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Effects of Fingered Citron (*Citrus medica* var. sarcodactylis) Essential Oil on Improvement in Diet-Induced Hyperlipidemia Syrian Hamsters

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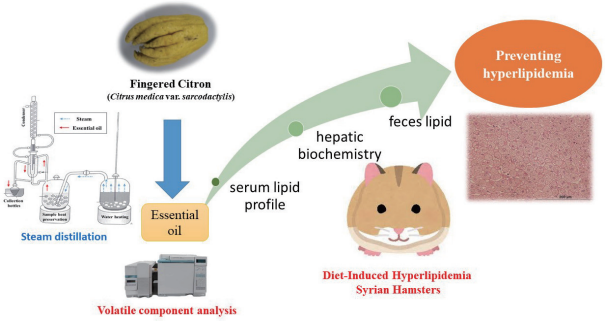
Abstract: Preventing hyperlipidemia and the risk of cardiovascular disease are attractive to public health. Essential oils are extremely promising nutrients for use in the treatment of hyperlipidemia, whose effectiveness is closely related to its volatile composition. We extracted fingered citron essential oil (FCEO) with steam distillation, analyzed the chemical composition, and evaluated its effects on hyperlipidemia. We identified 25 volatile compounds of FCEO with GC/MS, of which the main constituents were limonene and γ-terpinene. This study explored the protective effects of FCEOs against diet-induced hyperlipidemia Syrian hamsters. FCEOs treatment ranges from 0.03% to 0.05% with a daily diet. As of 12 weeks later, we found that the administration of the FCEOs improved the serum total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C) levels ($p < 0.05$). Further, LDL-C/HDL-C (high-density lipoprotein cholesterol) ratios were significantly reduced (39.02–68.07 vs. 80.27). Simultaneously, the FCEOs had improved lipid metabolism and histopathology in the liver. These actions suggest the potential of FCEO as a valuable source of nutraceuticals in diet-based therapies.



Key words: essential oil, hyperlipidemia, LDL-C/HDL-C, lipid metabolism

1 Introduction

The incidence and prevalence of cardiovascular diseases (CVDs) continue to rise. According to the World Health Organization, about 17.5 million people die annually from CVDs, accounting for 31% of all deaths in the world[1)]. The primary mechanism driving CVDs is atherosclerosis caused by dyslipidemia and a pro-inflammatory state. Therefore, lifestyle modifications, particularly a healthy diet, are important steps in primary prevention of CVDs. Diet plays a crucial role since increased lipid intake leads to inflammation and higher levels of reactive oxygen species (ROS) and pro-inflammatory cytokines IL-1 (Interleukin-1) and IL-6 (Interleukin-6) resulting in reduced secretion of Paraoxonase 1 (PON1) by the liver and decreased Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ)[2, 3)]. It is well established that an increased plasma level of low-density lipoprotein cholesterol (LDL-C) is the primary risk factor of development of coronary heart disease and atherosclerosis. In dyslipidemias, hepatic LDL-C receptors become incompetent. As LDL-C circulates increasingly through the body, its degree of oxidation increases and contact with the vascular endothelium is prolonged, thus elevating the athero-

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genic effect[4, 5].

In addition to a balanced diet, dietary supplements may contribute to improved health status. Phytotherapy uses plant-derived drugs to target health issues. Natural plant supplements lead to significant hypolipidemic and improved health by regulated enzyme activity[6–9]. Plant-based products rich in active chemical substances, including polyphenols, flavonoids, carotenoids, catechins, and essential oils, offer alternative strategies for preventing CVDs[8, 9]. Aromatic plants are those that produce and accumulate volatile compounds in secretory structures, such as trichomes, secretory cells, secretory ducts, and cavities[9]. Essential oils are volatile compounds produced by these plants. Essential oils are usually recovered by steam distillation of the raw plant material, which imparts a unique odor to the oil. The type of distillation, whether simple, fractionated, or steam distillation, depends on the boiling points and volatility of the products to be separated[10–13]. Essential oils are water-immiscible and contain more than 15 different chemical substances; most of these substances are low-molecular-weight odorants (below 300 Da), mainly monoterpenes, sesquiterpenes, terpene alcohols, and terpenoids, which belong to the terpene chemical family[13, 14].

