ORYZA OIL & FAT CHEMICAL CO., LTD.

ALPHA LIPOIC ACID

Ingredient for weight loss, beauty and anti-oxidative products

■ALPHA LIPOIC ACID-P

(Powder、Food Grade)

■ALPHA LIPOIC ACID-P８０

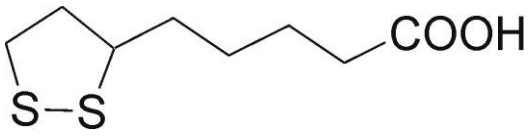
(Powder、Food Grade)

■ALPHA LIPOIC ACID-WSP７

(Water-soluble Powder、Food Grade)

■ALPHA LIPOIC ACID-L１

(Liquid、Food Grade)



■ALPHA LIPOIC ACID-PC

(Powder、Cosmetic Grade)

■ALPHA LIPOIC ACID-PC８０

(Powder、Cosmetic Grade)

■ALPHA LIPOIC ACID-WSPC７

(Water-soluble、Cosmetic Grade)

■ALPHA LIPOIC ACID-LC１

(Liquid、Cosmetic Grade)

ORYZA OIL&FAT CHEMICAL CO., LTD.

ver. 4.0 YF

ALPHA LIPOIC ACID

Ingredient for weight loss, cosmetics and anti-oxidative preparations

1. Introduction

α-Lipoic acid (thioctic acid) is a potent anti-oxidant that has been widely used in food supplement preparations. α-Lipoic acid has been used to alleviate peripheral pain in severe diabetic patients and its application in food preparations is getting popular. According to ***"Standards Concerning the Scope of Pharmaceutical Products"*** by PFSB Notification No. 0331009 dated March 31, 2004, the Ministry of Health, Labor & Welfare has revised and re-categorized α-lipoic acid as an ***"additive to be used in general food preparations or beverages".***

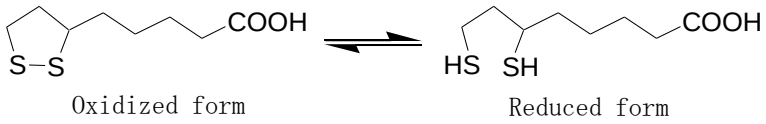


Fig. 1. α-lipoic acid

α-Lipoic acid (Fig. 1) is usually present in the mitochondrial matrix in the cells of organisms where cells metabolisms and energy production take place. *Adenosine triphosphate* (ATP), the energy required for cellular activities, is produced from metabolism of glucose *via* series of pathways, namely glycolysis, citric acid cycle, electron transfer and oxidative phosphorylation as shown in Fig. 2. Pyruvic acid produced from glycolysis is converted to acetyl CoA, a substrate for ATP production by *pyruvate dehydrogenase*, the enzyme that catalyzes the conversion. α-Lipoic acid has been found to enhance the action of pyruvate dehydrogenase. α-Lipoic acid normally exists in the reduced form in living organisms, and catalyzes oxidative decarboxylation process converting pyruvate to acetyl CoA. Hence, α-lipoic acid is essential for energy production in cells.

At Oryza Oil & Fat Chemical Co., Ltd., innovative process has been developed for the production and commercialization of α-lipoic acid enabling its application in the food industry. In addition, liquid form α-lipoic acid with high water dispersibility has been developed for its increasing demand in the beverages industry. Meanwhile, studies have been carried out in Oryza Oil & Fat Chemical Co., Ltd. to evaluate the various beneficial effects of α-lipoic acid, *e.g.* skin whitening effect, inhibition of adipocytes production and growth promoting effect on muscle cells.

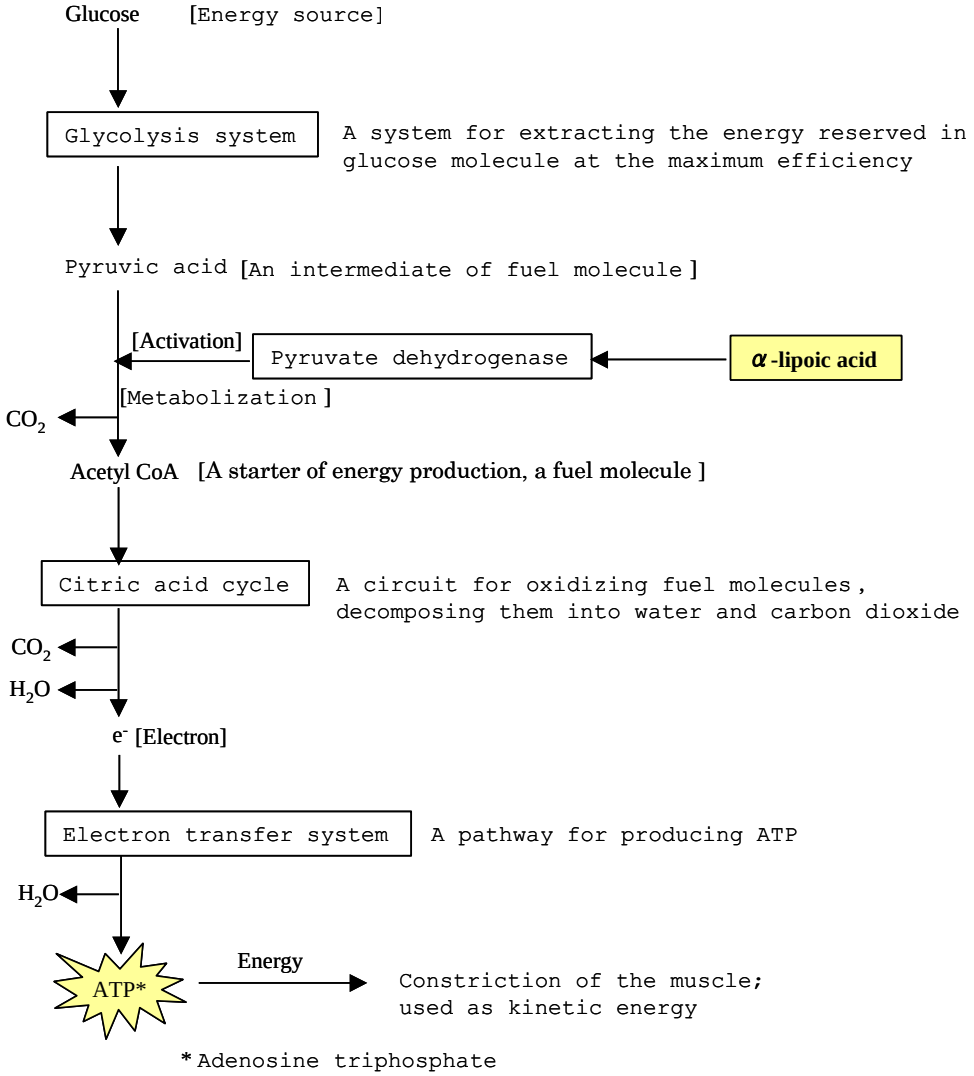


Fig. 2. Energy Production from Glucose and Site of Action of α-Lipoic Acid

2. Promotion of Weight Loss

Breakdown of Fats and Promote the Maintenance of Lean Muscle

Study suggested that α-lipoic acid enhances glucose utilization by increasing insulin sensitivity in advanced diabetic patients.[1] Meanwhile, Burke *et. al*.[2] found that co-ingestion of α-lipoic acid with creatine and small amount of sucrose enhances muscle total creatine content. Creatine is important for the production of energy and lipid catabolism in muscles. As skeletal muscle tissue is the major site for glucose following a meal, α-lipoic acid that enhances glucose uptake by skeletal muscle is potentially useful in weight reduction and long term prevention against obesity.

In 2004, anti-obesity effect of alpha-lipoic acid was reported to suppress appetite and enhance activity of brown adipose tissue in *Nature Medicine* that is famous science journal[3].

Furthermore it was reported alpha-lipoic acid enhances uncoupling of mitochondrial protein in muscle cells[4]. So enhancement of energy consumption can be expected.

1) Saengsirisuwan V., Perez F. R., Sloniger J. A., Maier T., Henriksen E. J. Interaction of exercise training and α-lipoic acid on insulin signaling in skeletal muscle of obese Zucker rats. *Am. J. Physiol. Endocrinol. Metab*. **287**, E529-536 (2004).

2) Burke D. G., Chilibeck P. D., Parise G., Tarnopolsky M. A., Candow D. G. Effect of α-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. *Int. J. Spot. Nutr. Exerc. Metab*. **13**, 294-302 (2003).

3) Kim M. S., Park J. Y., Namkoong C., Jang P. G., Ryu J W., Song H. S., Yun J. Y., Namgoong I. S., Ha J., Park I S.. Lee I. K., Viollet B., Youn J. H., Lee H. K., Lee K. U. Anti-obesity effects of α-lipoic acid mediated by suppression of hypothalamic AMP-activated protein kinase. *Nat. Med.*, **10**, 727-733 (2004).

