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Antidyslipidemic Activity of Hot-water Extracts from Leaves of *Cinnamomum osmophloeum* Kaneh

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The antidyslipidemic activity of hot-water extracts of *Cinnamomum osmophloeum* leaves (COE) were evaluated on hamsters fed a high-fat diet. Oral administration of COE to hyperlipidemic hamsters reduced the total cholesterol (TC), triglyceride (TG) and low-density lipoprotein (LDL-C) levels. Compared with hyperlipidemic hamsters, the plasma TC and TG levels of hamsters fed with COE at a dosage of 100 mg/kg body weight for 5 and 10 weeks were significantly reduced to 12.63% and 34.25%, and 33.88% and 36.88%, respectively. Plasma LDL-C was also reduced to 27.77% after 10 weeks feeding with the same regimen. Standard diagnostic tests indicated that the extracts did not cause damage to hamster liver or kidneys. Based on these results, it is concluded that COE possesses antidyslipidemic activity. The composition of COE was characterized. Two main compounds, kaempferol 3-*O*-*β*-D-apiofuranosyl-(1 → 2)-α-L-arabinofuranosyl-7-*O*-α-L-rhamnopyranoside (1) and kaempferitrin (2) were identified in the hot-water extracts. Their contents were 7.56% and 9.95%, respectively. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: Cinnamomum osmophloeum Kaneh; hot-water extract; total cholesterol; triglyceride; flavonol glycosides; antidyslipidemic activity.

INTRODUCTION

The genus *Cinnamomum* comprises about 250 species that are indigenous to Asia and Australia (Cheng *et al.*, 2006). The native name for *Cinnamomum osmophloeum* Kaneh (Lauraceae) is 'indigenous cinnamon tree'. It is an endemic hardwood grown in Taiwan at elevations of 400–1500 m (Chao *et al.*, 2005). One distinguishing characteristic of *C. osmophloeum* is that the composition of the essential oil of the leaves is similar to that of C. cassia. Several previous studies have demonstrated that the essential oil of *C. osmophloeum* leaves possesses a broad range of bioactivity against different kinds of organisms including bacteria (Cheng *et al.*, 2004), termites (Chang *et al.*, 2001), mites (Chen *et al.*, 2002), mildew (Chen and Chang, 2002) and fungi (Wang *et al.*, 2005). Recently, Wang and coworkers (Wang *et al.*, 2008) found that the essential oil and its dominant compound, cinnamaldehyde, possessed strong xanthine oxidase inhibitory activity and had an antihyperuricemia effect in mice. Furthermore, Sheng and his co-workers approved that cinnamaldehyde possessed the activation activity for peroxisome proliferator-activated receptors γ and α (PPARγ/α), and could improve insulin resistance, and to reduce fasted glucose, FFA, LDL-C, and AST levels in high-caloric diet-induced obesity (DIO) and db/db mice (Sheng *et al.*, 2008). They also demonstrated the hot-water extract prepared from cinnamon bark could increase the expression of PPARγ/α and their target genes such as LPL, CD36, GLUT4 and ACO in 3T3-L1 adipocyte *in vitro* (Sheng *et al.*, 2008).

In addition to essential oil, the leaves of *C. osmophloeum* contain abundant flavonol glycosides (Fang *et al.*, 2005). Epidemiological studies indicate that flavonoids and flavonol glycosides have various biological activities, such as decreasing the risk of cardiovascular diseases (Woodman and Chan, 2004), cancer chemoprevention activity (Rao *et al.*, 2009) and cholesterol-lowering effects (Kurowska and Manthey, 2004). In addition, there is considerable evidence suggesting a relationship between dyslipidemia and the manifest characteristics of metabolic syndrome X. Dyslipidemia has been well documented and is characterized by an 'atherogenic lipoprotein phenotype' or 'lipid triad'. Low-density lipoprotein (LDL) is one of the five major groups of lipoproteins, which in order of size, largest to smallest, are chylomicrons, VLDL, IDL, LDL and HDL, that enable lipids such as cholesterol and triglycerides to be transported within the water-based bloodstream. Medically, estimates of cholesterol content carried by LDL particles are used as an index to predict the blood cholesterol condition. Besides, higher levels of LDL particles bring about medical problems such as cardiovascular disease, they are often called the bad cholesterol particles (Colpo,

