Cytochrome P450 (CYP)-mediated drug–drug interactions are major causes for terminating the development of particular drugs or withdrawals of drugs from the market, due to adverse effects. Inhibition of CYP activity is a major cause of drug-drug interactions, since it results in accumulation of drugs which could otherwise be converted into less toxic products. Inhibition of glutathione S-transferases (GSTs) by drugs and other xenobiotics may also result in toxicities and adverse drug reactions, since GSTs are primary detoxification enzymes.

The aim of the investigations was to evaluate the drug-drug/food and -herb interaction between plant derived components, CYPs and GSTs, all important drug metabolizing enzymes. Curcumin, a yellow pigment and major component of curry a potential drug candidate, and a commonly used spice, was used as a model compound in these studies. Thirty-four curcumin analogues and seven medicinal plants from Ghana were analogously studied for drug-drug/food -herb interaction potential. High performance liquid chromatography (HPLC) and spectrophotometric assays were used to evaluate CYP and GST inhibitory activities. Our results suggest that inhibition of CYP3A4 and to a lesser extent CYP2C9 by curcumin has the potential to cause clinically significant drug-drug interactions. The curcumin analogues might have better prospects than curcumin since most of them have weaker CYP and GST inhibitory activities. Quantitative structure-activity relationship analysis suggested structural features of the curcumin analogues related to the observed activities. Most of the medicinal plants from Ghana lacked strong potential to inhibit the CYPs and GSTs. These results are important for companies developing curcumin as a drug, and will guide further design and synthesis of curcumin analogues with less CYP and GST inhibitory activities. Additionally, Food and drugs board in Ghana and countries were these medicinal plants are used will be informed of their potential harmful effects.

MSc Regina Appiah-Opong.

Thesis title: ‘Drug biotransformation enzyme interactions. Studies with Curcumin, Curcumin analogues and other plant-derived components’

Promoter: Prof. dr. N.P.E. Vermeulen, Molecular Toxicology Section, Vrije Universiteit Amsterdam. Tel.: 020-5987590; email: npe.vermeulen@few.vu.nl