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Research Article

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)

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ABSTRACT

The consumption of fruits/vegetables as sources of nutrients is important for healthy growth and development of the body. When used in combination with certain drugs, there is a tendency for interaction to occur, which is due to different bioactive phytochemical constituents which alter the activities of drugs transporters (efflux and influx transporters) and metabolizing enzymes, resulting to deviations in the expected pharmacological activity of the drug. The present study was aimed to investigate the effect of uziza *(Piper guineense)* and pineapple (*Ananas comosus)* extracts on the oral exposure of fexofenadine in rats. Pharmacokinetic parameters of fexofenadine were determined in rats following an oral (10 mg/kg) administration of fexofenadine in the presence and absence of pineapple and uziza extracts (10 mL/kg given orally) compared to the control group given fexofenadine alone. The combined use of pineapple decreased the oral exposure (AUC)of fexofenadine by 47% while uziza extract increased the oral exposure (AUC) of fexofenadine by 31% as compared to the group that received fexofenadine alone (control group). There was a reduction in peak plasma concentration of fexofenadine when co-administered with pineapple and uziza by 3% and 61% respectively compared to control. The reduction is indicative of delayed absorption by phytochemical constituents of *Piper guineense* (uziza) and pineapple juice extracts. A 10% decrease in clearance rate was observed for the group that received fexofenadine and pineapple extract as compared to the group that received fexofenadine alone while clearance rate was increased to about 56% in the group that received uziza extract. An increase in half life was observed for the group that received pineapple while a decrease was observed for the group that received uziza as compared to control respectively. In conclusion, pineapple juice significantly enhanced the oral exposure of fexofenadine in rats likely by the inhibition of P-glycoprotein-mediated cellular efflux while uziza extract reduced fexofenadine oral exposure by inhibition of organic anion transporting polypeptides (OATPs) during the intestinal absorption suggesting that the combined use of pineapple or uziza-containing diet with fexofenadine may require close monitoring for potential drug–diet interactions.

KEYWORDS: fruit/vegetable-drug interactions, pharmacokinetics, bioavailability, drug absorption, drug transporters.

INTRODUCTION

Diets and nutritional habits are important factors influencing human health and disease. Studies have suggested that regular consumption of fruits and vegetables may reduce risk of some diseases[1]. However, it is worth noting that most fruits and vegetables are rich sources of numerous bioactive compounds such as phytochemicals.

However, some dietary compositions play important roles in clinically significant food–drug interactions as they can influence drug absorption and disposition[2,3]. Therefore, potential interactions may occur when patients taking medicines regularly also consume certain fruits or vegetables[4]. Drug-nutrient interactions can be defined as modifications of pharmacokinetics or pharmacodynamics of a drug or impairment in nutritional status due to the addition of a drug[4]. Food/nutrient-drug interaction is said to be significant if it modifies the final therapeutic outcome. These interactionscan lead to two main clinical effects: decreased bioavailability of a drug, which subsequently results to treatment failure; or an increased bioavailability, which increases the risk of adverse effects and toxicities[5,6].

Fexofenadine is a non-sedating histamine H1-receptor blocker used for the treatment of seasonal allergic rhinitis[7]. It has been implicated as a substrate for the efflux transporter, P-glycoprotein (P-gp), in addition to the influx transporter, organic anion transporting polypeptide (OATP). Further to this, data has revealed that several furanocoumarins and bioflavonoids found in fruit juices are potent inhibitors of OATP transporters and P-gps[8]. Previous clinical studies involving fexofenadine demonstrated a significant reduction in bioavailability upon oral co-administration with fruit juices such as grapefruit, orange, and apple juice[9]. This is due to a significant inhibition of OATP and P-gps[8]. In rats, fexofenadine is excreted unchanged in the urine, bile, and gastrointestinal tract, indicative of limited metabolism, making it an ideal candidate to investigate transport processes[8].

