CHARPTER II

REVIEW OF RELATED LITERATURE AND RESEARCH

Metabolic syndrome

Metabolic syndrome (MetS) is well known as many other names such as insulin resistance syndrome (DeFronzo and Ferrannini, 1991), Reaven syndrome, syndrome X (Reaven, 1988), deadly quartet (Kaplan, 1989) and cardiometabolic syndrome (Castro, et al., 2003). MetS is a cluster of metabolic disorder that came together in a single individual which increasing the risk of type 2 diabetes mellitus and cardiovascular disease. (Rosenson, 2005). This syndrome includes central obesity, insulin resistance, high fasting blood glucose, hypertension, impaired glucose tolerance (Simmons, et al., 2010) , elevated triglyceride level (Spranger, et al., 2003) and low HDL-C (high density lipoprotein cholesterol) level (Sorrentino, 2005) as well as a systemic pro-inflammatory and prothrombotic state (Grundy, et al., 2004). World Health Organization (WHO) suggested for the above syndrome to be named it the metabolic syndrome in 1998 (Alberti and Zimmet, 1998). Moreover, MetS is also involved with an increased risk of non-alcoholic fatty liver disease (NAFLD) (Vanni, et al., 2010), that is one cause of a fatty liver. In case of NAFLD, deposited fat in the liver is not due to excessive alcohol use and kidney dysfunction (Palanisamy, et al., 2010). The causes of MetS are very complex and have various factors involved. The most important factors that cause of this disease include abdominal obesity and insulin resistance (Reaven, 2003). In addition, genetics (Storgaard, et al., 2006), aging (Sairam, et al., 2006), smoking (Wannamethee, et al., 2006), hormonal imbalances, inflammatory cytokine levels (Zhang, et al., 2007) and an inappropriate lifestyle which includes physical inactivity (Pietilainen, et al., 2008) and the consumption of high calorie intake, high fat diet (Doucet, et al., 1998), high carbohydrates and the glycemic index feeding (McKeown, et al., 2004) are also considered to be pathogenic factors for MetS.

Other conditions associated with MetS are non-alcoholic fatty pancreatic disease (Fraulob, et al., 2010), polycystic ovarian syndrome (Rasgon, et al., 2005) and

sleep apnea (Lam and Ip, 2009). A previous study has shown the endothelial dysfunction associated with insulin resistance can lead to hypertension (Sorrentino, 2005). Almost causes that lead to MetS were bad lifestyle and unhealthy diet (Pitsavos, et al., 2006) and these induce pathophysiological changes all over the body. Therefore, it is important to study the progression and treatment tactics for MetS.

Diagnostic criteria used for metabolic syndrome

There were several criterias from many organizations for the diagnosis of MetS, including World Health Organization (WHO) 1999 (Alberti and Zimmet, 1998), European Group for the Study of Insulin Resistance (EGIR) 1999 (Balkau and Charles, 1999), American College of Endocrinology (ACE) 2002 (Einhorn, et al., 2003) and National Cholesterol Education Program Adult Treatment Panel III 2001 (NCEP, 2001). Additionally, in 2005 there were criteria from two more institutes for diagnosis of MetS; International Diabetes Federation (IDF) (Alberti, et al., 2005) and American Heart Association (AHA) with National Heart Lung and Blood Institutes (NHLBI) of the United States of America (Grundy, et al., 2005). However, the diagnosis of the MetS in adult most commonly used is the criteria of National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) 2001. The NCEP ATP III described five components of MetS, including abdominal obesity, high triglycerides level, low HDL-C level, elevate blood pressure and increase fasting plasma glucose. It requires the presence of at least three of the five factors for diagnosis MetS, which are 1) waist circumference greater than or equal to 102 cm or 88 cm in male and female respectively, 2) triglycerides greater than 150 mg/dl or drug treatment, 3) HDL-C less than 40 mg/dl in male or less than 50 mg/dl in female or drug treatment, 4) blood pressure greater than 130/85 mmHg or drug treatment and 5) fasting plasma glucose greater than 110 mg/dl or drug treatment.

An NCEP ATP III criterion of MetS has been shown to be better than other criteria, although it does not incorporate inflammatory variables. The NCEP ATP III has underlined two important indexes that more closely related to insulin resistance; waist circumference estimating of fat accumulation in abdomen (Abate and Garg, 1995) and high fasting plasma glucose concentration (Matthews, et al., 1985). Many studies found that according to this criteria hypertriglyceridemia and low HDL-C

levels are most closely related to increasing the risk of both insulin resistance and cardiovascular disease (Gordon, et al., 1989).

Epidemiology of the metabolic syndrome

The MetS is a main public health problem and the prevalence is increasing throughout the world (Zimmet, et al., 2005). Increasing prevalence of this syndrome is depending on age, nationality, gender, population characteristics, countries, lifestyle and diet (Sarkar, et al., 2006; Romaguera, et al., 2010). MetS was presented in both women and men in USA (Ervin, 2009), Singapore (Termizy and Mafauzy, 2009) and Australia (Cameron, et al., 2007) and showed the increased prevalence in women, while Japan shown increased rates in men (Arai, et al., 2006).

