Review Article

# ศักยภาพของเคอร์คูมินและเตเตระไฮโดรเคอร์คูมินต่อกระบวนการเมแทบอลิซึมของน้ำตาลและไขมันในตับที่เกี่ยวข้องกับภาวะเบาหวานและภาวะไขมันพอกตับ

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## บทคัดย่อ

ตับเป็นอวัยวะสำคัญในร่างกาย มีหน้าที่ในการเมแทบอลิซึมสารภายในร่างกาย สารอาหาร และสารแปลกปลอมต่างๆ กระบวนการเมแทบอลิซึมน้ำตาลและไขมันในตับเกี่ยวข้องกับโรคต่างๆ อาทิ โรคเบาหวานและโรคไขมันพอกตับ ขมิ้นชัน (*Curcuma longa*) เป็นพืชที่พบการใช้ทั่วไปทั้งเป็นเครื่องเทศและยาสมุนไพร สารสำคัญที่มีสีเหลืองในขมิ้นชันคือ เคอร์คูมิน (curcumin) ซึ่งมีเตตระไฮโดรเคอร์คูมิน (tetrahydrocurcumin หรือ THC) เป็นเมแทบอไลท์ออกฤทธิ์ที่ไม่มีสี สารทั้งสองนี้มีรายงานฤทธิ์ที่เกี่ยวข้องกับกระบวนการเมแทบอลิซึมน้ำตาลและไขมันในภาวะเบาหวานและไขมันพอกตับ โดยเคอร์คูมินสามารถกระตุ้น AMP-activated protein kinase (AMPK) และ ยับยั้งยีนที่เกี่ยวข้องกับกระบวนการสร้างน้ำตาล phosphoenol pyruvate carboxy kinase (PEPCK) และ glucose 6-phosphatase (G6Pase) ในเซลล์ตับ ส่วนสารสกัดขมิ้นชันซึ่งมีสารสำคัญที่ประกอบด้วย เคอร์คูมิน ดีเมท็อกซี่เคอร์คูมิน (demethoxycurcumin) บิสดีเมท็อกซี่เคอร์คูมิน (bisdemethoxycurcumin) และ เออาร์-เทอร์เมอโรน (ar-turmerone) สามารถลดระดับน้ำตาลในเลือดของหนูถีบจักรเบาหวาน KK-A$^{y}$ ได้ เตตระไฮโดรเคอร์คูมินสามารถลดระดับน้ำตาล อินซูลิน ฮีโมโกลบิน HbA1c และระดับไขมันในเลือด ตลอดจนสามารถเพิ่มระดับ HDL ในหนูขาวที่ถูกชักนำภาวะเบาหวานชนิดที่ 2 และยังมีผลลดสมรรถนะของเอนไซม์ 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) ในหนูขาวที่มีภาวะคลอเรสเตอรอลสูง (hypercholesterolemic rats) ได้ ในขณะที่เคอร์คูมินลดระดับไขมันชนิดต่างๆ ในหนูแฮมสเตอร์ที่ถูกชักนำภาวะไขมันพอกตับ ด้วยอาหารอุดมไขมัน และมีรายงานว่าสามารถกระตุ้นสมรรถนะของกระบวนการเบต้าออกซิเดชั่นได้ด้วย สารสกัดขมิ้นชันสามารถลดการสร้างคลอเรสเตอรอลและเพิ่มการเปลี่ยนคลอเรสเตอรอลเป็นกรดน้ำดี (bile acids) ได้ในหนูขาวที่มีภาวะคลอเรสเตอรอลในเลือดสูง (hypercholesterolemia) โดยผ่านกลไกการลดการแสดงออกของ HMG-CoA reductase และเพิ่มการแสดงออกของ cytochrome P450 7A1 (CYP7A1) และ LDL receptor ซึ่งส่งผลลดระดับคลอเรสเตอรอลในกระแสเลือด แม้ว่าทั้งเคอร์คูมินและเตตระไฮโดรเคอร์คูมินจะแสดงผลในเชิงบวกต่อกระบวนการเมแทบอลิซึมที่เกี่ยวข้องกับภาวะเบาหวานและภาวะไขมันพอกตับในสัตว์ตัวแบบต่างๆ แต่ข้อมูลดังกล่าวยังไม่ชัดเจนเพียงพอที่จะสนับสนุนสารทั้งสองในการชะลอหรือควบคุมภาวะโรคที่เกี่ยวข้องกับกระบวนการเมแทบอลิซึมในตับ ดังนั้นจึงต้องมีการศึกษาเพิ่มเติมเพื่อบ่งชี้กลไกสำคัญของเคอร์คูมินอยด์ทั้งสองนี้ในการควบคุมภาวะดังกล่าวต่อไป

