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Effects of *Eleutherococcus senticosus* Cortex on Recovery from the Forced Swimming Test and Fatty Acid β-Oxidation in the Liver and Skeletal Muscle of mice

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Abstract: Objective: The root and stem barks of *Eleutherococcus senticosus* have been used to treat emotional and physical fatigue in China, Russia, Korea, and Japan. The effects of *E. senticosus* on recovery from physical fatigue and the expenditure of energy currently remain unclear. We herein examined the effects of *E. senticosus* extract on recovery from physical fatigue after the forced swimming test as well as fatty acid β-oxidation in the liver and skeletal muscle of mice.

Methods: *1) Physical fatigue; E. senticosus* extract (500 and 1000 mg/kg, twice daily) was administered orally to ICR male mice for 7 consecutive days. After swimming had been performed for 15 min, each mouse was placed on the cover of a 100-mm culture plate, and the time for each mouse to move away from the cover was measured. *2) Fatty acid β-oxidation in the liver and skeletal muscle; E. senticosus* extract (500 and 1000 mg/kg) was administered orally twice daily to C57BL/6J male mice for 21 consecutive days. The initial and final body and liver weight were measured, and then fatty acid β-oxidation activity in the liver and skeletal muscle was measured by methods using [1-^{14}C] palmitic acid.

Key Findings: Recovery times after forced swimming were shorter in *E. senticosus* extract (500 and 1000 mg/kg)-treated mice than in vehicle-treated mice. The body and liver weight had no effect by the oral administration of *E. senticosus* extract, vitamin mixture and L-carnitine. Fatty acid β-oxidation activity in skeletal muscle was increased by *E. senticosus* extract (500 and 1000 mg/kg).

Conclusion: *E. senticosus* may enhance recovery from physical fatigue induced by forced swimming by accelerating energy changes through fatty acid β-oxidation in skeletal muscle.

Keywords: Anti-fatigue, *Eleutherococcus senticosus*, Fatty acid β-oxidation in the liver and skeletal muscle, Forced swimming.

INTRODUCTION

The root and stem barks of *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim. (Araliaceae) have traditionally been used to control blood pressure, as a tonic, and for mental and emotional issues as analeptics or agents to cope with stress. Previous studies demonstrated that the root and stem barks of *E. senticosus* exerted protective effects against stress-induced physiological and physical changes [1-4], and also influenced immune functions [5-8], mast cell-dependent anaphylaxis [9], anti-metastatic actions [10], and the endocrine system [11-13]. Exposure to stress causes changes in biogenic monoamine levels in the brain, which consequently induce the formation of gastric ulcers [14] and increase noradrenaline, dopamine, and 5-hydroxytryptamine turnover [15]. Glucocorticoids are the main mediators of stress responses and modulate many signaling events in immune responses [16-22]. Thus, exposure to stress has been linked to the autonomic nervous, endocrine, and immune systems [23, 24]. We previously reported that various extracts of *E. senticosus* cortex inhibited reductions in natural killer activity and elevations in blood corticosterone levels induced by forced swimming stress [25]. Recovery from the physical fatigue caused by acute exercise generally occurs with rest and the consumption of a high calorific drink or diet. The excess consumption of a high calorific drink or diet is known to cause metabolic syndrome, hyperlipidemia, and obesity. Metabolic syndrome and obesity have been attributed an imbalance between energy intake and expenditure. Furthermore, dietary fats or carbohydrates have been suggested to promote the storage of body fat. Therefore, inhibiting the digestion and/or absorption of dietary fats or carbohydrates and accelerating energy expenditure are key factors in the treatment of metabolic syndrome. The acceleration of energy availability has been shown to enhance recovery from fatigue and prevent metabolic syndrome. In the present study, we examined the effects of *E. senticosus* extract or its extract plus a vitamin mixture on recovery from physical fatigue after a forced swimming test as well as fatty acid β-oxidation in the liver and skeletal muscle of mice.