Pineapple (*Ananas comosus)* is a tropical fruit consumed worldwide. It contains bromelain, a cysteine protease. Bromelain is known inhibitor of CYP2C9 activity[10]. Phytochemical screening of pineapple juice have revealed the presence of carbohydrates, tannins, flavonoids, coumarins, quinones, terpenoids, phenols and alkaloids[11,12]. Uziza (*Piper guineense)*, a plant from the family- Piperaceae and from genus-piper, is commonly called Ashanti pepper in West Africa. It is utilised in pepper soup preparation in the Southern part of Nigeria. The seeds are also used to prepare soups for mothers from the point of

delivery to prevent post partum contraction[13]. *Piper guineense* has been shown to contain alkaloids, flavonoids, saponins, phenols and tannins[14]. In addition uziza contains piperine, myristicine, elemicine, safrole and dillapiol[15]. To the best of our knowledge, minimal data exists with regards to possible interactions of drugs with common fruits and vegetables commonly consumed in Nigeria. This work investigates the potential nutrient-drug interaction involving *Piper guineense* (uziza) and Pineapple (*Ananas comosus)*, with fexofenadine in rats.

MATERIALS AND METHODS

Chemicals

Methanol (JHD, China), distilled water, formic acid, tween 80, Methylated spirit (JHD, China), fexofenadine HCl 120mg tablets USP (Fexet® **G**Getz Pharma limited). All chemicals used were of analytical grade.

Fruit/Vegetable Sample collection/processing

Pineapple *(Ananas comosus*), uziza *(Piper guineensis*) were purchased from Choba, Port Harcourt, Rivers State. About 50 g of pineapple fruit (50 mg) was washed, peeled and mashed to a pulp with a mortar and pestle, and then the pulp was filtered to extract the juice. Leaves of *Piper guineense* (uziza) (33 g) were washed, cut in small pieces, and squeezed to obtain a liquid extract.

Pharmacokinetic study

Fifteen (15) healthy male albino rats with weight range 125-185g used for this study were obtained from the animal house of Department of Pharmacology and Toxicology, University of Port Harcourt, Rivers State, Nigeria. The animals were placed in standard cages and housed in a controlled environment for at least two weeks for acclimatization. Animal ethics and proper handling methods were strictly adhered to. The cages were cleaned daily, ensuring proper and adequate bedding using saw dust. The animals were fed daily with standard diets and water *ad libitum*. The animals were starved a night before the experiment and fed afterwards.

The animals were divided into three (3) groups containing 5 animals each. The animals in the first group were given 10 mg/kg of fexofenadine plus water (which corresponds to the clinical dose in humans). The second group received 10 mg/kg fexofenadine plus 10 mL/kg of pineapple juice, while the third group received 10 mg/kg fexofenadine plus 10 mL/kg of uziza extract. This was done according to the method previously described by Kamath et al[8]. At predetermined intervals of 0,1, 2, 4, 8, and 10 hours, blood samples were withdrawn from the rat tail vein in heparinized tubes and plasma was obtained by centrifugation at 4000 rpm for 10 minutes and stored in a freezer until analyzed. A drug free plasma sample was used as blank. To 5µl aliquot of the plasma sample, 15µl of 0.1% formic acid and 45 µl of 99.99 % methanol were added respectively and centrifuged at 4000 rpm for 5 minutes. The supernatant was collected and analyzed using the UV spectrophotometer (UV-Visible SP6 Pye Unicam) at a wavelength of 220nm.The fexofenadine concentration in each sample analyzed was then calculated using a calibration curve constructed from the absorbance of the following standard fexofenadine concentrations of 1200, 600, 300, 150, 75, 37.5, 18.75 µg/mL

