



Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited



Open  Access

Research Article

Evaluation of Drug-Diet Interaction between *Psidium guajava* (Guava) fruit and Metoclopramide

Cecilia Nwadiuto Amadi* and Patience Onyinye Aghalibe

Department of Experimental Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Rivers State, Nigeria.

ABSTRACT

Studies have showed that phytochemicals present in fruit juices alter the oral bioavailability of drugs by inhibition of metabolising enzymes and transport proteins. The present study aimed to investigate the effect of *Psidium guajava* on the oral exposure of metoclopramide in rabbits. Pharmacokinetic parameters of metoclopramide were determined in rabbits following an oral (0.5mg/kg) administration of metoclopramide in the presence and absence of *Psidium guajava* (5mL/kg, given orally). Compared to the control group given metoclopramide alone, the combined use of *Psidium guajava* increased the oral exposure (AUC) of metoclopramide by 13% with a corresponding 177 % increase in C_{max} and half-life (71%). Furthermore, T_{max} decreased from 2h to 1h which might have contributed to the elevated plasma drug concentration in the first two hours in the presence of *Psidium guajava*. There was a significant increase in C_{max} (177%) and K_a (207%) which could be attributed to enhanced absorption via inhibition of P-gp resulting to increased bioavailability of the drug. In contrast, there was a significant decrease in elimination rate (88%) and a decrease in clearance rate (17%) attributable to inhibition of P450 enzymes (CYP2D6) by the phytochemical constituents. *Psidium guajava* enhanced the oral exposure of metoclopramide in rabbits likely by the inhibition of P-glycoprotein-mediated efflux during the intestinal absorption and inhibition of P450 enzyme system during metabolism, suggesting that the combined use of *Psidium guajava* or *Psidium guajava*-containing diet with metoclopramide may require close monitoring for potential drug-diet interactions.

Keywords: metoclopramide, *Psidium guajava*, diet-drug interaction, P-glycoprotein, P450 enzymes.

Article Info: Received 09 Feb 2019; Review Completed 05 March 2019; Accepted 06 March 2019; Available online 15 March 2019



Cite this article as:

Amadi CN, Aghalibe PO, Evaluation of Drug-diet interaction between *Psidium guajava* (Guava) fruit and Metoclopramide, Journal of Drug Delivery and Therapeutics. 2019; 9(2):144-147 <http://dx.doi.org/10.22270/jddt.v9i2.2441>

*Address for Correspondence:

Cecilia Nwadiuto Amadi, Ph.D. Department of Experimental Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Rivers State, Nigeria.

INTRODUCTION

Adequate consumption of fruits and vegetables may reduce risk of some diseases like cancer.¹ Certain phytochemical constituents in fruits and vegetables play an important role in significant food-drug interactions as they can affect drug absorption and disposition.² The concomitant use of drug regimens with foods, herbs and nutrients predisposes an individual to drug-food/herb/fruit interactions.³ However, such interactions can result to treatment failure or drug toxicities.⁴ Reports have indicated that a large proportion of the human population takes at least one pharmacologically active agent on a regular basis.

Metoclopramide increases gastrointestinal motility and hence used as a prokinetic agent in the management of drug-induced nausea and vomiting, diabetic gastroparesis and migraine headaches.⁵ Metoclopramide is well absorbed orally with a bioavailability of about 35% -100% and a half-life of 3-4 h in man.⁵

Psidium guajava L (Guava) is an important staple fruit and medicinal plant cultivated and consumed in tropical and sub-tropical countries. It is known to be used in folk medicine

around the globe.^{6,7} *Psidium guajava* contains a number of bioactive metabolites, such as phenolics, flavonoids, carotenoids, terpenoids, and triterpenes.⁸ Studies have demonstrated the effects of guava extracts on drug transport. For example, Junyaprasert et al.⁹ showed that the fruit extract showed a potent inhibitory effect on P-gp -mediated efflux in Caco-2 cells. They also indicated *Psidium guajava* to inhibit efflux transport in rat ileum suggestive of a possible interaction with P-gp substrates, such as digoxin, metoclopramide, fexofenadine, indinavir, vincristine, colchicine, and paclitaxel in the small intestine.⁹ Therefore, our study investigated the effect of *Psidium guajava* on the pharmacokinetics of metoclopramide in rabbits to establish a preclinical fruit-drug interaction model.