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# The Potential of Curcumin and Tetrahydrocurcumin in Hepatic Lipid and Glucose Metabolism Related to Diabetes Mellitus and Non-Alcoholic Fatty Liver Diseases: A Review

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## Abstract

The liver is a crucial organ for metabolizing endogenous substances, dietary substances, and xenobiotics in the body. Several diseases such as diabetes mellitus (DM) and non-alcoholic fatty liver disease (NAFLD) are associated with the deterioration of hepatic glucose and lipid metabolism. Turmeric or *Curcuma longa* is an herbal plant that is commonly used as a spice and a traditional medicine. The main yellow active compound in turmeric is curcumin, in which tetrahydrocurcumin (THC) is its active colorless metabolite. Both compounds have exhibited a protective effect for lipid and glucose metabolism as presented in both DM and NAFLD. Curcumin induced AMP-activated protein kinase (AMPK) inhibited genes-related gluconeogenesis, phosphoenol pyruvate carboxy kinase (PEPCK) and glucose 6-phosphatase (G6Pase) in hepatocytes. Active compounds that contained tumeric extract including curcumin, demethoxycurcumin, bisdemethoxycurcumin, and ar-turmerone lowered the blood glucose level of KK-$A^y$ mice. THC reduced the levels of glucose, insulin, hemoglobin A1c (HbA1c), and lipid including the HDL level in the blood of DM2-induced rats. Moreover, THC decreased 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) activity in the hypercholesterolemic rats. Curcumin lowered the lipid levels of NAFLD-induced hamsters that were fed a high fat diet with induction of beta-oxidation process. In addition, the turmeric extract also exhibited the potential to reduce cholesterol synthesis and accelerate the change of cholesterol into bile acid. This occurred in the rats with hypercholesterolemia via an inhibitory pathway of HMG-CoA reductase with activation of cytochrome P450 7A1 (CYP7A1) and LDL receptor expression, resulting in the decline of blood cholesterol level. Although curcumin and THC have exhibited positive effects on the metabolism of DM and NAFLD in animal models, evidence supporting mechanisms that delay progression or manage these diseases is still incomplete. Hence, further studies are required to clarify the key regulatory mechanisms that use these two curcuminoids in liver related diseases.curcuminoids in liver related diseases.

**Keywords:** *Curcuma longa*, curcumin, diabetes mellitus, non-alcoholic fatty liver disease, tetrahydrocurcumin
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## Introduction

The liver is a crucial organ with various functions in the body. It plays a role in metabolism of endogenous and exogenous substances, e.g., drugs, dietary substances, and xenobiotics, etc., production and storage of necessary biochemicals, decomposition and detoxification to maintain the homeostasis, and regulating energy balance (Rowland et al., 2013). These roles include lipid, glucose, and cholesterol metabolism. The pathways of fatty acid oxidation, lipogenesis, and gluconeolysis have been extensively reviewed (Bechmann et al., 2012; Xiao and Lewis, 2012; Iqbal and Hussain, 2009; Tessari et al., 2009; Cariou and Staels, 2007).

Because of its multidimensional functions, dysfunction of the liver leads to many diseases (Mueller et al., 2012; Frye et al., 2006). Several hepatic pathological conditions are implicated by metabolic abnormalities (Fabbrini et al., 2010). Prevalence of obesity and metabolic syndrome are rising to pandemic levels in some countries (Finucane et al., 2011; Grundy, 2008). Alteration of lipid and glucose metabolism and abnormal actions of insulin are now considered to be involved in the pathogenesis of some liver diseases such as non-alcoholic fatty liver disease (NAFLD) (Parekh and Anania, 2007). NAFLD is the most common chronic liver disease in affluent societies (Loomba and Sanyal, 2013; Welsh et al., 2013). Although steatosis itself does not significantly change the liver enzyme functions, it can progress to the severe form called non-alcoholic steatohepatitis (NASH). Hence, the pathways of lipid and glucose metabolism are necessary for understanding the pathologies of metabolic hepatic diseases, such as NAFLD with the nuclear receptor signaling, that acts as metabolic and toxicological sensors to regulate energy and metabolism (Jiang et al., 2015; Matsusue et al., 2014; Serviddio et al., 2013)

Turmeric or *Curcuma longa,* a common herbal plant found in Asia, is commonly used as a food ingredient and as a traditional medicine (Lestari and Indrayanto, 2014). Curcumin and tetrahydrocurcumin (THC) are the main active compound and its major colorless metabolite, respectively (Pari and Murugan, 2007). Activities of these two compounds have been reported in several diseases such as digestive disorder, toxic hepatitis, and inflammation (Yiu et al., 2011; Aggarwal and Harikumar, 2009; Pari and Amali, 2005). The protective effects of both compounds from turmeric in the pathways on the diseases involving lipid and glucose metabolism have been reported in several models (El-Moselhy et al., 2011; Yiu et al., 2011; Chanpoo et al., 2010; Kim et al., 2009). Therefore, the effects of curcumin and THC against liver diseases warrant further study.

