Marchetti et al., 2008*). Transporter inhibitors were used as a strategy to overcome TKIs drug resistance where significant increase in drug exposure was found (*Marchetti et al., 2008*; *Beretta et al., 2017*). TKIs are mainly metabolized in the liver with reported PK variability, which

can be attributed to differences in profiles of the liver metabolizing enzymes, namely CYP450s (*Scheffler et al., 2011*; *Li et al., 2007*). It can, therefore, be inferred that factors altering CYP450 enzymes or ABC transporters such as disease states, drugs (drug-drug interactions), or food (food-drugs interactions), should be considered when prescribing TKIs.

Drug-food interactions can result from the interaction of drugs with some natural constituents such as alkaloids and flavonoids, as well as other artificial components which are present in daily consumed food and drinks (*Bansal et al., 2009*; *Li et al., 2016*; *Li, Revalde & Paxton, 2017*; *Abdallah et al., 2015*; *Kamenickova & Dvorak, 2012*). Alteration in CYP enzymes and ABC can consequently alter the PK parameters of their substrates, i.e., bioavailability, tissue penetration, biliary excretion with a possible occurrence of drug-related toxicities (*Bansal et al., 2009*; *Li et al., 2016*; *Li, Revalde & Paxton, 2017*; *Abdallah et al., 2015*). Fruits and vegetables are known to be rich sources of bioactive flavonoids which can have different inhibitory effects on CYP450 metabolizing enzymes such as CYP3A4 and transporter proteins including P-gp (*Bansal et al., 2009*; *Li et al., 2016*; *Li, Revalde & Paxton, 2017*; *Abdallah et al., 2015*). The inhibition of P-gp by flavonoids can be comparable to that by verapamil and cyclosporine, two very well-known P-gp inhibitors (*Bansal et al., 2009*). For example, flavonoids, such as quercetin, increases the maximum serum concertation (C_{max}) and prolong the $t_{1/2}$ of paclitaxel (*Choi, Jo & Kim, 2004*). In addition to quercetin, other flavonoids such as kaempferol was able to increase tamoxifen C_{max} in female rats and both C_{max} and F in male rats (*Piao, Shin & Choi, 2008*; *Shin, Choi & Li, 2006*).

A well-known drug-food or beverage interaction is found with the co-administration of ERL or GEF and grapefruit, among other fruits (*Mouly et al., 2017*). Grapefruit, pomegranate, star fruit, and Seville oranges are known CYP450 inhibitors (*Mouly et al., 2017*; *Molden & Spigset, 2007*; *Hidaka et al., 2004*). They are inhibitors of the enzyme CYP3A4, a main ERL and GEF metabolizing enzyme (*Li et al., 2007*; *Mouly et al., 2017*; *Molden & Spigset, 2007*; *Hidaka et al., 2004*). It is thought that this action is mediated through a spiro-ortho-ester component, BAS 100, which is a potent CYP34A inhibitor (*Molden & Spigset, 2007*; *Hidaka et al., 2004*; *Smith et al., 2008*). Other juices such as orange, grapefruit, and apples are known to inhibit the activity of the influx transporters expressed in enterocytes and hepatocytes (OATP 1A2, 1B1, and 2B1), which can cause a drastic decrease in substrate drugs plasma levels (*Mouly et al., 2017*). Thus, it is advisable to stop consuming any of the above mentioned fruits or their products while on ERL or GEF therapy (*Li et al., 2007*; *Collado-Borrell et al., 2016*). Similar food/beverage drug interaction were reported with the coadministration of green tea and ERL, as well as the Chinese medicinal plant (*Marsdenia tenacissima*) and GEF (*Han et al., 2014*; *Maher et al., 2017*).

Flavoured bottled water (FW), carbonated (sparkling) and still, are gaining popularity among consumers in recent years (*Lorenc et al., 2019*; *Bilek et al., 2014*; *Brown et al., 2007*). It was reported that retail sales of FW have increased by 72% in 2018 (*Purdy, 2019*). FW is water mixed with natural or artificial flavouring agents (*Bilek et al., 2014*; *Brown et al., 2007*). In conjunction with flavouring agents, still FW can contain sweetening agents like aspartame, antioxidant agents like ascorbic acid, acidifying agents like citric acid,
and preservatives like sodium benzoate (*Bilek et al., 2014*). Compared to still FW, carbon dioxide and sodium bicarbonate are extra components found in carbonated FW (*Bilek et al., 2014*; *Cuomo et al., 2009*). However, carbon dioxide is mainly lost in the air once the bottle of carbonated FW is opened and a very small amount reaches the stomach upon consumption (*Cuomo et al., 2009*). A study by *Kamenickova & Dvorak (2012)* indicated that FW can contain fruits or herbal extracts among other ingredients which may influence the transcriptional activity of CYP enzymes. Also, FW which contains lemon, green tea, ginseng, guava, or passion fruit components may cause the activation of CYP1A2, increasing the chances of food-drug interactions (*Kamenickova & Dvorak, 2012*).

Although some argue that extrapolating the results of experiments on animal's PK to that of human's PK is not always appropriate due to the differences in some CYP enzyme isoforms, *Matsubara et al. (2004)*, indicated that similarities between human and rat can exist, like the similarity found between human CYP3A4 and rat CYP3A62 isoform. Although the activity of multidrug resistance-associated protein (MRP) in rat hepatocytes showed higher activity than human hepatocytes, humans hepatocytes exhibited higher BCRP activity than rat hepatocytes (*Li et al., 2008*). However, no species difference in the activity P-gp was found between rat and human hepatocytes (*Li et al., 2008*).

Therefore, in this study we aimed to investigate preclinically the effect of different flavours of still FW on the PK parameters of ERL and GEF, in Wistar rat.

MATERIALS & METHODS

Experimental animals

Fifty healthy male Wistar rats weighing 250 ± 30 g were obtained from the animal house, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Rats were randomly divided into ten cages ($n = 5$). All individualized ventilated cages (IVC) type IV used in this study were of $20''L \times 11''W \times 9''$ in dimension capable of hosting 4–5 rats. Cages density, bedding, and sanitation frequency was similar in all cages. Cages were housed at room temperature (25 °C) and at an average relative humidity of 50%. Daily observation of all rats was required to ensure that all animals maintained good health. All animal experiments strictly followed the guidelines of the Ethical Committee for Performing Studies on Animals, King Saud University, Riyadh, Saudi Arabia, protocol number KSU-SE-19-13.