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2005). The alteration in LDL particle size appears to be a fundamental part of the pathogenesis of insulin resistance syndrome (Gray *et al.*, 1997). In the present study, the antidyslipidemic activity of *C. osmophloeum* hot water leaf extract was investigated by using hamsters fed a high-fat diet (Rizvi *et al.*, 2003). The major components in the hot-water extracts were also characterized and quantified.

MATERIALS AND METHODS

Plant materials and chemicals. The leaves of C. osmophloeum were collected in May 2009 at Hui-Sun Experimental Forest Station, which is located in the middle of Taiwan. The plants were authenticated by Dr Yen-Hsueh Tseng (Professor of Department of Forestry, National Chung-Hsing University). The voucher specimen [Tseng4518] was deposited in the herbarium of the same university. All chemicals and solvents used for separation were HPLC grade. Deionized water was prepared using a Milli-Q water purification system (Millipore, MA). All the solutions were filtered through 0.45 μm membranes (Schleicher & Schuell, Germany) and degassed by an ultrasonic bath before use. Gemfibrozil with a purity ≥99%, purchased from Sigma-Aldrich (StLouis, MO, USA), was used as the reference cholesterol lowering drug.

Plant extract preparation. Air-dried and powdered leaves (950 g) of *C. osmophloeum* were extracted by boiling for 1 h with 15 L hot distilled water. After filtration with cheesecloth, the filtrates were collected and concentrated by lyophilization, yielding 150 g of COE (yield = 16%, w/dry weight of leaves).

Animals and experiment protocol. Animal experiments were designed in accordance with the *Guidebook for the Care and Use of Laboratory Animals* of The Chinese-Taipei Society of Laboratory Animal Science and approved by the same society. Forty male Golden Syrian hamsters 7 weeks old, weighing 100–120 g were housed in individual plastic cages and subjected to a 12 h light/dark cycle, relative humidity of 60% and a temperature at 25 °C. Experimental diets were provided a standard laboratory diet (LabDiet® 5001 Rodent diet, Purina Mills LLC, St Louis, MO, USA). The animals were given free access to regular rodent chow and water for 4 weeks; hamsters were weighed and randomly assigned into five groups of eight animals each before commencement of the study. Before being given the treatment extract or reference drug, the animals were fed a high-cholesterol diet that contained 0.2% cholesterol (Sigma-Aldrich Co., product number C8503); control animals were fed a normal diet. After 4 weeks, blood samples were collected from the orbital sinus of hamsters under anesthesia. The extent of hyperlipidemia in the control and high-cholesterol (HChol) groups was significantly different ($p < 0.05$). The control and HChol groups were given only 1 mL distilled water containing 0.5% Tween-80. The COE and the reference drug, gemfibrozil, groups were given them suspended in 1 mL distilled water containing 0.5% Tween 80 and then orally administered to the hamsters daily. The control group was fed a normal diet, and the HChol group was given a high-cholesterol diet that contained 0.2% cholesterol. Food intake was recorded daily and the animals were weighed weekly. The dosages of leaf extracts and gemfibrozil were adjusted weekly according to the average body weight of each hamster. Hamsters were fed a high-cholesterol diet and orally administered *C. osmophloeum* leaf extracts at dosages of 500 mg/kg body weight (bw) per day (HChol-CO500) or 100 mg/kg bw per day (HChol-CO100). The positive control group (HChol-gem20) was fed a high-cholesterol diet and orally administered 20 mg/kg bw per day of gemfibrozil. The hamsters were fed these experimental diets for 5 and 10 weeks. At the end of the treatment period, the animals were anesthetized and killed by inhalation of 2% isoflurane, and blood samples were collected from the orbital sinus and cardiac puncture. Plasma samples were then prepared. All plasma samples were used for analysis of total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), creatinine and blood urea nitrogen (BUN). All analyses were carried out in triplicate according to the spectrophotometry of Chiron Diagnostics Corporation (Oberlin, OH, USA) using the Express Plus Automatic Clinical Chemistry Analyzer (Chiron).