The biosynthetic pathway of terpene compounds comprises four stages[15]. The first involves the formation of isopentenyl pyrophosphate (IPP), the C5 unit of biological isoprene. The mevalonate pathway is the main route for synthesizing IPP and its allylic isomer, dimethylallyl pyrophosphate. A second synthesis pathway, the methylerythritol phosphate pathway, is also present. In the second step, the C5 units condense to generate three larger prenyl pyrophosphates (geranyl pyrophosphate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate). Then, in the third step, these three pyrophosphates undergo a wide range of cyclization and rearrangement reactions to produce the parent carbon skeletons for each terpene class. The final stage involves oxidation, reduction, conjugation, and other transformations that convert the carbon skeletons into thousands of terpene metabolites[15, 16]. As natural products, they have also been studied as phytogenic additives, since they contribute to the better use of nutrients and, consequently, improve performance by stimulating the appetite and secretion of endogenous digestive enzymes[17–19]. They also improve the integrity of the intestinal epithelium and show antimicrobial, and anthelmintic effects[20, 21].

The fingered citron (Citrus medica var. sarcodactylis) originates from Asia, including India and China. In China, most fingered citron was used as traditional Chinese medicine due to its medicinal and aromatic properties. The exocarp of its fruit is abundant in essential oils. Generally essential oils are able to pass through the skin, mucosa, and cell membranes and enter the systemic body circulation, which have been attributed to its high biological activity[19, 21]. Essential oils have been found to have favorable effects on cardio-metabolic disorders, such as atherosclerosis and hypertension, by modulating the serum lipid profile, endothelial inflammation, and oxidative stress, as well as controlling vasomotor tone through modulation of the nitric oxide pathway[3, 10–12, 22]. We then analyzed the chemical constituents of FCEO using gas chromatography/mass spectrometry (GC/MS) and evaluated its effects on lipidemia metabolism in a hamster model.

2 Materials and Methods

2.1 Materials

The chemicals and solvents used in this study, including sodium sulfate, cholesterol, casein, cellulose, methionine, choline bitartrate, and *n*-alkane mix solutions, were provided by Shimakyu Chemical Ind. Ltd. (Osaka, Japan), Sigma-Aldrich (St. Louis, MO, USA), and ECHO Chemical Co., Ltd. (Miaoli, Taiwan). The triglyceride (TG), total cholesterol (TC), LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels were determined using commercial enzyme assay kits (Randox, Crumlin, UK).

2.2 Essential oil extraction and analysis

Fingered citron fruit was harvested from trees at local farms in Mingjian Township, Nantou County, Taiwan. The fruit (1 kg) were added to 5 L of distilled water and homogenized. Steam distillation was then performed for 3 h to collect the essential oils (Fig. 1). The essential oils were dehydrated with anhydrous sodium sulfate and filtered. The essential oil samples obtained were dried to remove any water molecules by passing them through anhydrous sodium sulfate. They were then weighed and the yields were calculated. The products were stored at −20℃ until further use. For the GC/MS assessment of the essential oils, a gas chromatograph (Agilent 6890 GC) equipped with a DB-1 fused-silica capillary column (length 60 m × 0.25 mm i.d.; inner film thickness 0.25 μm) and coupled to a mass spectrometer (Agilent model 5973 N MSD) was used. The analysis followed the modified procedure described by Lin et al.[22]. (2019), The injector temperature was maintained at 250℃. The carrier gas flow rate was 1 mL helium/min. The electron energy was 70 eV at 230℃. The constituents were identified by matching their spectra with those recorded in an MS library (Wiley 7n). In addition, an *n*-alkane (C_5–C_{25}) reference mixture was used to calculate retention indices in relation to those of authentic standards or those in the literature. The relative content of each compound was calculated as a percentage of the total chromatographic area and the results were expressed as the means of triplicate experiments.

