CHAPTER I

INTRODUCTION

Obesity and overweight are defined as an accumulation of excess body fat, to an extent that may impair health. The prevalence of obesity has been continually rising for two decades (Centers for Disease Control and Prevention, U.S. Obesity Trends 1984–2002) both in the developed and in the developing nations while the United States has the highest rates of obesity in the developed world. From 1991 to 2002, the prevalence of obesity, as defined by a body mass index (BMI) greater than 30 kg/m^2, increased 74% (Atlanta GA: Centers for Disease control., 2005). From 2003-2004, 17.1% of children and adolescents aged 2 to 19 years, were overweight and 32.2% of adults aged 20 years or older were obese (NCHS., 2006; Ogden *et al*., 2006). In Thai population, the document from Ministry of Public Health in 2005 showed the increasing overweight and obesity at the prevalence rate of 30% and 9%, respectively (Manosoontorn, 2005). This sudden rise in obesity prevalence has been attributed to the combination of an excessive nutrient intake and a sedentary lifestyle.

Obesity has been shown to predispose to various diseases, particularly cardiovascular diseases, diabetes mellitus type 2, sleep apnea and osteoarthritis (NHLBI, 2000). Data from the National Health Care for Communities survey indicate that in the United States, obesity is associated with greater morbidity and poorer health-related quality of life (Sturm and Wells, 2001). According to the prevalence of overweight and obesity is increasing worldwide at an alarming rate, the WHO has estimated that the cost for obesity is 2 to 7 percent of the annual health

budget. Thus, obesity is now a public health and policy problem worldwide because of its prevalence, large economic costs and burdens.

Obesity raises the risk of developing cardiovascular disease partly through its effects on established vascular risk factor such as hypertension, dyslipidemia, insulin resistance, glucose intolerance and type 2 diabetes. This portends an enormous global burden of obesity related cardiovascular morbidity and mortality in the many years. It has been established that sympathetic nervous system plays an important regulating role in metabolic and cardiovascular function in obesity (Bray *et al*., 1989; Young and Landsberg, 1977). Such cardiovascular complications could be reinforced by sympathetic activation associated with obesity (Karason *et al.*, 1999). At present, heart rate variability (HRV) measurement has been accepted as a well-accepted noninvasive tool for the evaluation of cardiac autonomic nervous system (ANS) activity. Previous studies showed that cardiac autonomic function varied in women depending on their regional body fat distribution (Gao *et al.*, 1996). A decreased HRV, an expression of increased cardiac sympathetic activity, is associated with sudden cardiac death (Sztajzel, 2004) and has been reported in obese subjects at rest (Tentolouris *et al*., 2003).

Hyperlipidemia has been linked to many cardiovascular diseases and is associated with an increase in sudden death (Jouven *et al*., 2001; Wyne, 2003). Increased plasma free fatty acid levels resulted from an exaggeration in lipolytic activity of increased visceral fat accumulation (Goldstein, 2002), is a common finding in obese subjects. It has been reported that elevated plasma free fatty acid concentrations causes a stimulation of the cardiac autonomic nervous system and thus also has a proarrhythmic role (Oliver and Opie, 1994; Paolisso *et al*., 2000).

Although the mechanism underlying the cardiac sympathetic overactivity in obesity has not been elucidated, a role of plasma free fatty acid concentrations has been proposed.

Curcuminoids, a natural yellow-orange pigments present in the rhizomes of the turmeric (*Curcuma longa* Linn), is widely used as a spice for its coloring, flavoring and traditional remedy for treating sprains and inflammation in Asian countries. Several biological actions of natural curcuminoids have been reported including anti-oxidant, anti-carcinogenic, anti-inflammatory, anti-bacterial and hypoglycemic effect (Ammon and Wahl, 1991). With respect to lipid-lowering effects, curcuminoids prevent liver triglyceride accumulation and epididymal adipose tissue weight gain and decrease plasma VLDL-triglyceride in high fat model of obesity (Rao *et al*., 1970; Babu and Srinivasan, 1997; Asai and Miyazawa, 2001; Akrishnan *et al*., 2001). However, whether or not curcuminoids can decrease plasma free fatty acid levels in obesity has been not studied.

