CHAPTER I
INTRODUCTION

1.1 Rationale and background

Hypertension is a common cardiovascular disorder that causes of morbidity and mortality worldwide. Hypertension can be primary or essential, with no identifiable underlying cause, but has been linked to family history of hypertension and various risk factors including, obesity, high blood glucose, age, smoking, high salt diet and physical inactivity. The remaining minority of patients have “secondary” hypertension where a cause is identified and linked to diseases of the renal, endocrine, vascular, pulmonary and central nervous systems (Chiong *et al.*, 2008). The prevalence of hypertension increases in worldwide, approximately 40% of adults aged 25 and above had been diagnosed with hypertension; the number of people with the condition rose from 600 million in 1980 to 1 billion in 2008 (WHO, 2013). In Thailand, the prevalence of hypertension and prehypertension weighted to the national 2004 population from a nationally representative sample of 39,290 individuals aged ≥ 15 years was 22.0% and 32.8%, respectively, with a higher prevalence in men compared to women (Aekplakorn *et al.*, 2008). Remarkably, hypertension is the major risk factor of burden of disease (Bundhamcharoen *et al.*, 2011), the document from the Bureau of Epidemiology of the Ministry of Public Health of Thailand showed that the rate of mortality in Thai population in 2010-2012, (21,142 deaths per 100,000) from heart diseases and 3,684 deaths per 100,000 from hypertension (MOPH, 2013). The data suggest that prevalence of hypertension is rising rapidly, and spreads across regions in Thailand and all around the world. The increase in cardiovascular risk inherent to hypertension leads to premature morbidity and mortality. Prevention of blood pressure combined with lifestyle interventions or pharmacological treatments are associated with reductions in the risk of stroke and coronary events and appear to reduce to a lesser degree of the incidences of other complications (Williams, 2009).

Angiotensin II (Ang II) and nitric oxide (NO) have been reported to be a key factor in regulation of blood pressure (Zhou *et al.*, 2004). Inhibition of NO production stimulates the activation of the renin-angiotensin-aldosterone system (RAAS) which leads to elevation of arterial blood pressure and reproduces many aspects of the pathological conditions related to the hypertension (Koyanagi *et al.*, 2000; Priviero *et al.*, 2007). Therefore, restoration of Ang II and NO imbalance might be an important component to prevent/or treatment of vascular pathophysiology in hypertension. In this study, two experimental models have selected for studying the beneficial effect of dietary antioxidant on the prevention of hypertension. The first model is the N^{ω} –nitro-L-arginine metyl ester (L-NAME)-induced hypertension. Chronic administration of L-NAME, a NO synthase inhibitor, reduces NO production and leads to endothelial dysfunction. This model mimics a primary hypertension found in humans. The second model is the 2kidney-1clip (2K-1C) renovascular hypertension. This model has a clinical consequence of excessive stimulation of the RAAS and mimics a secondary hypertension occurred in humans.

Hypertension is strongly associated with vascular dysfunction and remodeling (Anderson *et al.*, 2000; Humphrey, 2008; Lemarie *et al.*, 2010). Compelling data from molecular and cellular experiments, together with animal studies, implicate a role for oxidative stress in hypertension. Hypertension may be both a cause and an effect of hypertension (Puddu *et al.*, 2008). Reactive oxygen species (ROS) play a physiological role in controlling endothelial function, vascular tone and cardiac function, and play pathological roles in inflammation, hypertrophy, proliferation, apoptosis, migration, fibrosis and angiogenesis. All of these important processes and artributable to the endothelial dysfunction, increased contraction of vascular smooth muscle (VSM) and structural remodeling causing increased peripheral resistance and elevated blood pressure (Dollery *et al.*, 1995; Forstermann, 2008; Lee and Griendling, 2008). Previous studies have demonstrated that a group of zinc endopeptidases called matrix metalloproteinase (MMPs) play an important role in vascular dysfunction and remodeling in many cardiovascular diseases, including hypertension (Bouvet *et al.*, 2005; Castro *et al.*, 2008; Galis and Khatri, 2002). Increased MMP activation leads to the degradation of extracellular matrix (ECM) proteins in the blood vessels and promotes the migration and proliferation of vascular smooth muscle cells (VSMCs) (Newby, 2006). ROS-induced MMP-2 and MMP-9 activation have been of particular interest in investigations into the role of vascular remodeling in hypertension (Bouvet *et al.*, 2005; Castro *et al.*, 2009; Walter *et al.*, 2008).