Compound isolation and index compound quantification. The COE was separated by analytical high-performance liquid chromatography (HPLC) using an Agilent1100 (Agilent, Germany) system with a 100 μL fixed loop, and a UV detector. A Luna C18 column (4.60 mm × 250 mm, 5 μm particle size, Phenomnex, Torrance, CA) with a three solvent system, 1% phosphoric acid with deionized water (solvent A), methanol (solvent B) and acetonitrile (solvent C). The linear gradient program was as follows: 82% A, 3% B and 15% C in the first 0 min, held for 10 min, changed to 77% A, 3% B and 20% C over 40 min, then changed to 100% B at 30 min, held for 5 min. The mobile phase flow rate was 0.4 mL/min, and the detector was monitored at 254 nm. All the chromatographic operations were carried out at ambient temperature (25 °C). Two major compounds were obtained from the hot-water extracts at retention times of 36.0 min (**1**) and 37.9 min (**2**). The structures of **1** and **2** were then elucidated using spectroscopic analysis. UV and IR data were acquired on a Bio-Tek μQuant MQX200 Microplate Spectrophotometer and a PerkinElmer Spectrum 100 FT-IR spectrometer, respectively. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Varian Unity Inova-600 MHz spectrometer using DMSO-d_6 as solvent. The HREIMS data were performed with a Thermo/Finnigan Quest MAT 95XL mass spectrometer. For calibration curves, appropriate volumes of the standard stock solutions (2 mg/mL) were diluted with deionized water, and five concentration levels (100, 250, 500, 1000 and 2000 μg/mL) were analysed. For quantification, the peak areas were correlated with the concentrations according to the calibration curve. All data are expressed as mean ± standard deviation of triplicate independent experiments ($n = 3$).

Statistical analysis. The main treatment effects were analysed by one-way analysis of variance (ANOVA) followed by Duncan's multiple range test using a Statistical Analysis System software (SAS Institute, Cary, NC). The significance level was set at $p < 0.05$. Data were expressed as mean ± SD.

RESULTS

Effects of *C. osmophloeum* on body weights of hamsters

This study investigated the effects of oral administration of hot water extract of *C. osmophloeum* leaves (COE) on a hyperlipidemic hamster model. During the experiment period, the body weights and daily food intake of the hamsters increased normally and did not show any difference among the various groups (Table 1). All the experimental animals had normal physical appearance and health throughout the experimental period. At weeks 5 and 10 after the start of the treatment regimen the animals were anesthetized and blood samples were collected and examined for estimation of the hypolipidemic effects of COE.

Regulation effects of *C. osmophloeum* on TC and TG levels

Table 2 shows the changes in plasma TC and TG levels. At the time for starting treatment with water extracts and gemfibrozil (week 0), the control group had a TC of 85.6 ± 8.2 mg/dL and the HChol group had extremely high TC levels of 219.8 ± 24.2 mg/dL. The high TC levels of the HChol group hamsters in comparison with the control group indicated that the HChol group was suitable for use as an animal model for antihyperlipidemic assay. The results revealed that the plasma TC and TG of hamsters were lowered by daily feeding with hot water extracts of *C. osmophloeum* at dosages of 100 mg/kg bw per day (HChol-CO100) and 500 mg/kg bw per day (HChol-CO500) for 5 and 10 weeks. The HChol-CO100 group had plasma TC and TG concentrations of 197.8 ± 47.2 and 126.1 ± 34.1 mg/dL after 5 weeks of treatment, which were 12.6% and 50.9%, respectively, less than those of the HChol group ($p < 0.05$). At week 10, the plasma TC and TG levels of HChol-CO100 were 153.2 ± 25.5 and 137.2 ± 78.6 mg/dL, which was less than 34.2% and 33.9%, respectively, of the levels in the HChol group.In the higher dosage group (HChol-CO500) more pronounced effects were observed. At week 10, the plasma TC and TG levels of HChol-CO500 were decreased to 40.3% (139.2 ± 17.2 ng/dL and 120.8 ± 49.3 ng/dL). After 5 and 10 weeks, gemfibrozil, a proven cholesterol reducer used clinically, significantly reduced the plasma TC levels of the hyperlipidemic hamsters ($p < 0.05$) (Khan *et al.*, 2008).