Study design

Four weeks before drug administration, cages were divided into five groups, two cages per group ($n = 10$), and rats had free access to commercial standard food and either water (group I, control group) or one of the FW (tested groups). Four types of FW, (Aquafina®, a product of Pepsi-Cola®, Saudi Industrial Projects Company, Jeddah, Saudi Arabia) with different flavours, specifically berry (group II), peach (group III), lime (group IV), and pineapple FW (group V) were used. Other components found in FW used in this study include water, preservatives (sodium phosphate, potassium sorbet, sodium benzoate), acidifiers (citric acid, maleic acid), sweeteners (aspartame, potassium acesulfame, allose), acidity regulator (sodium citrate), and antioxidant agent (calcium disodium EDTA). An estimation of the average amount of water and FW consumed by

rats in each treatment group is depicted in Table S1. The parallel design was used in this study to avoid animals' physiological changes that could occur in the cross-over design, possibly affecting PK profiles of drug substances. All animals involved in the study were deprived from food, but not water/FW, for at least 12 h before drug administration. Water and FW groups were then randomly subdivided ($n = 5$/each), where one cage of water or FW received one dose of ERL (20 mg/kg), and the other cage received GEF (20 mg/kg) suspended in 0.5% carboxymethyl cellulose through oral gavage; ERL and GEF were obtained from Pfizer Inc. (New York, USA). Drugs were administered to the rats between 7:00 am and 8:00 am. Rats were separately weighed from day one of water/FW consumption prior to drug administration for accurate dose calculation (Fig. S1). Blood samples (0.3 mL) were collected from each rat immediately prior to dosing (0 time) and at predetermined time points (0.5, 1, 2, 3, 5, 24, and 48 h) post drug administration. Blood samples were withdrawn and processed as described previously (*Maher et al., 2017*; *Maher, Alzoman & Shehata, 2016*; *Maher, Alzoman & Shehata, 2018*). Specifically, blood samples were withdrawn from the retro-orbital sinus into a series of heparinized tubes. Plasma was separated from collected blood samples by centrifugation at 4,500 rpm for 30 min where the centrifuge was maintained at 4 °C, and then stored at -20 °C until the day of analysis. Plasma samples were diluted as described previously, then ERL and GEF concentrations were determined from plasma samples using UPLC-MS/MS system, Waters Xevo TQ-S (Waters, Singapore), equipped with Acquity UPLC C 18 column (100 × 1.0 mm, 1.7 μm particle size) (Waters, Dublin, Ireland) (*Maher, Alzoman & Shehata, 2016*). A mixture of acetonitrile: water (80: 20, v/v), with 0.1% formic acid was used as a mobile phase at a flow rate of 0.2 mL/min (*Maher, Alzoman & Shehata, 2016*). Quantitative determination of ERL or GEF was conducted using a linear calibration curve between the range of 0.025-100 ng/mL with a correlation coefficient of 0.99. Quantitation of the analytes was performed using the multiple reaction monitoring (MRM) with positive ionization at m/z 447.25 > 128.08 (GEF), m/z 394.20 > 278.04 (ERL), and m/z 426.26 > 175.07 for the internal standard domperidone (DOM). The carry-over effect commonly encountered during the UPLC-MS/MS analysis, previously evaluated as an important validation parameter during method development and validation, did not exceed 15% for concentrations above lower limit of quantification (LLOQ) and 20% for concentrations at LLOQ level.

PK analysis

In all treated rats, ERL and GEF PK analyses were performed using non-compartmental analysis (NCA) with the aid of Excel 2010, PKSolver Add-In. C_{max} and t_{max} were obtained from the corresponding plasma concentration–time curve (Figs. 1A and 1B). Linear regression of the terminal phase of log-linear plasma concentration–time curve, using three points for ERL and four points for GEF (Figs. S2A and S2B), was used to estimate the terminal elimination rate constant (λ_z) and calculate $t_{1/2}$ from the formula, $t_{1/2} = 0.693/\lambda_z$. The area under the plasma concentration–time curve from time 0 to the last sampling time t, 48 h (AUC_{0-t}) was calculated using the trapezoidal rule. The apparent oral clearance (CL/F) was calculated as followed: CL/F = dose/$AUC_{0-\infty}$, where CL was drug clearance, F was drug bioavailability, dose was 20 mg/kg for ERL or GEF, and $AUC_{0-\infty}$ is the area
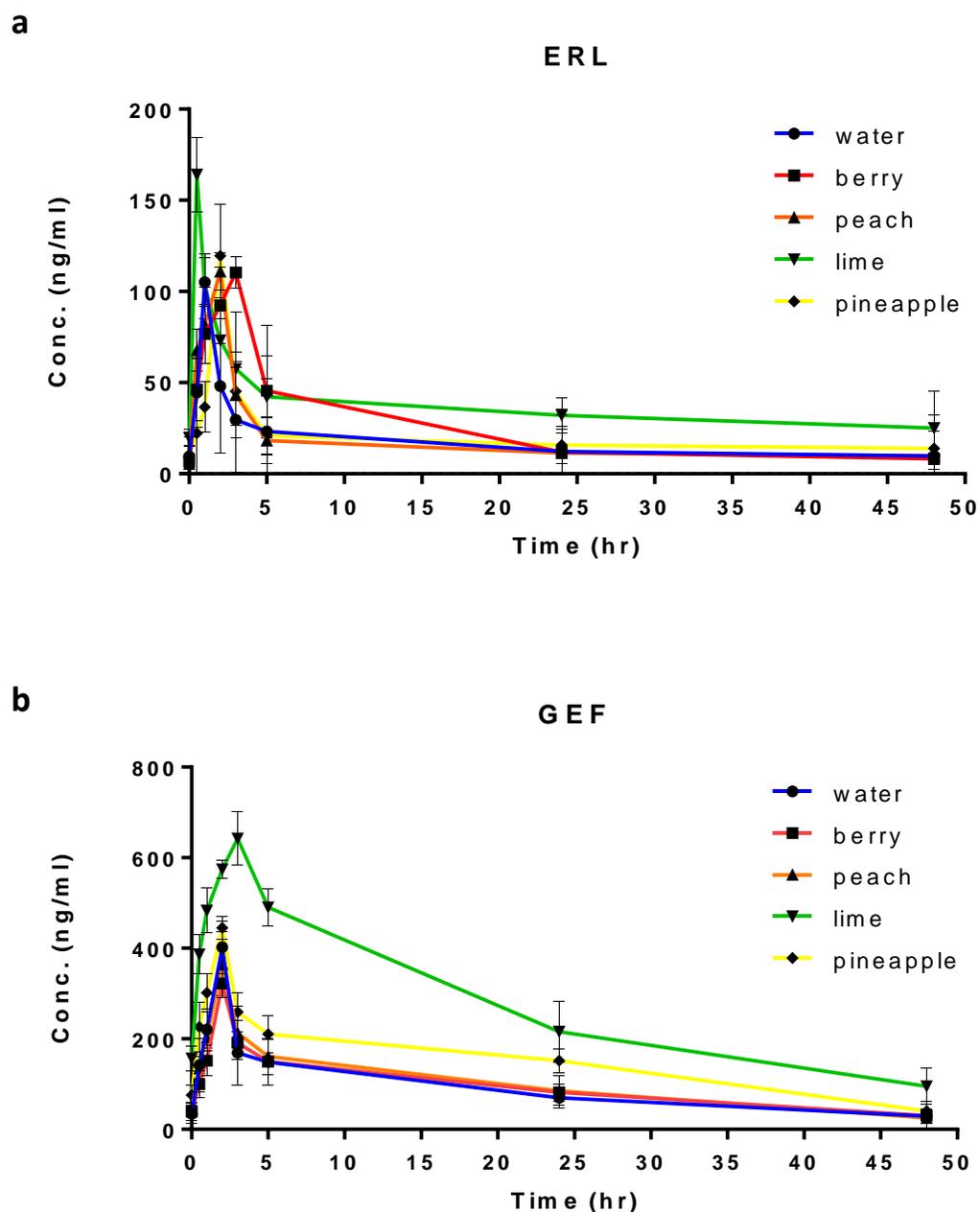
Figure 1 **Plasma concentration-time profile after oral administration of 20 mg/kg of ERL (A), or GEF (B) in rats, along with different types of FW ($n = 5$) per group.** Suitable dilutions of plasma samples were made before actual analysis.

under the plasma concentration–time curve from time 0 to ∞. $AUC_{0-\infty}$ was also derived by summing up AUC_{0-t} and the area obtained by extrapolation from time t to ∞. The latter area was calculated from the division of the last measured concentration (C_{last}) by λ_z. The ranking by which FW was considered to have the highest to the lowest impact

on ERL or GEF PK parameters is based on the number of PK parameters affected by the coadministration of FW with each drug.