MATERIALS AND METHODS

Materials

Metoclopramide 10mg tablets USP (TEVA UK Limited, Eastbourne), methylated spirit (JHD, China), Sulphuric acid (99%), Sodium hydroxide and acetonitrile were obtained from Loba Chemie Pvt. Ltd. All other chemicals were of

reagent grade and all the solvents used were of high-performance liquid chromatography (HPLC) grade.

Preparation of *Psidium guajava* fruit

Psidium guajava (guava) fruit (4 kg) was obtained from Choba, Port Harcourt, Nigeria in July. The sample was washed with clean tap water to remove dirt. The fruit was cut in small sizes and blended into a pulp with an electronic blender.

Pharmacokinetic studies in rabbits

Five local strains of health adult male rabbits (1.88 ± 0.7 kg) were used in the experiment. Animal ethics and proper handling methods were strictly adhered to. They were kept in the animal house of the department of Experimental Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Port Harcourt, Nigeria for two weeks with free access to food and water before the experiment. Animals were fasted for 12 h prior to dosing and fed approximately 4 h post-dose.

Experiment was carried out in two phases.¹⁰ In phase 1, each rabbit was given 0.5mg/kg of metoclopramide¹¹ via oral route. At pre-determined intervals of 0.5, 1, 2, 4, 5.5, and 7 h, blood samples were aseptically withdrawn from the marginal ear vein of the rabbits. Blood samples were collected into heparinized tubes, and centrifuged for 20 minutes at 4,000 rpm. Aliquots of aspirated supernatant plasma were stored in a freezer until analyzed. The rabbits were again allowed free access to food and water for one week, during which the drug was assumed to have been removed from the animal system. The animals were then used for the next phase of the experiment.

After the withdrawal of blood in the first phase, the rabbits were allowed a one-week drug 'wash-out' period before the commencement of the second phase and during this period, they had free access to food and water. It was assumed that all the drugs must have been eliminated within this period ($T_{1/2}$ of metoclopramide = 3-4 h). The second phase started on the 8th day by the administration of 0.5mg/kg of metoclopramide orally to each rabbit and almost immediately, 5mL/kg of *Psidium guajava* pulp was administered orally to each rabbit. Blood samples were collected at similar time intervals and analyzed as described above. For each animal, the plasma concentration of metoclopramide was compared when the drug was administered alone to when it was administered concomitantly with *Psidium guajava* pulp. The results were plotted as metoclopramide plasma concentration versus time to obtain a plasmatic curve, from which the pharmacokinetic parameters were calculated.

HPLC Assay

The plasma concentrations of metoclopramide were determined by the HPLC method reported by Cossu et al. (2008). In a centrifuge test tube (10 ml), 250 μ l of 1 M sodium hydroxide solution were added to 0.5 ml of plasma and the mixture was shaken on a vortex for 30 sec. Methylene chloride (5 mL) was added for drug extraction, and the mixture was stirred again for 2 min and centrifuged for 7 min at 4,000 rpm. Following centrifugation, the organic phase was transferred into a flask and evaporated at reduced pressure. The residue was reconstituted in 200 μ l of acetonitrile and 0.01 N sulphuric acid 20/80 (v/v) solution, and sonicated for 5 min. The resultant turbid solution was centrifuged and the supernatant analyzed by HPLC (Rayleigh model LT 100) to determine the amount of metoclopramide extracted. Separation and quantification were made on a 250 4.6 mm (i.d.) ODS Waters XTerraTM column (5 mm

particle size), preceded by a ODS XTerraTM, 5 mm, guard column (Waters, Milan, Italy). A 100 μ L amount of calibration plasma standard or extracted sample was directly injected onto the column and eluted with mixtures of acetonitrile and 0.01 N sulphuric acid solution 15/85 (v/v), at a flow rate of 1.5 ml/min over 15 min. All determinations were performed at room temperature. Detection was accomplished using a variable UV/Vis detector (Hewlett- Packard 1050 series) set at 213 nm wavelength. Peak areas determined with a 3390 integrator were used for data acquisition and processing (Hewlett- Packard, Waldbronn, Germany). The calibration curve from the standard samples was linear over the concentration range of 0 to 100 ng/mL. The intra-day ($n = 5$) and inter-day ($n = 5$) coefficients of variation were less than 15% and the detection limit was 1 ng/mL.