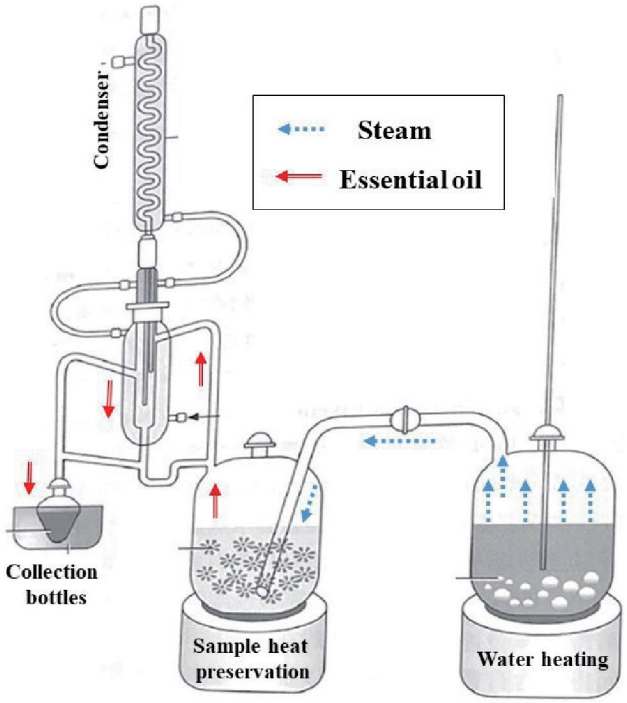

Fig. 1 Photographic images of steam distillation.

2.3 Animals and treatments

Male hamsters (5 weeks old, n = 24) were purchased from the National Laboratory Animal Center, Taipei City, Taiwan. The animals were housed in a temperature-controlled environment with a 12 h light/dark cycle at the animal facility of Hungkuang University. Before the experiments, the hamsters were acclimatized for one week to the environment and diet. The animal experiment was approved by the Ethics Committee for the Care of Animals and Animal Experiments of Hungkuang University (the affidavit indicating approval of the animal protocol used is attached). The hamsters were randomly assigned to one of four treatment groups (n = 6/group): (1) the normal group (NOR), which was fed the AIN-76A rodent diet; (2) the 3EO group, which was fed the AIN-76A rodent diet with 0.3% FCEO, 0.5% cholesterol, 12% corn oil, and 3% lard; and (3) the 5EO group, which was fed the AIN-76A rodent diet with 0.5% FCEO, 0.5% cholesterol, 12% corn oil, and 3% lard; and (4) the high-fat, high-cholesterol group (HFC), which was fed the AIN-76A rodent diet with 0.5% cholesterol, 12% corn oil, and 3% lard.

The experiment lasted for 12 weeks, during which the body weight and amount of food consumed were recorded every two days until the end of the experiment. After eight weeks of feeding, the hamsters were fasted for 12 h and then anesthetized with CO_2 to allow the collection of blood from their abdominal aortas. The blood was centrifuged (4,000 rpm, 4℃, 10 min) to separate the plasma, which was used later to determine the TG, TC, LDL-C, and HDL-C with commercially available assays (Randox, Crumlin, UK). After the animals were euthanized, their livers were dissected and rinsed with saline; the surface-adsorbed water was removed, and the samples were weighed. Lipids were extracted from the liver and feces of each hamster using chloroform–methanol (2:1, v/v). We then analyzed the TG, TC, glutathione peroxidase (GSH-Px), and superoxide dismutase (SOD) levels in the liver and neutral sterol levels in the feces.

Liver tissue samples were then carefully removed, minced, and fixed in 10% formalin. All samples were embedded in paraffin and cut into 4-μm-thick slices for evaluation of morphology and pathology. Each tissue sample was stained with hematoxylin and eosin and examined under a light microscope equipped with a charge-coupled device camera (BX-51, Olympus, Tokyo, Japan) by a veterinary pathologist.

2.4 Statistical analysis

All results were shown as mean ± standard deviation in the database (n = 6). One-way analysis of variance (ANOVA) was performed to determine statistical differences between groups. The Cochran–Armitage test was used for trend analysis of the dose effect of KOT supplementation. SAS 9.0 (SAS Institute, NC, USA) was used for the analyses. Results with a p-level of <0.05 were considered statistically significant.

