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Beneficial effects of curcumin on hyperlipidemia and insulin resistance in high-fat–fed hamsters

Eun-Mi Jang[a], Myung-Sook Choi[b], Un Ju Jung[c], Myung-Joo Kim[d], Hye-Jin Kim[b], Seon-Min Jeon[b], Su-Kyung Shin[b], Chi-Nam Seong[e], Mi-Kyung Lee[f,*]

[a]*Department of Nutrition Education, Graduate School of Education, Sunchon National University, Jeonnam 540-742, South Korea*
[b]*Department of Food Science and Nutrition, Kyungpook National University, Daegu 702-701, South Korea*
[c]*Institute of Human Nutrition, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA*
[d]*Department of Food Science and Nutrition, Daegu Polytechnic College, Daegu 706-022, South Korea*
[e]*Department of Biological Science, Sunchon National University, Jeonnam 540-742, South Korea*
[f]*Department of Food and Nutrition, Sunchon National University, Jeonnam 540-742, South Korea*

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Abstract

This study investigated the effect of curcumin (0.05-g/100-g diet) supplementation on a high-fat diet (10% coconut oil, 0.2% cholesterol, wt/wt) fed to hamsters, one of the rodent species that are most closely related to humans in lipid metabolism. Curcumin significantly lowered the levels of free fatty acid, total cholesterol, triglyceride, and leptin and the homeostasis model assessment of insulin resistance index, whereas it elevated the levels of high-density lipoprotein cholesterol and apolipoprotein (apo) A-I and paraoxonase activity in plasma, compared with the control group. The levels of hepatic cholesterol and triglyceride were also lower in the curcumin group than in the control group. In the liver, fatty acid β-oxidation activity was significantly higher in the curcumin group than in the control group, whereas fatty acid synthase, 3-hydroxy-3-methylglutaryl coenzyme A reductase, and acyl coenzyme A:cholesterol acyltransferase activities were significantly lower. Curcumin significantly lowered the lipid peroxide levels in the erythrocyte and liver compared with the control group. These results indicate that curcumin exhibits an obvious hypolipidemic effect by increasing plasma paraoxonase activity, ratios of high-density lipoprotein cholesterol to total cholesterol and of apo A-I to apo B, and hepatic fatty acid oxidation activity with simultaneous inhibition of hepatic fatty acid and cholesterol biosynthesis in high-fat–fed hamsters.

1. Introduction

A large number of studies are in progress to identify natural substances that are effective in reducing the severity of cardiovascular diseases (CVDs). In recent years, a few spices have been experimentally shown to impart several beneficial physiologic effects, of which the hypolipidemic and antioxidant influences have far-reaching health implications [1].

Curcumin is a major active component of *Curcuma longa* L, which has long been used widely as a spice and food-coloring agent in several foods such as curry, mustard, and potato chips [2,3]. Curcumin has many pharmacologic activities including anti-inflammatory properties, powerful antioxidant activity, and cancer-preventive properties [4]. A recent study showed that curcumin lowered blood glucose and glycated hemoglobin levels by lowering oxidative stress in diabetic rats [5]. In our previous study, curcumin was beneficial in improving insulin resistance and glucose homeostasis in *db/db* mice, which seems to be medicated through activation of glycolysis and inhibition of gluconeogenic and lipid metabolic enzymes in the liver [6]. Furthermore, several studies suggested that curcumin has hypocholesterolemic properties [7,8]. Arafa [9] reported that the hypocholesterolemic effect of dietary curcumin (0.5%, wt/wt) in high-cholesterol–fed rats could possibly be medicated through a local effect on cholesterol absorption or excretion through the bile, but not due to its antioxidant effect. Meanwhile, Srinivasan and Manjunatha [10] showed the hypolipidemic and antioxidant effects of curcumin (0.2%, wt/wt) in high-fat (30%)–fed rats. The 0.2% (wt/wt) dose of

* Corresponding author. Tel.: +82 61 750 3656; fax: +82 61 750 3608.
E-mail address: leemk@sunchon.ac.kr (M.-K. Lee).

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dietary curcumin used in animal study is equivalent to about 10 times of the corresponding turmeric [11].

