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Original Article

Hypolipidemic effects of *S*-(+)-linalool and essential oil from *Cinnamomum osmophloeum* ct. linalool leaves in mice

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ABSTRACT

Cinnamomum osmophloeum (土肉桂 tǔ ròu guì) ct. linalool is one of the chemotypes of the indigenous cinnamon in Taiwan. *S*-(+)-linalool is the major constituent of leaf essential oil (LEO) of *C. osmophloeum* ct. linalool. This study aimed to investigate its physiological effects including body weight changes, blood biochemical values, and histopathological changes in mice. The mice were treated with LEO, *S*-(+)-linalool, and *R*-(−)-linalool. Results demonstrated similar physiological changes in mice treated with LEO and *S*-(+)-linalool, but significantly different effects in the body weight, TG, TC and blood glucose of *R*-(−)-linalool group. *S*-(+)-linalool-treated mice gained less weight and had significant decrease in blood triglyceride levels. No histopathological changes were observed in livers, kidneys, and spleens of *S*-(+)-linalool-treated mice. Furthermore, there were no significant differences in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels between *S*-(+)-linalool-treated mice and the control group. In addition, LEO and *S*-(+)-linalool significantly inhibited lipid accumulation through down-regulation of 3T3-L1 adipocyte differentiation. Taken together, the results show that LEO and *S*-(+)-linalool from *C. osmophloeum* ct. linalool can contribute to body weight management without harmful side effects.

1. Introduction

Rapid increase in the prevalence of obesity is mainly caused by changes in lifestyle.[1] In addition, modern lifestyle leads to decrease in daily energy expenditure, and increase in consumption of unhealthy food. Other determinants of obesity may include antipsychotic drug,[2] inheritance,[3] corticosteroid medications,[4] and endocrine dyscrasia caused by insufficient rest or sleep. Obese individuals not only have alterations of posture, physiology,[5] and psychology,[6] but also higher rates of mortality[7] and chronic diseases, such as metabolic syndrome, cardiovascular diseases,[8] cancers,[9] diabetes, and hypertension.[10] In short, overweight is the leading cause of many diseases.

Adipocyte plays a significant role in the regulation of energy-metabolism system. In recent years, adipocyte has been taken as the basis to investigate development and treatment of obesity and related diseases. Adipogenesis involves preadipocyte proliferation and their differentiation into mature adipocytes.[11] The mechanisms of adipocyte differentiation and lipid accumulation in 3T3-L1 cells *in vitro* are similar to those of preadipocytes *in vivo*. 3T3-L1 preadipocyte cell line has become a useful model for investigating the modulation of adipogenesis.[12] Hence, 3T3-L1 cell was employed to evaluate the inhibitory effect of essential oil on lipogenesis.

Previous research has reported effects of essential oils from plants on appetite and weight loss.[13] *Cinnamomum osmophloeum* (土肉桂 tǔ ròu guì) ct. linalool is one chemotype of the indigenous cinnamon in Taiwan. Our previous study demonstrated that the leaves of *C. osmophloeum* ct. linalool can yield 4% (w/w) of essential oil, which contains about 90% *S*-(+)-linalool.[14]

However, the effect on reduction of body fat formation is still unknown. In this study, the weight control potency of leaf essential oil (LEO) from *C. osmophloeum* ct. linalool and its main constituents were evaluated using mice treated orally. Furthermore, inhibition of adipocyte differentiation and lipid accumulation in 3T3-L1 cells treated with LEO and its main constituent were also assessed.

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2. Materials and methods

2.1. Plant materials

C. osmophloeum (土肉桂 tǔ ròu guì) ct. linalool mature leaves were collected from Lienhuachih Research Center in Nantou County of central Taiwan. A voucher specimen (COLL) of each sample was deposited in the Laboratory of Wood Chemistry (School of Forestry and Resource Conservation, National Taiwan University). All samples were stored at 25 °C until analysis.