Changes of LDL-C/HDL-C ratio in the serum by treating with *C. osmophloeum* extracts

Effects of COE on serum HDL-C and LDL-C levels of hamsters are shown in Fig. 1A. The HDL-C levels were significantly higher in the HChol group (126.9 ± 40.1 mg/dL) than in the control (53.4 ± 8.1 mg/dL)

Table 1. Hamster body weight and daily food intake gain

Group	Body weight (g)			Daily feed intake (g/day)	
	Week 0	Week 5	Week 10	Week 5	Week 10
Control	100.4 ± 3.3[a]	121.2 ± 4.2[a]	137.2 ± 3.1[a]	7.4 ± 1.5[a]	8.3 ± 2.9[a]
HChol	99.3 ± 4.0[a]	114.8 ± 3.7[a]	134.8 ± 6.5[a]	7.3 ± 2.2[a]	8.4 ± 3.0[a]
HChol-Gem20	101.0 ± 3.4[a]	116.7 ± 5.4[a]	131.7 ± 5.7[a]	7.4 ± 3.2[a]	8.3 ± 1.3[a]
HChol-CO100	101.0 ± 2.0[a]	117.1 ± 5.9[a]	131.4 ± 4.5[a]	7.3 ± 1.0[a]	8.5 ± 1.9[a]
HChol-CO500	100.5 ± 1.9[a]	114.8 ± 6.8[a]	131.0 ± 7.1[a]	7.4 ± 2.6[a]	8.4 ± 2.5[a]

Control, normal diet (0% cholesterol); HChol, high-cholesterol diet; HChol-Gem20, gemfibrozil 20 mg/kg body weight (bw) per day and high-cholesterol diet; HChol-CO100, COE 100 mg/kg bw per day and high-cholesterol diet; HChol-CO500, COE 500 mg/kg bw per day and high-cholesterol diet.
Data are presented as mean ± SD ($n = 8$). Mean values within each column with different labels (a,b,c) are significantly different ($p < 0.05$).

Table 2. Effects of COE on hamster plasma TC and TG levels

Group	Week 0		Week 5		Week 10	
	Cholesterol (mg/dL)	Triglyceride (mg/dL)	Cholesterol (mg/dL)	Triglyceride (mg/dL)	Cholesterol (mg/dL)	Triglyceride (mg/dL)
Control	85.6 ± 8.2[a]	85.0 ± 19.6[a]	85.0 ± 19.6[a]	85.3 ± 16.4[a]	89.3 ± 5.2[a]	80.0 ± 11.9[a]
HChol	219.8 ± 24.2[b]	232.9 ± 92.9[c]	226.4 ± 24.1[c]	256.7 ± 61.5[c]	233.0 ± 15.1[c]	207.5 ± 71.4[c]
HChol-Gem20	235.7 ± 17.2[b]	148.1 ± 41.7[b]	191.8 ± 36.9[b]	133.8 ± 40.8[b]	116.3 ± 13.5[ab]	101.0 ± 26.0[ab]
HChol-CO100	243.5 ± 36.3[b]	147.0 ± 43.9[b]	197.8 ± 47.2[bc]	126.1 ± 34.1[b]	153.2 ± 25.5[b]	137.2 ± 78.6[b]
HChol-CO500	237.0 ± 48.6[b]	208.8 ± 79.7[bc]	190.7 ± 36.7[b]	163.6 ± 31.1[bc]	139.2 ± 17.2[b]	120.8 ± 49.3[b]

Control, normal diet (0% cholesterol); HChol, high-cholesterol diet; HChol-Gem20, gemfibrozil 20 mg/kg bw per day and high-cholesterol diet; HChol-CO100, COE 100 mg/kg bw per day and high-cholesterol diet; HChol-CO500, COE extracts 500 mg/kg bw per day and high-cholesterol diet.
Data are presented as mean ± SD ($n = 8$). Mean values within each column with different labels (a,b,c) are significantly different ($p < 0.05$).