Curcumin has, so far, no known dose-limiting toxicities and has been consumed by human in dosage of up to 12 g/d without any adverse effects [12]. The object of this study is to establish the mechanism responsible for the lipid-lowering effects of a low-dose curcumin (0.05%, wt/wt) and its beneficial effect on insulin resistance in a high-fat and high-cholesterol–fed hamster model, which has been extensively used for the study of diet-induced regulation of lipoprotein metabolism because the lipoprotein profiles of hamsters are more similar to humans than that of mice or rats [13].

2. Materials and methods

2.1. Animals and diets

Male Golden-Syrian hamsters (4 weeks old) were obtained from Charles River Laboratories (Wilmington, MA). The animals were all individually housed in stainless steel cages in a room at 22°C ± 2°C on a 12-hour light/dark cycle. All hamsters were fed a pelletized commercial chow diet for 1 week after arrival, and then randomly divided into 2 groups (n = 8) and fed a high-fat diet (10% coconut oil, 0.2% cholesterol, wt/wt) with or without curcumin. The composition of the experimental diet was based on the American Institute of Nutrition–76 semisynthetic diet [14,15]. The curcumin was given as a supplement based on a 0.05-g/100-g diet for 10 weeks. The hamsters had free access to food and water. At the end of the experimental period, the hamsters were anesthetized with ether after withholding food for 12 hours; and blood samples were taken from the inferior vena cava to determine the plasma biomarkers. After collecting the blood, the liver was removed, rinsed with a physiologic saline solution, and immediately stored at −70°C. The hamsters were all treated in strict accordance with the Sunchon National University guidelines for the care and use of laboratory animals.

2.2. Plasma biomarkers

The plasma glucose concentration was determined using an enzymatic kit (Asan, Seoul, Korea). The plasma leptin (Linco, St. Charles, MO) and insulin (Diagnostic System Laboratories, Webster, TX) levels were determined using a radioimmunoassay kit.

2.3. Homeostatic index of insulin resistance

Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the homeostasis of assessment, as follows [16]: HOMA-IR = (fasting glucose [millimoles per liter] × fasting insulin [μIU per milliliter])/22.5.

2.4. Plasma and hepatic lipid profiles

The concentrations of plasma cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (Sigma Diagnostics, St Louis, MO), and low-density lipoprotein cholesterol (LDL-C) (Daiichi Pure Chemicals, Tokyo, Japan) were determined using an enzymatic method, whereas the plasma free fatty acid concentration was determined using an enzymatic colorimetric method (Wako Chemicals, Richmond, VA). Non–high-density lipoprotein cholesterol concentration was calculated as the difference between total cholesterol (TC) and HDL-C. Plasma apolipoprotein (apo) A-I and B levels were measured using an immunoassay method (Nitto Boseki, Japan).

The hepatic lipids were extracted using the procedure developed by Folch et al [17], and the cholesterol and triglyceride concentrations were analyzed with the same enzymatic kit as used in the plasma analysis.

2.5. Preparation of samples

Blood samples from the inferior vena cava were collected in heparin-coated tubes. After centrifugation at 1000*g* for 15 minutes at 4°C, the plasma and buffy coat were carefully removed. The separated cells were then washed 3 times by resuspension in a 0.9% NaCl solution, and the centrifugation was repeated. The washed cells were lysed in an equal volume of water and mixed thoroughly. The hemoglobin concentration was estimated in an aliquot of the hemolysate using a commercial assay kit (No. 525-A, Sigma Chemical).

The enzyme source fraction in the liver was prepared according to the method developed by Hulcher and Oleson [18], with a slight modification. A 20% (wt/vol) homogenate was prepared in a buffer containing 0.1 mol/L of triethanolamine, 0.02 mol/L of EDTA, and 2 mmol/L of dithiothreitol (pH 7.0), and then centrifuged at 600*g* for 10 minutes to discard any cell debris; and the supernatant was centrifuged at 10 000*g* followed by 12 000*g* for 20 minutes at 4°C to remove the mitochondrial pellet. Thereafter, the supernatant was ultracentrifuged twice at 100 000*g* for 60 minutes at 4°C to obtain the cytosolic supernatant. The mitochondrial and microsomal pellets were then redissolved in 800 μL of a homogenization buffer; and the protein content was determined by the method of Bradford [19], using bovine serum albumin as the standard.