4) Dicter N., Madar Z., Tirosh O. α-lipoic acid inhibits glycogen synthesis in rat soleus muscle *via* its oxidative activity and the uncoupling of mitochondria. *J. Nutr*., **132**, 3001-3006 (2002).

(1) Promotion of Muscle Cell Growth (*in Vitro*)

The effect of α-lipoic acid on muscle cell lines, L6 cells, was examined. L6 cells were cultured with α-lipoic acid for 24 hours. Fig. 3 shown that cell production increases in the presence of α-lipoic acid. α-lipoic acid promote muscle growth and maintenance of healthy lean muscle.

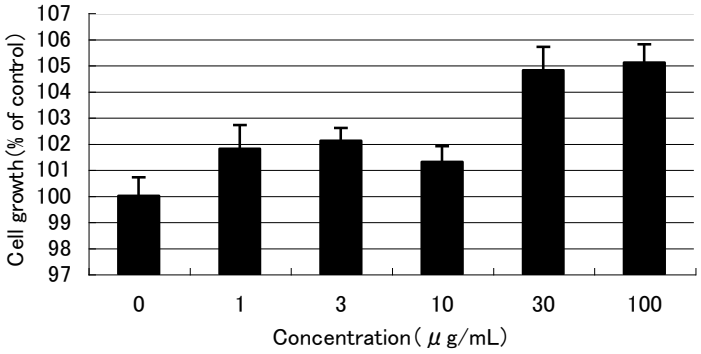


Fig. 3. Effects of α-Lipoic Acid on L6 Muscle Cells (Mean ± S.E., n=6)

【Method】

L6 cells ($5x10^4$ cells/ml) were suspended and cultured in D-MEM medium containing 10% bovine fetal serum, 100 units/ml of penicillin G and 100μg/ml of streptomycin. 100μl of the above suspension was distributed into 96-well microplate. Different concentrations of α-lipoic acid was added and the mixture was incubated for 24 hours. Degree of cell growth was determined by MTT assay.

(2) Promotion of Muscle Cell Growth (*in Vivo*)

Further study was prompted to examine the effect of α-lipoic acid *in vivo*. Mice were fed with diet containing α-lipoic acid for 24 days. Weight of the posterior limb (soleus muscle) was measured. Muscle weight increases in mice fed with diet containing α-lipoic acid (as illustrated in Fig. 4). α-Lipoic acid is effective in promoting muscle growth.

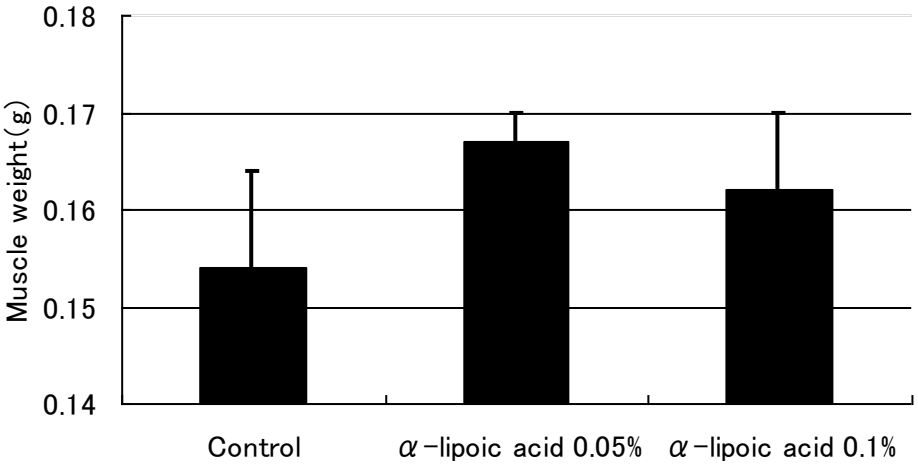


Fig. 4. Effects of Continuous Intake of α-Lipoic Acid on the Weight of the Soleus Muscle in Mice (mean ± S.E., n=6)

【Method】

Mice (ddy strain, male, 5 weeks old) were fed with diet (MF: Oriental Yeast Co., Ltd) containing α-lipoic acid (concentration 0.05% & 0.1%) for 24 days. Weight of soleus muscle was measured.

In another study conducted by Dicter N *et. al.*[3], α-lipoic acid shown to cause mitochondrial uncoupling and inhibition of glycogen synthesis. Glucose metabolism is regulated and weight maintenance is achieved.

3) Dicter N., Madar Z., Tirosh O. α-lipoic acid inhibits glycogen synthesis in rat soleus muscle *via* its oxidative activity and the uncoupling of mitochondria. *J. Nutr*. **132**, 3001-3006 (2002).

(3) Inhibition of Adipocytes Differentiation (*in Vitro*)

α-Lipoic acid has been shown to inhibit the differentiation of 3T3-L1 pre-adipocytes induced by a hormonal mixture or troglitazone[4]. Similar study was conducted at Oryza Oil & Fat Chemical Co., Ltd., the size of cell and internal oil vesicles were significantly reduced by α-lipoic acid (as illustrated in Fig. 5)

4) Cho K. J., Moon H. E., Moini H., Packer L., Yoon D. Y., Chung A. S. α-lipoic acid inhibits adipocyte differentiation by regulating pro-adipogenic transcription factors *via* mitogen-activated protein kinase pathway. *J. Biol. Chem*., **278**, 34823-34833 (2003).

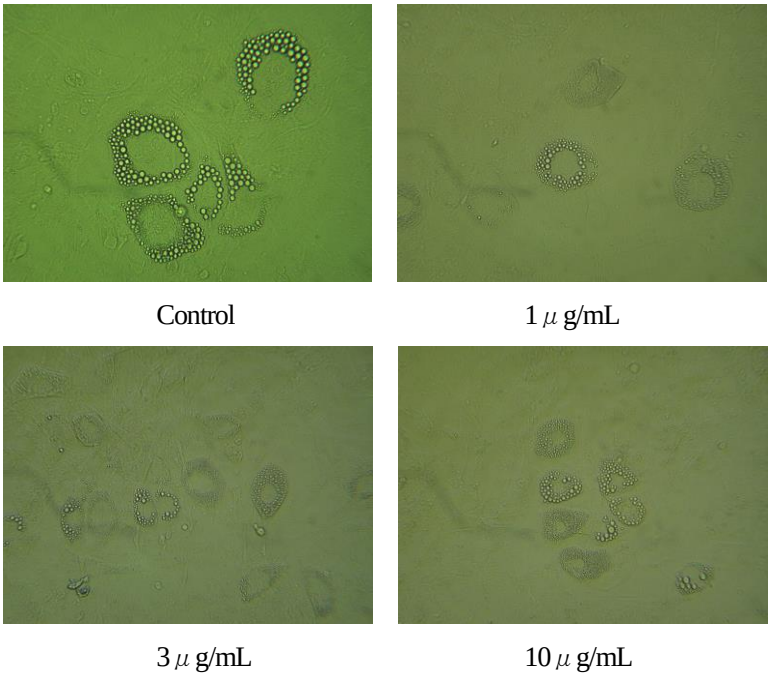


Fig. 5. Effects of α-Lipoic Acid on Adipocyte Differentiation

【Method】

3T3-L1 adipocytes ($5x10^4$ cells/ml) were incubated in D-MEM medium (high glucose) containing 10% bovine fetal serum for 2 days. The medium was then replaced by another medium containing insulin (1μg/ml), dexamethasone (0.25μM), isobutylmethylxanthine (0.5 mM) and different concentrations of α-lipoic acid. The new medium was further incubated for a total of 7 days. α-lipoic acid and insulin (1 μg/ml) was replaced every 2 days.

In adipocytes, an enzyme exists that converts glucose that is taken by insulin to triglyceride. The enzyme, glycerol 3-phosphate dehydrogenase (GPDH), is involved in this process to store excessive glucose-derived energy in fat cells. We studied the activity of α-lipoic acid on crude GPDH prepared from 3T3-L1 adipocytes and discovered that it has inhibitory activity (Fig. 6). Namely, α--lipoic acid prevents fat accumulation converted from excessive sugar.