In 2000, the prevalence of MetS in the Australia was 18.8% and 25.4% in males and females, respectively (Cameron, et al., 2007). In the USA population, 24% of males and 23.4% of females were diagnosed with MetS (Ford, et al., 2002). Many studies have shown that in 2005 and 2006, the prevalence in USA had increased to 34% in both men and women (Ford, 2005a; Ervin, 2009). It has been indicated that the prevalence of MetS in Asians are between 14-49% (Misra and Khurana, 2009). A recent study has shown that the prevalence of MetS is increasing in every continent which found that person was MetS in the range of 30% - 80% (Pudata and Konduru, 2011). While, in Thailand 2007, the prevalence of MetS was found in the group of professional and office workers 15.2% (Lohsoonthorn, et al., 2007) and rise to 32.6% in Thai adults 35 years and older (Aekplakorn, et al., 2011).

The prevalence of MetS is rapidly increasing in south Asian countries (Misra and Khurana, 2009) and worldwide, leading to increased morbidity and mortality due to diabetes mellitus type 2 and cardiovascular disease. A high prevalence of the MetS associated to type 2 diabetes mellitus and cardiovascular risk factors. In Japanese population, the deaths from ischemic heart disease increased by 3-4 folds which is caused by metabolic syndrome. (Lakka, et al., 2002). In addition, it has been reported that from July 1998 through August 2004 the population with MetS has mortality from cardiovascular disease 12-17% and 30-52% for diabetes (Ford, 2005b). While, Thailand has mortality from diabetes increased every year and rise to 7,749 deaths in 2012.

Abdominal obesity

Regular consumption of high fat and high carbohydrate diet is a major cause of obesity. Obesity is caused by an imbalance between caloric intake and caloric expenditure, lead to increase adipose tissue mass, especially visceral fat around the stomach and abdomen (Voshol, et al., 2009). An excess fat deposition in abdominal cavity will lead to the onset of MetS (Grundy, et al., 2005). The most classic sub-types of obesity are abdominal obesity (android obesity) and gluteal obesity (gynoid obesity) (Allison and Heshka, 1991). Waist circumference is an important index for prediction of the risk associated fat accumulation because it directly reflects a large amount of abdominal fat deposition. This criteria is a relatively sensitive indicator of the risk for metabolic and cardiovascular complicated in obesity more than body mass index (Abate and Garg, 1995). In addition, visceral fat deposition in abdomen and waist circumference show a strong association with type 2 diabetes (Anjana, et al., 2004).

Presently, abdominal obesity has been increasingly cited as a major health issue. In particular, abdominal obesity has been linked to central obesity and myocardial infarction (Yusuf, et al., 2004). This is relevant with type 2 diabetes mellitus, coronary heart disease (Kopelman, 2000) and it is a most importance cause of mortality and morbidity (Ogden, et al., 2006). Additionally, abdominal obesity associated with an increased risk factor of insulin resistance, dyslipidemia, hypertension (Stanhope and Havel, 2010) and cancer. There is strong evidences demonstrated that visceral adipose deposition is more closely associated with metabolic disease (Jensen, 2008).

Insulin hormone

Insulin is a polypeptide hormone that produced by pancreatic β-cells. It has several anabolic effects throughout the body. Glucose is the principal stimulus for insulin release from the β-cells of pancreas. The secretion of Insulin was stimulated by other substances such as amino acids, arginine and leucine, parasympathetic release of acetylcholine, sulfonylurea, cholecystokinin (CCK) (Cawston and Miller, 2010). The major function of insulin is to decrease blood glucose levels by promoting glucose uptake to other cells and increase glycogen synthesis in liver. Additionally, insulin

also plays a role in glucose metabolism regulation, lipogenesis stimulation, reduction of lipolysis and increasing amino acid transport into cells.

After a meal the blood glucose level rises, it is transported into the β-cells by a glucose transporter 2 (GLUT2). Inside the β-cells, glucose induces insulin release from insulin containing secretory granules into the circulation (Figure 2).

In classical pathway, insulin binds to its receptor on plasma membrane of liver, muscle, adipose tissue and others, then activates the intrinsic kinase activity of the intracellular domain of the receptor, leading to activation of cellular events mediated through the phosphorylation of insulin receptor substrates 1 (IRS-1). Phosphatidylinositol-3-kinase (PI3Ks) cascades contribute to the mechanism of insulin action. The glucose transporter 4 (GLUT4) located in intracellular vesicles then translocate and express on the cell membrane, resulting in the uptake of glucose into the cells, mainly the muscle cells (Figure 3).

In addition, this hormone stimulates glucose uptake from blood into fat tissue and other cells, then converts glucose to be glycogen that can be stored inside these cells. Therefore, the increase blood glucose level after meal can reduce to normal level (Winzell and Ahren, 2004). If these cells fail to respond to the normal actions of the insulin, so called insulin resistance, this will lead to hyperglycemia that found in diabetes mellitus type 2.

