CHAPTER I

INTRODUCTION

Curcuma comosa Roxb. is a plant in family Zingiberaceae. It is an indigenous plant of Thailand with a common name in Thai as Waan Chak Mod look (เต็ม สมิตินันท์, 2543). Rhizomes of *C. comosa* has been used extensively in Thai traditional medicine as an anti-inflammatory agent particularly for the treatment of female postpartum uterine inflammation and lower abdominal pain in male. Rhizomes of *C. comosa* comprise various chemical compounds include diarrylheptanoids (*trans*-1,7-diphenyl-5-hydroxy-1-heptene, *trans*-1,7-diphenyl-6-hepten-3-one-5-ol, *trans*-1,7-diphenyl-3-acetoxy-6-heptene, *trans*-1,7-diphenyl-6-heptene-3-one, *trans,trans*-1,7-diphenyl-1,3-heptadien-5-ol, *trans,trans*-1,7-diphenyl-4,6-heptadien-3-one (Jurgens et al., 1994), 1,7-diphenyl-5-hydroxy-(1*E*)-1-heptene, 5-hydroxy-7-(4-hydroxyphenyl)-1-phenyl-(1*E*)-1-heptene, 7-(3,4-hydroxyphenyl-5-hydroxy-1-phenyl(1*E*)-1-heptene) (Suksamrarn et al., 1997) and phloracetophenone glucoside (4,6-dihydroxy-2-*O*-(*β*-D-glucopyranosyl) acetophenone) (Suksamrarn et al., 1997). Many studies have revealed pharmacological effects of *C. comosa*, such as uterotrophic effect (Piyachaturawat et al., 1995a; อนุกูล สวัสดิ์พาณิชย์, 2537), estrogenic-like effect (Piyachaturawat et al., 1998; 1999), anti-inflammatory effect (Jantaratnotai et al., 2006; Sodsai et al., 2007). The results from those studies supported the traditional uses of *C. comosa* as medicinal herb. Other pharmacological effects of *C. comosa* have also been documented such as choleretic effect (Piyachaturawat et al., 1996) which is the effect of phloracetophenone glucoside, the aglycone part of a glucoside from *C. comosa* (Suksamrarn et al.,1997), cholesterol lowering effect (Piyachaturawat et al., 1996, 2000 and 2002), and nematocidal effect (Jurgens et al., 1994).

Cytochrome P450 (CYP) is the phase 1 drug metabolizing enzyme system. Phase 1 reactions convert the parent hydrophobic drug to a more polar metabolite by oxidation, reduction or hydrolysis. These reactions expose or introduce a functional group into the drug molecule and usually result in an increase hydrophilicity of the drug and hence a more readily excretable form. In addition, the product of phase 1 drug metabolism may act as a substrate for phase 2 metabolism, which is generally

the true detoxification pathways. CYP contributes to the metabolism of a variety of substrates both endogenous and exogenous compounds including therapeutic drugs, carcinogens, steroids, eicosanoids, etc. (Zhou et al., 2004). Thus the resultant increases in polarity usually facilitate excretion and is considered to be a detoxification process, but in some instances, a foreign compound is converted to a product which causes much greater cytotoxicity, mutagenicity or carcinogenicity (Guengerich and Shimada, 1991; Gibson and Skette, 2001). CYP can be induced by a large number of exogenous agents including drugs, alcohol, components in the diet, cigarette smoke, etc. (Park et al., 1996). CYP induction may result in increasing CYP content and/or CYP activity. Induction may either attenuate the pharmacological response or exacerbate the toxicity of a particular drug or both. In contrast, some CYP isoforms can be inhibited by various inhibitors. CYP inhibition can take place in several ways, including the destruction of enzymes, inhibition of enzyme synthesis or by complexing and thus inactivating enzymes. When two or more drugs are co-administered, drug interaction may occur by CYP inhibition. A large number of substrates, inducers and inhibitors of CYP play a major role in drug-drug interactions.

As mentioned above, *C. comosa* is an interesting plant with many pharmacological effects that is potential to be developed for medicinal purposes. Although herbal medicines have been claimed to be non-toxic because of their natural origin and long-term use as folk medicines, effects of several medicinal plants on CYP induction and/or inhibition have been reported (Moon et al., 2006; Zhou et al 2004). Thus, to develop *C. comosa* for a medicinal purpose with safety in term of drug-drug interaction, effects of this plant on CYP need to be investigated. If the constituents in *C. comosa* are inhibitors and/or inducers of CYP, administration of *C. comosa* may has an impact on the pharmacokinetics of any co-administered drugs that are metabolized by the particular CYP isoform. These may result in plasma drug level change, a loss of drug efficacy or an increase of drug toxicity. Therefore, effects of *C. comosa* on liver microsomal CYP preliminarily indicate the possibility of drug-drug interaction when *C. comosa* is used concomittanly with other medicines.

As it is well known that CYP play a role in carcinogenesis. Metabolic activation of procarcinogens is often catalyzed by CYP including CYP1A1, 1A2, 2B6 3A4 and 2E1 (Guengerich, 2001). For example, CYP1A1 activates polycyclic aromatic hydrocarbons (PAHs) to biological reactive metabolites that interact with

DNA resulting in carcinogenesis. Induction of some CYPs is a risk factor in several cancers since these enzymes can convert procarcinogens to carcinogens. Thus, effect *C. comosa* on CYP isoforms involving carcinogenic bioactivation is needed to be investigated. The induction effect of *C. comosa* on CYP isoforms that bioactivate procarcinogens will indicate an increase risk of carcinogens by *C. comosa*. On the other hand, *C. comosa* may be classified as an anti-carcinogenic agent if it inhibits CYP isoforms which bioactivate carcinogens.

So far, only one study investigated effect of total crude ethanolic extract of *C. comosa* on CYP (Suknoy, 2004). In this study effects of *C. comosa* hexane extract and ethanolic extract were examined on hepatic microsomal CYPs especially the pivotal isoforms involved in drug metabolism and activation of mutagens and/or carcinogens. These CYP isoforms include CYP1A1, 1A2, 2B1/2B2, 2E1 and 3A, using an *ex-vivo* study in rats. In addition, effect of *C. comosa* hexane and ethanolic extract on clinical blood chemistry and hematology were also investigated to confirm the previous toxicity data of this plant in rats.

Hypothesis

C. comosa hexane extract and ethanolic extract demonstrated an induction or/and inhibition effects on hepatic microsomal CYP as well as caused changes of clinical blood chemistry and hematology in rats.

Study design and process

1. Animal treatment: an *ex-vivo* study
2. Blood collecting
3. Determination of clinical blood chemistry and hematology
4. Preparation of liver microsomes
5. Determination of total CYP contents and CYP activities
6. Data analysis

Anticipated benefits from the study

1. A preliminary data of *C. comosa* hexane extract and ethanol effect on hepatic CYP450. Modulation of CYP indicated the possibility of *C. comosa* to increase and/or decrease risks of chemical-induced toxicities, mutagenesis and/or carcinogenesis.

Also the data provided the possibility of drug-drug interaction information of these extracts were taken concurrently with other medicines metabolized by CYP isoform that was modulated by this extract.

2. The clinical blood chemistry and hematology data in rats given *C. comosa* in this study would provided an additional subacute toxicity data of *C. comosa* in rats.