## Lipid and glucose metabolism related to diabetes mellitus (DM)

DM is a disease clinically characterized by chronic hyperglycemia and associated with long-term damage to several organs such as nerves, kidneys, eyes, heart, and blood vessels. The pathogenesis of DM results from deficiency in insulin secretion or/and insulin action. DM can be divided into 2 major categories. Type 1 DM or

insulin-dependent DM is caused by the inability to produce insulin due to autoimmune destruction of the β-cells of the pancreas. The other, type 2 DM or non-insulin-dependent DM, has a greater prevalent, and relates to insulin resistance that causes less response of liver, muscle, and adipose tissue to insulin (American Diabetes Association, 2012). Type 2 DM involves various metabolic pathways linked to other health problems and related to metabolic syndrome, including obesity, hyperlipidemia, hypertension, and cardiovascular disease (Birkenfeld and Shulman, 2014). The abnormality of glucose metabolism is considered to be the main cause of development of type 2 DM (Mera et al., 2011). These alterations include increase of glucose production and impairment to suppression of glucose, and change in glucose utilization (Meshkani and Adeli, 2009). The decreasing activity of enzyme in glucose metabolism such as liver glucokinase was also reported (Moore et al., 2012). Abnormal lipid profiles such as hypertriglyceridemia, accumulation of intermediate density lipoprotein, and small, dense LDL is also linked to this type of DM (Al-Jameil et al., 2014; Subramanian and Chait, 2012; Mooradian, 2009).

## Lipid and glucose metabolism related to non-alcoholic fatty liver disease (NAFLD)

NAFLD is defined as the disease with accumulation of lipid in hepatocytes and has histological changes resembling alcoholic fatty liver disease, but occurs in patients with no or low alcohol consumption (Loria et al., 2007). NAFLD ranges from simple steatosis through to the advanced stage called NASH which is approximately 20-30% of NAFLD patients (Rolo et al., 2012). Fibrosis of the liver to cirrhosis is the late stage by grading of NASH (Hübscher, 2006). NAFLD is the most liver disease presented in Western populations (Lomonaco et al., 2013). The major source of triglycerides accumulated in hepatocytes results from transportation of adipose fatty acid and *de novo* lipogenesis in the liver itself (Donnelly et al., 2005). The NAFLD patient has persistent increase of liver enzymes including aspartate aminotransferase (AST) and alanine aminotransferase (ALT). NAFLD is considered partly as a manifestation of the metabolic syndrome in the liver with abnormality-groups of symptoms such as insulin resistance, visceral obesity, dyslipidemia, and diabetes (Marchesini et al., 2001). The key to NAFLD pathogenesis is involved with the condition of insulin resistance that can progress to NASH in combination with other metabolic diseases resulting in increased gluconeogenesis and enhanced peripheral lipolysis. Consequently, free fatty acids are released from visceral adipose tissue into the plasma pool. The hepatic uptake of free fatty acids is increased, and finally an increase of triglyceride synthesis occurs, resulting in fat accumulation in the hepatocytes (Krawczyk et al., 2010).

## Turmeric plant and its active constituents

Turmeric (*Curcuma longa* Linn.) is a medicinal herb that is traditionally used as a spice and coloring in many dishes. *C. longa* belongs to the Zingiberaceae family which has been assigned as a rhizomatous and monocotyledonous

perennial herb. The turmeric plant is grown in hot, humid climates such as India, China, and South East Asia, including Indonesia, Thailand, Vietnam, and the Philippines. This plant can grow up to 1 meter in height with 6–10 distichously, elliptical leaves. The rhizome, which is the main part used for medicinal purpose has an intense yellow-color similar in appearance to the branched finger-shaped ginger root (Jayaprakasha et al., 2005).