Insulin resistance

Insulin resistance is a pathophysiological condition in which cells are unable to respond to the normal actions of insulin, which occurs when the pancreatic β cell produces insulin but target cells become resistant to insulin and are incapable to use it as effectively, leading to high blood glucose level. If insulin resistance exists, the β cells of pancreas will increase the secretion of insulin, resulting in hyperinsulinemia, leading to type 2 diabetes mellitus (Shoelson, et al., 2007). Insulin resistance is closely linked with abdominal obesity that caused by chronic intake of high fat and high sucrose diets (Sumiyoshi, et al., 2006). In central obesity people has found that the increasing of adipose tissue mass. It has been widely demonstrated that the increasing of adipose tissue expansion, leading to adipocytokine dysregulation, enhance the secretion of proinflammatory and inflammatory cytokines. Increasing inflammatory

and proinflammatory secretion includes tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6) and C-reactive protein (CRP) (Maachi, et al., 2004) and insulin resistance are associated with decrease in anti-inflammatory cytokine levels like adiponectin and leptin (Tilg and Moschen, 2006). These various inflammatory cytokine can acts on its receptor in skeletal muscle which activates Toll-like receptor signaling, IL receptor signaling, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and IκB kinase signaling, leading to reduce insulin signaling by inhibit IRS-1 phosphorylation (Coletta and Mandarino, 2011). Finally, glucose from blood is unable to uptake into the muscle cells, resulting in hyperglycemia thus promoting type 2 diabetes.

Oral glucose tolerance test

The simplest and most convenient glucose tolerance test is the oral glucose tolerance test (OGTT). OGTT is an assessment for the response of the insulin hormone on blood glucose level. This test is often used to test for diagnosis of type 2 diabetes (Bartoli, et al., 2011), demonstrated by a delayed response to an ingested glucose load. With an OGTT, the person overnight fasting (at least 8 but not more than 16 hours) before the fasting blood glucose is tested. After that person drinks a liquid containing with glucose (75g per kg of BW), then blood samples are taken up to four times within 2 hours for measuring the blood glucose level (Oka, et al., 2012). After 2 hours, normal person has plasma glucose concentration less than 140 mg/dl. If plasma glucose level is about 140-200 mg/dl person has impaired glucose tolerance (prediabetes) and if plasma glucose level remains above 200 mg/dl or still high this shows a sign of diabetes (Patel and Macerollo, 2010).