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MATERIALS AND METHODS

Materials

Extracts of *E. senticosus* root bark (Lot. No. 021212, Hokkaido, Japan) were provided by Nippon Funmatsu Pharmacy Co., Ltd. (Osaka, Japan). L-Carnitine (positive control) and a vitamin mixture [thiamine mononitrate (vitamin B_1) 54.9 mg; riboflavin (vitamin B_2) 21.9 mg; pyridoxine hydrochloride (vitamin B_6) 54.9 mg; *dl*-α-tocopherol succinate ester 113.5 mg; sodium L-ascorbate (vitamin C) 617.7 mg; nicotinamide 137.1 mg per 1000 mg] were also provided by Nippon Funmatsu Pharmacy Co., Ltd. [1-^{14}C]Palmitic acid (18.5 MBq) was purchased from NEN Life Science Products (MA, USA). A protein assay kit was purchased from Bio-Rad Lab. (CA, USA). Other chemicals used in this study were of reagent grade and purchased from Wako Pure Chemical Co. (Osaka, Japan).

Animals

Male C57BL/6J and ICR strain mice (5 weeks old) were obtained from Clea Japan (Osaka, Japan) and Japan SLC Co. (Shizuoka, Japan), respectively, housed for 1 week in a room with a controlled temperature of 25 ± 1 ºC and 60% relative humidity, and given free access to food and water during the experiments. Animal experiments were performed according to the ethical guidelines for Animal Experimentation by Ehime University and the Japanese Pharmacological Society, and the Guide for the Care and Use of Laboratory Animals of the National Institute of Health (USA). The Animal Studies Committee of Ehime University approved the experimental protocol (approval no. YA-8).

Measurement of Recovery Times in Mice after the Forced Swimming Test

As the evaluation of anti-fatigue actions, we measured the recovery time after forced swimming by the modified method of Kimura and Sumiyoshi [25]. Briefly, the water extract (500 or 1000 mg/kg body weight) of *E. senticosus* root bark, *E. senticosus* extract (250 or 500 mg/kg) plus the vitamin mixture (250 or 500 mg/kg), the vitamin mixture (500 or 1000 mg/kg), or L-carnitine (500 or 1000 mg/kg) was administered orally twice daily (7:00 and 19:00 h) to ICR male mice for 7 consecutive days. Swimming was performed for 15 min after the oral administration of the above samples, and each mouse was then placed on the cover of a 100-mm culture plate. The time for each mouse to move away from the cover was measured, and was defined as recovery from the physical fatigue induced by forced swimming.

Measurement of Fatty Acid β-Oxidation in the Liver and Skeletal Muscle Tissue of Mice

The water extract (500 or 1000 mg/kg body weight) of *E. senticosus* root bark, *E. senticosus* extract (250 or 500 mg/kg) plus the vitamin mixture (250 or 500 mg/kg), the vitamin mixture (500 or 1000 mg/kg), or L-carnitine (500 or 1000 mg/kg) was administered orally twice daily (7:00 and 19:00 h) to C57BL/6J male mice for 21 consecutive days. On day 22, mice were killed by exsanguination from the carotid artery under anesthesia with diethylether. The liver, skeletal muscle, and epididymal adipose tissues were quickly removed, and liver and epididymal adipose tissues weighed. Fatty acid β-oxidation activity in the liver or skeletal muscle was measured using the method of Sign *et al*. [26] and Murase *et al*. [27]. Briefly, the liver or skeletal muscle (100 mg) was washed in phosphate buffered saline (PBS, pH 7.0), cut into small pieces, and then homogenized on ice with 10 mM Hepes buffer (pH 7.2) containing 0.25M sucrose and 1 mM EDTA using an IKA ULTRA-TURRAX®T25 digital homogenizer (IKA Japan Co., Nara, Japan). The homogenate was centrifuged at 600 x *g* for 10 min, and the supernatant was used for the fatty acid β-oxidation assay. The reaction mixture [PBS (pH 7.4) containing [1-^{14}C] palmitic acid (0.1 μCi, 1.85 KBq), 0.25 mM CoA, 1 mM L-carnitine, 0.5 mM malic acid, 1 mM ADP, 1 mM $MgCl_2$, 1 mM dithiothreitol, bovine serum albumin (BSA, 0.2 mg/ml), and the supernatants of the liver and skeletal muscle homogenates (10 μg protein) in a total volume of 0.2 ml] was incubated for 10 min at 37 ºC. The reaction was stopped by adding $CHCl_3$-MeOH (2:1, v/v) (3 ml), conc. HCl (20 μl), and H_2O (0.6 ml). The reaction mixture was shaken for 5 min, and then centrifuged at 600 x *g* for 5 min. After centrifugation, the supernatant was extracted twice with *n*-hexane (1.4 ml) to remove residual radio-labeled palmitate. The radioactivity of the water layer was measured and expressed as mg protein.