2.6. Hepatic lipid–regulating enzyme activities

Fatty acid synthase (FAS) activity was determined by a spectrophotometric assay based on measuring the malonyl-coenzyme A (CoA)–dependent oxidation of nicotinamide adenine dinucleotide phosphate, reduced form (NADPH) according to the methods of Nepokroeff et al [20], with a slight modification. One unit of enzyme activity represented the oxidation of 1 nmol of NADPH per minute at 37°C. Phosphatidate phosphohydrolase (PAP) activity was determined by using the method of Walton and Possmayer [21]. The malic enzyme was determined as described by Ochoa [22]. One hundred fifty microliters of the cytosolic enzyme was mixed with 0.2 mmol/L triethanolamine buffer (pH 7.4), 1.5 mmol/L L-malate, 12 mmol/L $MnCl_2$, and 680 μmol/L

$NADP^+$, which was then measured for 1 minute at 340 nm (26°C) on a spectrophotometer. The glucose-6-phosphate dehydrogenase (G6PD) activity was determined using the method of Pitkanen et al [23], with a slight modification. A reaction mixture contained 55 mmol/L Tris-HCl buffer (pH 7.8), 3.3 mmol/L $MgCl_2$, 240 μmol/L $NADP^+$, 4 mmol/L glucose-6-phosphate, and 20 μL of the cytosolic enzyme. The activity measured the reduction of 1 mol NADP per minute at 340 nm using a spectrophotometer. β-Oxidation activity was measured spectrophotometrically by monitoring the reduction of NAD to NADH in the presence of palmitoyl-CoA as described by Lazarow [24], with a slight modification. The carnitine palmitoyltransferase was assayed spectrophotometrically by following the release of CoA-SH from palmitoyl-CoA using the general thiol reagent 5,5'-dithiobis (2-nitrobenzoate) as described by Bieber et al [25], with a slight modification. 3-Hydroxy-3-methylglutaryl (HMG)–coenzyme A reductase activities were determined in the microsome with [^{14}C]HMG-CoA as the substrate based on a modification of the method of Shapiro et al [26]. The activity was expressed as the synthesized mevalonate (picomoles per minute per milligram protein). Acyl CoA:cholesterol acyltransferase (ACAT) activities were determined by the rate of incorporation of [^{14}C]oleoyl-CoA into cholesterol ester fractions, as described by Erickson et al [27] and modified by Gillies et al [28]. The activity was expressed as synthesized cholesteryl oleate (picomoles per minute per milligram protein).

2.7. Plasma paraoxonase assay

Paraoxonase (PON) activity was assayed spectrophotometrically using the method described by Mackness et al [29], with minimal modification. Briefly, the assay mixture was consisted of 500 μL of a 5.5-mmol/L paraoxon substrate solution in a 0.1-mol/L Tris-HCl buffer (pH 8.0) containing 2 mmol/L $CaCl_2$ and 50 μL of plasma. The increase in absorbance was monitored photometrically for 90 seconds at 405 nm and 25°C using a spectrophotometer (DU-64; Beckman Instruments, Fullerton, CA).

2.8. Lipid peroxidation

As a marker of the lipid peroxidation production, the erythrocyte or hepatic malondialdehyde concentrations were measured using the method of Ohkawa et al [30]. Two hundred microliters of the erythrocyte and hepatic homogenate (20%, wt/vol) was mixed with 200 μL of 8.1% (wt/vol) sodium dodecyl sulfate, 1.5 mL of 20% (wt/vol) acetic acid (pH 3.5), and 1.5 mL of 0.8% (wt/vol) thiobarbituric acid. The reaction mixture was then heated at 95°C for 60 minutes. After cooling, the hepatic mixture was added to 1.0 mL of distilled water and 5.0 mL of a butanol-pyridine (15:1) solution. The reaction mixture was then centrifuged at 800*g* for 15 minutes; and the resulting colored layer was measured at 532 nm using 1,1,3,3-tetraethoxypropane (Sigma Chemical) as the standard.