Determination of Pharmacokinetic Parameters

Plasma metoclopramide concentrations were analyzed by a non-compartmental method. 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 7 hours [AUC (0-7)] by the linear trapezoidal method. The AUC from time 0 to infinity [AUC (0- ∞)] was calculated as AUC (0-7) plus AUC from 7 hours to infinity [AUC (7- ∞)], which was determined by dividing the final plasma drug concentration by K_{el} . C_{max} and the time to reach C_{max} (T_{max}) were obtained directly from the experimental data. Absorption rate constant (K_a) was derived by the method of back feathering from the graph of average serum concentration against time (absorption phase), using the relationship: slope = $-0.43K_a$. The rate of clearance of metoclopramide from plasma was determined using the relation: $CL_T = K_{el} \cdot V_d$; where V_d is the volume of distribution.

Statistical Analysis

Results were expressed as mean \pm standard error of mean. The significance of the difference between means of the control and test groups were determined using the Student's t-test. A P value of <0.05 was considered statistically significant.

RESULTS

Effect of *Psidium guajava* on the oral exposure of metoclopramide in rabbits

Pharmacokinetic parameters in the rabbits after oral administration of metoclopramide in the presence or absence of *Psidium guajava* are summarized in Table 2 and the plasma concentration-time profiles are presented in Figure 1. A graph showing percentage change in concentration due to *Psidium guajava* administration is shown in Figure 2. Administration of *Psidium guajava* to rabbits caused an increase in the oral exposure of metoclopramide. There was about 13% increased in AUC (0-7 h) in the group that received *Psidium guajava* and metoclopramide with a corresponding 177 % increase in C_{max} . Elimination rate decreased by 88% in the group that received *Psidium guajava*. Absorption rate constant increased by 207 % with a corresponding decrease in clearance rate (17%) resulting in drug accumulation. The half life of metoclopramide increased from 4.5 h to 7.7 h (71% increases). The time to reach peak plasma concentration was decreased from 2 h to 1h in the group that received *Psidium guajava*. This suggests that time to reach steady-state concentration may be reduced resulting in elevated plasma concentration of *Psidium guajava*. Percentage change in metoclopramide plasma

concentrations (0.5-7 h) are shown in figure 2. At 0.5 h, there was a 4 % decrease in concentration in the group that received *Psidium guajava*.

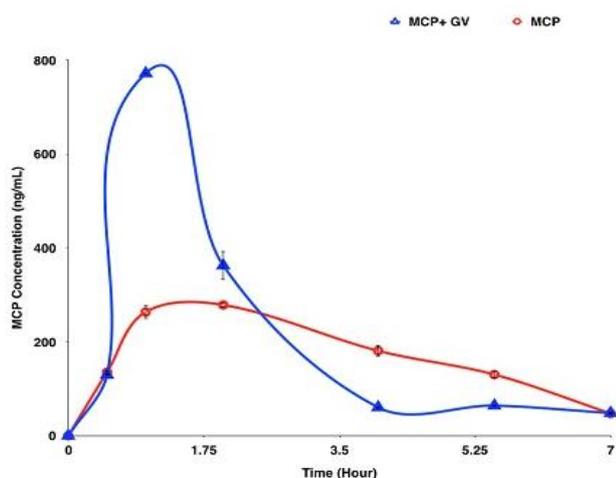


Figure 1: Mean plasma concentration-time profiles of metoclopramide after an oral administration of metoclopramide (0.5 mg/kg) to rabbits in the presence and absence of *Psidium guajava* (mean \pm SEM, $n = 5$). MCP (metoclopramide, 0.5 mg/kg, p.o.); MCP + GV (combined use with 5 mL mg/kg of *Psidium guajava*).

This increased by 193% and 30 % at the 1 and 2 hours respectively. However at 4 and 5.5 h, there was a 67 % and 103% decrease in concentration with a 2% increase at the 7th hour.