2.2. Chemicals

Trazodone hydrochloride effectively reduced the overeating and appetite without enhancing weight gain.[15] In this study, we use trazodone hydrochloride (Sigma, USA) dissolved in water (RO H_2O) as positive control, while *R*-(−)-linalool (Sigma, USA), *S*-(+)-linalool (separated and purified from LEO) and LEO were dissolved in corn oil (Sigma, USA). *S*-(+)-linalool was collected according to our previous report.[14]

2.3. Animals

Six-week-old male ICR mice (28–36 g) were purchased from BioLASCO Co. (Taiwan) and housed in plastic cages, each with four mice. Mice were allowed two weeks to adapt to the environment before the test. All mice were maintained under controlled temperature (22 ± 2 °C), and illumination (12 h light-dark cycle), with free access to food (LabDiet® 5001 Rodent diet, Purina Mills LLC, St. Louis, MO, USA) and water. To reduce the influence of light variations, all assays were conducted in a special noise-free room with controlled illumination. Mice were treated orally with corn oil (control) and 250 and 500 mg/kg of LEO of *C. osmophloeum* ct. linalool, 500 mg/kg of *S*-(+)-linalool and 500 mg/kg of *R*-(−)-linalool, and all samples were diluted by corn oil. The positive control group was administered with 75 mg/kg of trazodone hydrochloride dissolved in water (RO H_2O) (P.C.). Mice undergoing various treatments were administered with 0.2 mL sample for 14 days before being sacrificed. After sacrifice, blood, kidney, liver and spleen of mice were collected for further analyses.

Body weight change rate = [Body weight (g) − First day body weight (g)] × 100/First day body weight (g)

2.4. Sample preparation

Fresh mature *C. osmophloeum* ct. linalool leaves were cleaned with distilled water and then air dried at 25 °C. These samples (200 g each), in triplicate, were subjected to hydrodistillation for 6 h using a Clevenger-type apparatus. *S*-(+)-Linalool was separated and purified from *C. osmophloeum* ct. linalool LEO by 1100 series HPLC (Agilent, USA) equipped with a model pump and a UV detector (254 nm) and a 250 mm × 10 mm i.d., 5 μm silica gel column (Phenomenex, Torrance, CA). The mobile phase was solvent A, 100% *n*-hexane; and solvent B, 100% ethyl acetate. Elution conditions were 0–8 min of 85% A; 8–10 min of 85–0% A to B (linear gradient) at a flow rate of 4 mL/min. The resulting retention time of *S*-(+)-linalool was 6.05 min.

2.5. Blood biochemical analysis

The blood of mice was collected after being sacrificed and allowed to coagulate for 1 h at ambient temperature. Blood serum was obtained by centrifuging for 20 min at 4700 rpm and 4 °C with a refrigerated centrifuge. Blood glucose, total cholesterol (TC), and triglyceride (TG) levels displayed as mg/dL in serum were calculated using Commercial Spotchem™ II reagent strips and Spotchem™ EZ automated dry chemistry analyzer. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also tested and displayed as IU/L.

2.6. Pathological organization analysis

In this study, the organs of mice were subjected to histopathological examination by Appendix 1. Kidney, liver and spleen tissues taken from experimental animals were fixed in 10% neutral formalin, alcohol-dehydrated, paraffin-embedded and their sections were cut at 2 μm thickness by using rotary microtome (Leica RM 2145, Nussloch, Germany). Sections were stained with hematoxylin and eosin (H & E). Histopathological changes and pathological assessments were described objectively by Prof. Jiunn-Wang Liao (National Chung Hsing University) with an optical microscope (BX-51, Olympus Tokyo, Japan). According to the study of Shackelford et al.,[16] the degree of lesions in kidney, liver and spleen tissues were classified from 1 to 5 depending on severity: 1 = minimal (<1%); 2: slight (1–25%); 3 = moderate (26–50%); 4 = moderate/severe (51–75%); 5 = severe/high (76–100%).

2.7. 3T3-L1 adipocyte cell culture and differentiation

3T3-L1 adipocytes grew to confluence in 90% Dulbecco's Modified Eagle's medium (DMEM) and 10% fetal bovine serum (FBS) (culture medium). Confluent preadipocytes were cultured for 2 days in the culture medium, followed by further supplementation with 1 mL differentiation medium I (dexamethasone (1 μM), isobutylmethyl xanthine (1 mM) and insulin (10 μg/mL)). The cells were treated with test samples which mixed with LEO, *R*-(−)-linalool and *S*-(+)-linalool respectively in differentiation medium I. After 2 days, remove original medium 1 mL and exchange to 1 mL differentiation medium II (90 % DMEM, 10% FBS and 10 μg/mL insulin). Every 2 days replace the medium with differentiation medium II. Until differentiation day 8 in differentiation medium II, more than 90% of the cells had accumulated fat droplets, and test sample's effects on differentiation of 3T3-L1 cells were then assessed.