Statistical Analysis

All values are expressed as means ± standard errors of the mean (SEMs). Data were analyzed by a one-way ANOVA, and differences among means were analyzed using Dunnett's test. Differences were considered significant at $P<0.05$.

RESULTS

Effects of *E. senticosus* Root Bark Extract, *E. senticosus* Extract Plus the Vitamin Mixture, the Vitamin Mixture, and L-Carnitine on Recovery Times in Mice after the Forced Swimming Test

Recovery times after the forced swimming test were shorter in *E. senticosus* root bark extract (500 and 1000 mg/kg)-treated mice than in vehicle-treated mice (control) (Table **1**). Furthermore, recovery times after the forced swimming rest were significantly shorter in *E. senticosus* extract plus the vitamin mixture (500 and 1000 mg/kg)-, the vitamin mixture (500 and 1000 mg/kg)-, and L-carnitine (1000 mg/kg)-treated mice than in control mice (Table **1**).

Effects of *E. senticosus* Root Bark Extract, *E. senticosus* Extract Plus the Vitamin Mixture, the Vitamin Mixture, and L-Carnitine on Body and Adipose Tissue Weights in Mice

No significant differences were observed in body or liver weights between the vehicle-, *E. senticosus* extract (500 and 1000 mg/kg)-, *E. senticosus* extract plus the vitamin mixture (500 and 1000 mg/kg)-, the vitamin mixture (500 and 1000 mg/kg)-, and L-carnitine (500 and 1000 mg/kg)-treated mice (Table **2**). On the other hand, adipose tissue weights were

Table 1. Effects of *Eleutherococcus senticosus* root bark extract, *E. senticosus* extract plus the vitamin mixture, the vitamin mixture, and L-carnitine on recovery times in ICR male mice subjected to forced swimming.

Group	*n*	Recovery Times after Forced Swimming (min)
Experiment 1		
Swimming mice (Control)	6	34.20 ± 3.02
E. senticosus root bark extract		
(500 mg/kg, twice daily)	6	19.33 ± 3.07*
(1000 mg/kg, twice daily)	6	8.14 ± 3.95*
Experiment 2		
Swimming mice (Control)	7	39.27 ± 2.45
E. senticosus extract plus the vitamin mixture [a)]		
(500 mg/kg, twice daily)	6	19.40 ± 3.44*
(1000 mg/kg, twice daily)	6	11.25 ± 4.56*
Experiment 3		
Swimming mice (Control)	6	28.26 ± 5.14
Vitamin mixture [a)]		
(500 mg/kg, twice daily)	6	25.42 ±3.27
(1000 mg/kg, twice daily)	6	10.32 ±2.15*
Experiment 4		
Swimming mice (Control)	6	33.7 ± 3.55
L-carnitine [a)]		
(500 mg/kg, twice daily)	6	25.74 ± 5.89
(1000 mg/kg, twice daily)	6	13.39 ± 2.93*

[a)]Vitamin mixture (vitamins B_1, B_2, B_6, C, E, nicotinamide) acts as redox in energy metabolism. L-Carnitin also acts as β-oxidation of long chain fatty acid. Vitamin mixture and L-carnitine were used as energy metabolic agents.
Values are means ± SE. Each experimental data were analyzed by one-way ANOVA; differences among means were analyzed using Dunnett's test. *Significantly different from vehicle treated mice (control), $P<0.05$.