Turmeric contains several phytochemicals in the essential oil fraction (5.8%) obtained by stream distillation. This part is a rich source of phenolic compounds called curcuminoids (3–5%). Besides the major active compound curcumin (diferuloylmethane), other minor constituents such as demethoxycurcumin and bisdemethoxycurcumin, which give the yellow pigmentation to the *C. longa* plant, particularly to its rhizomes, have been isolated (Esatbeyoglu et al., 2012; Jayaprakasha et al., 2005). The chemical components in the essential oil were also reported, including curcumin (3–4%), α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%) (Chattopadhyay et al., 2004). Under a hydrogenation process, mixtures of derivative hexahydrocurcumin and THC have also been obtained. THC is one of the major active metabolites of curcumin, and identified in liver and intestinal cytosol from humans and rats studies. However, it was still not clear whether THC is as active as curcumin itself (Anand et al., 2007; Ireson et al., 2002)

## The activities of turmeric extract, curcumin, and tetrahydrocurcumin in various diabetic and non-alcoholic fatty liver models related to lipid and glucose metabolism

Liver diseases pose a major medical problem worldwide and a wide variety of herbs have been studied for the management of liver-related diseases. As a traditional herbal plant in many countries, *C. longa*, popularly known as Haldi (Hindi) in India, claims the use of its powder against a wide variety of diseases (Aggarwal et al., 2007). Recently, the pharmacological properties for health promotion including the liver protection properties of curcuminoids have gained increasing attention (Esatbeyoglu et al., 2012). Curcumin is used in traditional medicine, and there has been increasing research interest in its metabolite THC against liver diseases (Vera-Ramirez et al., 2013). The activities of curcumin and THC have been studied on several diabetic and non-alcoholic fatty liver models, described below.

### *In vitro anti-diabetic mechanism model*

Rat Reuber hepatoma H35 cells (or known as H35 cells or rat H4IIE cells) are a differentiated rat liver cell line that expresses liver enzymes (with exception of evidence for glycogenesis) and is widely used in studies of hepatic insulin-response and resistance (Hectors et al., 2012). Suppressive effects of curcumin and THC on dexamethasone-induced phosphoenol pyruvate carboxy kinase (PEPCK) and glucose 6 phosphatase (G6Pase) gluconeogenic gene expression was observed in H4IIE rat hepatoma cells while neither curcumin nor THC improved

insulin receptor (IR) activation, glucose uptake in skeletal muscle cells, inhibition of $\alpha$-glucosidase activity, or suppression of dipeptidyl peptidase-4 activity (Kim et al., 2009). Therefore, the suggestion of a potential mechanism mediating glucose-lowering effects of curcuminoids through suppression of hepatic gluconeogenesis was noted. The curcuminoids increased the phosphorylation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase (ACC) in H4IIE and Hep3B human hepatoma cells line with 400 times (curcumin) to 100,000 times (THC) the potency of metformin (Kim et al., 2009).

***In vivo diabetes mellitus models***

The beneficial effects of curcumin and its derivatives were reported in several rodent *in vivo* diabetic models (El-Moselhy et al., 2011; Na et al., 2011; Karthikesan et al., 2010a; Karthikesan et al., 2010b). In a type 2 diabetic KK-$A^y$ mouse model, turmeric extract, with curcumin, demethoxycurcumin, bisdemethoxycurcumin, and arturmerone as the main constituents suppressed an increase of blood glucose level. These observations suggested an enhanced ability to activate peroxisome proliferator-activated receptor gamma (PPAR-$\gamma$) (Kuroda et al., 2005; Nishiyama et al., 2005). A single treatment of THC has been reported to reduce the change of plasma glucose, insulin, haemoglobin, and glycosylated haemoglobin (HbA1c) in a type 2 diabetic rat model (Karthikesan et al., 2010b). Additionally, the water and ethanolic extract of *C. longa* showed preventive effects toward oxidative stress in the rodent-DM model with improvement in serum AST and ALT levels (El-Masry, 2012). The anti-oxidant effect of THC in induced hepatotoxicity in rat was also noted (Pari and Amali, 2005).

Dyslipidemia is an implication of DM. The rising concentration of plasma lipid and lipoprotein, and lowering of HDL cholesterol level are characteristics of uncontrolled blood glucose levels found in a diabetic patient (Mooradian, 2009). In a streptozotocin-nicotinamide-induced diabetic rat model, THC decreased the level of total cholesterol, free fatty acids, triglycerides, and phospholipids with improvement of plasma lipoproteins, *i.e.*, LDL-C, VLDL-C, and HDL-C (Karthikesan et al., 2010a). 3-Hydroxy-3- methyl-glutaryl coenzyme A reductase (HMG-CoA reductase) is a rate-limiting step enzyme in hepatic cholesterol biosynthesis which catalyzes HMG-CoA into mevalonate (Brown and Goldstein, 1980). An increase of HMG-CoA reductase activity was observed in the diabetic rats, in association with insulin resistance (Seo et al., 2008), that led to excessive production and accumulation of cholesterol, and subsequently caused formation of foam cells which can develop to atherosclerosis. The ratio of HMG-CoA to mevalonate was used for determination of HMG-CoA reductase activity. An increase of this ratio determines the decreasing activity of HMG-CoA enzyme. In the diabetic rat model, THC elevated the HMG-CoA/mevalonate ratio in both liver and kidney, and the far greater effect was noted by the combined treatment of THC with an antioxidant, chlorogenic acid (Karthikesan et al., 2010a). These results indicated that THC suppressed activity of HMG-CoA reductase,

corresponding to a previous report (Yiu et al., 2011).