In the present study, we hypothesized that curcuminoids could decrease autonomic dysfunction in obese rats. The animal model of high-fat diet was used to induce obesity. HRV measurement was performed to determine cardiac ANS activity. As there is a link between obesity and a generalized metabolic disorder of which insulin resistance is an indicator, HOMA index was calculated to determine the whole body insulin sensitivity. The purpose of this study was to investigate the changes of lipid profiles and insulin sensitivity in high-fat diet induced obese rats and whether or not these changes could prevent by curcuminoids administration. Also, we determined the alteration of cardiac autonomic activity associated with high-fat diet. Furthermore, whether or not curcuminoids could decrease cardiac autonomic

dysfunction induced by high-fat diet and if so this effect was related to the lipid-lowering effects.

LITERATURE REVIEW

Epidemiology of Obesity

Obesity is defined as an excess accumulation of body fat associated with increased fat cell size and number (Ali and Crowther, 2005). In terms of body mass index (BMI), the World Health Organization (WHO) and the U.S. National Institute of Health (NIH) define overweight as a BMI of 25 to 29.9 kg/m^2 and obesity as a BMI of 30 kg/m^2 or greater. The prevalence of overweight and particularly obesity continues to rise and is reaching epidemic proportions in both developed and developing nation (Ali and Crowther, 2005). Additionally, the National Heart, Lung and Blood Institute (NHLBI) recommends that a waist circumference of 88 cm or more (35 in. or more) in women or 102 cm or more (40 in. or more) in men, or alternatively, a waist-to-hip ratio (WHR) higher than 0.80 in women or 0.95 in men, is used as an adjunct to BMI to classify high-risk obesity (NHLBI., 1998). The current state of a rapidly increasing prevalence of obesity appears to have emerged largely from increased intake of calorie-dense foods, highly palatable diet and a technology-driven life of convenience and leisure at a time when physical activity is minimized (Nieves *et al*., 2003). A growing of obesity epidemic appears to be associated with an increasing prevalence of risk factors for cardiovascular disease and type 2 diabetes mellitus, includes hypertension and reduced glucose tolerance (Kahn *et al.*, 2001). Also, obesity has been identified as the key etiological condition that predisposes to the development of the metabolic syndrome (MS) (Kahn and Flier, 2000), which is present in 25-50% of United Stated population. This constellation of metabolic abnormalities includes glucose intolerance (type 2 diabetes, impaired glucose

tolerance, or impaired fasting glycemia), insulin resistance (IR), central obesity, dyslipidemia and hypertension, all well documented risk factor for cardiovascular disease (CVD) (Eckel *et al*., 2005). Thus, obesity is now recognized as a serious health problem worldwide.

Obesity and Cardiovascular disease

The obesity is characterized by profound hemodynamic and metabolic alterations (Bjorntorp *et. al*., 1997). It causes or exacerbates many health problems, both independently or associated with other disease (Kopelman *et al*., 2000). Although linked with CVD for centuries, obesity was named major modifiable coronary risk factors by the American Heart Association only with the last decade. In epidemiologic studies, obesity has been associated with an increased risk of coronary heart disease, stroke, venous thromboembolism and congestive heart failure (Robinson and Thomas, 2006). Obesity is also associated with several novel risk factors for CVD and diabetes such as fibrinogen and plasminogen activator inhibitor-1 and in inflammatory markers such as interleukin-6 and C-reactive protein (Robinson and Thomas, 2006).

