CHAPTER I

INTRODUCTION

Herbal medicines have received great attention as alternative medicines in recent years and been sold as dietary supplement or health food. Asiatic Pennywort, called *Centella asiatica* (L.) Urban in Umbelliferae family, has been used as a traditional herbal medicine in native countries like Sri Lanka, Madagascar, South Africa, India and Thailand, for hundreds of years. It is a perennial, herbaceous creeper growing to 50 cm. with fan shaped leaves (Singh, 1969). The active compounds isolated from *C. asiatica* are the triterpene acid and their glycosides, including asiatic acid, madecassic acid, asiaticoside and medecassoside (Inamdar et al., 1996). Asiaticoside which is the most abundant triterpene glycoside is effective in wound healing (Shukla et al., 1999). Additionally, there are several therapeutic effects, such as burning wound healing, heart enhancement (มาโนช วามานนท์ และ เพ็ญนภา ทรัพย์เจริญ, 2538), anti-oxidant effect (Hamida et al., 2002), cardio protective effect (Gnanapragasam et al., 2004), learning and memory improvement (Sulochana et al., 2005), decreasing the lipid peroxidation in brain (Veerendra and Gupta, 2002), anti-cancer activity (Bunpo et al., 2005). Therefore, this plant was subjected to extensive studies aiming to develop *C. asiatica* as an alternative drug.

A research group in the Faculty of Pharmaceutical Sciences, Chulalongkorn University has been granted the Research Funding in the name of "Research and Development of Standardized Pharmaceutical and Cosmetic products from Medicinal Plants *Centella asiatica* to Industrial Production Scale". From 2003 to 2005, the standardized extract of *C. asiatica* has been established with well-defined ratio of the active ingredient. The extract was claimed to be able to attenuate learning and memory deficit induced by bilateral common arteries occlusion in both Morris Water Maze and Step-down test. Then long term study on the toxicology and other pharmacological aspects are still required before performing clinical study in human. In addition to the safety information of this extract regarding subchronic/chronic toxicity, the study on the effect of the extract on cytochrome P450 (CYP) would be important in term of the possibility of drug-drug interaction when the extract was co-administered with medicines that are metabolized by CYPs.

During the research and development process of a new compound, drug-drug interaction study is one of the essential processes in pre-clinical and clinical studies particularly effect of the compound on CYP enzymes. CYP is an enzyme system in phase I metabolism, that play an important role in detoxification or in the other hand, metabolic activation of xenobiotics so as to be further detoxified by the conjugative reactions of phase II metabolism then readily excreted from the body. Thus inhibition and/or induction of CYP enzymes by any compounds may lead to the change of plasma level of drugs that are metabolized by CYPs administered resulting in an increase of side effects /drug toxicity or in the other hand decrease of drug efficacy. Therefore, an attempt to develop the standardized extracted of *C. asiatica* for use clinically, safety study regarding drug-drug interaction should be clarified.

In addition to the drug-drug interaction issue, effect of the standardized extract of *C. asiatica* on CYP would address whether this extract affects human susceptibility to exogenous mutagens/pro-carcinogen. This is due to the fact that many CYP isoforms play a role in xenobiotic bioactivations. As a result, this study investigated effects of the standardized extract *C. asiatica* on CYP isoforms that play key role in drug metabolism and the bioactivation of mutagens and/or carcinogens. Such CYP isoforms included CYP1A1, 1A2, 2B1/2B2, 2E1 and 3A.

Hypothesis

The standardized extract of *C. asiatica* demonstrated an inductive and/or inhibitory effects on rat hepatic microsomal CYPs.

Study design and process

1. Animal treatment: an *in vivo* study
2. Preparation of rat liver microsomes.
3. Determination of total CYP contents and CYP activities in rat liver microsomes.
4. Inhibitory effect of the standardized extract of *C. asiatica* on CYPs: an *in vitro* study.
5. Data analysis.

Anticipated benefits from the study

1. The possibility of drug-drug interaction when the standardized extract of *C. asiatica* was taken simultaneously with other medicines metabolized by CYP isoform was assessed.

2. A preliminary data of the standardized extract of *C. asiatica* whether it possessed an inductive and/or inhibitory effects on hepatic CYP, of which isoforms involving in various bioactivation reactions of certain drugs, chemicals as well as environmental toxicants resulting in reactive metabolites. This would be useful to estimate the possibility of the standardized extract of *C. asiatica* to increase and/or decrease risks of chemical-induced toxicities, mutagenesis and/or carcinogenesis.