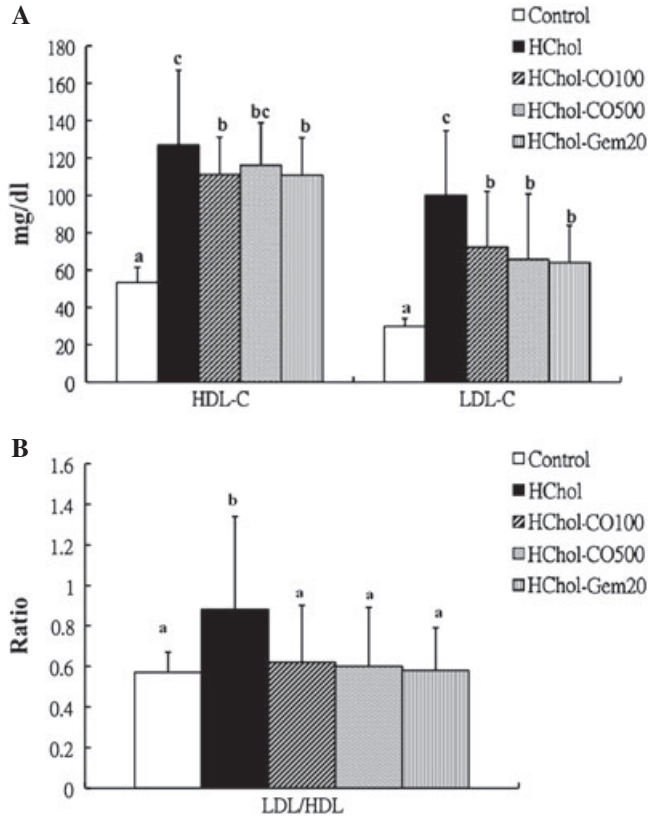

Figure 1. HDL-C, LDL-C plasma level changes and LDL/HDL ratio of hamsters fed with COE for 10 weeks. (A) The effects of COE on serum HDL-C and LDL-C levels of hamster. (B) Feeding hamsters with a high cholesterol diet for 10 weeks led to a significant increase in the ratio of LDL-C to HDL-C. Control, normal diet (0% cholesterol); HChol, high-cholesterol diet; HChol-Gem20, gemfibrozil 20 mg/kg bw per day and high-cholesterol diet; HChol-CO100, COE 100 mg/kg bw per day and high-cholesterol diet; HChol-CO500, COE 500 mg/kg bw per day and high-cholesterol diet. Data are presented as mean ± SD (n = 8). Mean values within each column with different labels (a, b, c) are significantly different ($p < 0.05$).

group because both HDL-C and LDL-C levels are typical cholesterols, which are increased by a high-cholesterol diet. The major type of cholesterol decreased by COE treatment was LDL-C (Fig. 1A). As expected, the HChol group had higher LDL-C levels than the control group at weeks 5 and 10. Inhibitory effects of LDL-C secretion were dose-dependent. The COE treatments at dosages of 100 mg/kg bw and 500 mg/kg bw resulted in a significant decrease in the serum LDL-C levels by week 10, 27.8% and 34.4%, respectively, compared with those of the HChol group ($p < 0.05$). LDL-C has been proven to increase the risk of atherosclerosis. The ratio of LDL-C to HDL-C was, thus, used as another criterion to evaluate the efficiency of hypolipidemia. A low LDL-C/HDL-C ratio represents a higher percentage of HDL-C in TC levels, therefore representing a reduced risk of atherosclerosis. It is well established that a low LDL-C level is beneficial to human health, reducing the risk of developing cardiovascular disease (Sacks *et al.*, 2002). Figure 1B shows that hamsters fed a high cholesterol diet for 10 weeks led to a significant increase in the ratio of LDL-C to HDL-C compared with that of the control group, the ratio increased from 0.57 ± 0.10 to 0.88 ± 0.46. However, the ratio of LDL-C to HDL-C in the groups treated with extracts was almost equal to the control groups (Fig. 1B). This result demonstrates that hamsters fed with COE increased their HDL-C levels and significantly decreased their LDL-C level. Statistical analyses show that the ratio of LDL-C to HDL-C was less in the HChol-CO100 and HChol-CO500 groups than in the HChol group ($p < 0.05$).

