

# DEVELOPMENT OF *IN VITRO* SPECIFIC ASSAYS FOR SCREENING OF DRUG HERB PHARMACOKINETICS INTERACTIONS FOR COMMONLY USED MALAYSIAN HERBS

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## INTRODUCTION

Herbal products are popular in the treatment of many diseases. Since they are natural products, they contain phytochemicals with capabilities to inhibit or induce drug-metabolising enzymes including cytochromes P450 (CYPs). This project aimed to develop *in vitro* enzyme assays as activity markers for major human liver microsomal CYP isoforms; to elucidate modulatory effects of commonly used Malaysian herbs on CYP activities; to determine herbal constituents involved in the interactions; and to predict clinically significant pharmacokinetic interactions in *in vivo* settings.

## METHODOLOGY

A total of eight HPLC (high-performance liquid chromatography) and fluorescence-based assays that served as CYP activity markers were established and used to examine modulatory effects by herbal components. Herbs investigated included *Andrographis paniculata* (hempedu bumi), *Centella asiatica* (pegaga), *Orthosiphon stamineus* (misai kucing), *Labisia pumila* (kacip Fatimah) and *Eurycoma Longifolia* (Tongkat Ali).

## RESULTS

Different herbs inhibited different CYP isoforms with varying degrees. *A. paniculata* exhibited moderate degree of inhibition towards CYP3A4 but andrographolide, its major constituent, did not inhibit significantly any isoform. *C. asiatica* caused greater degree of inhibition in CYP2C9 and CYP2C19 compared to other isoforms with its two constituents, asiatic acid and madecassic acid, demonstrating moderate to potent inhibition. *O. stamineus* selectively inhibited CYP3A4 with less inhibition observed in CYP2C19 and CYP2D6. One of its constituents, eupatorin, was found to inhibit CYP3A4 and CYP2D6 potently, implying potential risk for drug-herb interaction. *L. pumila* dichloromethane extract caused potent inhibition in CYP2C8 and CYP2C9

with  $K_i$  values below 1  $\mu\text{g/ml}$ , indicating likelihood of interaction. Moderate inhibition was also found in CYP2C19 and CYP1A2. Eurycomanone, the active constituent of *E. Longifolia*, did not exhibit significant inhibition on the CYP isoforms examined, indicating negligible risk of interaction.

## CONCLUSION

The five local herbs investigated showed differential effect on CYP activities. Our data show a significant potential for CYP-mediated drug-herb interactions for both *L. pumila* and *O. stamineus*. The other three herbs, *A. paniculata*, *C. asiatica* and *E. Longifolia*, however demonstrate much lesser risk of interaction.