2.9. Statistical analysis

All data are presented as the mean ± SE. The data were assessed by a Student *t* test using the statistical package from the SPSS (Chicago, IL) program. Statistical significance was considered at *P* less than .05. The correlation analysis was by the Pearson test.

3. Results

3.1. Body weight and plasma leptin level

Body weight was not significantly different between the groups (Fig. 1). Curcumin did not affect food intake and fat pad mass in high-fat–fed hamsters (data not shown). However, supplementation with curcumin significantly lowered plasma leptin concentration compared with the control group (Fig. 2).

3.2. Plasma and hepatic lipids and apolipoproteins

Supplementation with curcumin significantly lowered the plasma free fatty acid, TC, and triglyceride concentrations compared with the control group (Table 1). The level of non–HDL-C was significantly lowered, whereas the levels of plasma HDL-C and apo A-I were significantly elevated, in the curcumin group compared with the control group (Table 1). Although curcumin did not affect plasma LDL-C and apo B levels, it elevated HDL-C/TC and apo A-I/apo B ratios compared with the control group. The hepatic cholesterol and triglyceride concentrations were significantly lower in the curcumin group than in the control group by 14.4% and 11.6%, respectively (Table 1).

3.3. Hepatic lipid–regulating enzyme activities

The activities of hepatic lipid–metabolizing enzymes are presented in Table 2. The hepatic fatty acid β-oxidation activity was significantly higher in the curcumin group than

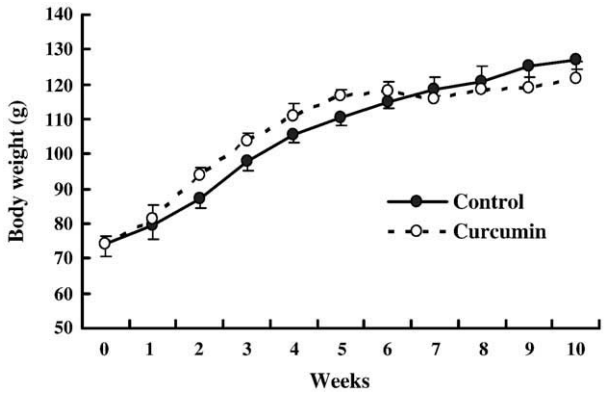

Fig. 1. Effect of curcumin supplementation on body weight in high-fat–fed hamsters. Hamsters were fed high-fat diet (10% coconut oil, 0.2% cholesterol, wt/wt) without (black circle) and with (white circle) curcumin (0.05%, wt/wt) for 10 weeks. Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test.

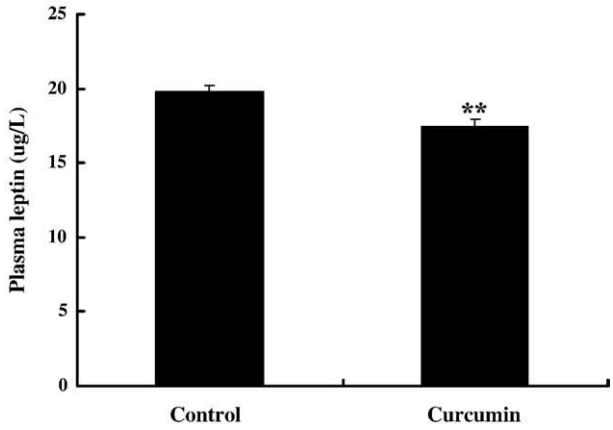

Fig. 2. Effect of curcumin supplementation on the plasma leptin concentration in high-fat–fed hamsters. Plasma leptin level was assessed by radioimmunoassay. Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test. $^{**}P < .01$, different from control group.

in the control group by 116%, whereas the FAS activity was significantly lower. Hepatic G6PD, malic enzyme, and PAP activities were not different between groups.

The curcumin supplement significantly inhibited hepatic HMG-CoA reductase and ACAT activities compared with the control group by 25% and 31%, respectively.