In addition to the amount of excess fat, the regional distribution of such fat also appears to influence cardiovascular health. Abdominal fat accumulation appears to be more important predictor than gluteofemoral fat of atherogenic dyslipidemia (specifically, the combination of elevated triglyceride, small dense LDL and low HDL cholesterol), hypertension and coronary heart disease (CHD), as well as of type 2 diabetes (NHLBI, 1998). Epidemiologic study has been reported that obesity individuals with accumulation of abdominal fat are at particular risk of cardiovascular

complications such as hypertension, ischemic heart disease and stroke (Lamarche, 1998). However, the underlying mechanism relating obesity to these cardiovascular events is not clear. According to the concept that the sympathetic nervous system plays an important role in regulating body fat by modulating thermogenesis and fat metabolism, the relationship between sympathetic nervous system activity and obesity has been proposed. Overfeeding has been shown to stimulate sympathetic activity in experimental animal models (Young and Lansberg, 1977; Young *et al*., 1982). In addition, an increased renal sympathetic nerve system activity was reported in genetically obese Zucker rats (Morgan *et al*., 1995). Kassab *et al*. (1995) showed that sodium retention and hypertension in high-fat diet induced obese dogs were significantly attenuated with bilateral renal denervation. They suggested that the increased renal efferent sympathetic nerve activity might contribute to the observed sympathetic activation in obesity. Such data agreed with the study of Rocchini *et al*. (1999) which found that combined alpha- and beta- blockade reduced arterial pressure to a significantly greater extent in obese animals compared to lean animals, and clonidine prevented onset of weight gain-induced hypertension. Sowers *et al*. (1982) reported increase of plasma and urinary catecholamine levels in obese humans. Furthermore, these obese subjects had exaggerated plasma norepinephrine levels in response to an upright posture and isometric handgrip. Using microneurographic technique, Grassi *et al.* (1995) demonstrated that postganglionic muscle sympathetic nerve firing rates in obese normotensives were twice that of lean controls, and this activation occurred in the absence of any blood pressure elevation. These findings were in accord with the reports that body fat was the major determinant of muscle sympathetic nerve discharge in human (Scherrer *et al*., 1994). Thus, the marked

sympathetic activation observed in obese normotensive subjects has been proposed as one of the factors facilitating, in the long term, the development of hypertension, a condition much more frequent in overweight than in lean people ("Race, education and prevalence of hypertension", 1977; Stamler *et al.*, 1978).

Heart Rate Variability (HRV)

Obesity is known to increase the risk of ischemia heart disease and other cardiovascular complications (Hubert *et al.*, 1983; Must *et al*., 1999), which may be, in part, due to sympathetic nervous system activation (Laederach-Hofmann *et al*., 2000; Matsumoto *et al.*, 2001; 1999; Muscelli *et al.*, 1998; Oparil and Oberman, 1999). In addition, prevalence of premature ventricular contractions, resulting in a risk of arrhythmia and sudden death has been reported to frequency occur in obese patients (Messerli, 1987). Interestingly, prolongation of the QT interval is the most important electrocardiographic abnormality, has also been found to be associated with both obesity (Blunberg, 1992; El-Gamal *et al.*, 1995) and abdominal fat deposition (Corbi *et al.*, 2002; Peiris *et al*., 1991; Park and Swan, 1997). As the QT interval is influence by autonomic tone, a perturbation of the ANS and its imbalance consisting of either increased sympathetic or reduced vagal activity may result in ventricular tachyarrhythmias and sudden death (Zipes and Wellen, 1998). Despite the relative consistent findings of autonomic disturbance in obesity, previous studies have not focused on the autonomic activity of the heart itself.

Heart rate variability (HRV) is a noninvasive electrocardiographic marker reflecting the activity of the sympathetic and vagal components of the autonomic nervous system on the sinus node of the heart. It expresses the total amount of

variations of both instantaneous heart rate and RR interval (interval between QRS complexes of normal sinus depolarization) (Stein *et al.*, 1994; Van Ravenswaaij-Arts CMA *et al*., 1993). Analysis of HRV consists of a series of measurements of successive NN interval (RR interval) variations of sinus origin which provide information about autonomic tone (Bonnemeier *et al*., 2003). In most clinical applications, HRV is analyzed by time, frequency domain methods.