Statistical analysis

Results were presented as mean $\pm$ SD. PK parameters of all treated groups following the consumption of FW were compared with control (rats having free access to water), using one-way ANOVA and Bonferroni's multiple comparisons test. Statistical significance was obtained with p-values ≤ 0.05.

RESULTS

Effect of FW on the PKs of ERL

Following four weeks of FW consumption, results show that lime FW was the only FW causing a significant increase in ERL's C_{max} (95% increase) (Fig. 2A). On the other hand, a significant increase in t_{max} was found with almost all tested FW, showing three times increase with berry FW and two times increase with peach and pineapple. The only decrease in t_{max} was found with lime FW, which was not statistically significant (Fig. 2B). Also, a significant change in $t_{1/2}$ with almost 49% decrease with berry, and about 41%, 65%, and 113.8% increase was noticed with peach, lime, and pineapple FW, respectively (Fig. 2C). While berry FW was only able to increase AUC_{0-48} by 42.35%, pineapple FW increased the $AUC_{0-\infty}$ by 86%. Lim FW, on the other hand, was able to increase both AUC_{0-48} and $AUC_{0-\infty}$, of about 111% and 200%, respectively (Figs. 2D and 2E). Regarding the apparent oral clearance, lime and pineapple FW caused a significant decrease of 65% and 30%, respectively (Fig. 2F). Results revealed that peach FW had no significant effect on other measured PK parameters including C_{max}, AUC_{0-48}, $AUC_{0-\infty}$, and CL/F. However, compared with other types of FW, lime FW had the most significant effect on ERL PK with the maximum increase in C_{max}, AUC_{0-48} and $AUC_{0-\infty}$, along with maximum decrease in ERL apparent clearance (Table S2).

Effect of FW on the PKs of GEF

Four weeks of FW consumption by animals followed by GEF administration resulted in a significant change in C_{max} relative to control. There was a 58% increase in C_{max} found with lime and an 18% decrease with berry FW (Fig. 3A). Moreover, there was an almost 50% significant increase in t_{max} with lime (Fig. 3B). None of the tested FW caused a significant change in $t_{1/2}$ (Fig. 3C). Two types of FW, lime and pineapple, had significantly affected GEF apparent bioavailability and increases in AUC_{0-48} and $AUC_{0-\infty}$ were recorded. Consequently, a significant reduction in CL/F occurred. As with ERL, the maximal effect on $AUC_{0-\infty}$ and was found with lime FW with almost 203% increase in both AUCs (Figs. 3D and 3E) followed by pineapple FW with almost 65% and 61% increase in AUC_{0-48} and $AUC_{0-\infty}$, respectively. Thus, a significant reduction of the apparent clearance of almost 67% and 40% of GEF was recorded with lime and pineapple FW, respectively (Fig. 3F). Table S3 summarizes the main PK parameters of GEF following the intake of FW.
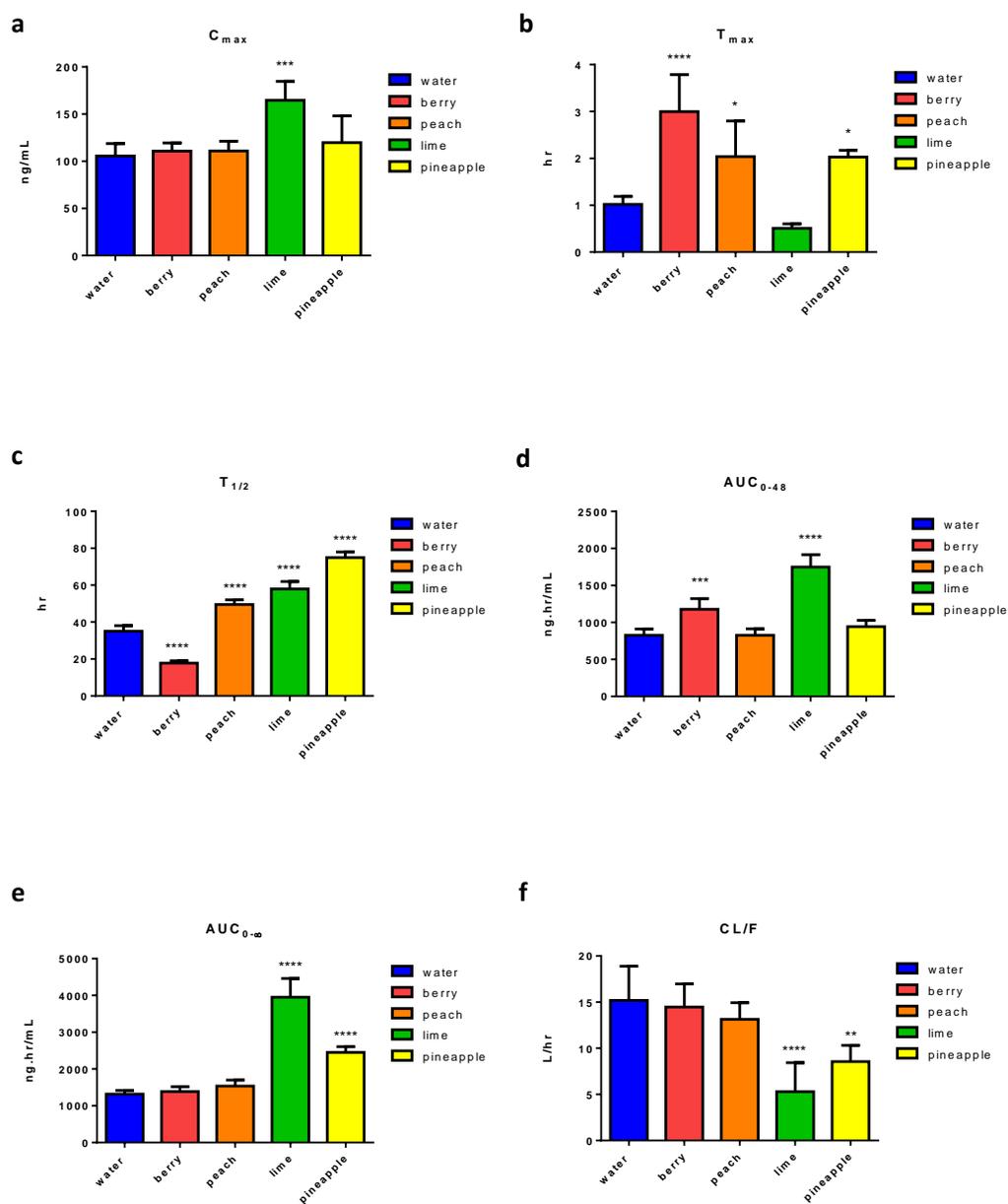
Figure 2 **Main pharmacokinetic parameters of ERL following four weeks administration of different types of FW in rats relative to control ($n = 5$) per group.** Statistical significance was obtained with p-values ≤ 0.05, where $*$ $P \leq 0.05$, $**$ $P \leq 0.01$, $***$ $P \leq 0.001$, and $****$ $P < 0.0001$.