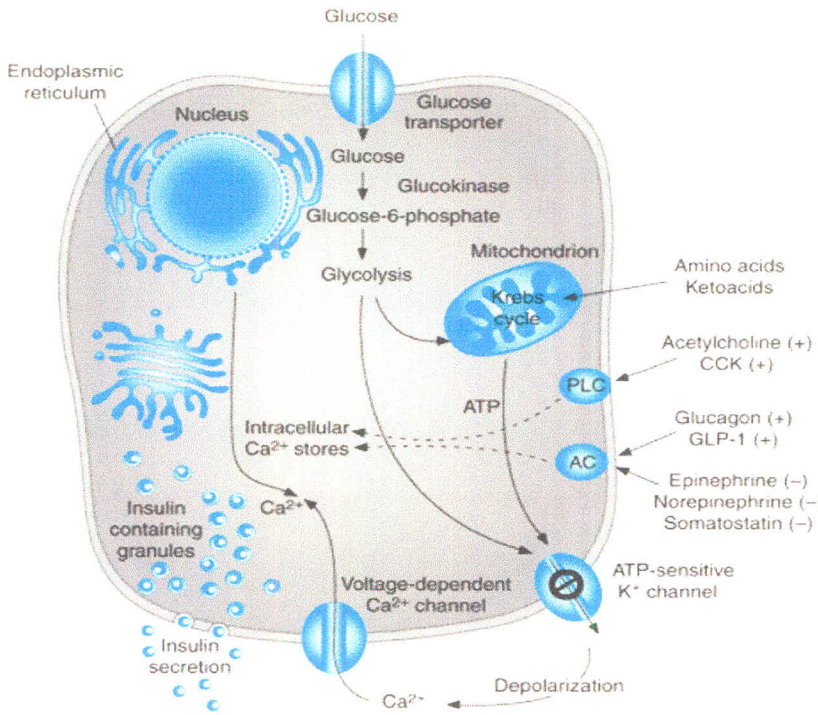


Figure 2 Regulation of insulin hormone release

Source: http://physiology.md.chula.ac.th/website/hormones_insulin.html

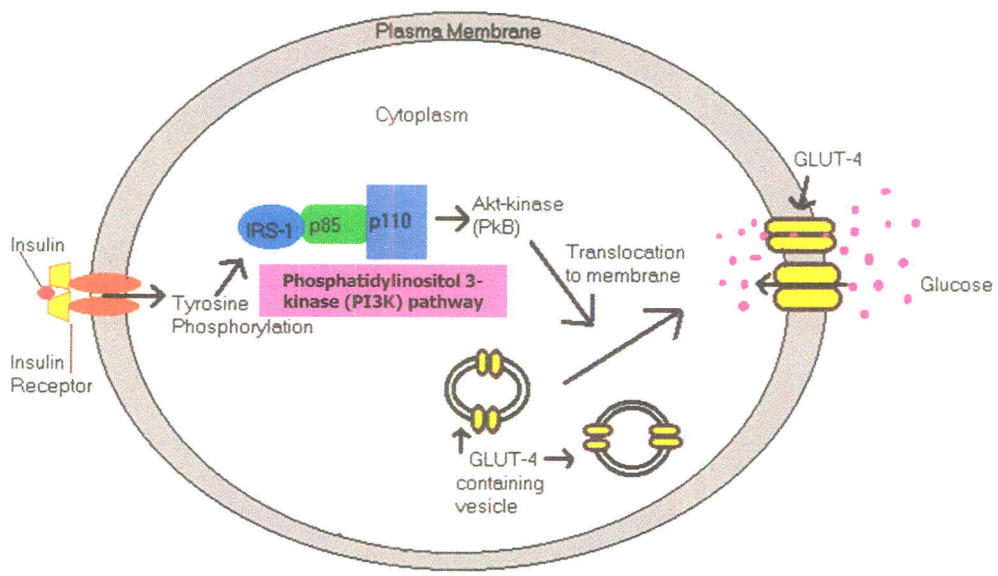


Figure 3 Insulin receptor signaling and action

Source: http://student.biology.arizona.edu/honors2003/group05/bg.html

Hypertension

Hypertension or high blood pressure is a chronic condition in which the arteries have consistently elevated blood pressure. Mainly cause of hypertension is the increased peripheral resistance which mainly attributed to narrow of small arteries and arterioles (Folkow, 1982). High blood pressure has an important role in relationship between insulin resistance, MetS, dyslipidemia and cardiovascular disease. It has been reported that insulin resistance condition is the major cause of hypertension which be a characteristic that is common pathophysiological of obesity (Modan, et al., 1985). In the high carbohydrate diet induced obesity, the increasing of peripheral vascular resistance in hypertension may be associated with insulin resistance (Samuelsson, et al., 2008). More than 50% of patients with hypertension are insulin resistance. Hyperinsulinemia can affect the increase of cholesterol and fatty acid metabolism (Muller-Wieland, et al., 1998), resulting in elevated of triglycerides and cholesterol accumulation in cells and blood vessel, leading to narrow of arterioles and increased peripheral vascular resistance, and developed to hypertension. Therefore hypertension can be used as an index of the criteria for diagnosis MetS (Reaven, 2005).

Dyslipidemia

Dyslipidemia is a major disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. It is elevation of total cholesterol, low-density lipoprotein cholesterol (LDL-C) and triglycerides concentrations and low high-density lipoprotein cholesterol (HDL-C) concentration in the blood that contributes to the development of atherosclerosis and it increases the risk for coronary heart disease and stroke (Messier, et al., 2004). With excessive intakes of carbohydrates and peripheral insulin resistance, glucose from blood is unable to convert into glycogen at the liver thus decreasing glucose uptake into cells. Therefore, the increase glucose concentration in circulation, enhances a conversion of glucose to triglyceride, resulting in an over accumulation of triglyceride in the liver, adipose tissue, muscle and other cells (Marques-Lopes, et al., 2001). High fat intake stimulates triglyceride hydrolysis via lipoprotein lipase resulting in increased plasma free fatty acid (FFA) concentrations (Kim and Kim, 2009) (Figure 4). The high levels of plasma FFA is buffered by cells such as skeletal muscle and liver, resulting in fat

accumulation in skeletal muscle and deposition of triglyceride and cholesterol esters in liver. Besides that high blood triglyceride concentration results in an increase transferring of triglyceride from VLDL to HDL and subsequently increases in HDL clearance and decreases HDL concentration (Zivkovic, et al., 2007). In obese person, an increase adipose tissue mass enhances a release of FFA into the circulation, resulting in the storage of triglyceride in the liver which may lead to hepatic insulin resistance (Spranger, et al., 2003). In addition, nonalcoholic steatohepatitis (NASH) is a form of liver disease which have dyslipidemia associated with the MetS, including high triglyceride, cholesterol and LDL-C level and low HDL-C concentration (Koruk, et al., 2003).