1. Time domain analysis

Time domain methods are analyzed on the basis of calculation of the changes in heart rate over time or the intervals between successive normal cardiac cycles (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Malik, 1995; Kleiger *et al*, 1992). From a continuous ECG recording, each QRS complex is detected, and the normal RR intervals, due to sinus depolarization, or the instantaneous heart rate are then determined. The calculated time domain variables may be simple or more complex based on statistical measurement. The simple time domain variables include the mean RR interval, the mean heart rate, the difference between the longest and shortest RR interval and the difference between night and day heart rate. The statistical time domain variables are divided into two categories: those derived directly from RR interbeat intervals and those calculated from the differences between successive RR intervals. Table 1 summarizes the most commonly used variables of the time domain (Sztajzel *et al*., 2004).

Table 1 Time domain parameters.

Variable	Units	Description
SDNN	ms	standard deviation of all RR intervals
SDANN	ms	standard deviation of the averages of RR intervals in all 5-minute segments of the entire recording
RMSSD	ms	square root of the mean of the sum of the squares of differences between adjacent RR interval
SD (or SDSD)	ms	standard deviation of differences between adjacent RR intervals
pNN50	%	percent of difference between adjacent RR intervals that are greater than 50 ms

The time domain variables calculated from RR interbeat intervals are SDNN, SDANN and SD. SDNN is a global index of HRV and reflects all the long-term components and circadian rhythms responsible for variability in the recording period. SDANN is an index of variability of the average of 5-minute intervals over 24 hours while SD is generally considered to reflect the day/night changes of HRV. RMSSD and pNN50 are the most common time domain variables based on interval differences. These measurements correspond to short-term HRV changes and are not dependent on day/night variations (Tsuji *et al*., 1996; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Malik, 1995; Kleiger *et al*, 1992). They reflect alterations in autonomic tone that are predominantly vagally mediated.

2. Frequency domain methods

Frequency domain (power spectral density) method is determined by using spectral analysis to quantify the signal's frequency content. This method yields information about the amount of variance (power) in the heart's rhythm expressed by periodic oscillations of heart rate at various frequencies. Most studies have assessed power spectral analyses using a nonparametric method, the fast Fourier transformation (FFT) (Wan *et al*., 2003a; 2003b) which has served to quantitatively evaluate the function of various cardiovascular control and identify key frequency regions that appear reflective of specific autonomic nervous system activity.

The power spectrum consists of frequency bands ranging from 0 to 0.5 Hz and can be classified into four band: ultra low frequency band (ULF), the very low frequency band (VLF), the low frequency band (LF) and the high frequency band (HF). From short term ECG recordings of 2 to 5 min, three main spectral components are classified; very low frequency (VLF), low frequency (LF), and high frequency (HF) components. An ultra low frequency (ULF) component, in addition to VLF, LF and HF, is characterized with long term ECG recordings of 24 hours. The spectral components are evaluated in terms of frequency (Hz) and amplitude which is assessed by the power spectral density of each component. The absolute value of spectral component is usually expressed in ms squared (ms^2). LF and HF components may also be expressed in normalized units (nu) which represent the relative value of each power component in proportion to the total power minus the VLF component (Pagani *et al.*, 1986; Malliani *et al*., 1991; Shimoguchi, 1990). Table 2 lists some of the common components examined in spectral analysis (Sztajzel *et al*., 2004; Terathongkum and Pickler, 2004).

Table 2 Frequency domain parameters.