Effects of *C. osmophloeum* extracts on serum GOT, GPT, BUN and creatinine levels

It was demonstrated that COE was able to decrease plasma TC and TG levels effectively, but whether it had other adverse effects on hamsters was still unclear. Therefore glutamate oxaloacetate transaminase (GOT) and glutamic pyruvic transaminase (GPT) levels were measured. GOT and GPT are released into the blood from liver cells when the cells are damaged and are regularly used to diagnose liver and heart disease. Plasma GOT and GPT levels in hyperlipidemic hamsters did not increase when they were fed COE (Table 3). However, the HChol group had higher plasma GOT and GPT levels than the control group after 10 weeks. In addition, the HChol group revealed a higher plasma blood urea nitrogen (BUN) level (32.0 ± 11.2 mg/dL) than the control group (25.1 ± 2.9 mg/dL). But there was no significant difference between the COE treated groups and control. Similar results were also found for creatinine levels in plasma (Table 3).

Characterization of composition of hot-water extracts of *C. osmophloeum* leaves

Finally, the composition of COE was analysed by HPLC. Figure 2 shows the HPLC chromatogram of COE. Two main compounds (compounds 1 and 2) were isolated from the hot-water extract and characterized. According to the MS and NMR analyses, compounds 1 and 2 were identified as kaempferol 3-O-β-D-apiofuranosyl-(1 → 2)-α-L-arabinofuranosyl-7-*O*-α-L-rhamnopyranoside (1) and kaempferitrin (2); spectral data were consistent with the literature (Rao *et al.*, 2005). The standard calibration curves (peak area vs concentration) of compound 1 and compound 2, were in the range 100–2000 μg/mL. The linear regression curves were $y = 29.25x + 2298.8$ ($R^2 = 0.9941$) for compound 1 and $y = 23.837x + 2833.8$ ($R^2 = 0.9852$) for compound 2 and revealed a good linearity. According to HPLC analysis, the contents of compounds 1 and 2 in COE were 7.56% and 9.95%, respectively.

DISCUSSION

The antidyslipidemic activity of hot-water extracts from the leaves of *C. osmophloeum* was evaluated in this study. According to the results obtained, *C. osmophloeum* extracts possessed significant reducing effects on TC, TG and LDL-C without changing the LDL-C/HDL-C ratio in hamster plasma. If the LDL-C/HDL-C ratio was lowered, then the content of HDL-C had a much higher percentage in TC levels, while on the contrary, the atherosclerotic risk factor LDL-C was lowered. Even administered at a low dosage (100 mg/kg bw per day) of hot-water extract to the hamsters, it expressed a remarkable effect on cholesterol-lowering activity.