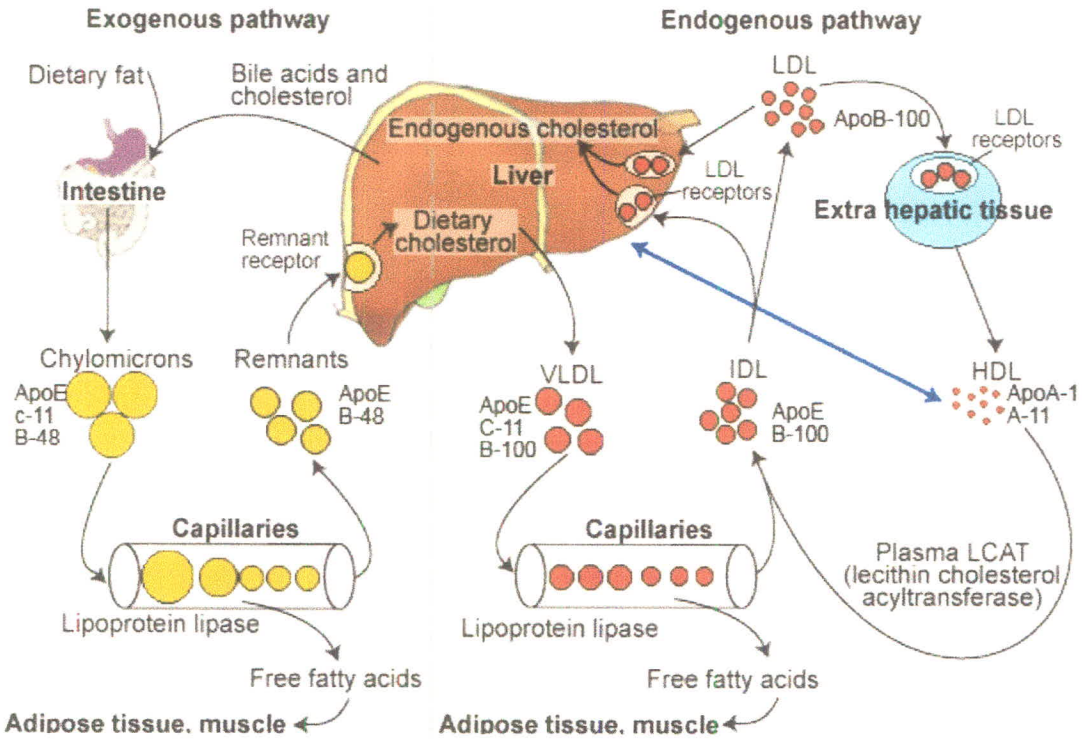


Figure 4 Pathways of lipid transport: Fat absorption from the intestine entering the circulation as chylomicrons. Then chylomicron is metabolised to chylomicron remnants and free fatty acids (FFA), FFA is converted to triglyceride and be accumulated in adipose tissue and muscle cells while chylomicron remnants transport to the liver. Additional, when cholesterol metabolism enters the liver, it is converted to very low density lipoprotein (VLDL) into the blood circulation. After that the lipoprotein lipase removes the FFA from VLDL become to intermediate lipoprotein (IDL). IDL is converted to low density lipoprotein (LDL) by hepatic triglyceride lipase. LDL is to deliver cholesterol to cells which cells take up cholesterol by LDL receptors. Additionally HDL is synthesized and secreted by the liver and small intestine. If excess cholesterol from cells, it is transported to the liver by HDL.

Source: http://www.elu.sgul.ac.uk/rehash/guest/scorm/294/package/content/liver_Lipopotein.html

High Fat and high sucrose diet induce metabolic syndrome

The development of MetS is most commonly caused by consumption of excessive carbohydrates such as sucrose and fructose includes consume a lot of fat (Lutsey, et al., 2008). Increasing consumption of high fat diet is a factor responsible for obesity and insulin resistance (Shulman, 2000). High fat diet fed rodent such as lard and coconut oil increased body weight, liver triglycerides deposition, plasma triglyceride level, free fatty acid concentration (Buettner, et al., 2006), visceral fat accumulation (Lin, et al., 2000), systolic blood pressure and induced endothelial dysfunction (Nicol, et al., 2005). Previous study reported that the effect of high fat diet consumption induced lipid disorder and insulin resistance in mice (Cong, et al., 2008).

Sucrose, a dietary source of fructose (Tappy and Le, 2010) has become an important tool used to mimic human MetS in animal model. High sucrose intake in rodents induced the development of onset of MetS, including central obesity, increased blood glucose, triglyceride, free fatty acids levels (Coelho, et al., 2010), hyperinsulinemia and impaired glucose tolerance (Lombardo, et al., 1996). It has been reported that sucrose feeding increased systolic blood pressure, developed hepatic steatosis (Huang, et al., 2010) and elevated insulin resistance in rats (Melancon, et al., 2006).

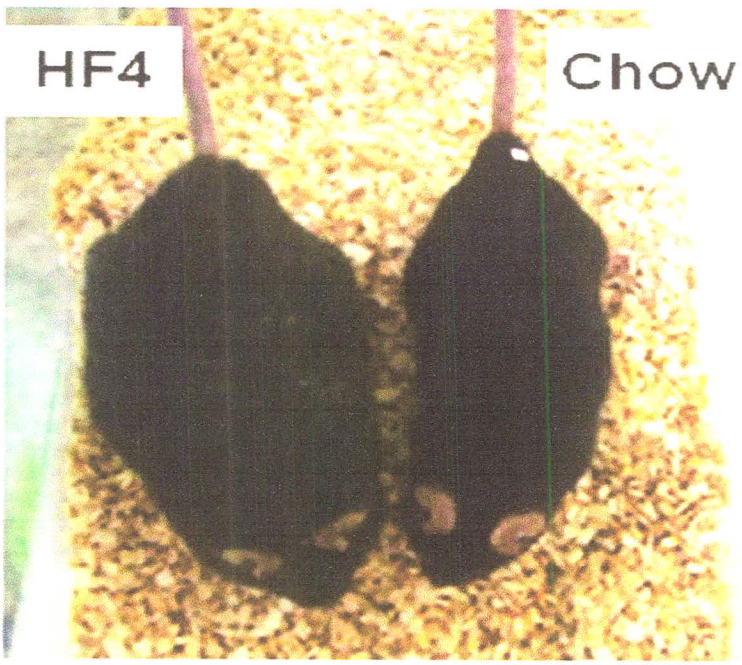
Moreover, rodents fed on high sucrose and high fat diet had enlarge body weight, visceral fat accumulation, hyperglycemia, hyperinsulinemia, dyslipidemia and hyperleptinemia (Murase, et al., 2001). In addition, combination of fat and sucrose also caused hepatic steatosis and elevated hepatic lipogenic enzyme (VanSaun, et al., 2009). Many studies have shown that the mice fed on varied content between 10-30% of sucrose with varied between 20%-60% fat diet able to induced MetS (Parekh, et al., 1998; Murase, et al., 2001; Sato, et al., 2010). Therefore, in animal model induce MetS by high fat high sucrose diet have been used to mimic the human diet more closely.