Variable	**Units**	**Description**	**Frequency range**
Total power	ms^2	variance of all RR intervals	<0.4 Hz
ULF	ms^2	ultra low frequency	<0.003 Hz
VLF	ms^2	very low frequency	<0.003-0.04 Hz
LF	ms^2	low frequency power	0.04-0.15 Hz
LFnu *	nu	LF power in normalized units	
HF	ms^2	high frequency power	
HFnu *	nu	HF power in normalized units	0.15-0.4 Hz
LF/HF ratio		ratio of low-high frequency power	

* LF and HF powers in normalized values (nu).

Normalized units are obtained as follows:

$$\text{LFnu or HF nu} = \frac{\text{LF or HF } (ms^2)}{\text{Total power } (ms^2) - \text{VLF } (ms^2)} \times 100$$

Under normal circumstances, the HF component is generally defined as a marker of vagal modulation and abolished by atropine infusion (Sztajzel *et al*., 2004; Pomeranz *et al*., 1985). This component is respiration-mediated and thus determined by the frequency of breathing. The LF component is modulated by both the sympathetic and parasympathetic nervous system. It is virtually abolished by total autonomic blockade (Pomeranz *et al.*, 1985) and is strongly affected by the oscillatory rhythm of the baroreceptor system (Fallen *et al*., 1988). In practical term, an increase of the LF component (tilt, mental and/or physical stress, sympathomimetic pharmacological agents) has been generally considered to be a consequence of sympathetic activity (Sztajzel *et al*., 2004). The LF/HF ratio is an index of sympathovagal balance and can be used as a measure of this balance. In a normal adult in resting condition, the LF/HF ration is generally between 1 and 2.

HRV has gained importance in recent years as a technique employed to explore the autonomic nervous system, which plays an important role in the pathophysiology of arrhythmogenesis. There is a consistent association of decreased HRV with increased cardiac and/or arrhythmogenic mortality, both sudden and non-sudden (Cripps *et al*., 1991; Bigger *et al*., 1993; Quintana *et al.*, 1997). However, because HRV deals with RR interval variations, its measurement is limited to patients in sinus rhythm and to those with a low number of ectopic beats.

Cardiac Autonomic Nervous System and Obesity

Study using the power spectral analysis of heart rate demonstrated that cardiac autonomic function varied depending on the regional body fat distribution in women (Gao *et al*., 1996). In addition, cross-sectional studies also showed the strongest

association with the changes in HRV and the change in waist circumference (Lemieux *et al.*, 1996). Study in healthy subjects found significant correlations between HRV and obesity indices (fat mass, percentage of fat content and waist/hip ratio) at rest. The higher levels of obesity indices were significantly associated with the lower LF spectral power whereas RMSSD was negatively related to obesity indices. These findings suggested the involvement of central obesity in autonomic regulation (Kim *et al*., 2005).

Cardiac autonomic dysfunction has been reported in obese subjects (Valensi *et al.*, 1995). It had been reported that an obese person might have an autonomic function disturbance in parasympathetic activity as well as in sympathetic activity. Analyses of beat-to-beat interval variations on a continuous electrocardiogram and cardiovascular reaction during breathing and handgrip exercise demonstrated that reduced HRV in obese subjects indicated depression in parasympathetic activity whereas the significant increase of blood pressure during handgrip reflected over-reactivity of sympathetic nervous system (Zahorska-Markkiewicz *et al*., 1993). Study in childhood obesity, (Martini *et al.*, 2001) demonstrated significantly low 24-hour and nighttime HF normalized units, and time-domain measures of vagal activity. Additionally, the obese children had significantly greater 24-hour and nighttime LF/HF ratio. Likewise, Tentolouris *et al*. (2003) reported that in obese women, increased sympathetic nervous system activity as expressed by an increased LF/HF ratio was correlated with a high plasma norepinephrine level. Thus, decrease of HRV which reflect abnormalities of autonomic input to the heart, represents a stage of increased risk of cardiac events in obesity.