2.8. Oil-red staining of culture cells

After 8-day differentiation, 3T3-L1 cells were stained using Oil Red staining method. The cells were washed with phosphate buffered saline (PBS) and then fixed with 10% formaldehyde for 1 h to stabilize the cells in the dish. The fixed cells were washed several times with PBS buffer. To each well, 1 mL of Oil Red (0.5 g Oil-red powder dissolved 100 mL isopropanol) was added and cells were incubated at ambient temperature for 15 min. The plates were rinsed three or four times with ddH_2O and photographed under a light microscope with a digital camera. The stained dye of cells was extracted with isopropanol (1 mL/well) and measured spectrophotometrically at 510 nm with the plate reader.

2.9. Statistical analysis

Data are expressed as mean ± S.E. in this study. For the difference analysis, various data were tested using one-way ANOVA and Scheffe's multiple ranges procedure with the SPSS software (Statistics 17.0). Different letters denote significant difference at the level of $p < 0.05$ according to the Scheffe's test.

3. Results

3.1. Effect of LEO and linalool on body weight changes in mice

Mice were treated with various samples once a day for 14 days. On day 2, the body weight change rate (5.7%) of mice treated with 500 mg/kg *R*-(−)-linalool already exceeded that of the control group (3.1%) (Fig. 1A). On day 14, the body weight change rate (10.3%) of *R*-(−)-linalool-treated mice became the highest in all groups. On day 9, the body weight change rate (2.5%) of mice treated with *S*-(+)-linalool and LEO was obviously lower than that of the control group (3.9%) (Fig. 1A). Furthermore, mice treated with trazodone hydrochloride had a marked decrease (3.9%) in body weight on day 4 (Fig. 1B).

3.2. Effect of LEO and linalool on the changes in blood biochemical parameters in mice

The TG, TC, glucose, AST and ALT levels of mice were analyzed. There were no significant differences in levels of TG, TC and glucose between mice treated with 250 and 500 mg/kg LEO and the control group (Table 1). However, the TG level of mice treated with 500 mg/kg *R*-(−)-linalool (172.8 ± 11.0 mg/dL) was 40% higher than that of the control group (123.6 ± 18.7 mg/dL). The levels of TC and glucose of the 500 mg/kg *R*-(−)-linalool group were 168.3 ± 11.8 mg/dL (25%) and 204.4 ± 2.4 mg/dL (18%), which were higher than those of the control group (135.3 ± 5.9 and 172.6 ± 8.0 mg/dL), respectively. *S*-(+)-linalool group not only maintained normal levels of TC and glucose but also caused a 25% fall in TG levels (91.2 ± 4.3 vs. 123.6 ± 18.7 mg/dl). The plasma AST and ALT values of mice treated with *S*-(+)-linalool were similar to those of the control group, but different from those of trazodone hydrochloride-treated mice (AST and ALT are 548.6 ± 76.8 and 84.0 ± 6.6 IU/L, respectively). In addition, we also found the result of relative organ weight (Fig. 2) of livers, kidneys, and spleens in mice tested with LEO from *C. osmophloeum* ct. linalool and *S*-(+)-linalool exhibited no difference to control group. Histopathological changes of livers, kidneys, and spleens in mice treated with LEO from *C. osmophloeum* ct. linalool and *S*-(+)-linalool were not observed, but the mice