3.4. PON activity and erythrocyte and hepatic lipid peroxide levels

As shown in Fig. 3, plasma PON activity was significantly higher in the curcumin group than in the control group by 1.7-fold. The PON activity was positively correlated with plasma HDL concentration ($r = 0.483$, $P < .05$). Supplementation of curcumin significantly lowered lipid peroxide levels in the erythrocyte and liver compared with the control group by 41.2% and 45.6%, respectively (Fig. 4).

Table 1
Effect of curcumin supplementation on lipid, lipoprotein cholesterol, and apolipoprotein profiles in high-fat–fed hamsters

	Control	Curcumin
Plasma		
Free fatty acid (mmol/L)	1.29 ± 0.07	1.07 ± 0.04*
Triglyceride (nmol/L)	3.20 ± 0.22	2.39 ± 0.19*
TC (mmol/L)	9.32 ± 0.24	7.51 ± 0.36**
HDL-C (mmol/L)	3.67 ± 0.13	4.28 ± 0.18*
LDL-C (mmol/L)	1.07 ± 0.12	0.91 ± 0.57
Non–HDL-C (mmol/L)[a]	5.16 ± 0.12	3.15 ± 0.29**
HDL-C/TC (%)[b]	41.47 ± 1.51	56.12 ± 4.95*
Apo A-I (g/L)	1.49 ± 0.02	1.75 ± 0.02***
Apo B (g/L)	0.29 ± 0.01	0.27 ± 0.02
Apo A-I/apo B	5.18 ± 0.48	6.65 ± 0.28*
Liver		
Cholesterol (μmol/g)	10.14 ± 0.36	8.68 ± 0.39*
Triglyceride (μmol/g)	6.72 ± 0.17	5.94 ± 0.25*

Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test.
$^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .001$, different from control group.

[a] Non–high-density lipoprotein cholesterol concentration was calculated as the difference between TC and HDL-C.

[b] (HDL-C/TC) × 100.

Table 2
Effect of curcumin supplementation on hepatic lipid–regulating enzyme activities in high-fat–fed hamsters

	Control	Curcumin
β-Oxidation (nmol/[min mg protein])	5.91 ± 0.23	13.20 ± 1.05***
FAS (nmol/[min mg protein])	0.34 ± 0.03	0.27 ± 0.02*
G6PD (nmol/[min mg protein])	4.43 ± 0.28	4.81 ± 0.20
Malic enzyme (nmol/[min mg protein])	59.16 ± 2.59	60.70 ± 3.99
PAP (μmol/[min mg protein])	2.84 ± 0.19	2.38 ± 0.14
HMG-CoA reductase (pmol/[min mg protein])	52.12 ± 2.34	39.86 ± 1.39**
ACAT (pmol/[min mg protein])	64.64 ± 4.02	44.11 ± 1.88***

Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test. β-Oxidation indicates free fatty acid β-oxidation.
$^{*}P < .05$, $^{**}P < .01$, and $^{***}P < .001$, different from control group.