Table 2. Effects of *Eleutherococcus senticosus* root bark extract, *E. senticosus* extract plus the vitamin mixture, the vitamin mixture, and L-carnitine on body and liver weights in C57BL/6J male mice.

Group	*n*	Initial Body Weight (g)	Final Body Weight (g)	Liver Weight (mg)
Normal	16	22.3 ± 0.24	24.1 ± 0.63	1281.6 ± 28.8
E. senticosus root bark extract				
(500 mg/kg, twice daily)	8	22.4 ± 0.19	25.1 ± 0.48	1335.7 ± 40.6
(1000 mg/kg, twice daily)	8	22.3 ± 0.18	23.9 ± 0.30	1285.6 ± 22.4
E. senticosus extract plus				
Vitamin mixture [a)]	8	22.2 ± 0.34	23.2 ± 0.44	1217.1 ± 16.9
(500 mg/kg, twice daily)				
(1000 mg/kg, twice daily)	8	22.6 ± 0.19	23.7 ± 0.28	1248.6 ± 23.0
Vitamin mixture [a)]				
(500 mg/kg, twice daily)	8	22.4 ± 0.21	23.7 ± 0.32	1282.6 ± 35.5
(1000 mg/kg, twice daily)	8	22.3 ± 0.42	23.0 ± 0.61	1229.8 ± 35.8
L-carnitine [a)]				
(500 mg/kg, twice daily)	8	22.2 ± 0.26	24.0 ± 0.13	1205.1 ± 27.2
(1000 mg/kg, twice daily)	8	22.6 ± 0.24	24.5 ± 0.48	1225.1 ± 39.4

[a)]Vitamin mixture (vitamins B_1, B_2, B_6, C, E, nicotinamide) acts as redox in energy metabolism. L-Carnitin also acts as β-oxidation of long chain fatty acid. Vitamin mixture and L-carnitine were used as energy metabolic agents.
Values are means ± SE.