DISCUSSION

In this study, we investigated the effect of different flavours of still FW on the PKs of ERL and GEF in male Wistar rats. Like other TKIs, ERL and GEF are susceptible to CYP3A4-mediated metabolism and are actively transported by transporters like P-gp, BCRP, OATPs (*Scheffler et al., 2011*; *Johnston et al., 2014*; *Marchetti et al., 2008*; *Agarwal et al., 2010*; *Bauer et al., 2018*; *Chen et al., 2011*). Thus, altering CYP enzymatic activity and/or
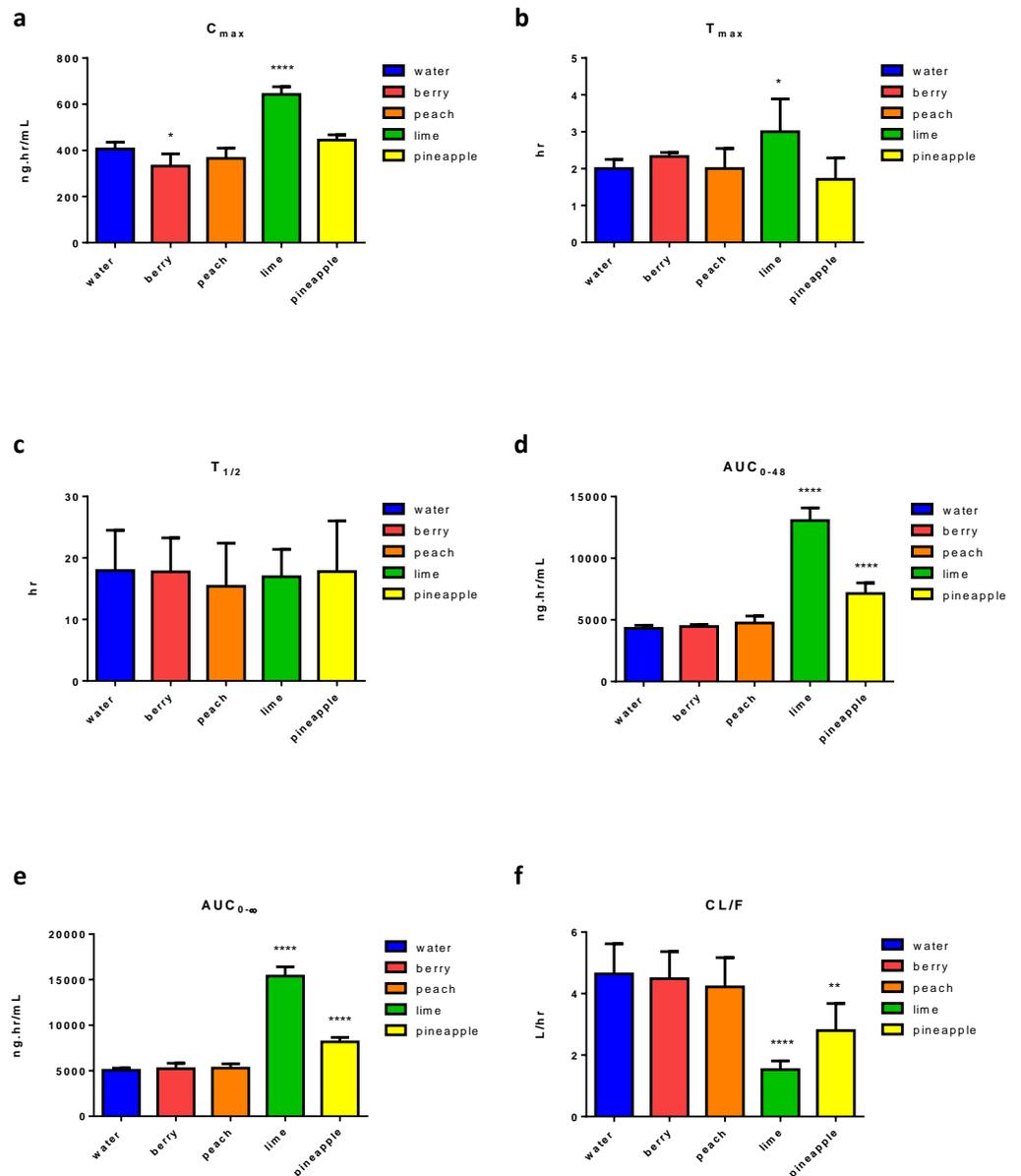
Figure 3 **Main pharmacokinetic parameters of GEF, following four weeks administration of different types of FW in rats relative to control ($n = 5$) per group.** Statistical significance was obtained with p-values ≤ 0.05, where * $P \leq 0.05$, ** $P \leq 0.01$, *** $P \leq 0.001$, and **** $P < 0.0001$.

protein transporters could significantly affect ERL or GEF exposure with consequent impact on therapeutic efficacy and/or drug-related toxicities.

A previous study suggests a possible gender specific differences in PK parameters between male and female rats knowing that CYP2C11, CYP2C13, and CYP3A2 are expressed in male rats whereas CYP2C12 is expressed in female rats, which can cause a difference in drug metabolism (*Czerniak, 2001*). Moreover, female rat oestrus cycle can have an effect

on liver metabolic enzyme, thus male rats were chosen in this study to eliminate any other possible variabilities that can effect ERL and GEF PKs (*Kulkarni et al., 2012*).

Tested FW altered most of ERL and GEF measured PK parameters, and the impact was in the following order: lime > pineapple > berry > peach for both ERL and GEF. Tables S2 and S3 revealed that peach FW had the least effect on ERL and no significant effect on GEF PKs. Berry FW significantly affected the exposure (AUC_{0-48}) of ERL, but no effect was found with GEF. Despite that both pineapple and lime FW had a significant effect on most ERL and GEF measured PK parameters, lime FW increased drug exposure (increased C_{max}, $AUC_{0-\infty}$) and decreased CL/F more extensively than pineapple FW.