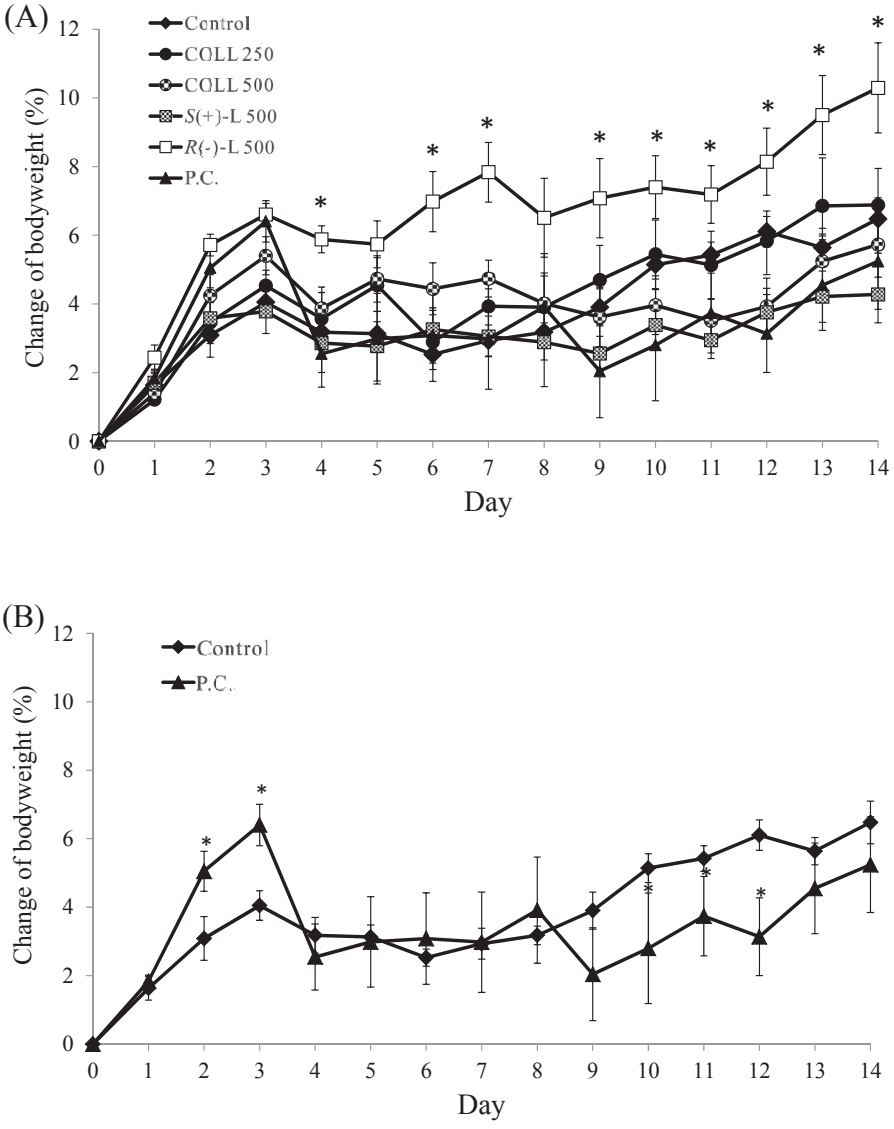

Fig. 1. Weight change of mice. (A) Weight change of mice in each group which was treated orally with corn oil (Control), 250 mg/kg and 500 mg/kg leaf essential oil of *Cinnamomum osmophloeum* ct. linalool (COLL 250, COLL 500), 500 mg/kg *S*-(+)-linalool (*S*(+)-L 500), 500 mg/kg *R*-(−)-linalool (*R*(−)-L 500) and 75 mg/kg the anxiolytic drug trazodone hydrochloride (P.C.), respectively. (B) Comparison of weight change in two groups mice, one was treated with corn oil (Control) and the other was treated with anxiolytic drug trazodone hydrochloride (P.C.). Data are expressed as mean ± S.E. ($n = 8$). $^*p < 0.05$ according to the Scheffe's test.

Table 1
Effects of the essential oils from leaf of *Cinnamomum osmophloeum* ct. linalool on blood biochemical values in mice.

Groups	TG*	TC*	Glu*	AST*	ALT*
Control	123.6 ± 18.7^{b}	135.3 ± 5.9^{b}	172.6 ± 8.0^{b}	290.6 ± 56.2^{b}	54.0 ± 4.3^{b}
COLL 250	129.8 ± 4.2^{b}	117.3 ± 14.0^{b}	166.8 ± 6.5^{b}	360.2 ± 8.2^{b}	55.8 ± 5.3^{b}
COLL 500	107.2 ± 8.1^{b,c}	113.0 ± 12.3^{b}	174.4 ± 13.2^{b}	378.2 ± 63.7^{b}	57.8 ± 2.6^{b}
S(+)-L 500	91.2 ± 4.3^{c,d}	117.8 ± 8.1^{b}	161.0 ± 8.3^{b}	297.4 ± 26.6^{b}	60.0 ± 2.4^{b}
R(−)-L 500	172.8 ± 11.0^{a}	168.3 ± 11.8^{a}	204.4 ± 2.4^{a}	280.0 ± 33.1^{b}	59.6 ± 2.8^{b}
P.C.	62.6 ± 5.3^{d}	112.0 ± 2.0^{b}	168.4 ± 3.4^{b}	548.6 ±76.8^{a}	84.0 ± 6.6^{a}