There are several enzymes involved in lipid metabolism. Lecithin-cholesterol acyltransferase (LCAT) is a plasma enzyme that converts free cholesterols into cholesteryl esters. This step is required for HDL maturation (Sorci-Thomas et al., 2009). Lipoprotein lipase (LPL) is the rate-limiting enzyme for catalyzing hydrolysis of triglycerides-rich lipoproteins including VLDL and chylomicrons in the blood circulation (Mead et al., 2002). In the diabetic rats, the plasma LCAT and LPL activities were decreased while a single treatment of THC and the co-treatment of THC with chlorogenic acid improved these enzyme activities (Karthikesan et al., 2010a). Additionally, twelve week-treatment of curcumin at a dose of 200 mg/kg improved type 1 diabetes mouse pancreatic islets, the pathological organ of type 1 DM, by increasing numbers of pancreatic islets (Chanpoo et al., 2010). The cellularity of $\beta$-cell pancreatic islets of type 2 diabetic rat was additionally increased after THC treatment (Karthikesan et al., 2010b).

***In vivo NAFLD and NASH models***

NAFLD is a wide spectrum of disease that starts with accumulation of triglyceride in hepatocytes, known as fatty liver or hepatic steatosis, and can progress to the stage of NASH with inflammation, fibrosis, or the severe stage, cirrhosis (Narasimhan et al., 2010). In previous study, curcumin supplement exhibited a hypolipidemic effect in high-fat fed hamsters. These effects included reduction of the levels of free fatty acid, total cholesterol, and triglyceride, and elevation of both HDL-C and apolipoprotein A1 (ApoA-I). Curcumin showed the potential to stimulate hepatic fatty acid oxidation by decreasing plasma leptin levels that may attenuate a leptin resistance state (Jang et al., 2008).

HMG-CoA reductase is a key enzyme for cholesterol synthesis in the liver. In the hypercholesterol-treated rat model, the turmeric extract down-regulated the expression of HMG-CoA reductase while cholesterol 7$\alpha$-hydroxylase (CYP7A1), which is the enzyme for bile acid synthesis from cholesterol, was elevated. These findings indicated the potential of *C. longa* to decrease cholesterol synthesis and to increase cholesterol conversion into bile acids. Moreover, the turmeric extract increased the expression level of the LDL receptor, which mediates endocytosis of LDL-C into the liver by binding to the LDL receptor on cell surface of hepatocytes, leading to increased capacity to remove LDL-C from plasma (Yiu et al., 2011).

In a methionine and choline deficient diet (MCD) induced NASH model, mice fed with curcumin-supplemented controlled diet exhibited normal liver histology. Moreover, the supplementation of curcumin to the MCD for 4 weeks improved the histopathological appearance of hepatic inflammation and necroinflammatory lesions by decreasing of the number and size of intrahepatic inflammatory foci with significant reduction of serum ALT level (Leclercq et al., 2004). However, curcumin had neither effect on hepatic lipid stores nor expression of acyl-coA oxidase mRNA, the rate limiting enzyme for peroxisomal $\beta$-oxidation (Leclercq et al., 2004).

## Conclusions

Curcumin and THC from *C. longa* have beneficial effects related to lipid and glucose metabolism in both of DM and NAFLD in animal models by various pathways including suppression of hepatic gluconeogenesis *via* activation of AMPK. These result in lowered expression of PEPCK and G6Pase, decreased cholesterol synthesis, and increased cholesterol conversion into bile acid by suppression of HMG-CoA reductase with up-regulation of CYP7A1 and LDL receptor, and other pathways such as neogenesis of pancreatic islets, reduced enzyme activities (*i.e.* LCAT, LPL, fatty acid synthase, and acyl-CoA cholesterol acyltransferase), and enhanced β-oxidation process. However, there is not enough evidence to fully understand the key mechanisms to delay progression and to treat either DM or NAFLD. Therefore, further studies are needed for clarifying impacts of both curcumin and THC on liver-related diseases, in particular DM and NAFLD.

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