A literature review indicated that the concomitant consumption of fruits/vegetables can influence the PK parameters of some drugs, and hence highlights the problem of drug-juice interactions (*Sasaki et al., 2017*; *Mallhi et al., 2015*). This influence can be mainly attributed to the potential inhibitory effect of juice components on CYP metabolizing enzymes, drug transporters including P-gp, and OATPs (*Sasaki et al., 2017*; *Mallhi et al., 2015*). It was reported previously that lime juice has a similar effect on drugs to grapefruit juice due to the similarly in the polyphenol and bergamottin contents which can act as inhibitors to the CYP3A4 and CYP2C9 enzymes (*Karmakar et al., 2015*; *Bailey, Dresser & Bend, 2003*; *Steuck, Hellhake & Schebb, 2016*; *Hanley et al., 2011*). CYP3A4 and P-gp, which is usually present in the GI system and the liver, have overlapping substrates as well as inhibitors inferring that P-gp might also be inhibited by grapefruit juice (*Bailey, 2010*). Accordingly, lime juice may have similar drug interactions to those reported with grapefruit, i.e., increase in the bioavailability of co-administered medications (*Dahan & Altman, 2004*; *Hollander et al., 1995*). In this respect, it is noteworthy to mention that the bioavailability of dasatinib's, a known TKI, usually increases following the ingestion of grapefruit juice (*Fleisher et al., 2015*). Thus, the lime FW-induced increase in the bioavailability of ERL/GEF could be attributed to the inhibition of CYP3A4-mediated metabolism and/or transporter proteins.

Pineapple juice also has an inhibitory effect on the activity of CYP2C9 enzyme due to its bromelain content (*Hidaka et al., 2008*). Some of the reported pineapple juice-drug interactions were found with diclofenac, warfarin, and tolbutamide, all of which are CYP2C9 substrates (*Hidaka et al., 2008*). Although pineapple has no reported modulatory effect on CYP3A4 enzymes, pineapple-induced increases in ERL/GEF bioavailability could be attributed to the mucus disrupting property of bromelain. Being a proteolytic enzyme, it could increase the muco-penetration and diffusion of drugs through the mucous barriers, increasing the systematic exposure (*Murgia et al., 2018*). Also, a study by Amadi et al., indicates that pineapple can possibly have an inhibitory effect on P-gp and OATP transporters, and thus can increase the exposure of drugs that are substrates to these transporters such as fexofenadine (*Amadi & Barileela, 2018*). While P-gp found on the intestinal epithelium act as efflux proteins, decreasing the bioavailability of drugs substrate, OATP are influx proteins that can influence the absorption of drug substrates and increase bioavailability (*Amadi & Barileela, 2018*). The increase in ERL and GEF exposure in our study indicates that pineapple juice might have a favourable inhibition of P-gp over OATP (*Amadi & Barileela, 2018*).

The effect of different types of berry juice on drug metabolizing enzymes was also studied previously (*Mallhi et al., 2015*). It was reported that cranberry juice can inhibit CYP3A4 or CYP2C9 (*Mallhi et al., 2015*; *Uesawa & Mohri, 2006*; *Ushijima et al., 2009*). However, studies indicated that it is unlikely that cranberry juice can cause a significant drug interactions with drug metabolized by CYP3A4 or CYP2C9 (*Wanwimolruk et al., 2012*; *Pham & Pham, 2007*). Other berries such as black raspberry and blueberry are reported to be weak inhibitors of CYP3A1 and CYP3A4, respectively (*Mallhi et al., 2015*; *Dreiseitel et al., 2008*). This might justify the different effect berry FW has on ERL's exposure as compared to lime FW, and the negligible effect on GEF PKs except for the C_{max}. This may also be the case for peach FW, where a previous report has only described the down-regulatory effect of peach supplementation on CYP2A and CYP2b1/2, but not on CYP3A4 (*Canistro et al., 2016*).

Although it is possible that the dose of flavouring agent used could have influenced the PK parameters of ERL and GEF differently, Table S1 shows that lime and pineapple FW were consumed less than berry and peach, probably due to the sour or bitter flavours of lime and pineapple compared to berry and peach. Yet, lime and pineapple had more impact on the PK of both drugs. Also, the literature indicates that weight or obesity can affect the PK parameters of drugs due to an alteration in CL and volume of distribution (V_d), and therefore $t_{1/2}$ (*Hanley, Abernethy & Greenblatt, 2010*). In our study, however, there was no significant difference in weights among rats in different FW groups ruling out the possible impact of the rats' weight on ERL and GEF PKs (Fig. S1).

Artificial sweetening agents such as aspartame, are another component of FW. To our knowledge, there was no reported drug interaction between aspartame and ERL or GEF. Also, other studies indicate that aspartame has no effect on hepatic CYP enzymes such CYP1A2, an enzyme involved in ERL metabolism, or CYP2A3 (*Li et al., 2007*; *Kamenickova et al., 2013*; *Vences-Mejia et al., 2006*). Thus, aspartame might not be involved in the metabolism of ERL and GEF. Further evaluation of aspartame's effect on ERL/GEF metabolism is needed.

ERL and GEF are weak bases that are better absorbed in an acidic pH, and thus alteration of gastric pH can affect their absorption rate (*Kumarakulasinghe et al., 2016*). Acidifiers and acid regulators are components of FW. A study by van Leeuwen et al., indicated that the concomitant use of cola and acidic beverage can significantly increase ERL mean drug exposure. However, the effect on patients were marginal and clinically irrelevant (*Van Leeuwen et al., 2016*). Also, Fotaki and Klein showed that carbonated beverages can change the stomach pH which in turn can affect drugs absorption, dissolution, and stomach emptying (*Fotaki & Klein, 2013*). Therefore, we cannot rule out the possible effect of acidifiers on ERL or GEF PK. In regards to the antioxidant EDTA, it was reported previously that it can prolonged gastric emptying and can act as an inhibitor of gastric acid, which could reduce drug exposure (*Shafer et al., 1985*). Such an effect was not observed in here, which can imply that their relatively low concentration in FW makes them not capable of inducing such an effect. Regarding preservatives such as sodium phosphate and potassium sorbate there were no reports to our knowledge that evaluated their effects on drug absorption or metabolism. Thus, further studies in this area are needed.

It is noteworthy to mention that the blood sampling time (up to 48 h) in this study was adequate to carry out a fair comparison of the overall-plasma concentration–time profile among different rat groups, which was the main purpose of our study. However, for more accurate estimation of the elimination phase, the total sampling time should have been further extended, particularly for ERL.

CONCLUSION

In conclusion, the present study indicates that drinking FW could be of significance in rats receiving ERL or GEF. Furthermore, our results indicate that lime FW had the highest impact on ERL and GEF PKs in terms of the number of PK parameters altered (C_{max}, t_{max}, $t_{1/2}$, AUC_{0-48}, $AUC_{0-\infty}$ and CL/F). The order by which the FW effected the PK parameters were as follows: lime > pineapple > berry > peach for both ERL and GEF. Peach had nearly negligible effect on ERL and no effect on GEF PKs. Therefore, it might be of clinical importance to evaluate the PK parameters of ERL and GEF in human subjects who consume FW while on therapy.

Funding
This work was funded by the Deanship of Scientific Research at King Saud University through the research group project no. RGPVPP-331. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures
The following grant information was disclosed by the authors:
Deanship of Scientific Research at King Saud University through the research group: RGPVPP-331.

Competing Interests
The authors declare there are no competing interests.