Data Analysis

Plasma fexofenadine concentrations were analyzed by a non-compartmental method. The concentration–time data for each study period 0–10 hours after completion of fexofenadine administration were fitted by a non linear least squares regression to the following equation, $C = C_0.e^{-(kt)}$, where C is the concentration at time t and C_0 is the concentration when t =0.The terminal elimination rate constant (K_{el}) was determined by log-linear regression. The apparent elimination half-life of the log-linear phase ($T_{1/2}$) was calculated as $0.693/K_{el}$. The area under the plasma drug concentration-time curve (AUC) was calculated from 0 to 10 hours [AUC (0-10)] by the linear trapezoidal method. The AUC from time 0 to infinity [AUC(0-∞)] was calculated as AUC (0-10) plus AUC from 10 hours to infinity [AUC(10-∞)].Cmax and the time to reach Cmax (Tmax) were obtained directly from the experimental data. The volume of distribution (Vd) was calculated for each treatment by dividing the dose of fexofenadine by the initial plasma concentration of fexofenadine when t is equal to zero. The clearance rate (Cl_T) was obtained by multiplying Vd by the elimination rate constant (K_{el}). The concentration maximum (Cmax) and the corresponding time (Tmax) were read off from the plasma concentration versus time curve. Results were expressed as mean ± SEM (standard error of the mean). Statistical analysis of data obtained was performed using chi-squared test and results were regarded as significant at $p < 0.05$.

RESULTS

The plasma concentration-time profiles of fexofenadine after an oral administration of fexofenadine (10 mg/kg) in the presence and absence of uziza juice (10 mL/kg) and pineapple juice (10 mL/kg were characterized in rats and illustrated in Figure 1. The plasma concentration of fexofenadine was quantifiable up to 10-h post dose. The mean pharmacokinetic parameters of fexofenadine were also summarized in Table 1. As shown in table 1, combined use of uziza and pineapple juices with fexofenadine affected the oral pharmacokinetics of fexofenadine compared to the control group given fexofenadine alone. For the group that received uziza juice, there was a significant ($p<0.05$) reduction in AUC (47% reduction) but this was in contrast to the result obtained with pineapple juice where there was a significant ($P<0.05$) increase in AUC (31% increase). The clearance rate was also increased in the group that received uziza as compared to control group while there was a reduction in the group that received pineapple juice. The peak plasma concentration occurred at 1 hour for all the three groups with reduction in peak plasma concentration of fexofenadine when co-administered with pineapple and uziza by 3% and 61% respectively compared to control. The elimination rate in the group of rats that received both fexofenadine and pineapple was 5% higher than the corresponding values obtained in the group that received fexofenadine alone. A 10% decrease in clearance rate was observed for the group that received fexofenadine and pineapple extract as compared to the group that fexofenadine alone while clearance rate was increased to about 56% in the group that received uziza extract. An increase in half life was observed for the group that received pineapple while a decrease was observed for the group that received uziza as compared to control respectively. Figures 2-4 show the log concentration graphs derived in the presence and absence of pineapple and uziza extracts. The slopes of the graphs were used to determine the absorption rate constants and half -lives respectively.

Table 1: Plasma pharmacokinetics parameters of fexofenadine with and without uziza/pineapple extract.

	AUC (mg.hr/mL)	T_{max} (hr)	K_{el} (hr)	Clearance (mL/hr)	$T_{1/2}$
Group F	1.268 ± 0.2*	1	0.074 ± 0.002*	0.625 ± 0.03*	2.79 ± 0.05*
Group FP	1.659 ± 0.2 *	1	0.078 ± 0.002 *	0.567 ± 0.02*	4.25 ± 0.07*
Group FU	0.677 ± 0.1*	1	0.056 ± 0.001*	0.972 ± 0.04*	1.95 ± 0.04*

Group F = group administered fexofenadine only, Group FP = group administered fexofenadine + pineapple extract, Group FU= group administered fexofenadine + uziza extract. *Significan p<0.05.