An imbalance of sympathetic/parasympathetic tone has been reported to be responsible for many cases of sudden death (Kleiger *et al*., 1987; Tsuji *et al*., 1994; Ryan *et al*., 1976). Despite the prevalence of alterations in cardiac autonomic function in obesity, the underlying mechanisms responsible for such sympathetic overactivity are not fully understood. Elevated plasma free fatty acid (FFA) levels have been linked to many cardiovascular diseases and are associated with an increase in sudden death (Jouven *et al*., 2001; Wyne, 2003). As consequence of increased visceral fat accumulation with a secondary exaggeration in lipolytic activity, elevated plasma free fatty acid concentrations is a common finding in obese subjects (De Fronzo and Ferrannini, 1991). Several studies have examined the effects of fatty acids on the cardiac autonomic nervous system activity. Verwaerde *et al*. (1999) showed that acute elevation of plasma free fatty acid concentrations caused tachycardia in dogs mainly because of impairment of parasympathetic control. In healthy subjects, Paolisso *et al*. (2000) reported that elevated plasma free fatty acid levels stimulated cardiac sympathetic nervous activity. Study in noninsulin dependent diabetic (NIDDM) patients showed that in raising plasma free fatty acid levels, a cardiac sympathetic overactivity occurred along with increase of catecholamine concentrations and mean arterial blood pressure (Manzella *et al*., 2001). Moreover, recent study have reported that elevated level of plasma free fatty acids induced by intralipid and heparin infusion in overnight fasting rats strongly link with the reduced vagal component of cardiac baroreflex and inversely correlate with baroreflex sensitivity (Shaltout and bdel-Rahman, 2005). In addition, spectral analysis of HRV showed that elevation of plasma free fatty acids significantly increased LFnu and

reduced HFnu, causing a significant increase in the LF/HF ratio, a measure of for sympathovagal balance (Shaltout and bdel-Rahman , 2005).

Curcuminoids

1. The Biological Source of Curcuminoids

Curcuminoids are natural yellow-orange pigments and present in the rhizomes of the turmeric. The term turmeric is used to refer both to the turmeric plant and to the spice derived from the rhizomes of the plant.

Turmeric was described as *Curcuma longa* by Linnaeus and the taxonomic position is as follows:

Class	Liliopsida
Subclass	Commelinids
Order	Zingiberales
Family	Zingiberaceae
Genus	*Curcuma*
Species	*Curcuma longa*

Curcuma longa Linn (turmeric) is a tropical plant native to south and southeast tropical Asia. It is a perennial herb having a short stem with large oblong leaves and bear ovate, pyriform or oblong rhizomes, which are often branched and brownish-yellow in color (Figure 1)(Chattopadhyay *et al*, 2004). Turmeric is widely consumed in the countries of origin for a variety of uses, including use as a dietary spice, as a dietary pigment and as an Indian folk medicine for the treatment of various illnesses (Araujo and Leon, 2001). In tropical regions of Asia, turmeric has been used as a traditional remedy for treatment of sprains and inflammation (Ammon, 1991). It is

also used in Hindu religious ceremonies in one form or another as part of the religious rites. Curcuminoids are responsible for the yellow color of turmeric, and comprise 3 to 6% of the turmeric plant's total composition.

(a) **(b)**

(c)

Figure 1 A stemless rhizomatous of *Curcuma longa* Linn and powder.

Curcuminoids which comprise 3 to 6% of the turmeric plant's total composition, are polyphenolic. Three major curcuminoids namely curcumin (curcumin I), dexamethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III) occur naturally in the rhizomes of the *Curcuma* species (Chearwae *et al*, 2006). Curcumin, as the major component, makes up 70 to 75% of the curcuminoids, demethoxy-curcumin 15 to 20% and bisdemethoxycurcumin about 3%. In addition, the tumeric contains dihydrocurcumin, diferuloilmethane, feruloil-p-cumaroilmethane, di-p-cumaroilmethane, α-and β-turmerones, α-pinene, β-pinene, camphene, limonene, terpinene, curzernone, curlone, campesterol, stigmasterol, β-sitosterol, cholesterol and fatty acids. The structures of 3 main curcuminoids isolated from turmeric powder are shown in Figure 2.