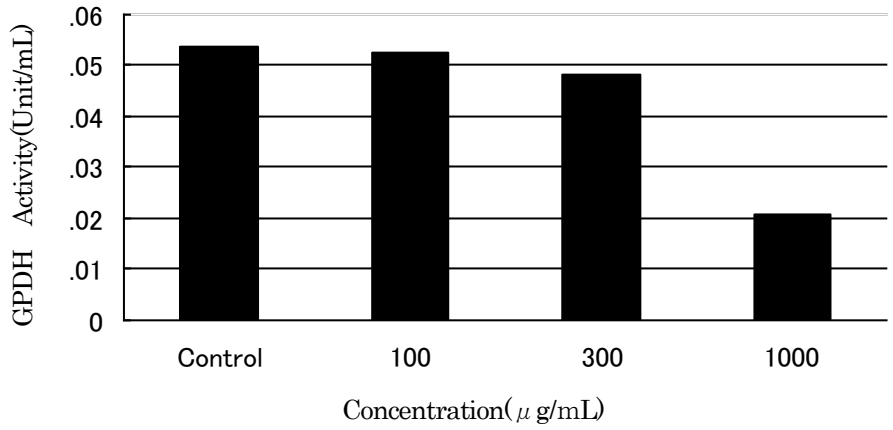


Fig. 6 Effect of α-Lipoic Acid on Fat Cell-derived GPDH activity (n=2-3)

【Method】

The lysate prepared from differentiated 3T3-L1 cells was used as the enzyme source. GPDH activity was measured by commercioally available kit (Primary Cell), Japan.

(4)Preventive effect on body weight gain in mice

We examined how α-lipoic acid influences weight gain in which were fed diet mice freely for 13 days with mild exercise. As shown in Fig. 7, the effect to prevent weight gain was weak by oral administration of α-lipoic acid (0.1%) only. However, α-lipoic acid supplementation with mild exercise significantly boosted its effect to prevent weight gain.

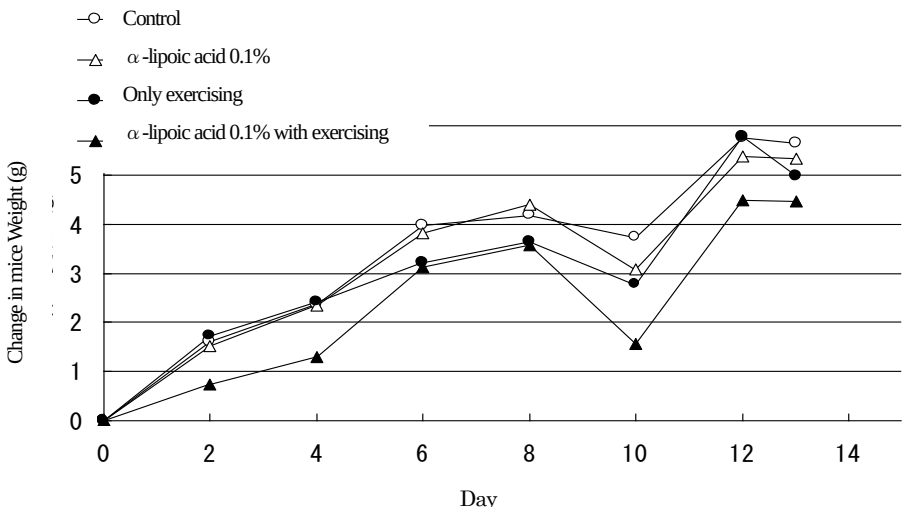


Fig. 7 Change in Mice Weight Fed α-Lipoic Acid Continuously with or without Exercise (n=5)

【Method】

Mice (ddY, male, 5 weeks old) were fed the diet (MF, Oriental Yeast) that includes α-lipoic acid (0.1%) for 13 days. Exercise was loaded with a treadmill (MK-770M, Muromachi Kikai) for ten minutes (5 rpm/min) once a day.

(5) Enhancement of lipid metabolism (*in vitro*)

We evaluated the effect of α-lipoic acid on the mRNA expression related to lipid metabolism (Table 1, Fig. 8) in human hepatocytes (HepG2) and muscle cells (L6). As shown in Fig. 9, α-lipoic acid enhanced mRNA expression of CPT, ACOX, AMPK and PPARα. On the other hand, α-lipoic acid enhanced mRNA expression of CPT, ACOX and AMPK. However, mRNA expression of PPARγ did not change. These results suggest that α-lipoic acid enhances lipid metabolism in liver and muscle.

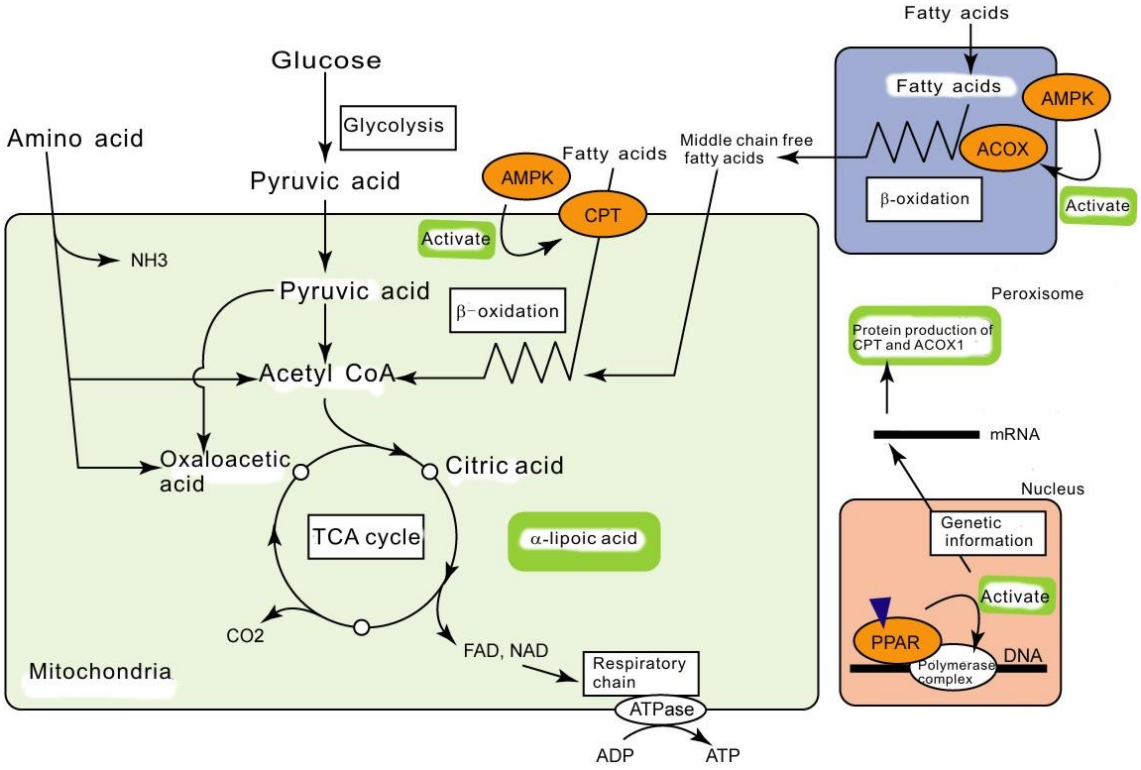


Fig. 8 Lipid and sugar metabolism in cells

Table 1. Evaluated mRNA

Name	gene	Function
Carnitin palmitoyl transferase	**CPT**	Key enzyme of mitochondrial β-oxidation. CPT incorporates fatty acid into mitochondrial matrix. The activation enhances β-oxidation.
Acyl CoA oxidase	**ACOX**	Key enzyme of peroxisormal β-oxidation. The activation enhances β-oxidation.
cAMP dependent protein kinase	**AMPK**	Hormone and stress responsible protein. Phosphorylates numerous proteins and regulates them. The activation inactivates stock cycle of energy and enhances energy consumption.
peroxisome proliferator-activated receptor	**PPAR**	PPARα enhances hepatic fat metabolism and PPARγ incorporates lipid in muscle cells.
β-actin	*β-actin*	Cytoskeletal protein. Used as standard gene.

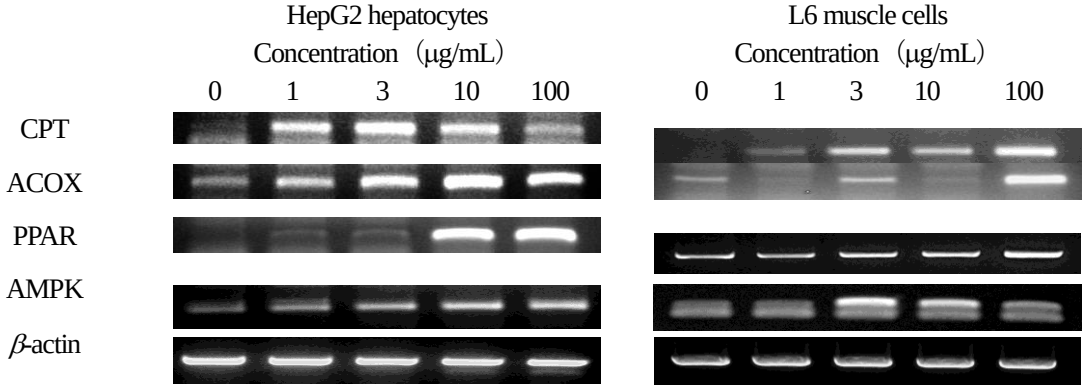


Fig. 9. Effect of α-lipoic acid on the expression mRNA related to lipid metabolism.