Animal models for metabolic syndrome

The MetS is one of the most important disorders that affect a major health issue and biomedical research. Epidemiology of MetS throughout the world has continuously increased (Zimmet, et al., 2005). Thus, it is imperative to develop animal models of MetS for research. There were several reports demonstrating the

multifactorial genetic disease animal models of MetS, such as Zucker diabetic fatty rats (Schmidt, et al., 2003) and db/db mice which have a mutation in leptin receptor gene, ob/ob mice which caused mutation in leptin gene (Enser, 1972), Goto-Kakizaki rats that are spontaneous none obese diabetic (Yasuda, et al., 2002), Otsuka long-Evans Tokushima fatty rats (Shima, et al., 1999) and Tsumura, Suzuki, Obese Diabetes (Hirayama, et al., 1999) that developed spontaneously type 2 diabetic mice. In addition, normal strain of animals induced with high fat and high carbohydrate diets have been used to mimic human MetS for example Wistar rats (Ble-Castillo, et al., 2012), Sprague-Dawley rats (Sahin, et al., 2007), ICR mice (Yun, et al., 2007) and C57BL/6J mice (Surwit, et al., 1988). These models can help determining the disorder from MetS and has been used in many researches. Among the various animal models available to study MetS, C57BL/6J mice are the most commonly used for several reasons. The previous studies show that C57BL/6J mice are able to develop severe obesity, hyperglycemia, hyperinsulinemia (Surwit, et al., 1988) and type 2 diabetes mellitus (Dissard, et al., 2013). The combined feeding studies require only 4-5 months to induce MetS in C57BL/6J mice (Surwit, et al., 1988; Gallou-Kabani, et al., 2007). Some research has shown that C57BL/6J mice received high fat high sucrose diet be able to progress hypercholesterolemia, hyperglycemia, hyperinsulinemia and increase visceral fat mass in a higher amount in comparison to the diabetes-resistance A/J mice (Rebuffe-Scrive, et al., 1993). Additionally, the combination of fat and sucrose in the diet induced diabetes and obesity in C57BL/6J (Surwit, et al., 1995). Recently, It has been indicated that in this strain mice induced obesity by high fat high sucrose diet could progress into the characteristic of non-alcoholic fatty pancreatic disease by increase pancreatic islet size, fat contained pancreas and liver, leading to hepatic fat accumulation and insulin resistance (Fraulob, et al., 2010). Moreover, this strain has been reported as a good model that can mimic human MetS (Figure 5). For these reasons, in this study, C57BL/6Mlac mice induce by high fat high sucrose diet will be used as a model of MetS.

(A)



(B)

Figure 5 The characteristic of C57BL/6 mice
The normal of C57BL/6 mice (A) and
diet-induced MetS of C57BL/6 mice (B)

Source: http://www.nlac.mahidol.ac.th/nlacwwwtha/spec_inC57BL_6.htm
http://high-fat-nutrition.blogspot.com/2012_09_01_archive.html

Kaempferia parviflora

Kaempferia parviflora Wall. ex Baker (*K. parviflora*), a plant in the family of Zingiberaceae, is also known as KraChai-Dum and referred to as Thai ginseng (Sudwan, et al., 2006). This native plant grows throughout tropical parts of North and Northeast of Thailand, especially Phitsanulok and Loei Province up to an altitude of about 500-700 m above sea level. *K. parviflora* is an herbaceous plant with underground rhizomes. Its rhizomes have dark purple to black color. The trunk has a height of about 30 cm. Its leaves are wide about 7-15 cm and 30-35 cm long. The *K. parviflora* can be grown throughout the year, however, the appropriate growing season is during March to May. After 10-12 months of growth it can be utilized (Department of Agriculture, 2009), and the rhizome has been used in various herbal medicine preparations (Figure 6).

The flavonoids (flavone) are the main active compounds of *K. parviflora*, found in the rhizome. Previous study reported that chemical structures of the eleven flavonoids have been isolated from *K. parviflora*, with many methoxyl groups are attached, including 3,5,7-trimethoxyflavone, 3,5,7,3′,4′-pentamethoxyflavone, 3,5,7,4′-tetramethoxyflavone, 5-hydroxy-3,7-dimethoxyflavone, 5,7,4′-trimethoxyflavone, 5-hydroxy-7,4′-dimethoxyflavone, 5-hydroxy-3,7,4′-tri-methoxyflavone, 5-hydroxy-3,7,3′,4′-tetramethoxyflavone, 5-hydroxy-7-methoxyflavone, 5,7-dimethoxyflavone and 5,7,3′,4′-tetramethoxyflavone (Sutthanut, et al., 2007) (Figure 7).