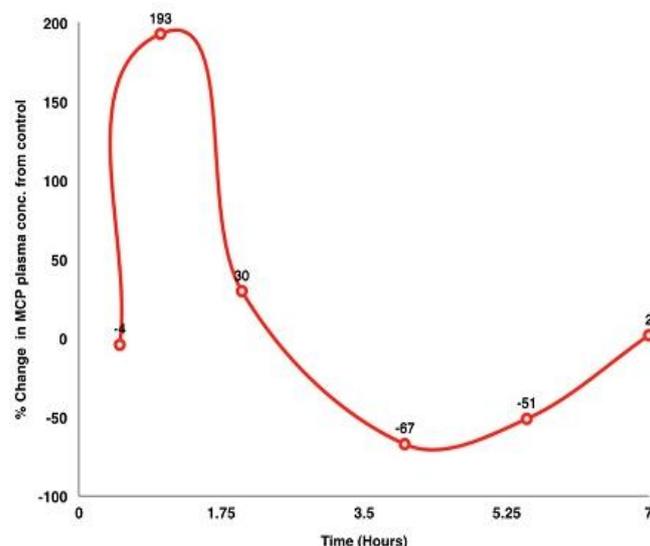


Figure 2: Percentage change in metoclopramide (MCP) plasma concentration (0-7 h) when co-administered with *Psidium guajava*.

Table 1: Pharmacokinetic parameters of metoclopramide after an oral administration of metoclopramide (0.5 mg/kg) to rabbits in the presence and absence of *Psidium guajava* (mean \pm SEM, $n = 5$). * $P < 0.05$, compared to the control given metoclopramide alone.

Parameters (unit)	AUC ng/h/ml	Tmax (hr)	Cmax (ng/ml)	Ka (hr)	Cl (L/hr/kg)	T _{1/2} (hr)	Kel (hr)
MCP	1230 \pm 150.00	2 \pm 0.05	278.5 \pm 24.20	0.27 \pm 0.01	0.81 \pm 0.03	4.50 \pm 0.04	0.75 \pm 0.01
MCP + <i>Psidium guajava</i>	1393 \pm 170.00	1 \pm 0.02	771.4 \pm 31.10*	0.83 \pm 0.02*	0.67 \pm 0.01	7.70 \pm 0.08*	0.09 \pm 0.01*
% Change in AUC from control	13%	-50%	177%	207%	-17%	71%	-88%

DISCUSSION

Bioactive phytochemicals in fruits and vegetables can be beneficial for health. However, these phytochemicals can influence the pharmacological properties of drugs by altering their absorption characteristics via interactions with drug transporters and drug-metabolizing enzymes.⁴ Efflux proteins found in the intestinal epithelium such as P-glycoprotein (P-gp) have been shown to reduce the absorption of certain compounds that are substrates hence decreasing their bioavailability.¹² In addition, the bioavailability of drugs could be decreased or increased when co-administered with other compounds that inhibit or induce enzymes that metabolise them. Studies have revealed that important constituents of certain fruits and vegetables significantly inhibit enzyme function *in vitro*.¹³ For example, studies have revealed that sevilla orange was shown to inhibit CYP3A4 and P-glycoprotein.¹⁴ Results from these studies implicated several furanocoumarins and bioflavonoids to be responsible for this inhibition.¹⁵ Furthermore, grapefruit juice has been demonstrated to increase the oral bioavailability of some therapeutic agents such as felodipine, nifedipine, saquinavir, and sildenafil.¹⁶⁻¹⁸ This increase was attributed to inhibition of intestinal CYP3A4 drug metabolism by phytochemicals present in

grape juice.^{17,18} Grapefruit was also reported to inhibit intestinal P-gp activity of certain drugs such as cyclosporine, hence increasing its oral bioavailability.¹³ These results strongly suggest that several furanocoumarins and bioflavonoids present in fruits are potent inhibitors of metabolising enzymes and drug transporters.