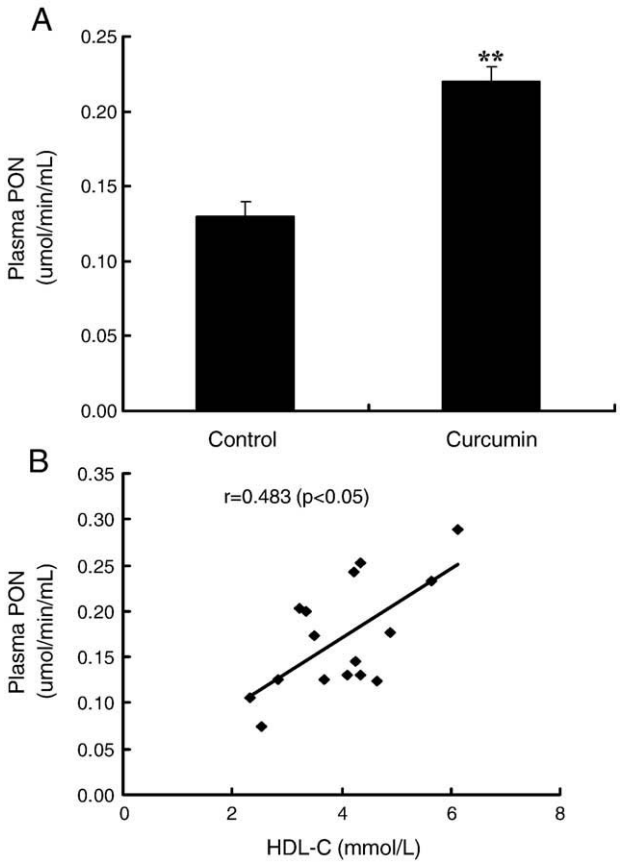

Fig. 3. Effect of curcumin supplementation on the plasma PON activity (A) and correlation between PON activity and HDL-C levels (B) in high-fat–fed hamsters. Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test. $^{**}P < .01$, different from control group. The correlation analysis was by the Pearson test.

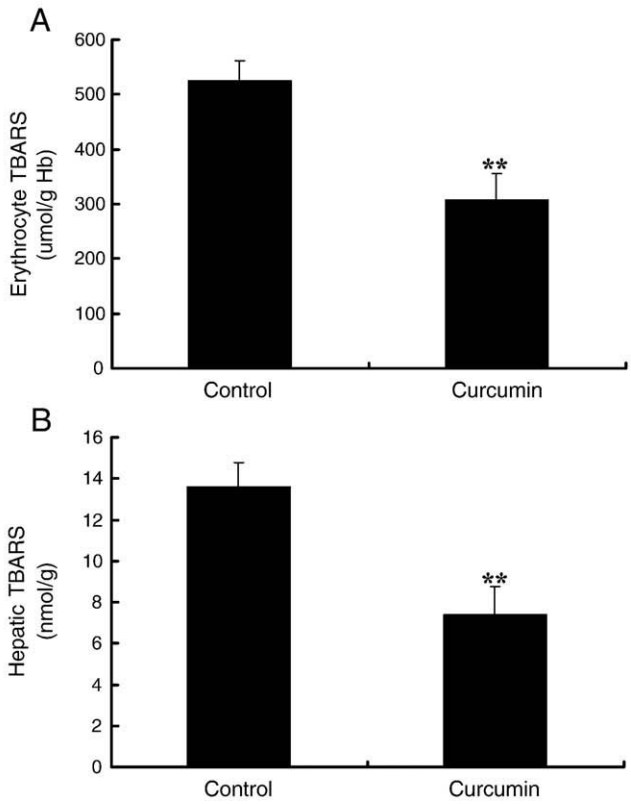

Fig. 4. Effect of curcumin supplementation on erythrocyte (A) and hepatic (B) lipid peroxide levels in high-fat–fed hamsters. As a marker of the lipid peroxidation, thiobarbituric acid reactive substance concentrations were measured. Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test. $^{**}P < .01$, different from control group.

3.5. Plasma glucose and insulin levels and insulin resistance index (HOMA-IR)

After 10 weeks of high-fat feeding, plasma glucose levels were elevated to greater than 11.0 mmol/L (198 mg/dL) (Table 3). The curcumin supplement did not alter the plasma glucose level in high-fat–fed hamsters; however, the plasma insulin level was significantly lowered by curcumin supplementation by approximately 25.4% (Table 3). Accordingly, HOMA-IR was significantly lower in the curcumin-supplemented group than in the control group by 25.9% (Table 3).

4. Discussion

This study demonstrated that the curcumin supplement (0.05%, wt/wt) markedly reduced the plasma levels of triglyceride and free fatty acid compared with the control group by approximately 25% ($P < .05$) and 18% ($P < .05$), respectively, in high-fat–fed hamsters. In the current study, supplementation of curcumin in high-fat–fed hamsters resulted in the suppression of the hepatic FAS activity with an increase in hepatic fatty acid β-oxidation activity. Interestingly, curcumin did not affect the activities of malic enzyme, G6PD, and NADPH generation enzymes for fatty acid synthesis, but predominately inhibited FAS. Fatty acid synthase is a key enzyme participating in energy reservation in vivo [31] and is related to various human diseases such as obesity and cancer [32]. Recently, FAS has been identified as a potential therapeutic target for obesity in experimental animal models [33]. Considering that the liver is the major site of fatty acid metabolism, actions of curcumin, such as down-regulated hepatic FAS and up-regulated fatty acid β-oxidation activity, appeared to play an important role on the prevention of hyperlipidemia in high-fat–fed hamsters. A hypothetical mechanism can be proposed for the decreased level of plasma free fatty acid in the curcumin-supplemented group. In high-fat–fed hamsters supplemented with curcumin, either the free fatty acid secretion into the plasma was markedly lowered or the plasma fatty acid removal occurred more rapidly to be used as substrate for fatty acid β-oxidation in tissues.