3 Results and Discussion

3.1 Composition of FCEO

This study employed steam distillation for the extraction of essential oils, with an extraction rate of 0.52%. This approach aligns with the principles of green chemistry, which ensures the release of no harmful substances to minimize the environmental impact[12]. This study used GC/MS to measure the volatile composition of FCEO and analyzed its content using the area normalization method. In this study we detected 25 volatile compounds in FCEO (Table 1), consisting of 11 monoterpenes (94.34%), 7 sesquiterpenes (1.71%), 2 terpene aldehydes (0.78%), and 5 terpene alcohols (2.27%). In general, monoterpenes predominate in essential oils, with an overall presence of more than 80%, in this study we discover limonene (47.90%) and γ-terpinene (30.93%) as the main component in FCEO. Most terpenoids are distinguished by their multicyclic structures with functional groups and a carbon skeleton. These functional groups of volatile terpenoids (alcohols, ketones, aldehydes, and esters) are responsible for the different odors of extracts and complex fragrances. Oxyfunctionalized terpene derivatives find broad applications in the flavor and fragrance industries. In addition to their perfuming power, these molecules such as linalool, 4-terpinenol, α-terpineol, and geraniol in FCEO possess medicinal prop-

Table 1 Composition of fingered Citron essential oils.

Compound	RI	Formula	MW	%
Monoterpene				
α-thujene	923	$C_{10}H_{16}$	136	1.90
α-pinene	940	$C_{10}H_{16}$	136	3.67
camphene	945	$C_{10}H_{16}$	136	0.01
sabinene	966	$C_{10}H_{16}$	136	0.43
β-pinene	981	$C_{10}H_{16}$	136	3.04
β-myrcene	986	$C_{10}H_{16}$	136	2.05
1-phellandrene	995	$C_{10}H_{16}$	136	0.94
limonene	1024	$C_{10}H_{16}$	136	47.90
β-ocimene	1060	$C_{10}H_{16}$	136	1.18
γ-terpinene	1051	$C_{10}H_{16}$	136	30.93
α-terpinolene	1092	$C_{10}H_{16}$	136	2.29
Sesquiterpene				
copaene	1368	$C_{15}H_{24}$	204	0.01
β-elemene	1384	$C_{15}H_{24}$	204	0.01
caryophyllene	1419	$C_{15}H_{24}$	204	0.36
α-bergamotene	1405	$C_{15}H_{24}$	204	0.29
germacrene-D	1483	$C_{15}H_{24}$	204	0.54
bicyclogermacrene	1484	$C_{15}H_{24}$	204	0.10
β-bisabolene	1501	$C_{15}H_{24}$	204	0.40
Terpene aldehydes				
neral	1209	$C_{10}H_{16}O$	152	0.40
geranial	1239	$C_{10}H_{16}O$	152	0.38
Terpene alocohols				
linalool	1088	$C_{10}H_{18}O$	154	0.25
4-terpinenol	1163	$C_{10}H_{18}O$	154	0.54
α-terpineol	1177	$C_{10}H_{18}O$	154	0.58
nerol	1209	$C_{10}H_{18}O$	154	0.43
geraniol	1234	$C_{10}H_{18}O$	154	0.47

* Abbreviation description: RI means the retention index, which was identified via the comparison of mass spectra.

erties, which, in synergy, make essential oils renowned in aromatherapy[14, 19]. Volatile terpenoids also appear to be involved in protecting plants against heat and oxidative stress[9].

3.2 Management of dyslipidemia

The lipid metabolism of hamsters is more similar to humans compared to that of other rodents. Hamsters do not develop aortic atherosclerotic lesions through dietary induction[23]. In this study, no hamsters died during the experimental period, and no eating disorders were observed. At the end of the experimental period, the four experimental groups did not show significant differences in feed consumption (Table 2). However, the 3EO group (2.35) and the 5EO group (2.33) showed lower food efficiency than the HFC group (3.46). In a previous study, we showed that essential oils reduce weight gain from high-fat diets and decrease food efficiency, which closely relates to the assimilation of fat and the conversion to energy[22].

Dyslipidemia is the condition of having an abnormal amount of lipids (TG, cholesterol, and phospholipids) in the blood. More specifically, it refers to increased TC, LDL-C, and TG levels and decreased HDL-C levels. A high-fat, high-cholesterol diet can easily cause hyperlipidemia and other chronic metabolic diseases[1, 24]. The serum TC (367.33 mg/dL vs. 256.53 mg/dL), TG (324.00 mg/dL vs. 201.25 mg/dL), and LDL-C (152.81 mg/dL vs. 64.62 mg/dL) concentrations in the HFC group were significantly higher than those in the NOR group (Table 3). The 3EO and 5EO groups showed significantly reduced serum TC (249.50–284.67 mg/dL), TG (238.50–254.33 mg/dL), and LDL-C (70.96–106.13 mg/dL) levels. However, HDL-C level did not show a significant difference.

