CHAPTER I

INTRODUCTION

The rationale for the study

Alcoholic liver disease (ALD) is a major disease of morbidity and mortality worldwide [1,2]. In Thailand, the liver disease is one of the diseases that can cause death of patients [3]. Some studies reported that a patient with cirrhosis and superimposed alcoholic hepatitis had 60 % of a 4-year mortality [4]. The dose and time dependences of excess alcohol consumptions lead to ALD [5]. Toxic by-products of alcohol metabolism are mainly generated in hepatocytes by three major enzymes; alcohol dehydrogenase, microsomal ethanol oxidizing system (MEOS) by cytochrome P450 2E1 and catalase [6]. These enzymes play the important roles to development pathogenesis of ALD. The mechanisms of liver damages are mainly composed of three pathways: 1) intestinal permeability alteration 2) oxidative stress production, and 3) immunogenic effect. A range pathological changes of ALD are characterized by a progression from steatosis to chronic hepatitis, fibrosis and cirrhosis [7,8,9].

Up to date, treatment options for alcoholic liver disease including fatty liver, fibrosis (hepatitis) and cirrhosis are problematic. At this time, there is still no effective medicine for ALD. Most patients contact professional physicians when they already have symptoms of ALD. Therefore, the principle of treatment focuses predominantly on reduction of decompositions caused by the disease and a liver transplantation. However, the transplantation has many limitations such as matched donate livers and cost expensively. The pathological progression of ALD are taken longer times depending on many genetic factors the alcohol consumption. The clinical treatments used for ALD are lifestyle modification, nutrition therapy, drug therapy, anti-tumor necrosis factor (anti-TNF) therapy and alternative medicines (e.g. silymarin, s-adenosylmethionine) [6, 10]. The choices of drug that have been used are corticosteroid, colchicine and propylthiouracil [4, 11,12, 13]. The effectivenesses of drug treatment in ALD are inconsistent in an individual patient.

Silymarin is probably the most widely used of complementary and alternative medicine in the treatment of the liver diseases. However, the potential benefit of silymarin remains a controversial issue [14]. Above this mention, there is an opportunity to find alternative medicines in Thailand. The idea of developing hepatoprotective agent from natural product has been investigated. Many clinical researches have reported the effect of several plants to treat liver diseases such as *Picrorhiza kurroa* (kutkin), *Camellia sinensis* (green tea), *Chelidonium majus* (greater celandine), *Glycyrrhiza glabra* (licorice), and *Allium sativa* [10]. Therefore, we are looking for the herbal plant in our country to use as a hepatoprotective agent.

Turmerics, *Curcuma longa* Linn are grown in southeast asia, the tropical countries, China, India as well as Thailand [15]. Major chemical constituents in turmeric comprise of volatile oil and the colouring compound, curcuminoids [16,17,18]. Curcuminoids are mixture of curcumin, monodemethoxycurcumin and bisdemethoxycurcumin [19]. For years, turmeric compound has been used as a spice, cosmetic ingredient, aromatic and herbal medicine [20]. Curcuminoids have variety of, pharmacological actions such as anti-inflammatory, anti-oxidant, anti-microbial and anti-cancer. Various studies have showed that curcumin, a mixture compound in curcuminoids, has antioxidant properties. The antioxidant activity of curcumin could be mediated through antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [21]. Moreover, the suppression of lipid peroxidation by curcumin could lead to the suppression of inflammation [22]. Its anti-inflammatory property appears to be modulated via the inhibition of induction of cyclooxygenase-2 (COX-2), lipoxygenase (LOX), inducible nitric oxide synthase (iNOS) and production of cytokines such as interferon-γ and tumor necrosis factor, and activation of transcription factors like NF-κB, and AP-1 [23]. The molecular basis of anti-cacinogenic and chemopreventive effects of curcumin is attributed to its effect on several targets including transcription factors, growth regulators, apoptotic genes, angiogenesis regulators and cellular signaling molecules. Traditionally, many countries have been applied turmeric and natural curcuminoids as a therapeutic preparation for many ailments. It is used to treat diseases associated to gastrointestinal tract such as dyspepsia, peptic ulcer, and liver disorders [24]. There are some published literatures shown that curcuminoids protect the animal livers from

variety of hepatoxic substances such as carbon tetrachloride, galactosamine, pentobarbital, l-chloro-2-4-dinitrobenzene, 4-hydroxy-nonenal and acetaminophen [10]. In Thailand, people also use turmeric in traditional treatments as well as an alternative treatment for gastrointestinal disorders. Moreover, turmeric is one of the list herbal medicine products in the national of essential medicines. It has been encouraged to use in hospitals. The properties of curcuminoids contribute to support the notion of their many biological cascades for ALD treatment.

We aim to determine a hepatoprotective effect of curcuminoids, the active mixture compounds in turmeric. Ethanol-induced hepatotoxicity rats will be use as animal model in this study in which the model resemble the chronic pathological process of ALD patient. Moreover, we will investigate the possibility of mechanism of action of curcuminoids as a hepatoprotective agent in HepG2 hepatoma cells culture. This finding may encourage the usage of curcuminoids from turmerics as the hepatoprotective treatment for ALD in our country.

Hypothesis

We hypothesized that curcuminoids have the hepatoprotective effects in ethanol induced toxicity rats and HepG2 cells and the mainly mechanism of curcuminoids as the hepatoprotective agent may involve an antioxidant and anti-inflammatory properties.

Objectives of the study

1. To evaluate effect of curcuminoids on liver function enzymes in ethanol fed rats.
2. To determine effect of curcuminoids on lipid peroxidation and antioxidant enzymes in rat microsomes.
3. To examine effect of curcuminoids on histological liver tissue in ethanol-induced toxicity rats.
4. To determine effect of curcuminoids on cytotoxicity, lipid peroxidation and nitric oxide (NO) production in ethanol-stimulated HepG2 cells.

Expected outputs of the study

To gain the knowledge of curcuminoids on ethanol induced toxicity in animals and cell culture, and understand the possibility mechanism of action of curcuminoids as a hepatoprotective agent.

Expected outcomes

Curcuminoids may be used in alcoholic liver disease patients as the hepatoprotective agent.