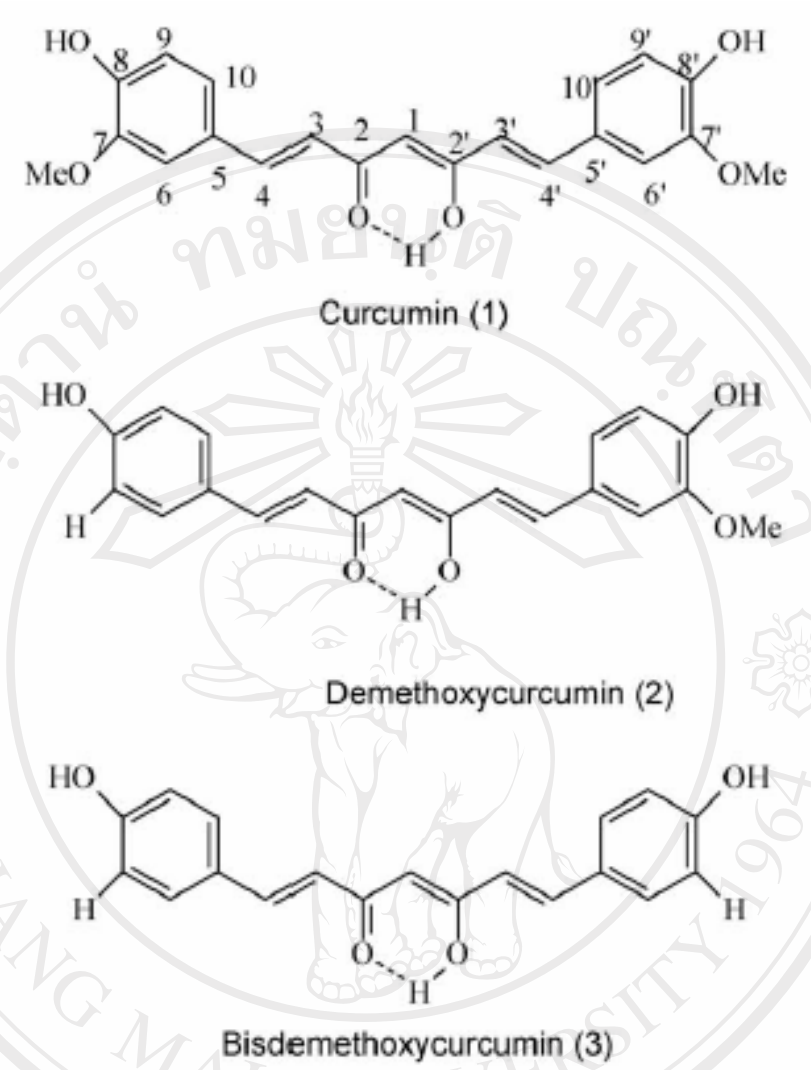

Figure 2 Chemical structures of curcuminoids

The properties of 3 curcuminoids are as follows:

1. 1, 7-bis (4–hydroxyl–3-methoxy phenyl)-6, heptadiene-3, 5 dione (1.11%) is called curcumin. Its formula is C_{21} H_{20} O_6 and molecular weight is 368. It has yellow-orange color and a little soluble in ether and quit soluble in ethanol, acetone propyleneglycol and benzene. Curcumin is the important active ingredient responsible for the biological activity of turmeric.

2. Ferulogl-(4-hydroxycinnamoil) – methane (0.86%) is called demethoxycurcumin. Its formula is C_{21} H_{18} O_5 and molecular weight is 338.

3. Bis–(4– hydroxycinnamoil) – methane (1.62%) is called bisdemethoxycurcumin. Its formula is C_{19} H_{16} O_4 and molecular weight is 308.