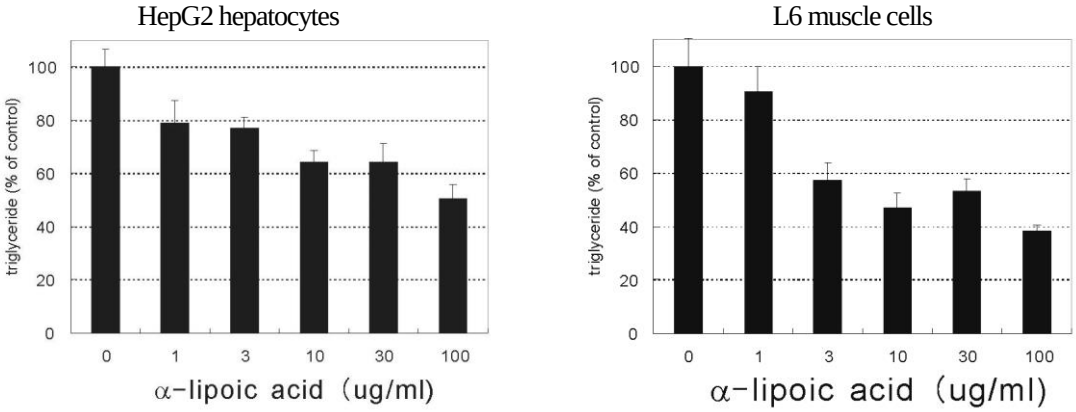


Fig. 10 Effect of α-lipoic acid on triglycride contents (mean±SE, n=6)

As a result of determination of cellular triglyceride, decrease in triglyceride was observed in bothe hepatocytes and muscle cells (Fig. 10). α-lipoic acid was suggested to decrease triglyceride by enhancement of expression of molecules related to β-oxidation.

【Method】

HepG2 or L6 cells were treated with a-lipoic acid for 24 hr. Cell lysates were obtained for determination of mRNA and triglycride.

(6) Continuous ingestion test in healthy men

In order to evaluate the effect of α-lipoic acid on bady weight in human, we conducted an ingestion test on our healthy male employees. Eight of them were taken 100 mg of α-lipoic acid and 10 employees took 200 mg for 4 weeks. After ingestion their obesity indexes and blood parameters were compared before and after the test.

In the group that took 100 mg of α-lipoic acid a day, their body fat ratio, impedance, fat amount, and hip sizes were reduced. There was a change in their serum parameters as well. Their blood sugar level was significantly lowered ($p<0.01$) and creatinine level was increased ($p<0.05$). (Table 2.)

In the group that took 200 mg of α-lipoic acid a day, body weight, body fat ratio, BMI, impedance, fat amount, hip size, and thickness of abdominal fat were reduced. Their blood sugar level and triglyceride were significantly lowered and creatinine level was increased ($p<0.05$). (Table 3.)

As described above, the intake of α-lipoic acid (100 or 200 mg/day) for 4 weeks improved the physical condition such as obesity indexes, blood sugar level, and serum creatinine level. This is caused by the effect of α- lipoic acid to increase muscle cells and prevention of fat store.

Table 2: Obesity indexes and blood parameters before and after taking α- Lipoic Acid (100 mg)

Parameters	**Before Taking**	**After Taking**	**The Number of The Improvement/All Example**
Wight（kg）	65.5±12.2	65.5±12.1	4 / 7
Body Fat（%）	19.1±5.8	18.6±5.9	6 / 7
BMI（kg/m^2）	22.2±4.0	22.2±4.0	3 / 7
Impedance（Ω）	490±66	480±55	5 / 7
Fat Content（%）	12.7±2.6	12.5±3.2	6 / 7
Degree of Obese (%)	0.9±18.3	0.9±18.2	4 / 7
Waist Size（cm）	77.2±10.9	77.6±12.1	2 / 7
Hip Size（cm）	95.5±8.9	92.1±7.3	7 / 7
Waist / Hips	0.81±0.06	0.84±0.08	2 / 7
Thickness of Addominal Fat（mm）	13.3±4.0	14.6±4.3	1 / 7
Blood Sugar（mg/dL）	87.3±100.7	69.3±18.0 $^{p<0.01}$	6 / 7
Cholesterol（mg/dL）	199.4±28.1	204.0±36.1	2 / 7
HDL- Cholesterol（mg/dL）	54.6±16.3	54.1±144.8	1 / 7
Triglyceride（mg/dL）	155.0±127.5	198.3±206.3	1 / 7
Phosphatide（mg/dL）	219.9±33.6	228.7±50.4	4 / 7
Creatinine（mg/dL）	0.82±0.11	0.87±0.131 $^{p<0.05}$	6 / 7
Total Protein（g/dL）	7.11±0.34	7.16±0.29	4 / 7

Values are shown with the average of 7 subjects (one subject stopped the test because of epigastric distress) with standard deviation.

Table 3: Obesity indexes and blood parameters before and after taking α - Lipoic Acid (200 mg)

Parameters	**Before Taking**	**After Taking**	**The Number of The Improvement/All Example**
Wight（kg）	71.0±15.3	70.4±14.0	6 / 10
Body Fat（%）	22.3±6.6	21.9±6.4	6 / 10
BMI（kg/m^2）	24.4±5.4	24.3±4.9	4 / 10
Impedance（Ω）	489±77	481±68	5 / 10
Fat Content（%）	14.6±5.8	14.3±5.2	6 / 7
Degree of Obese (%)	4.4±13.4	4.4±12.4	4 / 10
Waist Size（cm）	82.1±11.4	82.2±9.5	3 / 10
Hip Size（cm）	96.0±8.11	95.4±8.8	7 / 10
Waist / Hips	0.85±0.05	0.86±0.03	1 / 10
Thickness of Abdominal Fat（mm）	16.7±7.3	16.3±7.6	6 / 10
Blood Sugar（mg/dL）	97.0±28.4	94.0±29.9	5 / 10
Cholesterol（mg/dL）	200.2±26.6	203.1±26.5	4 / 10
HDL- Cholesterol（mg/dL）	58.4±22.7	57.3±20.3	3 / 10
Triglyceride（mg/dL）	164.4±117.7	118.1±65.5	4 / 10
Phosphatide（mg/dL）	238.3±41.4	230.6±33.5	5 / 10
Creatinine（mg/dL）	0.84±0.15	$0.86\pm0.16^{p<0.05}$	8 / 10
Total Protein（g/dL）	7.21±0.2	7.32±0.1	5 / 10

Value are shown with the average of 10 subjects with standard deviation.

