Dual Effect of Quercetin, the Anti-Metabolic Syndrome is Mediated by Adipocyte Activation

ABSTRACT

The metabolic syndrome is a metabolism abnormalities which has became a global health problem and a clinical condition which comprises various specific abnormalities including abdominal obesity, insulin resistance, dyslipidemia, and hypertension (Moller and Kaufman, 2005). These abnormalities have been found lately as a major and increasingly prevalent disorder (Grundy *et al*, 2004) that parallels the dramatic worldwide epidemic of type 2 diabetes and obesity. It is closely associated with insulin resistance and is highly associated with the risk of cardiovascular diseases.

The insulin-resistant metabolic syndrome affects a large number of Malang East Java populations and is associated with the increase rates of atherosclerotic cardiovascular disease (Sargowo, 2005). Over the past few years, much effort has been made to understand the interaction between insulin resistance and endothelial dysfunction (Mather *et al*, 2001) with particular emphasis on adipocyte-derived hormones (adipokines) and their effects on vascular homeostasis (Shuldiner *et al*, 2001; Cooke and Oka, 2002). The adipose tissue has emerged as a key secretory organ, releasing a number of bioactive molecules such as resistin, adiponectin, tumor necrosis factor-α (TNF-α), plasminogen activator inhibitor type 1, and the recently described leptin.5 These adipokines not only function prominently in the pathogenesis of the insulin-resistant syndrome but may also serve as important vasoactive factors, directly affecting endothelial function and vascular health (Gill *et al,* 2005). The ability of adipokines to directly affect vascular homeostasis might represent an important basic mechanism of cardiovascular diseases in patients with metabolic syndrome.

Leptin, which is encoded by of *ob* gene, is a plasma protein secreted by adipocytes and is involved in the control of body weight, mainly through its hypothalamic effects (Knudson, 2005). Recently, new peripheral roles for leptin have been identified, i.e., regulation of hematopoietic processes and proinflammatory immune responses (Lawton 2006), as well as stimulation of endothelial cell growth and angiogenesis (Lum and Roebuck, 2001). Moreover, the leptin receptor with the longest cytoplasmic domain (Ob-Rb), which is responsible for the leptin-mediated activation of the Janus kinases (JAK)2/STAT pathway, has been found to be expressed in various peripheral cells such as endothelial cells and cells from the immune system (Guzik *et al*, 2003; Tak and Firestein, 2001). The plasma concentrations of leptin are markedly increased in obese patient and is positively correlated with body fat mass (Shuldiner *et al*, 2001). As obesity is associated with hyperleptinemia, and also showed characteristic of metabolic syndrome, we hypothesized that leptin, in addition to its inflammation properties, exerts metabolic syndrome effect and promotes endothelial cell activation.

The etiopathology of the metabolic syndrome has not yet been fully elucidated. It seems to be the result of a complex combination of several etiologic factors that accompany central obesity and insulin resistance (Anderson *et al*, 2001). Recent studies have highlighted the involvement of a proinflammatory state that induces

insulin resistance and leads to clinical and biochemical manifestations of the metabolic syndrome. The pathomechanism leading to this pathologic acondition was suggested to involve an abnormal production of hormones and cytokines from the adipose tissue, namely an excessive production of proinflammatory mediators such as IL-6 and tumor necrosis factor-α (TNF-α) together with a lower secretion of the anti-inflammatory adipocytokine adiponectin (Dandona *et al*, 2005; Kadowaki *et al*, 2006).

Dietary patterns which include a high intake of food derived from plant, such as vegetables, legumes, and fruits, have been directly associated with the management and prevention of obesity, type 2 diabetes, and other cardiovascular risk factors (Van Dam *et al*, 2002; Estruch *et al*, 2006). These foods contain flavonoids, polyphenolic compounds reported to have protective effects against chronic pathologic conditions such as coronary events, high mortality due to cardiovascular diseases, and diabetes (Mink *et al*, 2007; Knekt *et al*, 2002). However, the epidemiological studies carried out to date remain inconclusive, and controversial data have been published concerning the protective effects of flavonoids diet against diabetes (Nettleton *et al*, 2006). It is difficult to ascertain whether flavonoids are really responsible for these beneficial health effects, as only limited studies have been made on food sourced flavonoids. And it is complicated to do such studies, as these food contains other components which can also contribute to these protective effects.

Quercetin is an isoflavone group which is commonly known as an active component in several plants. These plants (e.g. peanut, tomato, and onion) are frequently and easily found in most parts in Indonesia. Abundant sources of vitamin P active flavonoid pigments, quercetin, the 3-rhamnoside of quercetin (3,5,7,3`,4` pentahydroxylflavone) have been isolated from peanuts. Some researchers have shown that quercetin could function as a nutritional antioxidant, it inhibits ICAM-1, VCAM-1 expression in endothelial cell by down regulating both phorbol 12-myrestate 13-acetate (PMA) and TNFα-induced ICAM-1 expression via inhibiting both activator protein-1 (AP-1) activation and c-Jun NH3-terminal kinase (JNK) pathway. Furthermore, quercetin also induces the up-regulation MCP-1 expression in human umbilical vein endothelial cells (HUVECs), at the protein and trancription levels (Lakhanpal and Deepak, 2007).

The first year research result showed that 500 mg/ml leptin enhanced TNFα levels through increasing leptin receptor expression, ERK1/2 and NFκB activity on human endothelial cells. This result also demonstrated that 125 μM quercetin could reduced TNFα, levels in endothelial cells induced with high dose leptin. However, when quercetin concentration is increased to 625 μM, TNFα, levels tend to increase as well, although the increment might be associated with reducing leptin receptor density and activity of ERK1/2 and NFkB respectively.

This research will be conducted for two steps, on the first steps, we focus on the of interaction between quercetin and non-genomic topics through identification of the effect quercetin upon on gene of ET-1, ICAM-1, and VCAM-1 in human umbilical vein endothelial cells (HUVECs) by Reverse transcriptase PCR (RT-PCR) and Fluorescent In Situ Hybridization (FISH) methods. Second steps, research will be performed *in vivo* using diet-induced obese rat (*Rattus norvegicus* strain Wistar) to elucidate the dual effect of quercetin as a results of 1st year research.