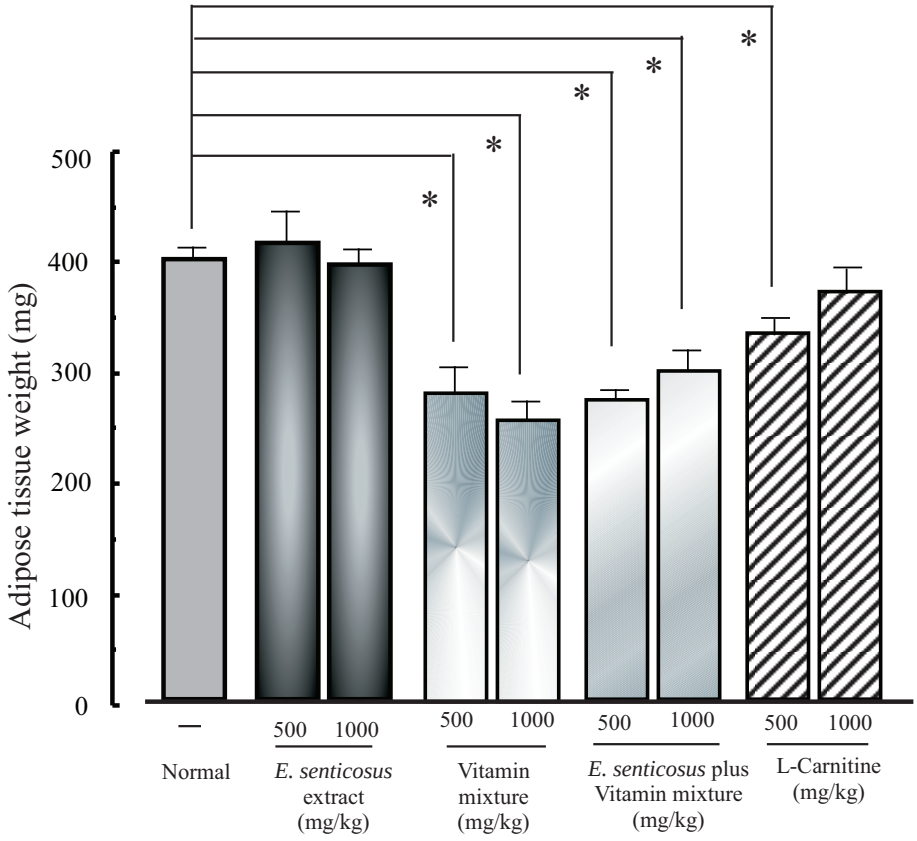

Fig. (1). Effects of *Eleutherococcus senticosus* root bark extract, *E. senticosus* extract plus the vitamin mixture, the vitamin mixture, and L-carnitine on adipose tissue weights in C57BL/J male mice. Values are means ± SE of 8-16 mice. *Significantly different from control mice, *P<0.05*.

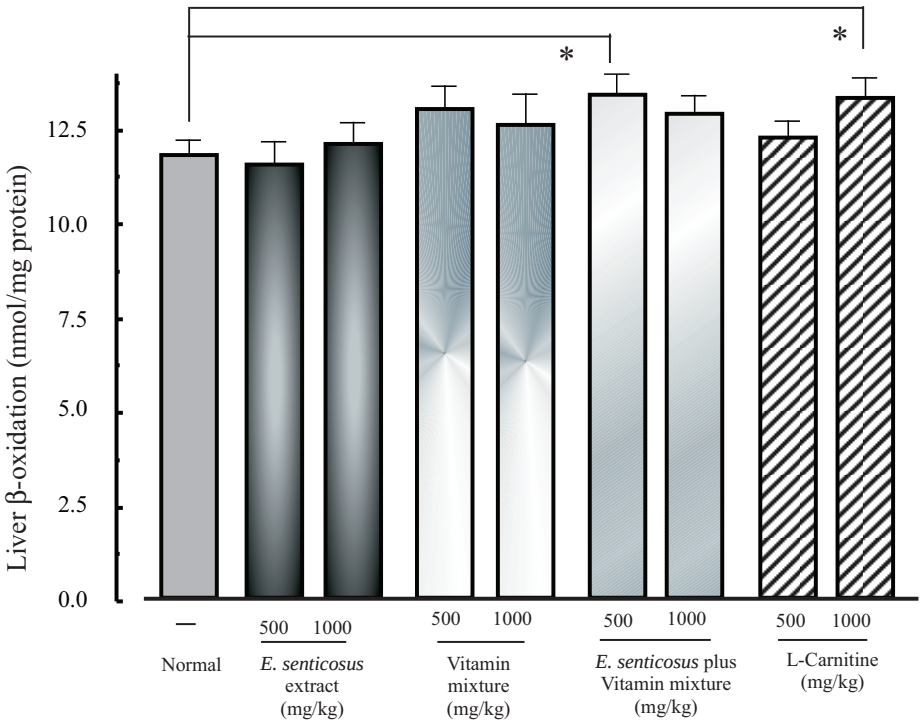

Fig. (2). Effects of *Eleutherococcus senticosus* root bark extract, *E. senticosus* extract plus the vitamin mixture, the vitamin mixture, and L-carnitine on β-oxidation in the liver of C57BL/J male mice. Values are mean ± SE of 8-16 mice. *Significantly different from control mice, *P<0.05*.