Author Contributions
- Aliyah Almomen conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Hadir M. Maher conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Nourah Z. Alzoman conceived and designed the experiments, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Shereen M. Shehata performed the experiments, authored or reviewed drafts of the paper, and approved the final draft.
- Amal Alsubaie performed the experiments, analyzed the data, authored or reviewed drafts of the paper, and approved the final draft.

Animal Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

Ethical Committee for Performing Studies on Animals, King Saud University, Riyadh, Saudi Arabia with protocol number KSU-SE-19-13.

Data Availability

Raw data is available as Supplemental Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.9881#supplemental-information.

REFERENCES

Abdallah HM, Al-Abd AM, El-Dine RS, El-Halawany AM. 2015. P-glycoprotein inhibitors of natural origin as potential tumor chemo-sensitizers: a review. *Journal of Advanced Research* **6(1)**:45–62 DOI 10.1016/j.jare.2014.11.008.

Agarwal S, Sane R, Gallardo JL, Ohlfest JR, Elmquist WF. 2010. Distribution of gefitinib to the brain is limited by P-glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2)-mediated active efflux. *Journal of Pharmacology and Experimental Therapeutics* **334(1)**:147–155 DOI 10.1124/jpet.110.167601.

Amadi CM, Barileela LK. 2018. Effect of pineapple (ananas comosus) and uziza (piper guineense) extracts on fexofenadine bioavailability: possible role of p-glycoprotein (p-gp) and organic anion transporting polypeptides (oatps). *International Research Journal of Pharmacy* **9(3)**:17–21.

Bailey DG. 2010. Fruit juice inhibition of uptake transport: a new type of food-drug interaction. *British Journal of Clinical Pharmacology* **70(5)**:645–655 DOI 10.1111/j.1365-2125.2010.03722.x.

Bailey DG, Dresser GK, Bend JR. 2003. Bergamottin, lime juice, and red wine as inhibitors of cytochrome P450 3A4 activity: comparison with grapefruit juice. *Clinical Pharmacology and Therapeutics* **73(6)**:529–537 DOI 10.1016/S0009-9236(03)00051-1.

Bansal T, Jaggi M, Khar RK, Talegaonkar S. 2009. Emerging significance of flavonoids as P-glycoprotein inhibitors in cancer chemotherapy. *Journal of Pharmacy & Pharmaceutical Sciences* **12(1)**:46–78 DOI 10.18433/J3RC77.

Bauer M, Matsuda A, Wulkersdorfer B, Philippe C, Traxl A, Ozvegy-Laczka C, Stanek J, Nics L, Klebermass EM, Poschner S, Jäger W, Patik I, Bakos E, Szakács G, Wadsak W, Hacker M, Zeitlinger M, Langer O. 2018. Influence of OATPs on hepatic disposition of erlotinib measured with positron emission tomography. *Clinical Pharmacology and Therapeutics* **104(1)**:139–147 DOI 10.1002/cpt.888.

Beretta GL, Cassinelli G, Pennati M, Zuco V, Gatti L. 2017. Overcoming ABC transporter-mediated multidrug resistance: the dual role of tyrosine kinase inhibitors

as multitargeting agents. *European Journal of Medicinal Chemistry* **142**:271–289 DOI 10.1016/j.ejmech.2017.07.062.

Bethune G, Bethune D, Ridgway N, Xu Z. 2010. Epidermal growth factor receptor (EGFR) in lung cancer: an overview and update. *Journal of Thoracic Disease* **2(1)**:48–51.

Bilek M, Matlok N, Kaniuczak J, Gorzelany J. 2014. Sugar and inorganic anions content in mineral and spring water-based beverages. *Roczniki Państwowego Zakladu Higieny* **65(3)**:193–197.

Brehmer D, Greff Z, Godl K, Blencke S, Kurtenbach A, Weber M, Müller S, Klebl B, Cotten M, Kèri G, Wissing J, Daub H. 2005. Cellular targets of gefitinib. *Cancer Research* **65(2)**:379–382.

Bronte G, Rolfo C, Giovannetti E, Cicero G, Pauwels P, Passiglia F, Castiglia M, Rizzo S, Vullo FLo, Fiorentino E, Van Meerbeeck J, Russo A. 2014. Are erlotinib and gefitinib interchangeable, opposite or complementary for non-small cell lung cancer treatment? Biological, pharmacological and clinical aspects. *Critical Reviews in Oncology/Hematology* **89(2)**:300–313 DOI 10.1016/j.critrevonc.2013.08.003.

Brown CJ, Smith G, Shaw L, Parry J, Smith AJ. 2007. The erosive potential of flavoured sparkling water drinks. *International Journal of Paediatric Dentistry* **17(2)**:86–91 DOI 10.1111/j.1365-263X.2006.00784.x.

Canistro D, Vivarelli F, Cirillo S, Costa G, Andreotti C, Paolini M. 2016. Comparison between in toto peach (Prunus persica L. Batsch) supplementation and its polyphenolic extract on rat liver xenobiotic metabolizing enzymes. *Food and Chemical Toxicology* **97**:385–394 DOI 10.1016/j.fct.2016.10.006.

Chen YJ, Huang WC, Wei YL, Hsu SC, Yuan P, Lin HY, Wistuba II, Jack Lee J, Yen C-J, Su W-C, Chang K-Y, Chang W-C, Chou T-C, Chou C-K, Tsai C-H, Hung M-C. 2011. Elevated BCRP/ABCG2 expression confers acquired resistance to gefitinib in wild-type EGFR-expressing cells. *PLOS ONE* **6(6)**:e21428 DOI 10.1371/journal.pone.0021428.

Choi JS, Jo BW, Kim YC. 2004. Enhanced paclitaxel bioavailability after oral administration of paclitaxel or prodrug to rats pretreated with quercetin. *European Journal of Pharmaceutics and Biopharmaceutics* **57(2)**:313–318 DOI 10.1016/j.ejpb.2003.11.002.

Collado-Borrell R, Escudero-Vilaplana V, Romero-Jimenez R, Iglesias-Peinado I, Herranz-Alonso A, Sanjurjo-Saez M. 2016. Oral antineoplastic agent interactions with medicinal plants and food: an issue to take into account. *Journal of Cancer Research and Clinical Oncology* **142(11)**:2319–2330 DOI 10.1007/s00432-016-2190-8.

Cuomo R, Sarnelli G, Savarese MF, Buyckx M. 2009. Carbonated beverages and gastrointestinal system: between myth and reality. *Nutrition, Metabolism & Cardiovascular Diseases* **19(10)**:683–689 DOI 10.1016/j.numecd.2009.03.020.

Czerniak R. 2001. Gender-based differences in pharmacokinetics in laboratory animal models. *International Journal of Toxicology* **20(3)**:161–163 DOI 10.1080/109158101317097746.

Dahan A, Altman H. 2004. Food-drug interaction: grapefruit juice augments drug bioavailability–mechanism, extent and relevance. *European Journal of Clinical Nutrition* **58(1)**:1–9 DOI 10.1038/sj.ejcn.1601736.

Dreiseitel A, Schreier P, Oehme A, Locher S, Hajak G, Sand PG. 2008. Anthocyanins and their metabolites are weak inhibitors of cytochrome P450 3A4. *Molecular Nutrition & Food Research* **52(12)**:1428–1433 DOI 10.1002/mnfr.200800043.