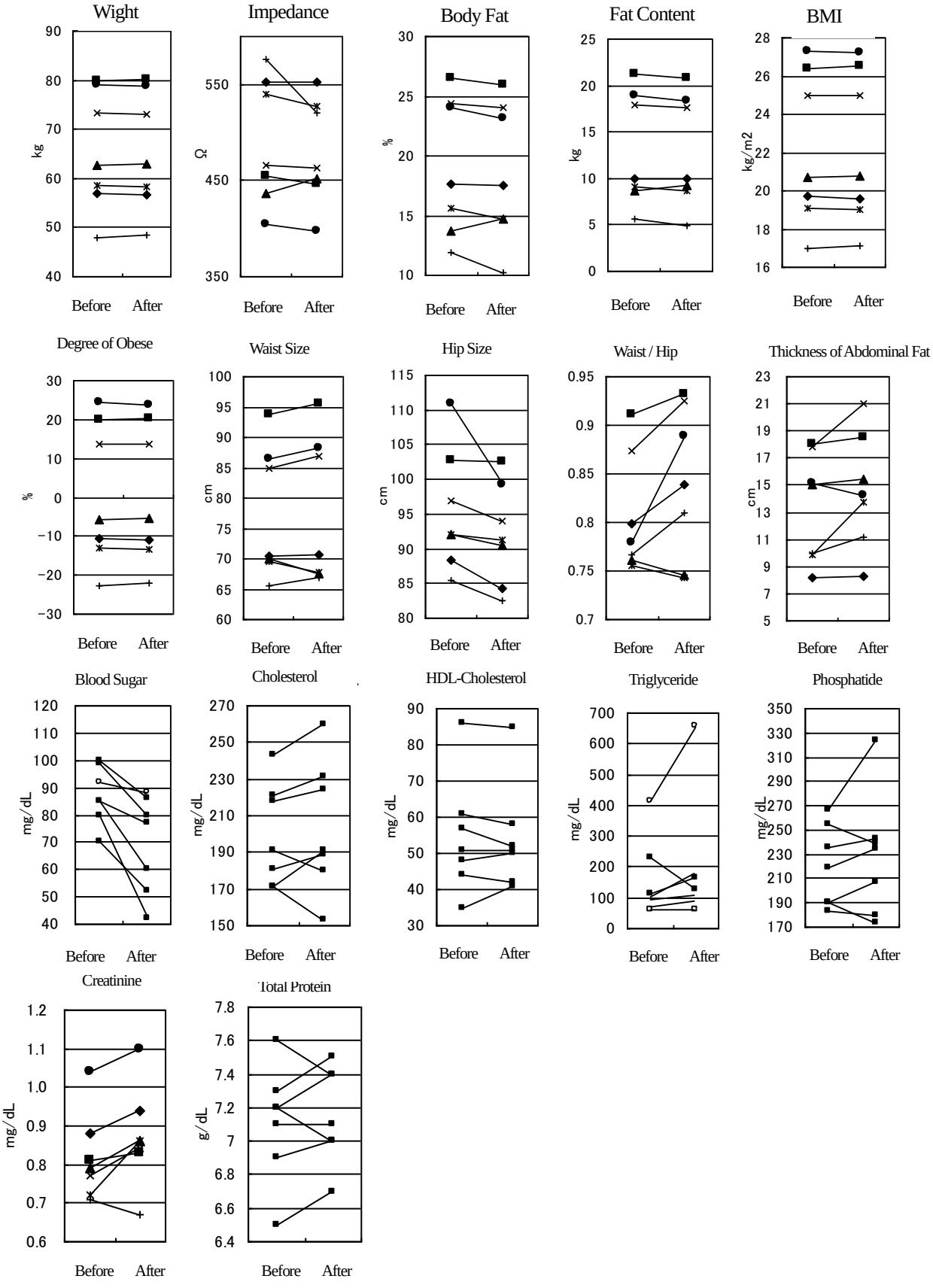


Fig. 11 Changes in obesity indexes and blood parameters before and after taking α-Lipoic Acid (100 mg)

3. Cosmeceutical Effects

(1) Skin-Whitening Effect

①Effect on melanin formation (*in vitro*)

The effect of α-lipoic acid on B16 melanoma cells was examined. As illustrated in Fig. 12, α-lipoic acid demonstrated a dose-dependent suppression effect on melanin formation. α-lipoic acid is a potentially useful skin whitening agent.

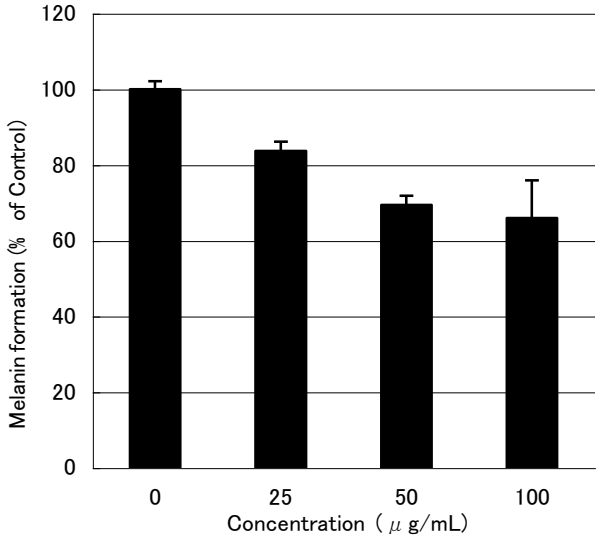


Fig. 12. Effects of α-Lipoic Acid on Melanocyte (B16) Growth (mean ± S.E., n=6)

【Method】

B16 melanoma cells ($5x10^4$ cells/ml) were suspended in MEM medium (containing 10% fetal bovine serum, 100 units/ml penicillin and 100μg/ml streptomycin) containing 2mM theophylline, and 500μl of the suspension was placed into a 24-well plate. Different concentration of α-lipoic acid (55μl) was added and the mixtures were incubated for 3 days. After incubation, PBS (300 μl) was added and cells were crushed by ultrasonication.

Crushed cell mixture was recovered on a 96-well plate and absorbance was determined at wavelength 415 nm (reference wavelength 700 nm).

②Activity to reduce pigmentation (*in vivo*)

We examined the effect of α-lipoic acid given continuously to brown guinea pigs according to following protocol. Then we studied how it reduces pigmentation caused by UV rays. As shown in Fig. 13, the color value on the radiation area of the control group (0 mg/kg of α-lipoic acid) on the 8th and 10th day after the start of UV exposure clearly lowered as compared to before exposure (day 0). In the group that took α-lipoic acid (25 and 50 mg/kg), the color value on the radiation area increased (Refer to the photo in Fig. 14.) This indicates that α-lipoic acid controls

pigmentation, proving that it performs skin-lightening activity with oral intake both *in vitro* and *in vivo*.

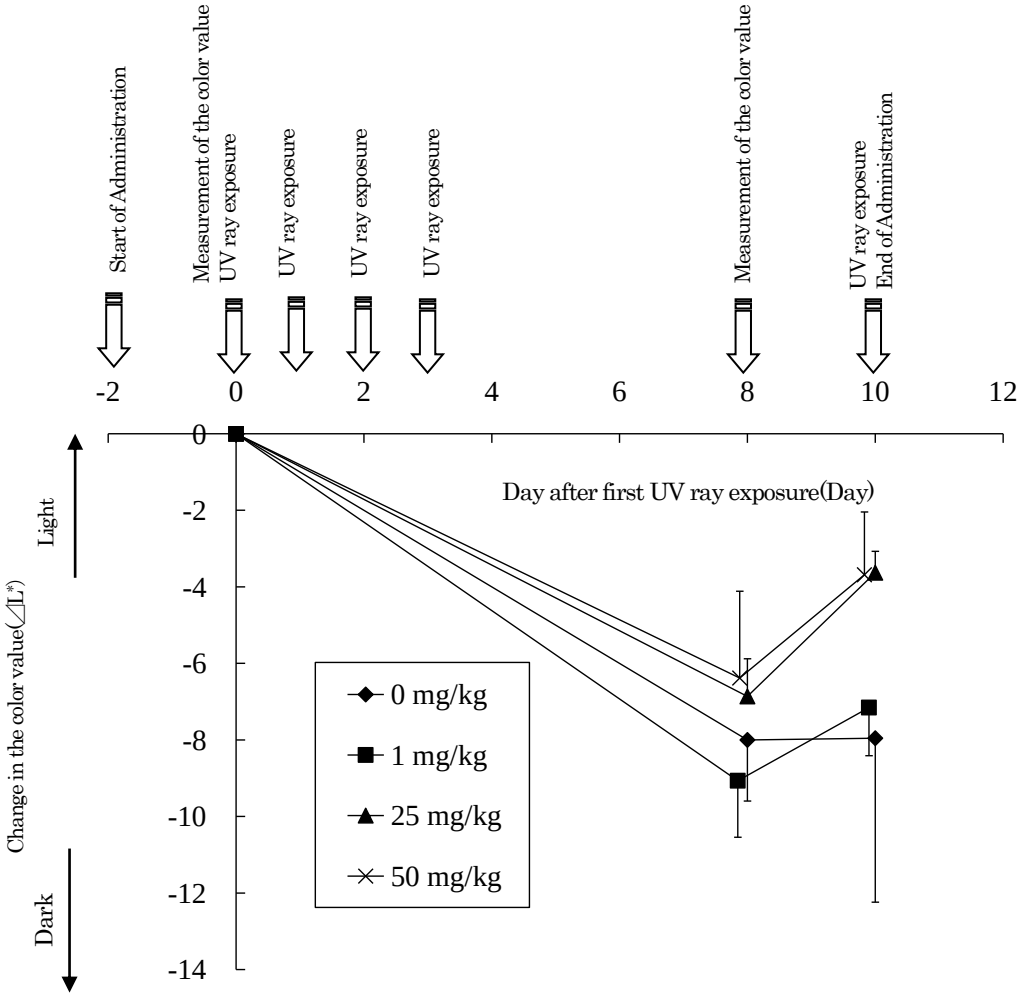
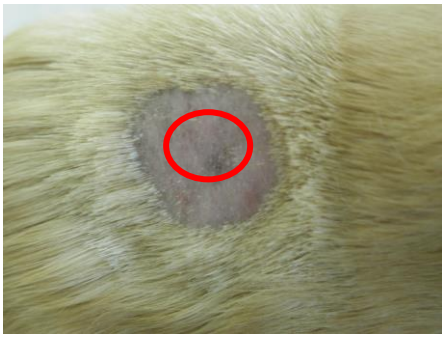