* TG: Triglyceride, TC: Total cholesterol, Glu: Glucose (mg/dL); AST: Aspartate aminotransferase, ALT: Alanine aminotransferase (IU/L). Data are expressed as mean ± S.E. ($n = 5$). Observations were made 14 days following the oral administration of corn oil (Control), 250 and 500 mg/kg leaf essential oil of *C. osmophloeum* ct. linalool (COLL 250, COLL 500), 500 mg/kg *S*-(+)-linalool (*S*(+)-L 500), 500 mg/kg *R*-(−)-linalool (*R*(−)-L 500) and 75 mg/kg the anxiolytic drug trazodone hydrochloride (P.C.). Different letters are significantly different at the level of $p < 0.05$ according to one-way ANOVA and Scheffe's test.

treated with *R*-(−)-linalool revealed non-specific histopathological changes of kidney (Fig. 3). Histopathological changes of kidney in trazodone hydrochloride-treated mice, accounting for 50% of mice studied, showed focal minimal to moderately severe fatty infiltration in the proximal tubules of the cortico-medullar junction of kidney (Fig. 4).

3.3. LEO from C. osmophloeum ct. linalool suppresses intracellular lipid accumulation during adipocyte differentiation

3T3-L1 cells were treated with various concentrations of LEO, *S*-(+)-linalool, and *R*-(−)-linalool. After differentiation, the cells were fixed and stained with Oil Red to examine neutral fat deposition. As shown in Fig. 5, the accumulation of lipid droplets within cells was greatly reduced by treatment with LEO, *S*-(+)-linalool, and *R*-(−)-linalool compared with the control group. Moreover, higher doses (100 μg/mL) had greater inhibition effect than lower ones (10 μg/mL), which was further supported by quantitative spectrophotometric analysis of cellular neutral lipid content. The level of lipid accumulation at higher treatment concentration was obviously decreased. However, there is no statistically significant difference between *S*-(+)-linalool- and *R*-(−)-linalool-treated groups.

4. Discussion

Owing to changes in dietary habits of modern lifestyle, people eat unhealthy food that caused hyperlipidemia, high cholesterol, and blood glucose increment, which are the main predisposing factors of cardiovascular diseases. This study presented the hypolipidemic effects of *S*-(+)-linalool and compared *S*-(+)-linalool with *R*-(−)-linalool in terms of physiological effects in mice. Previous research has found essential oils from *C. osmophloeum* ct. linalool have better yield and quality of *S*-(+)-linalool than other plants.[14]

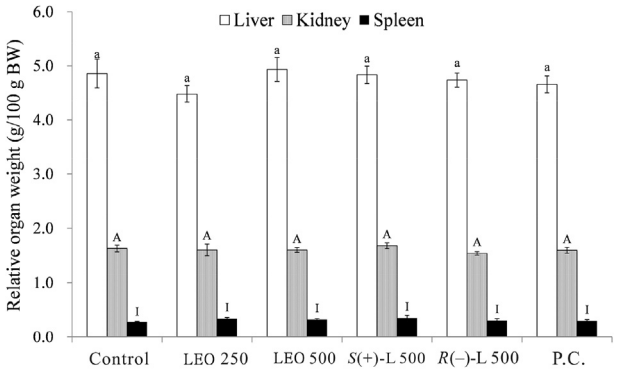

Fig. 2. Relative organ weight of livers, kidneys, and spleens in mice treated with corn oil (control), with 250 mg/kg and 500 mg/kg leaf essential oil of *Cinnamomum osmophloeum* ct. linalool (LEO 250 and LEO 500), 500 mg/kg *S*-(+)-linalool (*S*(+)-L 500), 500 mg/kg *R*-(−)-linalool (*R*(−)-L 500) and 75 mg/kg the anxiolytic drug trazodone hydrochloride (P.C.). Data are expressed as mean ± S.E. ($n = 8$). A, a and I means no significant difference at level of $p < 0.05$ according to one-way ANOVA and Scheffe's test in each group.