Metoclopramide is a gastro-prokinetic and antiemetic drug which acts as an antagonist at D₂ receptors in the chemoreceptor trigger zone in the central nervous system.¹⁹ Metoclopramide was administered in a tablet form, and therefore its absorption and metabolism may be affected by the activity of the excretory transporters and drug metabolizing enzymes. Several researches have indicated that the absorption of metoclopramide in small intestinal mucosa was mainly mediated by P-gp, and metoclopramide was mainly metabolized by CYP2D6.¹⁹⁻²¹ Therefore, the potential drug-drug interaction of metoclopramide mediated by CYP450 and P-gp might happen.

Important bioactive metabolites such as phenolics, flavonoids, carotenoids, terpenoids, and triterpenes, have been identified in *Psidium guajava*.⁸ Specifically, *Psidium guajava* contains flavonoids such as quercetin and phloretin which are known inhibitors of P-glycoprotein.⁴ Studies carried out by Junyaprasert et al.⁹ demonstrated the

inhibition of P-gp in rat ileum suggesting that *Psidium guajava* could interact with P-gp substrates in the small intestine.

In our study, co-administration of metoclopramide with *Psidium guajava* fruit increased the oral exposure (AUC and C_{max}) (Table 1) of metoclopramide in rabbits. The observed deviation in the pharmacokinetics of metoclopramide strongly suggests an inhibition of P-glycoprotein (P-gp) enzyme and P450 enzymes (CYP2D6) by the phytochemical constituents present in *Psidium guajava*. Inhibition of P-gp resulted to to enhanced absorption and consequently increased bioavailability. This may explain the observed significant increase in C_{max} (177%), K_a (207%) and non-significant increase in AUC (13%). On the other hand, inhibition of metabolism by P450 enzymes (CYP2D6) resulted in drug accumulation which could be responsible for the increase in half-life (71%) noted when *Psidium guajava* and the drug were administered together to the animals. This inhibition also explains the decreased elimination rate (88%) and decreased clearance (17%) observed when the drug was administered with the fruit. The alterations in the pharmacokinetic properties of metoclopramide could result in unwanted side effects and toxicities. The plasma concentration of metoclopramide (in the group that received *Psidium guajava*) increased maximally at 1 hour (193%) (Figure 2) and reduced afterwards indicative of the point of maximal inhibitory effect on P-gp. Considering the therapeutic importance of metoclopramide and its relative cheapness and availability, a possible co-administration may occur in patients.

Our data demonstrates preliminary evidence of the interaction between *Psidium guajava* and metoclopramide but the clinical significance of this is yet to be fully evaluated. In our opinion, *Psidium guajava* should be consumed with caution by patients taking metoclopramide to avoid toxicity/adverse effects of the drug. Furthermore, a large number of drugs are substrates for P-gp, the concomitant use of *Psidium guajava* or *Psidium guajava*-containing diets may provide some therapeutic benefits to enhance the pharmacokinetic features of poorly absorbable P-gp substrates.

CONCLUSION

Psidium guajava enhanced the oral exposure of metoclopramide possibly by the inhibition of P-gp-mediated efflux during intestinal absorption and inhibition of P450 enzymes (CYP2D6) during metabolism. This suggests that the combined use of *Psidium guajava* or *Psidium guajava*-containing diet with metoclopramide may require close monitoring for potential drug-diet interactions.

AUTHOR CONTRIBUTIONS: C.N.A designed the study, drafted the manuscript and interpreted the results. P.O.A and C.N.A collected test data.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

FUNDING: This research received no external funding.