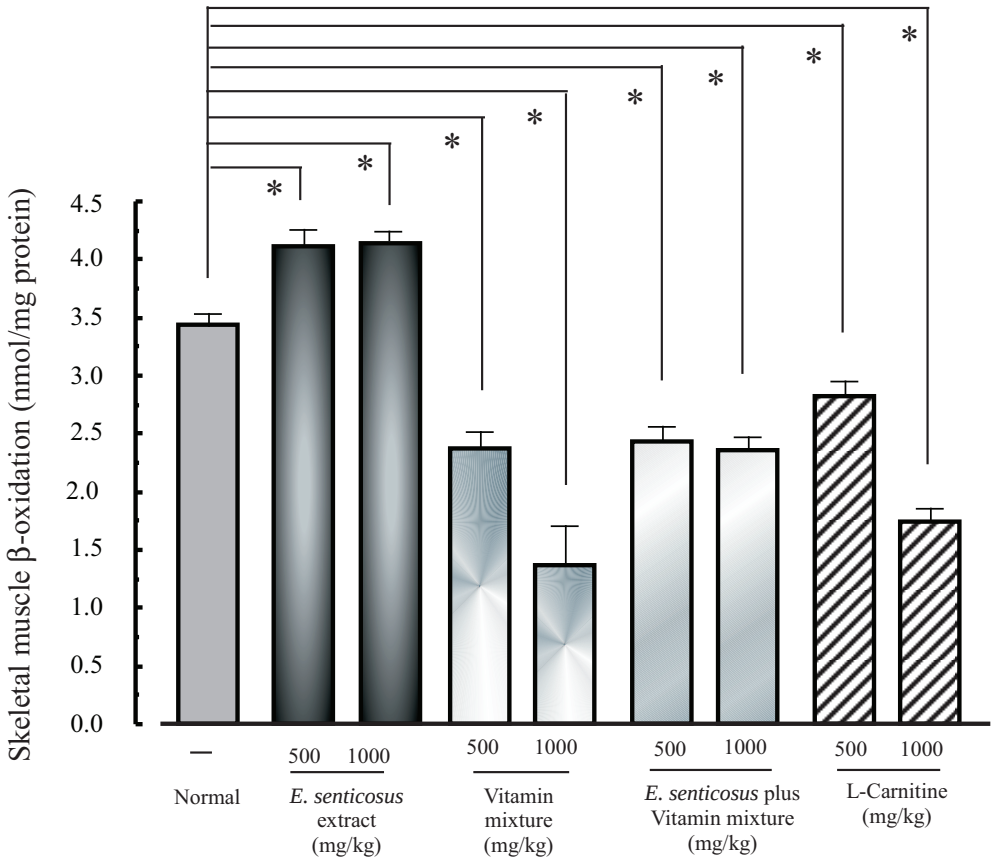

Fig. (3). Effects of *Eleutherococcus senticosus* root bark extract, *E. senticosus* extract plus the vitamin mixture, the vitamin mixture, and L-carnitine on fatty acid β-oxidation in skeletal muscle in C57BL/J male mice. Values are mean ± SE of 8-16 mice. *Significantly different from control mice, *P<0.05.*

significantly lower in the vitamin mixture (500 and 1000 mg/kg)-, *E. senticosus* extract plus the vitamin mixture (500 and 1000 mg/kg)-, and L-carnitine (500 mg/kg)-treated mice than in control mice (Fig. **1**). The oral administration of *E. senticosus* extract had no effects on adipose tissue weights (Fig. **1**).

Effects of *E. senticosus* Root Bark Extract, *E. senticosus* Extract Plus the Vitamin Mixture, the Vitamin Mixture, and L-Carnitine on Fatty Acid β-Oxidation Activity in the Liver and Skeletal Muscle of Mice

Fatty acid β-oxidation activity in the liver was higher in *E. senticosus* extract plus the vitamin mixture (500 mg/kg)- and L-carnitine (1000 mg/kg)-treated mice than in control mice, but remained unchanged in *E. senticosus* extract- and the vitamin mixture-treated mice (Fig. **2**). Fatty acid β-oxidation activity in skeletal muscle was increased by the oral administration of *E. senticosus* extract (500 and 1000 mg/kg) (Fig. **3**). Conversely, fatty acid β-oxidation activity in skeletal muscle was lower in the vitamin mixture-, *E. senticosus* extract plus the vitamin mixture-, and L-carnitine-treated mice than in control mice (Fig. **3**).