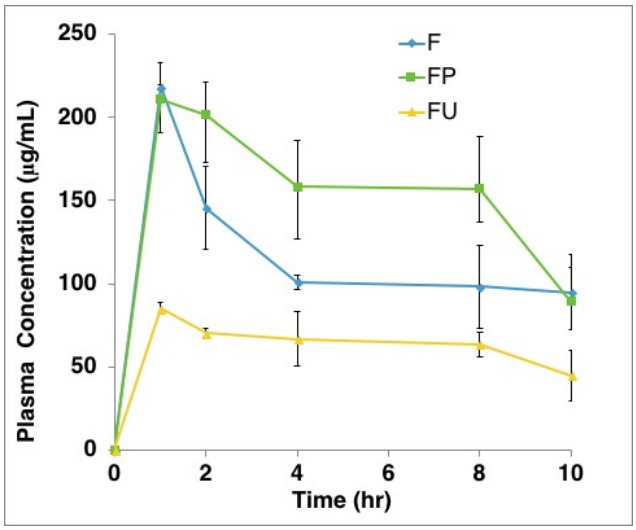

Figure 1: Mean plasma concentration of fexofenadine versus time with and without pineapple/uziza extract. F= fexofenadine, FP = fexofenadine + pineapple extract, FU= fexofenadine + uziza extract.

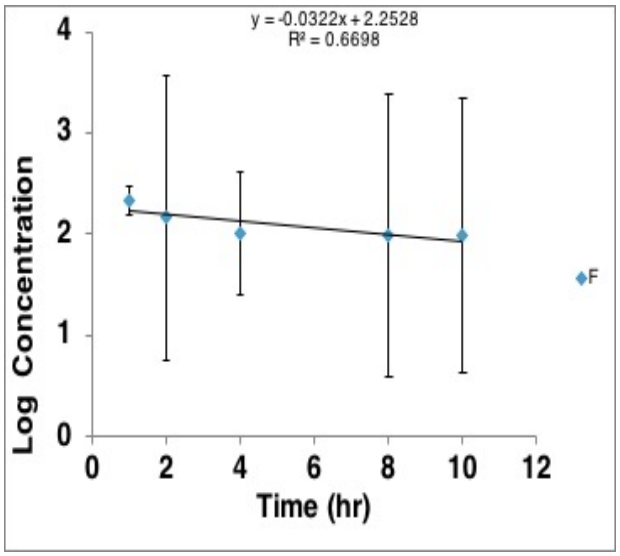

Figure 2: Graph of log concentration versus time for fexofenadine alone.

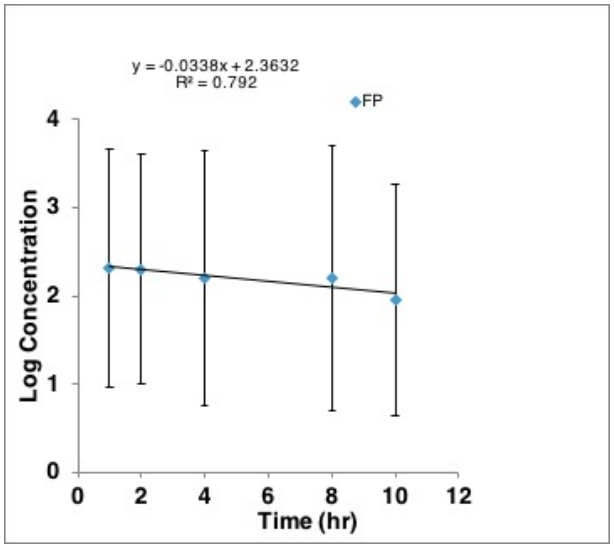

Figure 3: Graph of log concentration versus time for fexofenadine + pineapple extract.

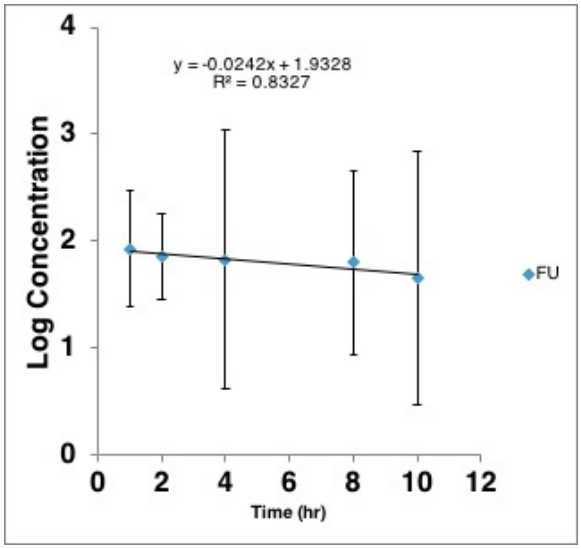

Figure 4: Graph of log concentration versus time for fexofenadine + uziza extract.