In recent years, growing interest in preventing cardiovascular disease using plant-based foods has generated numerous epidemiologic, pre-clinical and clinical studies (Hu and Willett, 2002). Such studies are important in extending our understanding of diet- cardiovascular disease relations beyond what we already know about individual nutrients.

Rice (*Oryza Sativa* L.) is one of the most commonly staple diets of Asian population. Rice bran is a major by–product obtained from the polishing process that produces white rice. Rice bran contains amounts of protein, dietary fiber and phenolic substances (Goufo and Trindade, 2014; Sereewatthanawut *et al.*, 2008; Wiboonsirikul *et al.*, 2007). Recent studies report protein hydrolysis extract from rice bran possessing free radical scavenging activity (Adebiyi *et al.*, 2009; Goufo and Trindade, 2014) Furthermore, rice bran enzymatic extract have shown the beneficial effect to attenuates dyslipidemia, insulin resistant, hypertension, and oxidative stress in obese rats (Boonloh *et al.*, 2015; Justo *et al.*, 2013; Justo *et al.*, 2013). Interestingly, previous studies done by our group found that rice bran protein (RBP) hydrolysates possess ACE-inhibitory activity, free radicals scavenging (Kokkaew and Thawornchinsombut, 2011), inducing vasorelaxion (Tuangpolkrung, 2012) and reducing inflammation via suppression of cytokine signaling pathways (Boonloh *et al.*, 2015). Nonetheless, there was no report on the antihypertensive effect of this antioxidative RBP.

Polyphenols play an important role in the maintenance of health and prevention of diseases. Curcumin (diferuloymethane) is an active ingredient of polyphenolic curcuminoids extracted from the rhizomes of turmeric (*Curcuma longa* Linn.) of the Zingiberaceae family. Curcumin (CUR) has been well recognized as a dietary spice for centuries and its pharmacological activity have been studied in various animal models and clinical investigations into, among others, its anti-inflammatory, anti-cancer, anti-diabetic, anti-hypertensive, anti-dementia and antioxidant properties (Bar-Sela *et al.*, 2010; Kim *et al.*, 2008; Nakmareong *et al.*, 2011; Sharma *et al.*, 2005; Sompamit *et al.*, 2009; Sreepriya and Bali, 2006). Previous studies have demonstrated that CUR inhibits VSMC migration and proliferation and collagen synthesis in vascular cell cultures stimulated with platelet-derived growth factor and in the experimental model of L-NAME-induced hypertension (Hlavackova *et al.*, 2011; Liu *et al.*, 2008). Furthermore, recent studies have shown that CUR reduces oxidative stress in a rat model of L-NAME hypertension (Liu *et al.*, 2008; Nakmareong *et al.*, 2011), however, the others mechanisms involved with these effects have not been clarified.

The present study was to investigate the mechanisms of dietary antioxidants, including RBP and CUR, on attenuation of high blood pressure, hemodynamic disturbance, oxidative stress, endothelial dysfunction and vascular structural changes during the development of hypertension in two experimental models of 2K-1C renovascular hypertension and L-NAME-induced hypertension in rats.

1.2 Objectives

1.2.1 To investigate the protective effect of RBP and CUR against in 2K-1C and L-NAME- induced hypertension and vascular structural changes in rats.

1.2.2 To evaluate the effects of RBP and CUR on alleviation of hypertension, endothelial dysfunction and vascular structural changes and oxidative stress in 2K-1C and L-NAME-induced hypertension in rats.

1.3 Scope of thesis

This study aimed to elucidate underlying mechanisms of RBP and CUR on the alterations of hemodynamic status, endothelial dysfunction, oxidative stress and vascular structural modifications in 2K-1C and L-NAME-induced hypertension in rats. The experimental model of hypertensive rats was induced by the 2K-1C renal arterial stenosis and L-NAME hypertension models.

1.4 Hypothesis

The antioxidant RBP and CUR could prevent the progression of high blood pressure, endothelial dysfunction, vascular structural changes and remodeling in 2K-1C and L-NAME-induced hypertension in rats by exerting effects through improvement of ROS formation, enhanced eNOS expression and suppression of matrix metalloproteinase expression.

1.5 Anticipated outcomes

Results obtained from this study will provide important information for development of RBP and CUR as supplement food products to promote good health and reduce cardiovascular risk of hypertension. In addition, RBP and CUR may be beneficial in term of therapeutic usage in combination with other drug treatment of hypertension in the future.