DISCUSSION

Brekhman and Dardmov [28] previously reported that the root bark of *E. senticosus* was used in Russia as an adaptogen, the properties of which increased non-specific body resistance to stress and fatigue. Furthermore, old Chinese medical books described the use of the root and stem barks of *E. senticosus* to treat beriberi, rheumatism, impotence, and physical and psychological fatigue from the Tang period (approximately the 8th century) in China [29]. We previously demonstrated that the extract of *E. senticosus* root bark prolonged swimming times and inhibited reductions in natural killer (NK) activity in splenic lymphocytes as well as increases in blood corticosterone levels in mice following the forced swimming test [25]. These findings suggest that the root bark extract of *E. senticosus* had stress-lowering and anti-fatigue effects, and inhibited stress-induced NK activity reduction and blood corticosterone elevation. It is well-known that insulin-resistant diabetes with obesity is closely associated with the decrease in the lipid utilization in liver and muscle [30-33]. Petersen *et al.* [30] reported that type 2 diabetes in the elderly subjects have severe insulin resistance in muscle as well as the accumulation of triacylglycerol in muscle and liver, and the decreases in both mitochondorial oxidative activity and mitochondorial adenosine triphosphate (ATP) synthesis. Xin *et al.* [34] reported that the transcriptional co-activator PPAR-γ co-activator-1α (PGC1-α)-dependent myokine, irisin [35] improve fatty oxidation and glucose ultilization in high-fat diet-treated mice. Furthermore it has been reported that natural products, sudachitin

(polymethoxylated flavone) [36] and tea catechin [27, 37, 38] improve glucose and lipid metabolism increasing mitochondorial biogenesis (fatty acid β-oxidation) in skeletal muscle and/or liver. Thus, the acceleration of fatty acid β-oxidation in the liver and skeletal muscle improves obesity, insulin-resistance diabetes by obesity through the reduction of adipose tissue. In the present study, we showed that the extract of *E. senticosus* root bark enhanced fatty acid β-oxidation in skeletal muscle without affecting body or adipose tissue weights, and accelerated recovery from the physical fatigue induced by forced swimming. The oral administration of *E. senticosus* root bark extract appears to have accelerated energy expenditure in the body by promoting fatty acid β-oxidation in skeletal muscle. On the other hand, the vitamin mixture, *E. senticosus* extract plus the vitamin mixture, and L-carnitine reduced fatty acid β-oxidation activity in skeletal muscle as well as adipose tissue without affecting body or liver weights. The reduction observed in adipose tissue cannot be explained by reductions in fatty acid β-oxidation in skeletal muscle after the oral administration of the three materials (the vitamin mixture, *E. senticosus* extract plus the vitamin mixture, and L-carnitine). Therefore, the three materials tested may have stimulated lipolysis and inhibited lipogenesis in adipose tissue, thereby reducing adipose tissue weight. Further studies are needed in order to determine the effects of the vitamin mixture and L-carnitine on lipolysis and lipogenesis in adipose tissue. Although *E. senticosus* plus the vitamin mixture and L-carnitine reduced fatty acid β-oxidation in skeletal muscle in the present study, that in the liver was accelerated. Murase *et al*. [27] previously reported that tea catechins reduced increases in adipose tissue weight induced by the consumption of a high-fat diet though the acceleration of fatty acid β-oxidation in the liver without affecting that in skeletal muscle. These findings indicate that the reductions induced in adipose tissue weight by *E. senticosus* plus the vitamin mixture and L-carnitine may have been due to the acceleration of fatty acid β-oxidation in the liver.

In conclusion, the root bark of *E. senticosus* may have enhanced recovery from the physical fatigue induced by the forced swimming test by accelerating energy changes through fatty acid β-oxidation in the skeletal muscle or liver. Further studies are needed in order to clarify the effects of *E. senticosus* on the relationship between high fat diet-induced obesity and the availability of energy expenditure through fatty acid β-oxidation in the liver or skeletal muscle, and also to isolate the active substance(s).

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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