In this study, mice were treated with various samples once a day for 14 days. Changes in body weight of mice were recorded daily, and changes of TG, TC, blood glucose and blood biochemical values were also examined. It was found that mice treated with *R*-(−)-linalool obviously gained more body weight than other groups. A similar result was published in Shen and coworkers' study on the effects of olfactory stimulation with scent of lavender oil and its active component, linalool, in rats.[13] It has been proven that linalool is almost *R*-(−)-linalool in lavender oil.[17] In contrast, *S*-(+)-linalool was significantly different from *R*-(−)-linalool. The body weight change rate of mice treated with *S*-(+)-linalool and LEO was obviously lower than that of the control group, but the effect of trazodone hydrochloride was different. The body weight of mice treated with trazodone hydrochloride decreased dramatically. However, the mechanism behind body weight loss caused by trazodone hydrochloride was still unclear and needs further investigation. In summary, LEO from *C. osmophloeum* ct. linalool has potent effect on body weight management.

High cholesterol and blood glucose are the pathogenic factors of cardiovascular diseases. The above-mentioned results showed that *R*-(−)-linalool increased both TG and TC levels, and it also led to increase in body weight of mice. This study also found that the TG of *R*-(−)-linalool treated mice was 40% higher than that of the control group. The levels of TC and blood glucose were 25% and 18% higher than those of the control group, respectively. Therefore, *R*-(−)-linalool may raise the risk of cardiovascular diseases. In contrast, *S*-(+)-linalool not only maintained normal TC and blood glucose but also caused a 25% decrement in TG. In addition, Jun[18] reported that linalool had the efficacy of decreasing TG in plasma.

The plasma AST and ALT values were often useful in medical diagnosis for liver damage and hepatotoxicity. Here, AST and ALT values of mice treated with *S*-(+)-linalool were similar to those of the control group, but different from those of trazodone hydrochloride-treated mice. The relative organ weight and gross finding of livers, kidneys, and spleens of mice treated with LEO from *C. osmophloeum* ct. linalool and *S*-(+)-linalool exhibited no difference compared with the control group. Non-specific histopathological changes and fatty infiltration in livers, kidneys, and spleens of LEO- and *S*-(+)-linalool-treated mice were not observed. Hence, *S*-(+)-linalool indeed reduced the risk of cardiovascular diseases.

This study used the 3T3-L1 cell line which is widely used as a model of adipocyte differentiation and adipose biology to determine the effects of *C. osmophloeum* ct. linalool LEO, *S*-(+)-linalool, and *R*-(−)-linalool on adipocyte differentiation. The accumulation