In Thailand, the rhizome of *K. parviflora* is used as a traditional medicine to treatment various diseases such as used for improving blood flow and impotence, increased vitality, decreased pain, muscle fatigue and numbness and treatment of gout and diarrhea (Department of Agriculture, 2009). It has been reported that in male rats treated with low (60 mg/kg) and moderate (120 mg/kg) doses of *K. parviflora* had courtship behavior during the first 10-minute period, while the rat treated with high (240 mg/kg) and chronic doses of *K. parviflora* showed reduced courtship behavior (Sudwan, et al., 2006) .

The flavonoids from rhizome extract of this plant had various biological and pharmacological effects. Among these flavonoids 5,7,4′-trimethoxyflavone and 5,7,3′,4′-tetramethoxyflavone exhibited anti-plasmodial activity against *Plasmodium falciparum* (Yenjai, et al., 2004). Potent anti-fungal activity against *Candida albicans*

and mild anti-mycobacterial activity have been pointed out for the compounds 3,5,7,4′-tetramethoxyflavone and 5,7,4′-trimethoxyflavone (Yenjai, et al., 2004). Moreover, 5-hydroxy-3,7,3′,4′-tetramethoxyflavone (3.6, 9.2, 16.1 and 16.3 μg/ml) had an effect on anti-inflammatory activity by suppressing of inducible nitric oxide synthase (iNOS) mRNA expression and prostaglandin E_2 (PGE_2) release but partly due to that of tumor necrosis factor-alpha (TNF-α) in the mouse macrophage cell line (RAW 264.7 cells) (Tewtrakul and Subhadhirasakul, 2008; Sae-wong, et al., 2009). There was a report found that the active component of *K. parviflora* extract (KPE) as well as 5,7,4-trimethoxyflavone had anti-cancer effect in human cholangiocarcinoma cell lines (Leardkamolkarn, et al., 2009).

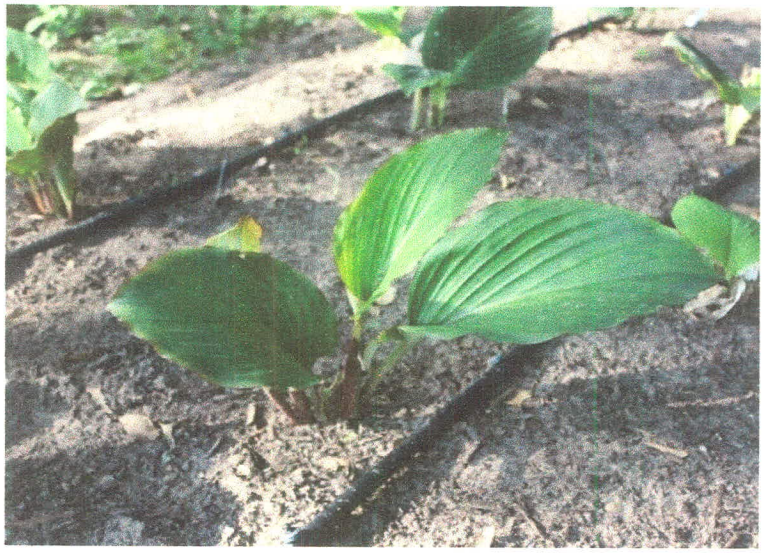
K. parviflora crude had been found to be effective in the treatment of allergy and allergic-related diseases (Tewtrakul and Subhadhirasakul, 2007), gastric ulcer (Rujjanawate, et al., 2005), leucorrhea and oral diseases (Chomchalow, et al, 2003). It also had anti-viral proteases (Sookkongwaree, et al., 2006) and inhibited cholinesterase activity (Sawasdee, et al., 2009). In addition, ethanolic extract of *K. parviflora* was found to be vasodilator, anti-oxidant and reduces ischaemic injury in rat isolated hearts (Malakul, et al., 2011a). The *K. parviflora* extract had effect on modulators the multidrug resistance in cancer cells by suppressed multidrug resistance associated-proteins (MRP)-mediated transport in A549 cells (Patanasethanont, et al., 2007). Moreover, KPE prevents endothelial dysfunction in rats with STZ-induced diabetes (Malakul, et al., 2011b) and modulated several CYP450 enzyme activities (Mekjaruskul, et al., 2012).

It was noted that *K. parviflora* extract at dose of 50 and 500 mg/kg/day had hepatoprotective and anti-inflammatatory effects in the Wistar rats (Chivapat, et al., 2010). For the chronic toxicity study of ethanolic rhizome extract from *K. parviflora*, it has been reported that the male Wistar rats were orally administered with *K. parviflora* extract at dose of 500 mg/kg BW for six months had significantly decreased body weight and triglyceride concentration. While female rats receiving the same dose had increased cholesterol and glucose concentration. Additionally, *K. parviflora* at dose of 500 mg/kg had no effect on histopathological lesion in visceral organs (Chivapat, et al., 2010) and the rat treated with 60, 120 and 240 mg/kg of *K. parviflora* extract did not effect on kidney and liver function (Sudwan, et al., 2006).

Recent studies reported that TSOD mice, a multifactorial genetic disease animal model in which obese type II diabetes mellitus develops spontaneously ingested with *K. parviflora* powder containing test feed (1 and 3% *K. parviflora* powder) had anti-obesity effect by suppressing visceral fat accumulation, improving dyslipidemia, insulin resistance, hypertension and peripheral neuropathy (Akase, et al., 2011). In contrast, *K. parviflora* powder did not affect on normal mice.