The present study showed that supplementation of curcumin in high-fat–fed hamsters for 10 weeks led to significant increases in both the plasma HDL-C and apo A-I concentrations by 17%. Epidemiologic observations and clinical trials have consistently documented a positive relation between LDL-C concentrations and CVD risk and a negative relation between HDL-C concentrations and CVD risk [34]. There are a number of factors that determine circulating HDL-C concentrations. Apolipoprotein A-I is the main structural protein of HDL, and its plasma concentration is positively correlated with HDL-C concentrations [35,36]. Although curcumin did not affect the plasma LDL-C and apo B levels, it favorably elevated the apo A-I/apo B ratio in high-fat–fed hamsters. Low values in the apo A-I/apo B ratio have been previously reported to be an indicator of a high risk of CVD in humans [37].

In addition, the supplementation of curcumin also elevated plasma PON activity, which is well known to be decreased by a proatherosclerotic diet [38]. Paraoxonase is a lipophilic antioxidant that is bound to HDL-C [39]. Paraoxonase in HDL fraction plays a pivotal role in the antioxidative/anti-inflammatory/antiatherosclerotic properties of HDL [40] and is inversely related to the risk of atherosclerosis and diabetes [41]. In this study, a positive correlation was found between PON activity and HDL-C concentration ($r = 0.483$, $P < .05$) in

Table 3
Effect of curcumin supplementation on the plasma glucose and insulin levels and HOMA-IR in high-fat–fed hamsters

	Control	Curcumin
Glucose (mmol/L)	12.25 ± 0.35	11.69 ± 0.36
Insulin (μIU/mL)	7.80 ± 0.45	5.82 ± 0.37**
HOMA-IR[a]	4.05 ± 0.30	3.00 ± 0.16***

Values are expressed as mean ± SE of 8 hamsters in each group. Statistical analysis was done by Student *t* test.
$^{**}P < .01$ and $^{***}P < .001$, different from control group.
[a] HOMA-IR was calculated as follows: (glucose [millimoles per liter] × fasting insulin [μIU per milliliter])/22.5.

the plasma. Malin et al [42] reported that one of the hypolipidemic drugs, pravastatin, increased PON gene expression with increases in HDL-C and apo A-1 level. Therefore, the current results and other's reports [43] indicate that the increased plasma PON activity accompanies an elevation of the HDL-C concentration.

As such, the current results demonstrated that curcumin is a potential cholesterol-lowering agent as indicated by decreased levels of TC and non–HDL-C in the plasma. The increase in the HDL-C and apo A-I concentration as well as PON activity by the curcumin supplement can be beneficial for the prevention of atherosclerosis. Recently, Roberts et al [44] reported that severe dyslipidemia in rats with a diet-induced chronic metabolic syndrome is associated with a marked up-regulation of hepatic ACAT activity and an elevated ratio of HMG-CoA reductase activity to cholesterol 7α-hydroxylase activity. Cholesterol 7α-hydroxylase controls the first limiting step in bile acid synthesis and indirectly regulates cholesterol biosynthesis and plasma LDL-C levels [45]. However, in the present study, there is no change in the plasma LDL-C concentration by curcumin supplement, which suggests that the hypocholesterolemic action of curcumin could partly be mediated by the down-regulation of biosynthesis. Zulet et al [46] reported that hepatic HMG-CoA reductase activity was elevated in rats fed a diet enriched in 10% coconut oil and 0.2% cholesterol. The elevation of this enzyme activity may be attributed to the higher availability of acetyl CoA, which stimulates the cholesterogenesis rate [47]. In the liver, HMG-CoA reductase is the rate-limiting enzyme in cholesterol biosynthesis; and ACAT is the primary enzyme responsible for intracellular esterification of cholesterol. Thus, curcumin supplementation seemingly inhibited the hepatic HMG-CoA reductase and ACAT, thereby lowering not only the hepatic cholesterol level but the plasma TC and non–HDL-C levels. It is plausible that curcumin can possibly limit the availability of body cholesterol for the later development of atherosclerosis in high-fat–fed hamsters.