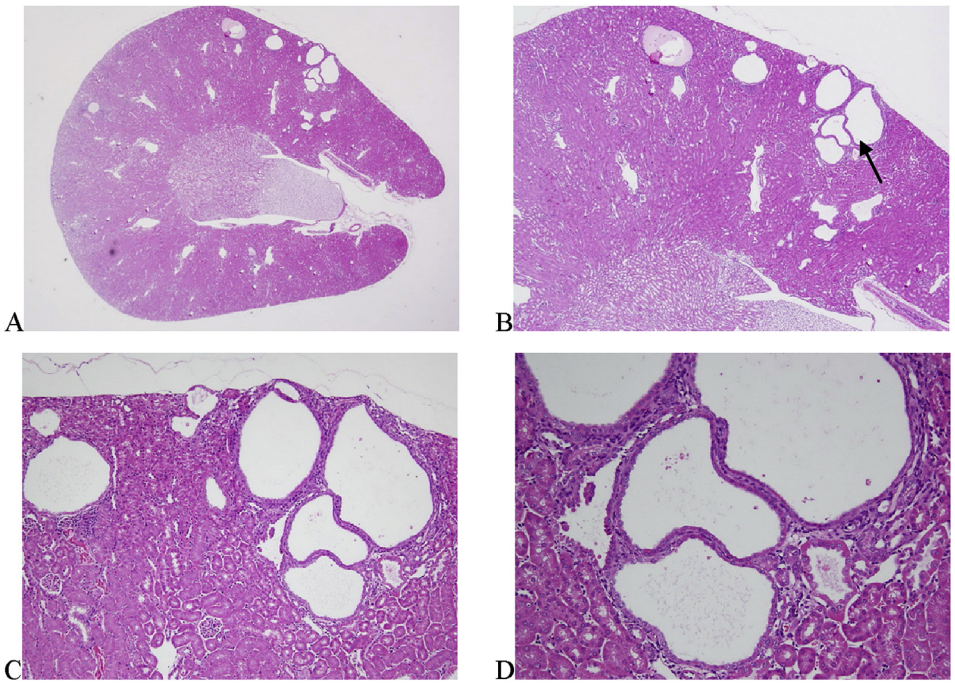

Fig. 3. Non-specific histopathological changes of kidney in mice treated with 500 mg/kg *R*-(−)-linalool. Focal, slight tubular cyst (arrow) was found in mice (A. 20×, B. 40×, C. 100×, D. 200×, animal code: 10-1). (H&E stain).

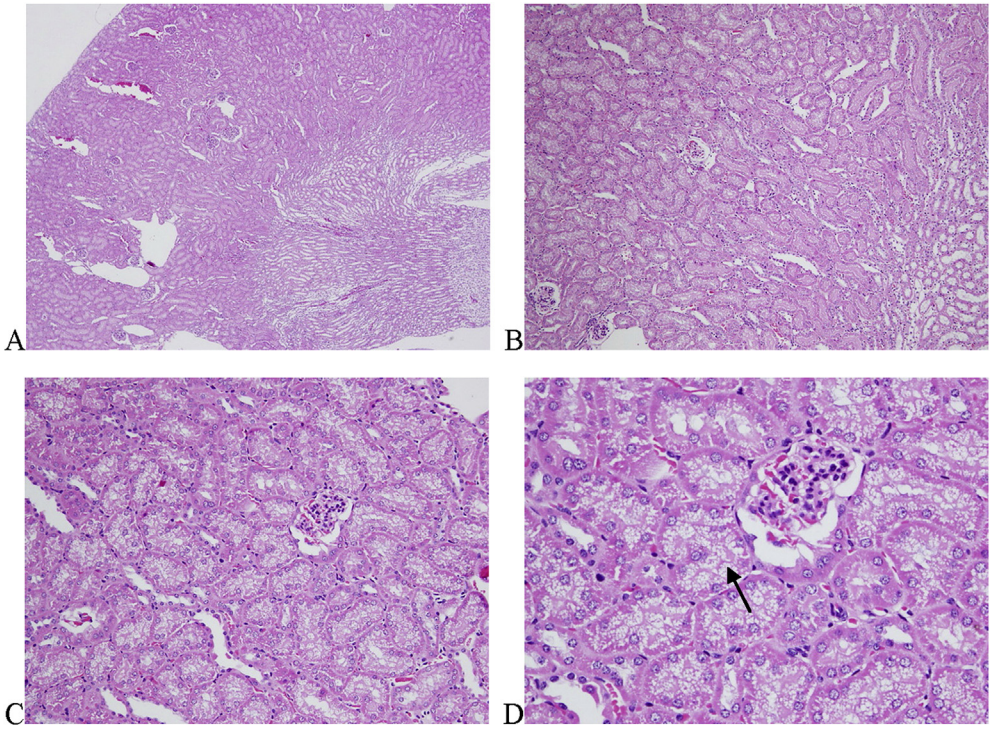

Fig. 4. Representative micrograph for histopathological findings in the kidney of trazodone hydrochloride-treated mice. The proximal tubules of cortico-medullar junction of kidney occur fatty infiltration (arrow). (A. 40×, B. 100×, C. 200×, D. 400×, animal code: 11-4). (H&E stain).

of lipid droplets within cells and quantitative spectrophotometric analysis of cellular neutral lipid content revealed that high dosage could significantly inhibit lipid production in the 3T3-L1 cell line. Moreover, no significantly different effect was observed between *S*-(+)-linalool- and *R*-(−)-linalool-treated groups. Therefore, it can be inferred that body weight gain of *R*-(−)-linalool-treated mice is resulted from the increase of food intake and the decrease of lipid metabolism.[17]