Moreover, *K. parviflora* extract (1% KPE mixed with normal chow diet) treatment was able to suppress an increase in body weight, visceral fat deposition and pancreatic lipase activity, as well as improved insulin resistance, hypertension and fatty liver disease in multifactorial genetic disease mice (Shimada, et al., 2011). Additionally, this plant is a promising candidate preventive agent for treating lifestyle-related diseases (Murata, et al., 2013).

For these reasons, the present study was designed to investigate the effects of *K. parviflora* extract on reduce various disorders in the early stage of the MetS by used in a dose of 10 and 100 mg/kg body weight represents low dose and high dose, respectively.



(A)

(B)

Figure 6 The characteristic of *Kaempferia parviflora* (*K. parviflora*)
The trunk and leaves of *K. parviflora* (A)
and the rhizome of *K. parviflora* (B)

Source: http://www.qsbg.org/Database/Botanic_Book%20full%20option/search_detailasp?Botanic_ID=2494
http://www.tejastropicals.com/blog/wp-content/uploads/2011/07/Kaempferia-parviflora-Krachai-Dom-8sm.jpg

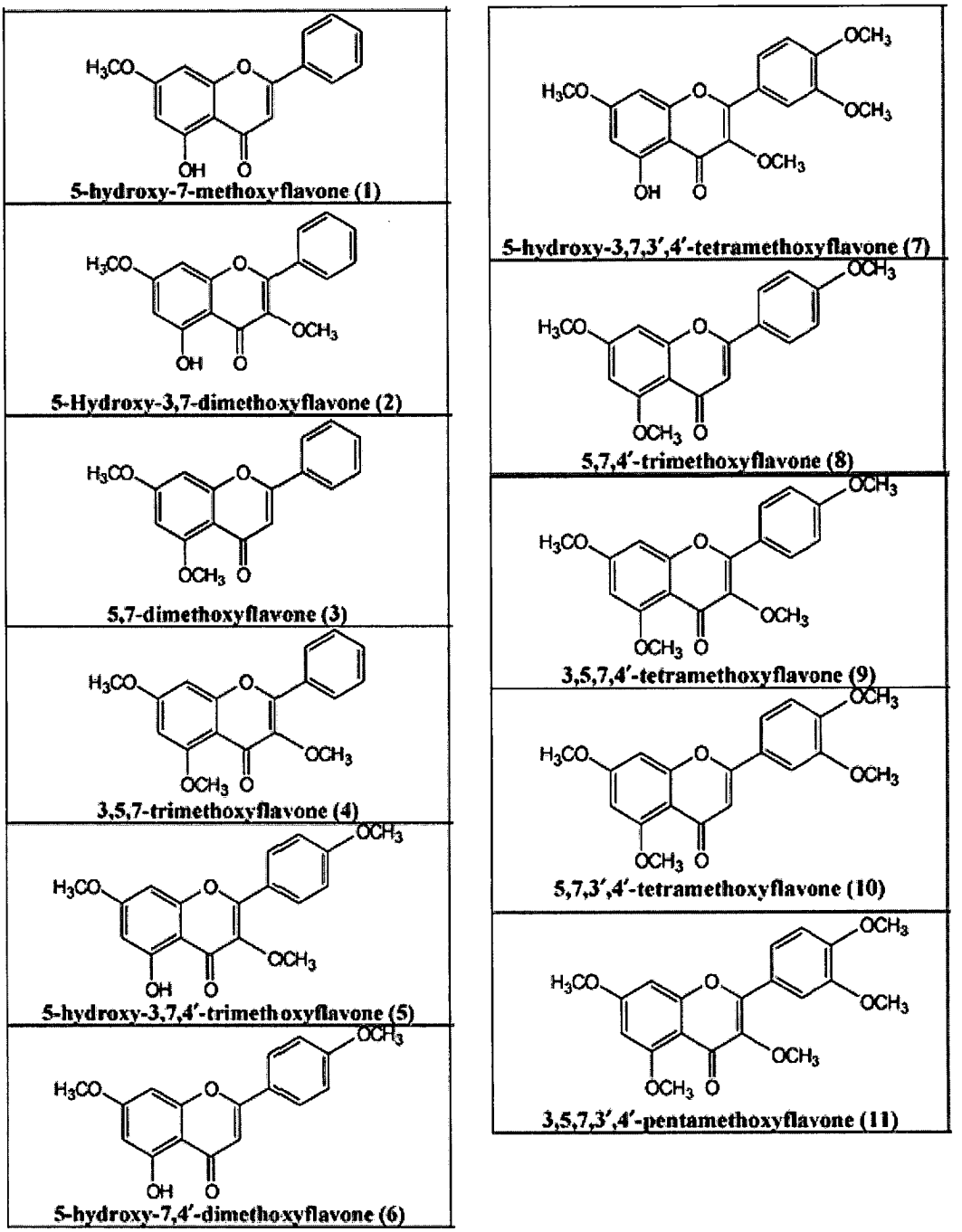


Figure 7 The main active compounds of *Kaempferia parviflora* (11 flavonoids)

Source: Sutthanut, et al., 2007