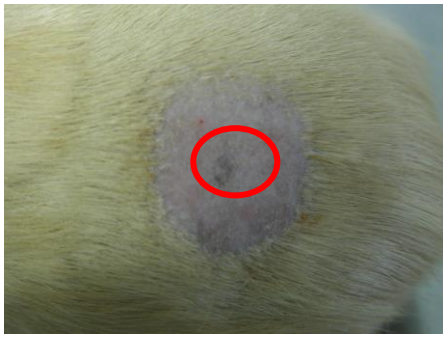
Fig. 13 Effect of α-Lipoic Acid on Pigmentation Formation caused by UV rays in Brown Guinea Pigs (average value +/- SD, n=3)

【Method】

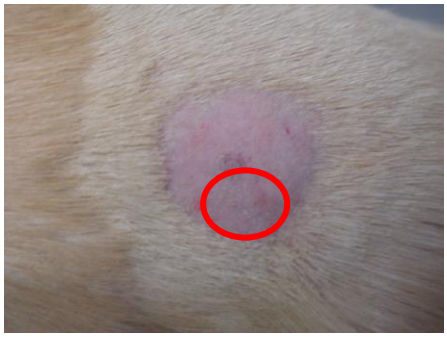
Brown guinea pigs (male, 4 weeks old)were given α-lipoic acid daily from 2 days before (day -2) UV ray radiation (day 0). UV rays (UV-B, 2,000 mJ/cm^2) ware radiated to the hair-shaved back of the guinea pigs using a UV-ray radiator (Solar Simulator manufactured by Ushio, Inc, Japan.) 4 times from day 0 to day 3. α-lipoic acid was given orally from day -2 to day 10 including the period of UV ray radiation. The color value (L* value) of the radiation area was measured using a spectro-color-difference meter (Nippon Denshoku Industries Co., Ltd.) before UV ray radiation (day 0) and 8th and 10th days after starting the radiation.



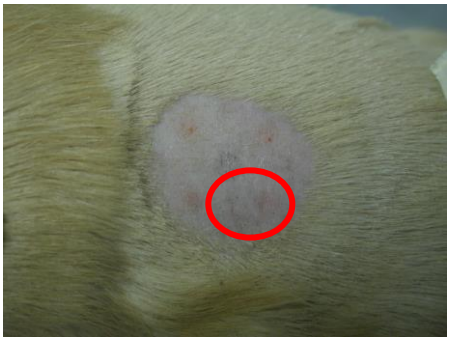
Control



1 mg/kg



25 mg/kg



50 mg/kg

Fig. 14 Radiation area on the 8th day after starting the radiation

(2) Skin-rejuvenating Effect

① Effect of α-Lipoic Acid on Neonatal Dermal Fibroblasts (*In Vitro*)

The effect of α-lipoic acid on neonatal dermal fibroblasts was examined using NB1RGB cells. Fig. 15 illustrates the effect of α-lipoic acid on fibroblasts cells proliferation. It is evident that α-lipoic acid stimulate growth of human fibroblasts thus promote skin suppleness and rejuvenate aging skin.

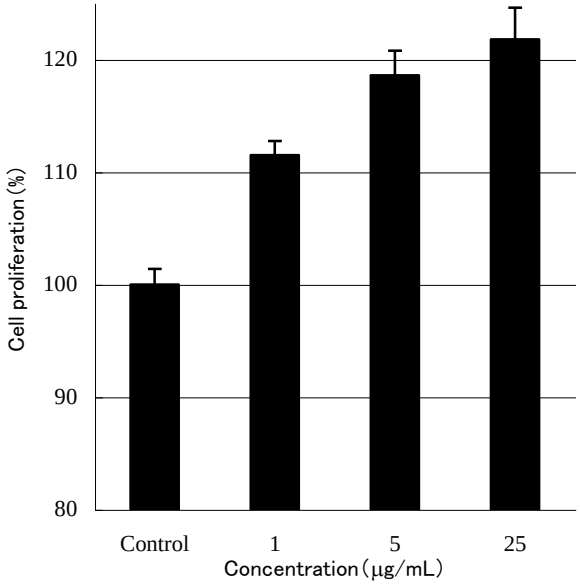


Fig. 15. Effects of α-Lipoic Acid on NB1RGB Fibroblast Growth (mean ± S.E., n=6)

【Method】

NB1RGB cells ($2x10^5$ cells/ml) were suspended in α-MEM medium (containing 10% bovine fetal serum, 100 units/ml penicillin and 100μg/ml streptomycin), and 100μl of the suspension was placed into a 96-well plate. Different concentration of α-lipoic acid (10 μl) was added and incubated for 2 days. Degree of cell growth was determined using MTT assay.

② Effect of α-Lipoic Acid on Skin Turnover Rate (*In Vitro*)

The effect of α-lipoic acid on skin turnover rate was examined using three-dimensional reconstructed skin cell model. As illustrated in Fig. 16, model treated with α-lipoic acid has a more uniformed distribution of skin cells. The granule containing cells are aligned in a flat monolayer. In contrast, the granule containing cell was hardly visible in controlled model. This suggested that α-lipoic acid promotes healthy skin turnover and promote skin suppleness.

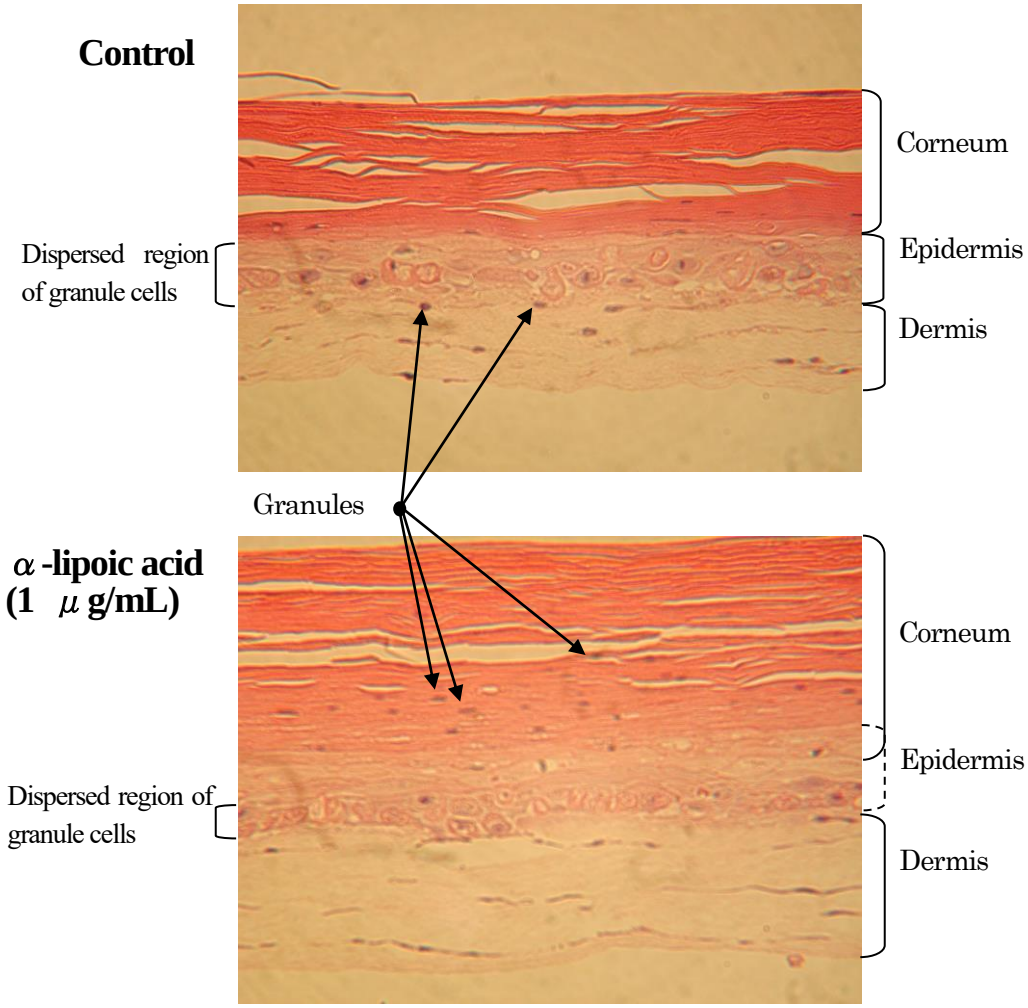


Fig. 16. Three-Dimensional Images of Artificially Reconstructed Skin Cell Model

【Method】

Reconstructed human skin model (TESTSKIN™: Toyobo Co., Ltd) was used. α-lipoic acid was injected into the dermal layer of skin and incubated for 6 days. The medium was replaced every 3 days. Cross section of tissue specimens were prepared after treatment in 10% formalin. Changes in specimens was observed under microscopic enlargement.