Because curcumin was beneficial in improving insulin resistance in *db/db* mice in our previous study [6], we tested whether it improves high-fat diet–induced insulin resistance in hamsters. High-fat intake generally increases energy storage mainly as a triglyceride and raises circulating free fatty acid level, which is sufficient to induce peripheral and hepatic insulin resistance [48]. This study demonstrated that curcumin improved the insulin resistance and plasma and hepatic lipid levels in high-fat–fed hamsters. Insulin resistance manifests with a reduced efficiency of insulin that inhibits hepatic glucose production and stimulates glucose utilization in skeletal muscle and adipose tissue. Subsequent high glucose levels result in compensatory hyperinsulinemia, which accounts for the elevation of HOMA-IR values [49,50]. Homeostasis model assessment is a useful index for insulin sensitivity/resistance that is derived from blood insulin and glucose concentration under fasting conditions [51]. In the present study, feeding a high-fat diet (10% coconut oil, 0.2% cholesterol) for 10 weeks resulted in elevating the plasma glucose level (>11 mmol/L) in hamsters. The plasma glucose level was not significantly different between groups; however, the insulin level was significantly lowered in the curcumin group compared with the control group. Accordingly, HOMA-IR was significantly improved in the curcumin group than in the control group by 26% ($P < .001$), which is correspondent to our previous findings in which the curcumin significantly attenuated HOMA-IR in type 2 diabetes mellitus *db/db* mice [6].

In the current study, the plasma leptin concentration was significantly lowered by the curcumin supplementation; however, the body weight and food intake were not different between groups. Leptin, a cytokine produced mainly by the white adipose tissue, is actively involved in the control of body weight and food intake. In hypothalamus, leptin stimulates anorexigenic pathways and decreases food intake [52]. Huang et al [53] have shown that acute intravenous leptin infusion decreases hepatic triglyceride secretion; increases hepatic fatty acid oxidation and ketogenesis; and, as a result, decreases hepatic triglyceride levels. Meanwhile, in obese nonalcoholic fatty liver disease patients, leptin levels are elevated and are directly correlated with the severity of hepatic steatosis [54], which brings up the concept of leptin resistance [55]. It is generally known that circulating levels of leptin are high in the obese, proportional to body mass index [56]. This study indicates that curcumin significantly lowers the triglyceride level and stimulates the hepatic fatty acid β-oxidation, with a simultaneous decrease in the plasma leptin concentration, in high-fat–fed hamsters. Thus, these results suggest that curcumin may attenuate the leptin resistance in diet-induced hyperlipidemic hamsters.

Finally, lipid peroxidation is also considered responsible for the impairment of endothelial cells, capillary permeability, and fibroblast and collagen metabolism [57]. Curcumin supplementation significantly lowered lipid peroxide levels in the erythrocytes and liver of high-fat–fed hamsters, thus suggesting a decreased rate of lipid peroxides formation.

5. Conclusion

In conclusion, the current results indicate that supplementation with curcumin in high-fat–fed hamsters lowered HOMA-IR; the plasma levels of insulin, leptin, triglyceride, free fatty acid, and TC; and hepatic cholesterol and triglyceride levels. Curcumin elevated the plasma levels of HDL-C and apo A-1 and the HDL-C/TC and apo A-1/apo B ratios. Accordingly, curcumin (0.5%, wt/wt) provided as a supplement appeared to play an important role in the prevention of diet-induced hyperlipidemia in a high-fat–fed hamster model by mediating suppression of fatty acid and cholesterol biosynthesis as well as stimulating fatty acid β-oxidation in the liver. Curcumin enhanced PON activity in plasma and lowered the lipid peroxidation in the erythrocyte

and liver, which suggests that curcumin may have a potential antioxidative effect.

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