Epidemiological evidence indicates that there is a strong association between the incidence of CVDs and a high level of LDL-C and a low level of HDL-C. Therefore, the LDL-C/HDL-C ratio is often calculated to estimate cardiovascular risk[24–26]. The differences in LDL-C/HDL-C ratios of the 3EO, 5EO, and HFC blends were 68.07, 39.02, and 80.27, respectively (Table 3). The preventive effect of 3EO on the estimated cardiovascular risk was superior to that of 5EO. On the other hand, a high level of TG has been associated with increased LDL-C particles and increased cardiovascular risk. On that basis, atherogenic dyslipidemia, defined as a high LDL-C/HDL-C ratio and hypertriglyceridemia, is associated with high cardiovascular risk[24, 25]. The greater the reduction in LDL-C levels is the greater the protective effect against atherosclerotic CVD.

When food energy is excessive, adipose tissue initiates lipogenesis through re-esterification of free fatty acids and de novo lipogenesis. TG deposition leads to adipose tissue hypertrophy, obesity, and finally adipocyte dysfunction, which affects its endocrine and immunological responses[2, 4]. Fatty liver disease disrupts lipid metabolism and increases liver fat synthesis and accumulation, resulting in a variety of liver dysfunctions[5]. The HTC (43.28 mg/g vs. 14.53 mg/g) and HTG (68.90 mg/g vs. 24.36 mg/g) levels in the livers of the HFC group were significantly higher than the levels in the NOR group (Table 4). Both 3EO and 5EO significantly reduced the HTC level (31.94–34.62 mg/g). However, no significant difference was observed in the improvement in HTG. In histological observations, the liver cells of the HFC group exhibited fatty infiltration and necrosis compared to those of the NOR group. Treatment with FCEO showed visible positive changes in the histopathological of liver cells (Fig. 2).

Table 2 Effects of fingered Citron essential oils on the growth properties of hyperlipidemia Syrian hamsters.

	NOR	3EO	5EO	HFC
Weight (g)	80.67 ± 1.53^{a}	96.00 ± 4.35^{b}	101.60 ± 7.82^{c}	105.83 ± 12.10^{c}
Daily weight gain (g)	0.06 ± 0.03^{a}	0.15 ± 0.05^{b}	0.14 ± 0.06^{b}	0.22 ± 0.06^{b}
Daily dietary intake (g)	6.90 ± 0.10^{a}	6.26 ± 0.50^{a}	6.05 ± 0.54^{a}	6.80 ± 0.13^{a}
Food efficiency (%)	0.85 ± 0.40^{a}	2.35 ± 0.75^{b}	2.33 ± 0.27^{b}	3.46 ± 0.88^{c}

* All data in each column with different letters (a–c) are significantly different ($p < 0.05$). Abbreviation description: NOR, feed with normal diet. 3EO, feed a high-fat, high-cholesterol diet containing 0.03% fingered citron essential oils. 5EO, feed a high-fat, high-cholesterol diet containing 0.05% fingered citron essential oils. HFC, feed a high-fat, high-cholesterol diet.

Table 3 Effects of fingered Citron essential oils on the serum lipid profile of hyperlipidemia Syrian hamsters.

Groups	NOR	3EO	5EO	HFC
Serum				
TG (mg/dL)	201.25 ± 16.52^{a}	238.50 ± 21.74^{ab}	254.33 ± 17.90^{b}	324.00 ± 24.21^{c}
TC (mg/dL)	256.53 ± 17.25^{a}	249.50 ± 15.78^{a}	284.67 ± 12.81^{b}	367.33 ± 32.18^{c}
HDL-C (mg/dL)	181.78 ± 12.42^{b}	155.90 ± 10.17^{a}	181.82 ± 9.56^{b}	190.36 ± 13.01^{b}
LDL-C (mg/dL)	64.62 ± 8.61^{a}	106.13 ± 9.51^{b}	70.96 ± 5.60^{a}	152.81 ± 19.48^{c}
LDL-C/HDL-C (%)	35.54 ± 6.16^{a}	68.07 ± 4.34^{b}	39.02 ± 2.42^{a}	80.27 ± 3.62^{c}

* All data in each column with different letters (a–c) are significantly different ($p < 0.05$). Abbreviation description: NOR, feed with normal diet. 3EO, feed a high-fat, high-cholesterol diet containing 0.03% fingered citron essential oils. 5EO, feed a high-fat, high-cholesterol diet containing 0.05% fingered citron essential oils. HFC, feed a high-fat, high-cholesterol diet. TG, triglyceride. TC, cholesterol. LDL, low density lipoprotein. HDL, high density lipoprotein.