4. Antioxidative Effects

The antioxidative effect of α-lipoic acid has been renown for years. Studies were carried out to confirm its anti-oxidative effect. As illustrated in Fig. 17 and Fig. 18, α-lipoic acid showed a dose-dependent antioxidative effect. α-lipoic acid is a potentially useful antioxidant for the prevention of degenerative diseases.

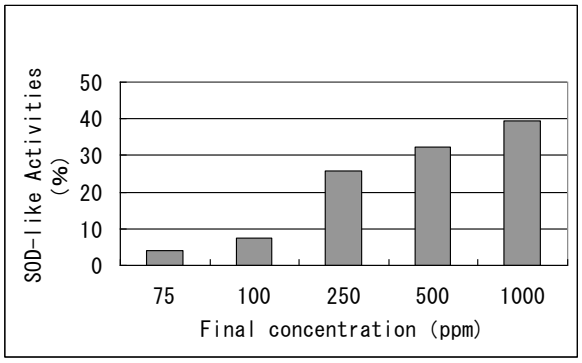


Fig. 17. SOD-Like Activities of α-Lipoic Acid

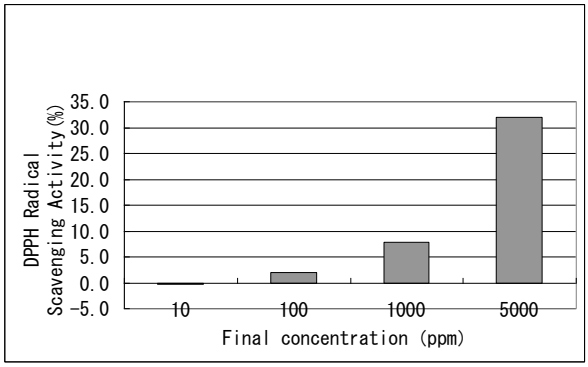
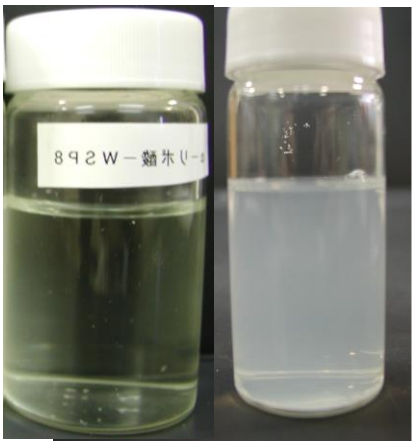


Fig.18. DPPH Radical-Scavenging Activities of α-Lipoic Acid

5. Water Soluble α-Lipoic Acid

We successfully developed solubilized α-lipoic acid powder with high water solubility (Alpha Lipoic Acid-WSP8, WSPC8). This powder can be used for enables in beverages (refreshments and soft drinks and liquid cosmetics). As shown in photos (Fig.19), WSP8 and WSPC8 can be dissolved in water quicker and kept the clearer as compared to conventional product. Moreover, the taste of α-lipoic acid(tingling sensation) has been reduced.



Modified product (WSP8 and WSPC8)　　conventional product

Fig. 19 Comparison of Water Solubility of Alpha Lipoic Acid-WSP8 and WSPC8

6. Absorption of α-lipoic acid

After oral administration of "α-lipoic acid-P" or "α-lipoic acid-WSP8" to rats equivalent to 30 mg/kg α-lipoic acid, serum concentration of α-lipoic acid was determined. As a result, serum concentration of α-lipoic acid given "α-lipoic acid-WSP8" revealed 3-times higher CMAX and AUC compared to those of "α-lipoic acid-P".

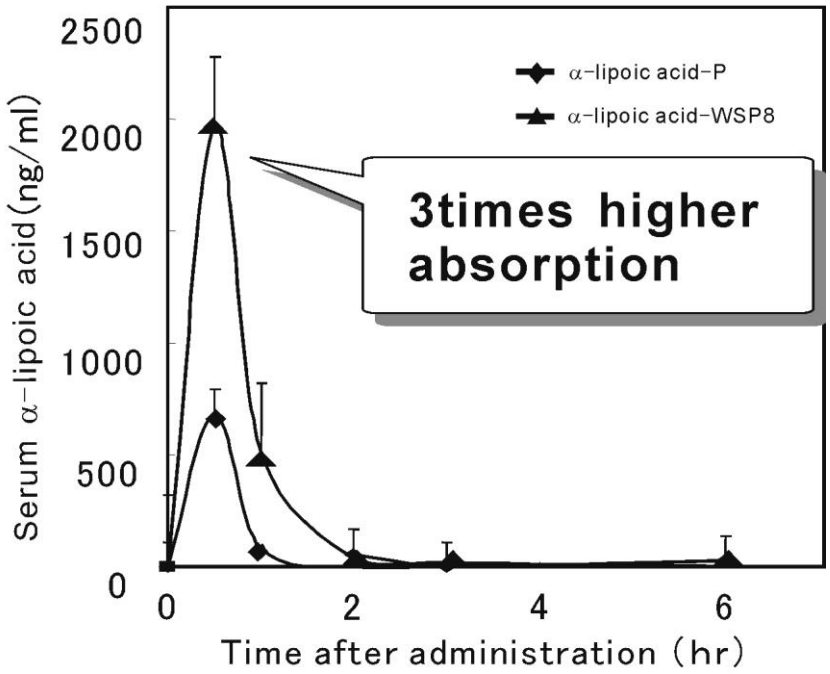


Fig. 20 Serum concentration of α-lipoic acid (From shield labo., Co. Ltd.)

7. Stabilities of ALPHA LIPOIC ACID

(1) Thermal Stability

Thermal stability of α-lipoic acid was examined. α-lipoic acid easily destroyed at temperature as low as 60ºC (as illustrated in Fig. 21). In general, there is a 25% loss of α-lipoic acid upon heating at temperature >60ºC. Caution is required when α-lipoic acid is used in food preparations due to its sensitivity to heat. Percentage loss during heating is important factor for consideration when determining the quantity to be used.

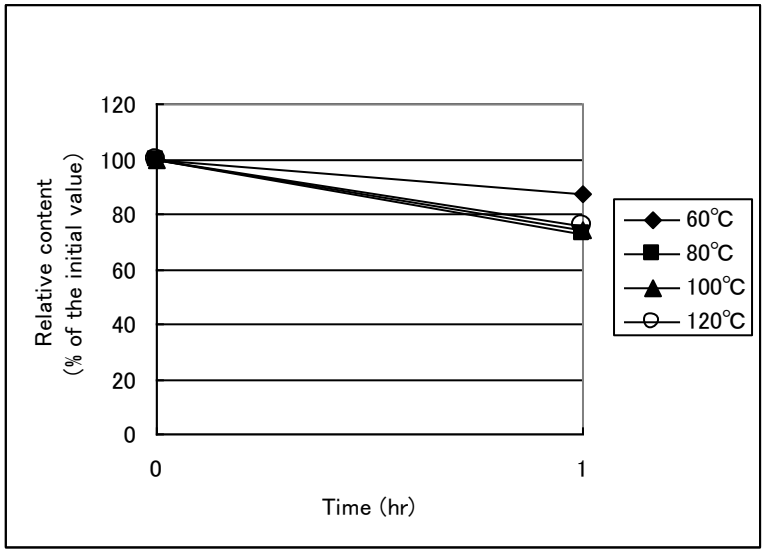


Fig. 21. Thermal Stability of α-Lipoic Acid

(2) pH Stability

The effect of pH on α-lipoic acid was examined at room temperature in dark for 1 day and 1 week. α-lipoic acid is highly remained stable at wide pH range, pH 3-10 (as shown in Fig. 22).