2. Biological Activities of Curcuminoids

2.1 Antioxidant Action

Curcuminoids have been found to have a number of antioxidant activities. Unnikrishnan and Rao (1995) demonstrated that curcuminoids provided a protection of hemoglobin from oxidation. *In vitro* study, curcuminoids inhibit the generation of reactive oxygen species (ROS) like superoxide anions, H_2O_2 and nitrite radical generation by activated macrophages (Sreejayan and Rao, 1994). Curcuminoids also decrease lipid peroxidation in liver microsomes, erythrocyte membranes and brain homogeates by maintaining the activities of antioxidant enzymes like superoxide dismutase, catalase and glutathione peroxidase (Reddy and Lokesh, 1992; 1994).

2.2 Anti-inflammatory Action

Pharmacological actions of curcuminoids as an anti-inflammatory agent have been demonstrated in both acute and chronic models of inflammation. Curcuminoids are effective against carrageenin-induced edema test (Srimal and Dhawan, 1973; Srihari *et al*., 1982; Srivastava and Srimal, 1985; and Brouet and Ohshima *et al*., 1995). Clinical study in rheumatic patients showed significant improvement of symptoms after administration of curcumin (Yegnanarayan *et al*., 1976). In addition, Huang *et al*. (1992) examined the inhibitory effects of curcumin on the proliferation of blood mononuclear cells and vascular smooth muscle cells (Huang *et al*., 1992). The anti-inflammatory activity of curcuminoids may underlie several mechanisms, including reduction of the release of ROS (Phan *et al*., 2001), inhibition of AP-1 and NF-KappaB and inhibition of the activation of the pro-inflammatory cytokines TNF-α (Bierhous *et al*., 1997).

2.3 Anti-Carcinogenic Action

Anticarcinogenic effects of curcumin in animal, as indicated by its ability to inhibit both tumor initiation induced by benzo (a) pyrene and 7, 12 dimethylbenz (a) anthracene and tumor promotion induced by phorbol esters (Deshpanda and Maru,1995; Huang *et al*., 1995). Curcumin also induces apoptosis and inhibits cell cycle progression, both of which prevent cancerous cell growth in rat aortic smooth muscle cells (Chen and Huang, 1998). In addition to its activity in preventing malignant transformation, and inhibiting tumor growth, curcumin has antimetastatic potential, as well. In this regard, curcumin downregulates matrix metalloproteinase

(MMP)-2 and upregulates tissue inhibitor of metalloproteinase (TIMP)-1, two common effect molecules involving in cell invasion (Shao *et al.*, 2002).

2.4 Lipid-Lowering Action

With respect to lipid metabolism, dietary curcuminoids reduce serum and liver cholesterol in cholesterol-fed rats (Rao *et al*., 1970; Babu and Srinivasan, 1997). Study of Asai *et al*. (2001) showed that dietary turmeric extract prevented liver triacylglycerol (TG) accumulation in mice. In another work, dietary curcumin decreased liver TG deposition and plasma VLDL-TG in high fat-induced obese rats. Curcumin also prevents the increase in fatty acid content in ethanol-induced liver damage (Akrishnan *et al*., 2001).

2.5 Action on Cardiovascular System

Curcumin decreases the severity of pathological changes and thus protects from damage caused by myocardial infarction (Nirmala *et al*., 1996). Study in rabbits with pressure overload found that curcumin improved cardiac function and counteracted myocardial collagen remodeling of failing heart (Yao *et al*., 2004). With respect to anti-atherosclerotic action, curcumin derivatives have been demonstrated to reduce aortic fatty streak formation in cholesterol-fed rabbits (Quiles *et al*., 2002). Also, curcumin inhibits the development of atheroscelrosis in gene-target apolipoprotein E (apoE) and LDLR-double-knockout mice, animal model of atherosclerosis (Olszanecki *et al*., 2005).