Fleisher B, Unum J, Shao J, An G. 2015. Ingredients in fruit juices interact with dasatinib through inhibition of BCRP: a new mechanism of beverage-drug interaction. *Journal of Pharmaceutical Sciences* **104(1)**:266–275 DOI 10.1002/jps.24289.

Fotaki N, Klein S. 2013. Mechanistic understanding of the effect of PPIs and acidic carbonated beverages on the oral absorption of itraconazole based on absorption modeling with appropriate in vitro data. *Molecular Pharmaceutics* **10(11)**:4016–4023 DOI 10.1021/mp4003249.

Han SY, Zhao HY, Zhou N, Zhou F, Li PP. 2014. Marsdenia tenacissima extract inhibits gefitinib metabolism in vitro by interfering with human hepatic CYP3A4 and CYP2D6 enzymes. *Journal of Ethnopharmacology* **151(1)**:210–217 DOI 10.1016/j.jep.2013.10.021.

Hanley MJ, Abernethy DR, Greenblatt DJ. 2010. Effect of obesity on the pharmacokinetics of drugs in humans. *Clinical Pharmacokinetics* **49(2)**:71–87 DOI 10.2165/11318100-000000000-00000.

Hanley MJ, Cancalon P, Widmer WW, Greenblatt DJ. 2011. The effect of grapefruit juice on drug disposition. *Expert Opinion on Drug Metabolism & Toxicology* **7(3)**:267–286 DOI 10.1517/17425255.2011.553189.

Hidaka M, Fujita K, Ogikubo T, Yamasaki K, Iwakiri T, Okumura M, Kodama H, Arimori K. 2004. Potent inhibition by star fruit of human cytochrome P450 3A (CYP3A) activity. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* **32(6)**:581–583 DOI 10.1124/dmd.32.6.581.

Hidaka M, Nagata M, Kawano Y, Sekiya H, Kai H, Yamasaki K, Okumura M, Arimori K. 2008. Inhibitory effects of fruit juices on cytochrome P450 2C9 activity in vitro. *Bioscience, Biotechnology, and Biochemistry* **72(2)**:406–411 DOI 10.1271/bbb.70511.

Hollander AA, Van Rooij J, Lentjes GW, Arbouw F, Van Bree JB, Schoemaker RC, Van Es LA, Van der Woude FJ, Cohen AF. 1995. The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients. *Clinical Pharmacology and Therapeutics* **57(3)**:318–324 DOI 10.1016/0009-9236(95)90157-4.

Johnston RA, Rawling T, Chan T, Zhou F, Murray M. 2014. Selective inhibition of human solute carrier transporters by multikinase inhibitors. *Drug Metabolism and Disposition: The Biological Fate of Chemicals* **42(11)**:1851–1857 DOI 10.1124/dmd.114.059097.

Kamenickova A, Dvorak Z. 2012. Effects of flavored mineral waters on AhR-CYP1A1 signaling pathway in primary human hepatocytes and in human hepatic and intestinal cancer cells. *Food and Chemical Toxicology* **50(6)**:1933–1939 DOI 10.1016/j.fct.2012.03.073.

Kamenickova A, Pecova M, Bachleda P, Dvorak Z. 2013. Effects of artificial sweeteners on the AhR- and GR-dependent CYP1A1 expression in primary human hepatocytes and human cancer cells. *Toxicology In Vitro* **27(8)**:2283–2288 DOI 10.1016/j.tiv.2013.10.001.

Karmakar S, Biswas S, Bera R, Mondal S, Kundu A, Ali MA, Sen T. 2015. Beverage-induced enhanced bioavailability of carbamazepine and its consequent effect on antiepileptic activity and toxicity. *Journal of Food and Drug Analysis* **23**(2):327–334 DOI 10.1016/j.jfda.2014.07.012.

Kulkarni KH, Yang Z, Niu T, Hu M. 2012. Effects of estrogen and estrus cycle on pharmacokinetics, absorption, and disposition of genistein in female Sprague-Dawley rats. *Journal of Agricultural and Food Chemistry* **60**(32):7949–7956 DOI 10.1021/jf204755g.

Kumarakulasinghe NB, Syn N, Soon YY, Asmat A, Zheng H, Loy EY, Pang B, Andrew Soo R. 2016. EGFR kinase inhibitors and gastric acid suppressants in EGFR-mutant NSCLC: a retrospective database analysis of potential drug interaction. *Oncotarget* **7**(51):85542–85550 DOI 10.18632/oncotarget.13458.

Ladanyi M, Pao W. 2008. Lung adenocarcinoma: guiding EGFR-targeted therapy and beyond. *Modern Pathology* **21**(Suppl 2):S16–S22 DOI 10.1038/modpathol.3801018.

Li Y, Revalde J, Paxton JW. 2017. The effects of dietary and herbal phytochemicals on drug transporters. *Advanced Drug Delivery Reviews* **116**:45–62 DOI 10.1016/j.addr.2016.09.004.

Li M, Yuan H, Li N, Song G, Zheng Y, Baratta M, Hua F, Thurston A, Wang J, Lai Y. 2008. Identification of interspecies difference in efflux transporters of hepatocytes from dog, rat, monkey and human. *European Journal of Pharmaceutical Science* **35**(1-2):114–126 DOI 10.1016/j.ejps.2008.06.008.

Li J, Zhao M, He P, Hidalgo M, Baker SD. 2007. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. *Clinical Cancer Research* **13**(12):3731–3737 DOI 10.1158/1078-0432.CCR-07-0088.

Li B, Zhao B, Liu Y, Tang M, Lue B, Luo Z, Zhai H. 2016. Herb-drug enzyme-mediated interactions and the associated experimental methods: a review. *Journal of Traditional Chinese Medicine* **36**(3):392–408 DOI 10.1016/S0254-6272(16)30054-1.

Lorenc W, Markiewicz B, Kruszka D, Kachlicki P, Baralkiewicz D. 2019. Study on Speciation of As, Cr, and Sb in bottled flavored drinking water samples using advanced analytical techniques IEC/SEC-HPLC/ICP-DRC-MS and ESI-MS/MS. *Molecules* **24**(4):Article 668 DOI 10.3390/molecules24040668.

Lu JF, Eppler SM, Wolf J, Hamilton M, Rakhit A, Bruno R, Lum BL. 2006. Clinical pharmacokinetics of erlotinib in patients with solid tumors and exposure-safety relationship in patients with non-small cell lung cancer. *Clinical Pharmacology and Therapeutics* **80**(2):136–145 DOI 10.1016/j.clpt.2006.04.007.

Maher HM, Alzoman NZ, Shehata SM. 2016. Simultaneous determination of selected tyrosine kinase inhibitors with corticosteroids and antiemetics in rat plasma by solid phase extraction and ultra-performance liquid chromatography-tandem mass spectrometry: Application to pharmacokinetic interaction studies. *Journal of Pharmaceutical and Biomedical Analysis* **124**:216–227 DOI 10.1016/j.jpba.2016.03.013.