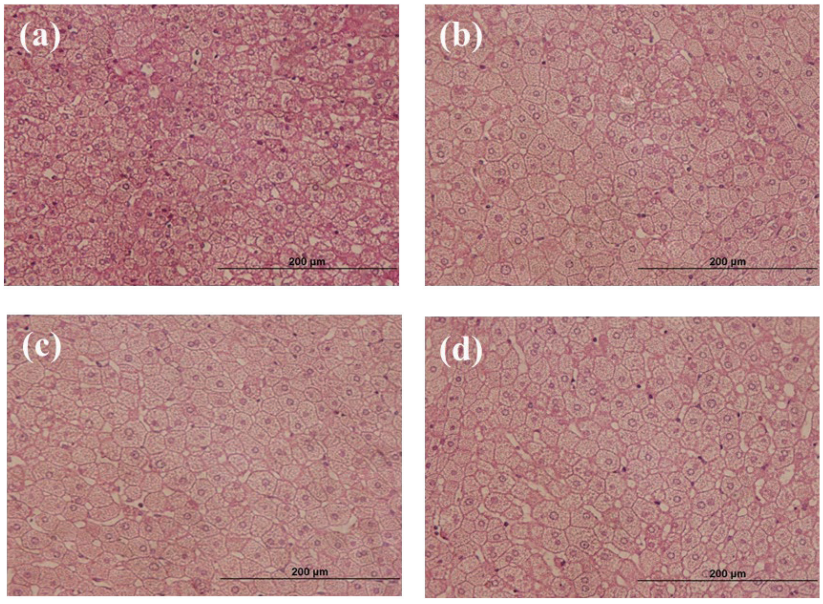

Fig. 2 Histopathological changes of fingered Citron essential oil on liver of hyperlipidemia Syrian hamsters (a: NOR, b: 3EO, c: 5EO, d: HFC) (H&E stain, 400X magnification).
Abbreviation description: NOR, feed with normal diet. 3EO, feed a high-fat, high-cholesterol diet containing 0.03% fingered citron essential oils. 5EO, feed a high-fat, high-cholesterol diet containing 0.05% fingered citron essential oils. HFC, feed a high-fat, high-cholesterol diet.

Table 4 Effects of fingered Citron essential oils on the serum lipid profile in hepatic biochemistry and feces lipid of hyperlipidemia Syrian hamsters.

	NOR	3EO	5EO	HFC
Liver				
HTG (mg/g)	24.36 ± 3.13^{a}	64.96 ± 4.41^{b}	66.57 ± 2.49^{b}	68.90 ± 3.38^{b}
HTC (mg/g)	14.53 ± 0.98^{a}	34.62 ± 2.64^{b}	31.94 ± 2.25^{b}	43.28 ± 3.67^{c}
HPL (mg/g)	15.34 ± 2.38^{a}	49.62 ± 3.63^{d}	36.97 ± 3.46^{c}	18.03 ± 2.14^{b}
SOD (U/g)	0.096 ± 0.012^{a}	0.084 ± 0.005^{a}	0.096 ± 0.006^{a}	0.108 ± 0.007^{a}
GSH-Px (U/g)	9.97 ± 0.83^{a}	12.11 ± 1.06^{b}	17.14 ± 0.81^{c}	12.02 ± 1.34^{b}
Feces				
Lipid content (%)	0.96 ± 0.10^{a}	2.13 ± 0.08^{b}	1.96 ± 0.08^{b}	1.06 ± 0.12^{a}
Neural sterol (mg/g)	1.81 ± 0.07^{a}	8.82 ± 0.31^{b}	9.61 ± 0.21^{c}	7.92 ± 0.42^{b}