Table 3. Plasma level change of HDL-C, LDL-C, GOT, GPT, BUN and creatinine of hamsters fed with COE for 10 weeks

Group	GOT (U/dL)	GPT (U/dL)	BUN (mg/dL)	Creatinine (mg/dL)
Control	43.0 ± 7.5[a]	65.9 ± 11.8[a]	25.1 ± 2.9[ab]	0.3 ± 0.1[b]
HChol	99.6 ± 34.3[b]	127.6 ± 19.0[b]	32.0 ± 11.2[b]	0.3 ± 0.0[b]
HChol-Gem20	49.6 ± 5.6[a]	70.2 ± 13.3[a]	19.3 ± 3.6[a]	0.2 ± 0.0[a]
HChol-CO100	62.9 ± 33.7[ab]	79.5 ± 30.8[a]	22.0 ± 2.3[a]	0.2 ± 0.1[ab]
HChol-CO500	53.1 ± 11.7[a]	71.5 ± 18.8[a]	18.8 ± 2.9[a]	0.2 ± 0.0[a]

Control, normal diet (0% cholesterol); HChol, high-cholesterol diet; HChol-Gem20, gemfibrozil 20 mg/kg bw per day and high-cholesterol diet; HChol-CO100, COE 100 mg/kg bw per day and high-cholesterol diet; HChol-CO500, COE 500 mg/kg bw per day and high-cholesterol diet. Data are presented as mean ± SD (n = 8). Mean values within each column with different labels (a,b,c) are significantly different ($p < 0.05$).

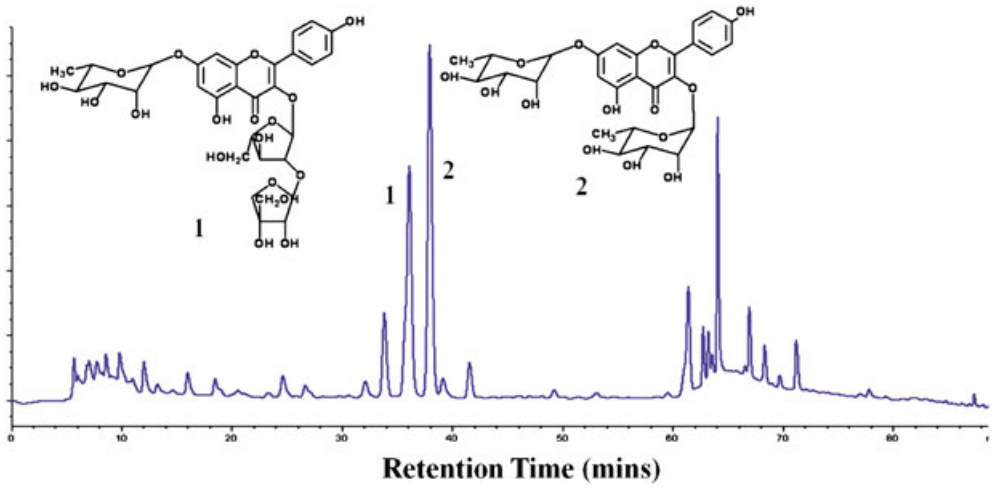

Figure 2. HPLC spectrum of the COE. **1**, kaempferol 3-O-β-D-apiofuranosyl-(1 → 2)-α-L-arabino-furanosyl-7-*O*-α-L-rhamnopyranoside **2**, kaempferitrin.

Moreover, the lipid concentration in plasma was reduced in a dose dependent manner by treatment with hot-water extracts of *C. osmophloeum* leaves. More cholesterol supplementation will lead to a burden on the liver metabolites and simultaneously increase the risk for developing hepatic fibrosis (Aguilera *et al.*, 2005; Jeong *et al.*, 2005; Papadia *et al.*, 2004).

According to the results observed in this study, the LDL-C levels in plasma of hamsters treated with extract were lower than those of the high cholesterol uptake only group (HChol). However, more investigations are needed to ascertain this effect. From the perspective of food science, a dosage of 100 mg/kg bw in the hamster corresponds to supplementing the diet of a human with a body weight of 70 kg and a height of 170 cm with COE at 854 mg daily (Reagan-Shaw *et al.*, 2008). Even administered at this low dosage as a hot-water extract, the leaves of *C. osmophloeum* expressed a remarkable cholesterol-lowering activity in the hamster. It is concluded that the COE might be a safe food supplement for treating dyslipidemia. Further investigations into bioavailability, clinical safety and so on should be conducted in the future.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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