REFERENCES

- Liu RH: Potential synergy of phytochemicals in cancer prevention: mechanism of action. *J Nutr* 2004; 134:3479S-85S.
- Evans AM: Influence of dietary components on the gastrointestinal metabolism and transport of drugs. *Ther Drug Monit* 2000; 22:131-136.
- Mallhi TH, Sarriff A, Adnan AS, Khan YH, Qadir MI, Hamza AA, Khan AH: Effect of Fruit/Vegetable-Drug Interactions on CYP450, OATP and p-Glycoprotein: A Systematic Review. *Tropical Journal of Pharmaceutical Research* 2015; 14:1927-1935.
- Rodríguez-Fragoso L, Martínez-Arismendi JL, Orozco-Bustos D, Reyes-Esparza J, Torres E, Burchiel SW: Potential Risks Resulting from Fruit/Vegetable- Drug Interactions: Effects on Drug-Metabolizing Enzymes and Drug Transporters. *J Food Sci* 2011; 76:R112-R124.
- Radwan AM, Determination of metoclopramide in serum by HPLC assay and its application to pharmacokinetic study in rats. *Analytical letters* 1998; 31:2397-2410.
- Jouad H, Haloui M, Rhiouani H, El Hilaly J, Eddouks M: Ethnobotanical survey of medicinal plants used for the treatment of diabetes, cardiac and renal diseases in the North centre region of Morocco (Fez-Boulemane). *J Ethnopharmacol* 2001; 77:175-82.
- de Wet H, Nkwanyana MN, van Vuuren SF: Medicinal plants used for the treatment of diarrhoea in northern Maputaland, KwaZulu-Natal Province, South Africa. *J Ethnopharmacol* 2010; 130:284-289.
- Qian H, Nihorimbere V: Antioxidant power of phytochemicals from *Psidium guajava* leaf. *J Zhejiang Univ Sci* 2004; 5:676-683.
- Junyaprasert VB, Soonthornchareonnon N, Thongpraditchoe S, Murakami T, Takano M: Inhibitory effect of Thai plant extracts on P-glycoprotein mediated efflux. *Phytother Res* 2006; 20:79-81.
- Nwafor SV, Esimone CO, Amadi CA, Nworu CS: *In vivo* interaction between ciprofloxacin hydrochloride and the pulp of unripe plantain (*Musa paradisiaca*). *Eur J Drug Metab Pharmacokinet* 2003; 28:253-258.
- Cossu M, Sanna V, Gavin E, Rassu G, Giunchedi PA: New Sensitive Reversed-phase High- performance Liquid Chromatography Method for the Quantitative Determination of Metoclopramide in Canine Plasma. *Analytical Letters* 2008; 41:767-778.
- Kunta JR, Sinko, PJ: Intestinal drug transporters: *In vivo* function and clinical importance. *Current Drug Metabolism*, 2004; 5:109-124.
- Kim RB: Organic anion-transporting polypeptide (OATP) transporter family and drug disposition. *European Journal of Clinical Investigation* 2003; 33:1-5.
- Greenblatt DJ: Analysis of drug interactions involving fruit beverages and organic anion transporting polypeptides. *Journal of Clinical Pharmacology* 2009; 49:1403-1407.
- Kamath AV, Yao M, Zhang Y, Chong S: Effect of Fruit Juices on the Oral Bioavailability of Fexofenadine in Rats. *Journal of Pharmaceutical Science* 2004; 94:233-239.
- Bailey DG, Malcolm J, Arnold O, Spence JD: Grapefruit juice - drug interactions. *Br J Clin Pharmacol* 1998; 46:101-110.
- Dresser GK, Bailey DG: The effects of fruit juices on drug disposition: A new model for drug interactions. *Eur J Clin Invest* 2003; 33:10-16.
- Lown KS, Bailey DG, Fontana RJ, Janardan SK, Adair CH, Fortlage LA, Brown MB, Guo W, Watkins PB: Grapefruit Juice increases felodipine oral availability in humans by decreasing intestinal CYP3A4 protein expression. *J Clin Invest* 1997; 99:2545-2553.
- Desta Z, Wu GM, Morocho AM, Flockhart DA: The gastroprokinetic and antiemetic drug metoclopramide is a substrate and inhibitor of cytochrome P450 2D6. *Drug metab Dispos* 2002; 30:336-343.
- Pottier, G., Marie, S., Goutal, S., Auvity, S., Peyronneau, M.A., Stute, S., Boisgard, R., Dolle, F., Buvat, I., Caille, F., Tournier, N: Imaging the Impact of the P-Glycoprotein (ABCB1) Function on the Brain Kinetics of Metoclopramide. *Journal of Nuclear Medicine* 2016, 57:309-314.
- Livezey MR, Briggs ED, Bolles AK, Nagy LD, Fujiwara R, Furge LL: Metoclopramide is metabolized by CYP2D6 and is a reversible inhibitor, but not inactivator, of CYP2D6. *Xenobiotica* 2014; 44:309-319.