Maher HM, Alzoman NZ, Shehata SM. 2018. Validated UPLC-MS/MS method for the quantification of dasatinib in plasma: application to pharmacokinetic interaction studies with nutraceuticals in Wistar rats. *PLOS ONE* **13**(6):e0199208 DOI 10.1371/journal.pone.0199208.

Maher HM, Alzoman NZ, Shehata SM, Abahussain AO. 2017. UPLC-ESI-MS/MS study of the effect of green tea extract on the oral bioavailability of erlotinib and lapatinib in rats: potential risk of pharmacokinetic interaction. *Journal of Chromatography B* **1049–1050**:30–40.

Mallhi T, Sarriff A, Adnan A, Khan Y, Qadir M, Hamzah A, Khan A. 2015. Effect of fruit/vegetable-drug interactions on CYP450, OATP and p-Glycoprotein: a systematic review. *Tropical Journal of Pharmaceutical Research* **14(10)**:1927–1935 DOI 10.4314/tjpr.v14i10.27.

Marchetti S, De Vries NA, Buckle T, Bolijn MJ, Van Eijndhoven MA, Beijnen JH, Mazzanti R, Van Tellingen O, Schellens JHM. 2008. Effect of the ATP-binding cassette drug transporters ABCB1, ABCG2, and ABCC2 on erlotinib hydrochloride (Tarceva) disposition in in vitro and in vivo pharmacokinetic studies employing Bcrp1-/-/Mdr1a/1b-/- (triple-knockout) and wild-type mice. *Molecular Cancer Therapeutics* **7(8)**:2280–2287 DOI 10.1158/1535-7163.MCT-07-2250.

Matsubara T, Kim HJ, Miyata M, Shimada M, Nagata K, Yamazoe Y. 2004. Isolation and characterization of a new major intestinal CYP3A form, CYP3A62, in the rat. *Journal of Pharmacology and Experimental Therapeutics* **309(3)**:1282–1290 DOI 10.1124/jpet.103.061671.

Molden E, Spigset O. 2007. Fruit and berries–interactions with drugs. *Tidsskrift For Den Norske Laegeforening* **127(24)**:3218–3220.

Mouly S, Lloret-Linares C, Sellier PO, Sene D, Bergmann JF. 2017. Is the clinical relevance of drug-food and drug-herb interactions limited to grapefruit juice and Saint-John's Wort? *Pharmacological Research* **118**:82–92 DOI 10.1016/j.phrs.2016.09.038.

Murgia X, Loretz B, Hartwig O, Hittinger M, Lehr CM. 2018. The role of mucus on drug transport and its potential to affect therapeutic outcomes. *Advanced Drug Delivery Reviews* **124**:82–97 DOI 10.1016/j.addr.2017.10.009.

Pham DQ, Pham AQ. 2007. Interaction potential between cranberry juice and warfarin. *American Journal of Health-System Pharmacy* **64(5)**:490–494 DOI 10.2146/ajhp060370.

Piao Y, Shin SC, Choi JS. 2008. Effects of oral kaempferol on the pharmacokinetics of tamoxifen and one of its metabolites, 4-hydroxytamoxifen, after oral administration of tamoxifen to rats. *Biopharmaceutics and Drug Disposition* **29(4)**:245–249 DOI 10.1002/bdd.593.

Purdy C. 2019. Americans want to drink more water. *Available at https://qz.com/1520602/americans-want-to-drink-more-water/*.

Sasaki T, Sato Y, Kumagai T, Yoshinari K, Nagata K. 2017. Effect of health foods on cytochrome P450-mediated drug metabolism. *Journal of Pharmaceutical Health Care and Sciences* **3**:Article 14.

Scheffler M, Di Gion P, Doroshyenko O, Wolf J, Fuhr U. 2011. Clinical pharmacokinetics of tyrosine kinase inhibitors: focus on 4-anilinoquinazolines. *Clinical Pharmacokinetics* **50(6)**:371–403 DOI 10.2165/11587020-000000000-00000.

Shafer RB, Levine AS, Marlette JM, Morley JE. 1985. Do calories, osmolality, or calcium determine gastric emptying? *American Journal of Physiology* **248(4 Pt 2)**:R479–R483.

Shin SC, Choi JS, Li X. 2006. Enhanced bioavailability of tamoxifen after oral administration of tamoxifen with quercetin in rats. *International Journal of Phamaceutics* **313(1–2):**144–149 DOI 10.1016/j.ijpharm.2006.01.028.

Smith NF, Baker SD, Gonzalez FJ, Harris JW, Figg WD, Sparreboom A. 2008. Modulation of erlotinib pharmacokinetics in mice by a novel cytochrome P450 3A4 inhibitor, BAS 100. *British Journal of Cancer* **98(10):**1630–1632 DOI 10.1038/sj.bjc.6604353.

Steuck M, Hellhake S, Schebb NH. 2016. Food polyphenol apigenin inhibits the cytochrome P450 monoxygenase branch of the arachidonic acid cascade. *Journal of Agricultural and Food Chemistry* **64(47):**8973–8976 DOI 10.1021/acs.jafc.6b04501.

Sullivan I, Planchard D. 2016. Next-generation EGFR tyrosine kinase inhibitors for treating EGFR-mutant lung cancer beyond first line. *Frontiers in Medicine* **3:**Article 76.

Torre LA, Siegel RL, Jemal A. 2016. Lung cancer statistics. *Advances in Experimental Medicine and Biology* **893:**1–19 DOI 10.1007/978-3-319-24223-1_1.

Uesawa Y, Mohri K. 2006. Effects of cranberry juice on nifedipine pharmacokinetics in rats. *Journal of Pharmacy and Pharmacology* **58(8):**1067–1072 DOI 10.1211/jpp.58.8.0007.

Ushijima K, Tsuruoka S, Tsuda H, Hasegawa G, Obi Y, Kaneda T, Takahashi M, Maekawa T, Sasaki T, Koshimizu T, Fujimura A. 2009. Cranberry juice suppressed the diclofenac metabolism by human liver microsomes, but not in healthy human subjects. *British Journal of Clinical Pharmacology* **68(2):**194–200 DOI 10.1111/j.1365-2125.2009.03436.x.

Van Leeuwen RW, Peric R, Hussaarts KG, Kienhuis E, NS IJ, De Bruijn P, Van der Leest C, Codrington H, Kloover JS, Van der Holt B, Aerts JG, van Gelder T, Mathijssen RHJ. 2016. Influence of the acidic beverage cola on the absorption of erlotinib in patients with non-small-cell lung cancer. *Journal of Clinical Oncology* **34(12):**1309–1314 DOI 10.1200/JCO.2015.65.2560.

Vences-Mejia A, Labra-Ruiz N, Hernandez-Martinez N, Dorado-Gonzalez V, Gomez-Garduno J, Perez-Lopez I, Nosti-Palacios R, Carranza RCamacho, Espinosa-Aguirre JJ. 2006. The effect of aspartame on rat brain xenobiotic-metabolizing enzymes. *Human and Experimental Toxicology* **25(8):**453–459 DOI 10.1191/0960327106het646oa.

Wanwimolruk S, Prachayasittikul S, Prachayasittikul V, Bernichi B. 2012. Effect of cranberry dietary supplements with different brands on human CYP3A4 enzyme. *EXCLI Journal* **11:**108–115.