DISCUSSION

The oral bioavailability of drugs is influenced by many factors including physicochemical properties of the drug, gastric emptying time, alteration in gastrointestinal pH, enzyme induction/inhibition. Complex phytochemicals in foods, herbs, fruits, and vegetables can be beneficial to human health; however, such phytochemicals can also impair the therapeutic efficacy of drugs by affecting their absorption characteristics via interactions with drug transporters and drug metabolizing enzymes[6].

Efflux proteins expressed on the epithelium of the intestines such as P-gp or MRP2 limit the absorption of drugs that are substrates subsequently reducing their bioavailability[16,17]. On the other hand, influx transporters like OATP or PEPT1, promote the absorption of substrates of these transporters[17, 18]. Some OATP substrates are substrates of P-gp and MRP2 as well[18]. An overlap of substrate specificities between influx and efflux transporters may influence the overall bioavailability of drugs[8]. Studies have revealed that important constituents of grapefruit significantly inhibit OATP-B function *in vitro*[19,20]. Sevilla orange was also shown to inhibit CYP3A4, P-glycoprotein, OATP-A and OATP-B[8,20,21]. However, studies have indicated that juices from a

number of fruits such as grapefruit, orange, and apple juice produced more significant inhibition of OATP transporters over P-gp[9,22]. Results from these studies implicated several furanocoumarins and bioflavonoids present in fruit juices to be responsible for this inhibition[8]. Fexofenadine has been indicated as a substrate of the efflux transporter, P-gp, as well as the influx transporter, OATP[23,24].

In our study, co-administration of fexofenadine with pineapple juice significantly increased the systemic exposure of fexofenadine in rats. This is similar to the results obtained by Jin and Han[2], where co-administration of fexofenadine with piperine resulted to increased the oral exposure (AUC) of fexofenadine by 180% to 190%. This is indicative of preferential inhibition of P-gp over OATP leading to increased bioavailability of fexofenadine with pineapple. In contrast, co-administrationof uziza juice with fexofenadine caused a decrease in the oral exposure (AUC and Ka) of fexofenadine in rats, suggesting preferential inhibition of OATP over P-gp. The inhibition of intestinal OATPs decreased the intestinal absorption/oral exposure of fexofenadine when co-administered with uziza juice. This observation is also consistent with results obtained by Kamath *et al* [8], where a co-administration of fexofenadine with orange and apple juice resulted in a significant reduction in fexofenadine oral bioavailability. The dose of 10 mg/kg used in our study corresponds to the 120 mg human dose utilized in the clinical study by Dresser et al[9]. Furthermore, as shown in Table 1, the clearance rate was increased in the group that received uziza as compared to control group while there was a reduction in the group that received pineapple juice. This trend is comparable to the previous work by Jin and Han[2], who observed the increased clearance of fexofenadine via the concomitant administration of piperine (20 mg/kg). The peak plasma concentration occurred at 1 hour for all the three groups with reduction in peak plasma concentration of fexofenadine when co-administered with pineapple and uziza by 3% and 61% respectively compared to control. The reduction in peak plasma concentration is indicative of delayed absorption by phytochemical constituents of *Piper guineense* and pineapple juice extracts. Further work investigating the bioavailability of fexofenadine with individual components of pineapple and uziza juices will be important in gaining a better insight to the influence of transport processes fexofenadine absorption.

CONCLUSION

Therefore, further investigation in humans is necessary in order to validate our findings. Pineapple juice significantly enhanced the oral exposure of fexofenadine likely by the inhibition of P-gp-mediated efflux during intestinal absorption over OATP while uziza juice reduced its exposure/bioavailability likely by preferential inhibition of OATP over P-gp. This impairment in the bioavailability of fexofenadine could result in reduced effectiveness of fexofenadine in patients (for uziza) or toxicity effects (for pineapple). This fruit juice–drug interaction rat model may be useful in prediction of potential food–drug interactions in humans for fexofenadine.

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