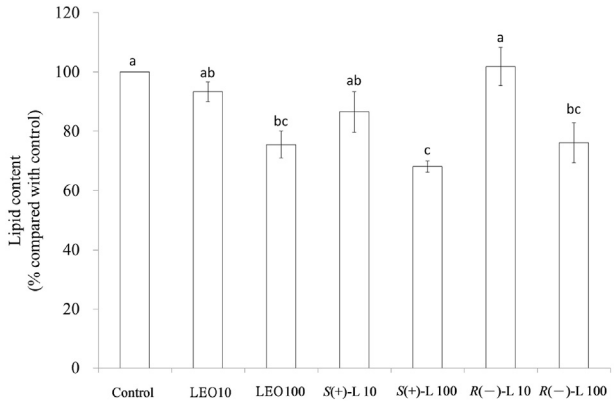

Fig. 5. Effects of essential oil from *Cinnamomum osmophloeum* ct. linalool leaf essential oil and its major constituent on suppressing adipogenesis. Data are expressed as mean ± S.E. ($n = 3$). Different letters are significantly different at the level of $p < 0.05$ according to the Duncan's test.

potency[22] similar to *R*-(−)-linalool, but it inhibited body weight gain. Taken together, the present findings demonstrated that *S*-(+)-linalool had the potential to be a low-cost health food for body weight management without side-effects.

Conflicts of interest

All contributing authors declare no conflicts of interest.

Acknowledgements

The authors thank Prof. Jiunn-Wang Liao (National Chung Hsing University) for assistance and critical suggestions in pathological organization analysis and Taiwan Forestry Research Institute for providing *C. osmophloeum* materials.

Appendix 1. Pathology – individual micro findings of mice

Organ	Histopathological finding	Animal code															
		Control								CO-LL 250							
		1–1	1–2	1–3	1–4	2–1	2–2	2–3	2–4	3–1	3–2	3–3	3–4	4–1	4–2	4–3	4–4
Kidney		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liver		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Organ	Histopathological finding	Animal code															
		CO-LL 500								*S* + L 500							
		5–1	5–2	5–3	5–4	6–1	6–2	6–3	6–4	7–1	7–2	7–3	7–4	8–1	8–2	8–3	8–4
Kidney		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Liver		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Organ	Histopathological finding	Animal code															
		R – L 500								P.C							
		9–1	9–2	9–3	9–4	10–1	10–2	10–3	10–4	11–1	11–2	11–3	11–4	12–1	12–2	12–3	12–4
Kidney		–	–	–	–		–	–	–	–	–	–	–	–		–	–
	Cyst, focal					3									1		
	Fatty infiltration, tubule, cortico-medullar area												4	–	2	3	1
Liver		–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Spleen		–	–	–		–	–		–	–	–	–	–	–	–	–	–

–: No significant lesions.
[1]: Degree of lesions was graded from one to five depending on severity: 1 = minimal (<1%); 2: slight (1–25%); 3 = moderate (26–50%); 4 = moderate/severe (51–75%); 5 = severe/high (76–100%).

5. Conclusions

In recent decades, obesity has become a global epidemic in both developed and developing countries. It is characterized by an increased adipose tissue mass and is associated with high health risk. The results obtained in this study demonstrated that LEO from *C. osmophloeum* (土肉桂 tǔ ròu guì) ct. linalool and *S*-(+)-linalool could reduce production and accumulation of lipid, and there are no pathological changes of liver, kidneys and spleen in mice. In addition, AST and ALT in mice treated with LEO and *S*-(+)-linalool did not change, and the levels of TG, TC and blood glucose remained normal. The results also revealed that *S*-(+)-linalool had the capability to inhibit intracellular lipid in 3T3-L1 adipocytes, indicating that *S*-(+)-linalool could play an essential role in controlling body weight. Compared with other plants' essential oils like onion oil,[19] garlic oil,[19] lemongrass oil[20] and cinnamon oil[21] which could reduce TG content, essential oil of *C. osmophloeum* ct. linalool could be more easily and rapidly obtained. Moreover, *S*-(+)-linalool from the essential oil of *C. osmophloeum* ct. linalool had anxiolytic

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