* All data in each column with different letters (a–c) are significantly different ($p < 0.05$). Abbreviation description: NOR, feed with normal diet. 3EO, feed a high-fat, high-cholesterol diet containing 0.03% fingered citron essential oils. 5EO, feed a high-fat, high-cholesterol diet containing 0.05% fingered citron essential oils. HFC, feed a high-fat, high-cholesterol diet. HTG, hepatic triglyceride. HTC, hepatic cholesterol. HPL, hepatic phospholipids. SOD, superoxide

Other studies have shown that reducing oxidative stress and inhibiting fat generation are promising treatment options for preventing dyslipidemia[5, 22]. Phosphatidylcholine is an essential component of cell membranes and lipoproteins. When phosphatidylcholine is depleted, the liver secretes less very-low-density lipoprotein cholesterol, causing lipids to accumulate in hepatic cells[27, 28]. The differences in hepatic phospholipids (HPL) between the NOR, 3EO, 5EO, and HFC blends were 15.34, 49.62, 36.97, and 18.03 mg/g, respectively (Table 4). Steatosis may increase oxidative stress, which is counteracted by cellular enzymatic systems (cytosolic and mitochondrial SOD, GSH-Px, catalase, and non-enzymatic antioxidant systems)[29]. The results showed that 3EO and 5EO significantly increased hepatic GSH-Px levels (249.50–284.67 U/g of the hamsters. Bile acids have been recognized as regulators of lipid metabolism and are responsible for cholesterol-lowering activity via the mechanism of increasing fecal sterol excretion. Excessive cholesterol in the liver is metabolized to produce bile acids, which are eliminated via the bile duct. Hepatic cholesterol-7α-hydroxylase is an enzyme that regulates the conversion of cholesterol to bile[30]. The results showed that 5EO significantly increased the fecal neutral sterol (9.61 mg/g vs. 8.82 mg/g in the 3EO group) level in the hamsters (Table 4).

3.3 Composition–activity relation

In this study, treatment with essential oils of the fingered citron led to reduced TG and TC levels in blood serum, a positive indicator of health. Several studies have assessed the antidyslipidemic potential of isolated compounds present in essential oils. Camphene and carvacrol increased lipoprotein lipase and reduced leptin concentration, there by promoting antihyperlipidemia[31]. Geraniol improved the lipid profile, as well as the expression of receptors and enzymes associated with lipid metabolism[32]. Linalool appears to affect the metabolism of LDL-C by decreasing oxidation and increasing its affinity for the LDL-C receptor[33]. In metabolic syndrome mice, β-caryophyllene improved blood glucose, the lipid profile, and the antioxidant system[34].

Essential oils can lead to hypocholesterolemia by inhibiting the regulatory enzyme of cholesterol synthesis, HMG-CoA reductase, produced in the liver[24]. The mechanism of action of limonene has been reported to result in 70% inhibition of HMG-CoA reductase at a post-transcriptional level, thereby interfering with cholesterol synthesis[35–37]. Liver cytochrome P450 transform limonene into a variety of products. In humans, the biotransformation of limonene occurs via four pathways: oxidation of endocyclic double bonds; oxidation of exocyclic double bonds; oxidation of the methyl side chain; and allylic oxidation of the C6 ring. Limonene is metabolized in the liver and transformed into perillyl alcohol, perillyl aldehyde, and perillyl acid, all of which can prevent protein isoprenylation by interfering with the isoprenoid pathway[38].

4 Conclusion

Essential oils for aromatic plants are natural, non-toxic, natural products with rich monoterpenes that can be utilized as aromatherapy and prevent numerous health problems. Current research focuses on essential oils to identify plant-derived and chemical components, and the bioactivity of essential oils depend on their pharmacokinetic, meta-

bolic, and pharmacodynamic profiles in the human body. We observed significant improvements in the hyperlipidemia of FCEO. But still, it is required to isolate the active principle(s)and elucidate the mechanism of hypolipidemic effects. Therefore, that shall be faced to increase consumer recognition and utilization to derive specific health benefits. Further and more thorough studies are needed to understand the full potential of FCEO.

Author Contributions

Writing—Original draft preparation, Formal analysis, Conceptualization, K.-M.Y.; Visualization, H.-C.C.; Writing—review and editing, Y.-C.C.; Validation, Conceptualization, C.-H.H.; Data curation, Methodology, L.-Y.L. All authors have read and agreed to the published version of the manuscript.

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