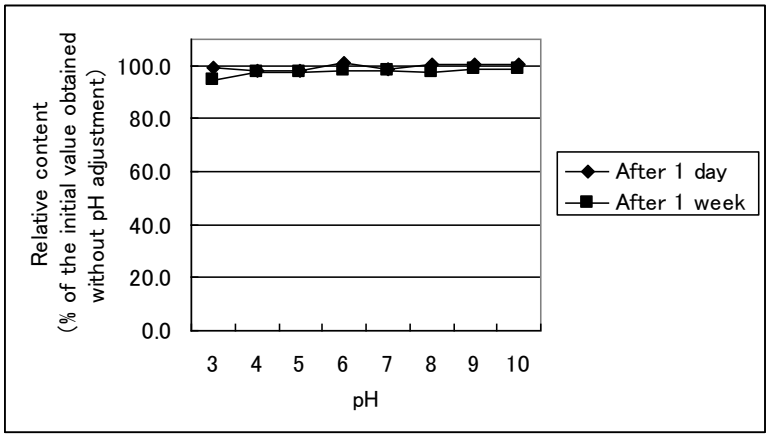


Fig. 22. Effect of pH on α-Lipoic Acid

8. Nutritional Information

	Results	Method
Moisture	0.2 g/100 g	Karl Fischer Reagent
Protein*1	0.0 g/100 g	Kieldahl method
Fat	99.8 g/100 g	Direct extraction method
Ash	0.0 g/100 g	Direct ashing method
Carbohydrate*2	0.0 g/100 g	
Energy*3	898 kcal/100 g	
Dietary fiber	< 0.0 g/100	Prosky method
Sodium	1 mg/100 g	Atomic absorption spectrophotometory

*1) N=6.25

*2) 100 – (moisture + protein + fat + ash)

*3) Factors for calculating the energy value : protein, 4; fat, 9; carbohydrate, 4; dietary fiber, 2

Tested by:SRL, Inc.

Date of issue of the test result report : September 2, 2004

Research result issue number : No. 200408200016

9. Safety Profile

(1) Acute Toxicity (LD_{50})

In the single-dose toxicity test in ddY mice, the LD_{50} values of α-lipoic acid were 405 mg/kg and 277 mg/kg in male and female mice, respectively. These values correspond to ingestion of 16.6 g and 24.3 g, of α-lipoic acid, in adult humans weighing 60 kg.

(2) Acute Skin Irritation Study in Rabbit

Following the OECD Guideline No. 404 (April 24, 2002)and Commission Directive 2004/73/EC, acute skin irritation study was perfomed by using 3 rabbits (New Zealand white). After application of α-lipoic acid (0.5 g) to the normal skin in the state of obstruction for 4 hours, irritation was judged by using the Draize method after 1, 24, 48, and 72 hours later and was calculated by using p.i.i. (primary irritation index).

As the result of the examination, slight erythematous was observed in 3 rabbits after 1 hour. Although erythematous was not observed after 24 hours, and recovery was confirmed. The p.i.i. of α- lipoic acid was confirmed with 0.0. Hence,α- lipoic acid was not found to be acute irritatable substance for the rabbit skins.

Tested by: Safepharm Laboratories Limited

Date of issue of the test result report : August 1, 2005

Research result issue number :1600/007

(3) Cumulative Skin Irritation Study in Guinea Pig

The 0.1%, 1% and 10% α- lipoic acid solutions(0.05mL) ,diluted with ethanol were applied at once a day for 14 days on the skin of 3 guinea pigs. Skin lesions were evaluated every day.

Under the experimental conditions adopted, the test substance was found to be non-irritant for the skins of guinea pig.

Tested by: Bozo Research Center Inc.
Date of issue of the test result report : August 23, 2005
Research result issue number : C-I168

(4) Acute Eye Irritation Study in rabbit

Following the OECD Guideline No. 405 (April 24, 2002) and Commission Directive 2004/73/EC, α-lipoic acid (70 mg) was administered into the eyes of 3 rabbits (New Zealand white) and the conditions of their eyes were observed without washing out 1, 24, 48, and 72 hours later and on the 7th, 14th, and 21st days.

On the eyes of all of rabbit, cloudiness of cornea, iris inflammation, and medium level stimulation on conjunctiva were observed. The eyes of one rabbit ware recovered to their normal conditions 7 days later and the others 21 days later.

According to the evaluation of the result using the standard determined by Kay, the mean value of maximum group was 26.0 that was observed 48 hours later. We confirmed that α-lipoic acid has medium level irritation on rabbit eyes (level 5 among levels 1 through 8).

Tested by: Safepharm Laboratories Limited
Date of issue of the test result report : August 1, 2005
Research result issue number : 1600/008

(5) Sensitization Test

Following the OECD Guideline No. 429 (April 24, 2002)and Commission Directive 2004/73/EC, sensibilization test (LLNA Assay) was perfomed in 10%, 25%, and 50% concentrations of α-lipoic acid by using the 4 mice at each group .

As a result of the examination, α-lipoic acid was not found to be sensitizing ability at 10,25,and 50%.

Tested by: Safepharm Laboratories Limited
Date of issue of the test result report : August 1, 2005
Research result issue number : 1600/009

(6) Mutagenicitiy Test (Ames test)

Following the OECD Guideline No. 471, and Commission Directive 2004/73/EC, Ames test was performed. The test was performed using by *Samonella typhimurium* TA1535, TA1537,TA98 and TA100,

and *Escherichia coli* WP2 urvA. Under the conditions with or without S9mix.

The result showed α-lipoic acid possessed no mutagenicitiy at the concentrations of 50 to 5000 μg/plate.

Tested by: Safepharm Laboratories Limited
Date of issue of the test result report : August 12, 2005
Research result issue number : 1600/010

(7) Residual Solvents

Assayed Items	Results	Detection Limits	Assay Method
Cyclohexane	Not Detected	5 ppm	GC-MS
Ethyl acetate	Not Detected	5 ppm	GC-MS
Methyl-*tert*-butyl ether			
Toluene	Not Detected	5 ppm	GC-MS
Acetone	Not Detected	5 ppm	GC-MS
Hexane	Not Detected	5 ppm	GC-MS
Dichloromethane	Not Detected	1 ppm	GC-MS

Tested by: Japan Food Research Center Foundation
Date of issue of the test result report : December 1, 2004
Research result issue number : No. 304110371-001

10. α-Lipoic Acid Polymers (Impurity)

(1) Structure of α-lipoic Acid Polymer

α-lipoic acid sometimes generates polymers (impurity) during heat-drying or purification process using ethanol. We analyzed the structure of α-lipoic acid polymer A (polymer generated during heat-drying) and α-lipoic acid polymer B (polymer generated in ethanol solution) at Osaka University Graduate School (professor: Nobutoshi Murakami). Fig. 23 shows the clarified structure of α-lipoic acid polymers A and B.

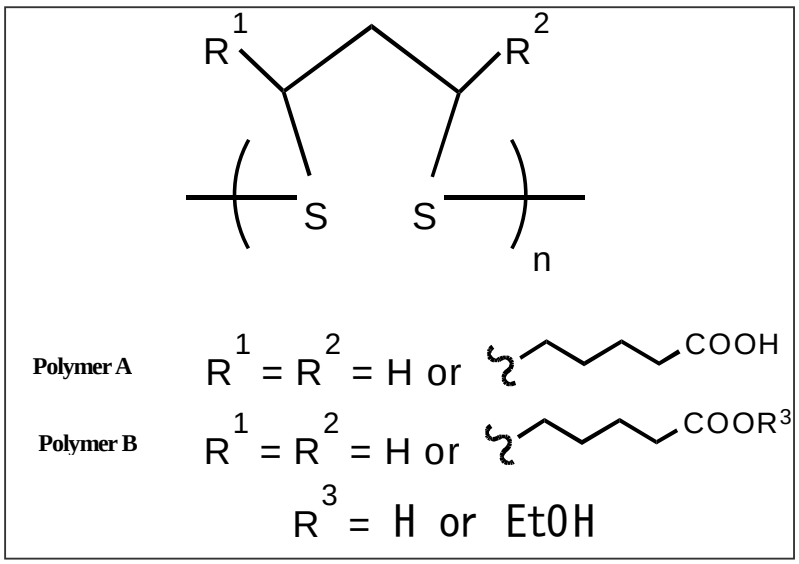


Fig. 23. Structure of α-lipoic acid Polymers A and B.

(2) Safety of α-lipoic acid polymer (Acute toxicity)

We conducted a single-dose test of α-lipoic acid polymer B in dog (beagle, male). α-lipoic acid polymer B (500 mg/kg) was given to dog, and overall condition was observed. Moreover hematologic test and biochemical examination of blood was performed. There was no change in its overall condition and no acute symptoms occurred in liver or kidney function within 24 hours after administration.

Ref.) Shimoda H. *et al.* Safety and structural analysis of polymers produced from manufacturing process of α-lipoic acid. *Shokuhin Eiseigaku Zasshi*, **125**, 125-31 (2007) in Japanese.

11. Recommended Daily Dose

ALPHA LIPOIC ACID: 50~100 mg/day

12. Applications of ALPHA LIPOIC ACID

Bland Names	Applications	Examples
ALPHA LIPOIC ACID-P, P80	The product is the powder of α-lipoic acid for foods.	Soft gel capsule, hard capsule, tablet, *etc*.
ALPHA LIPOIC ACID-WSP7	The product is water-soluble powder for foods. It is suitable for beverages.	Drinks (beverage, juice, *etc*.), soft gel capsule, hard capsule, tablet, candy, chewing gum, cookies, chocolate, jelly, *etc*.
ALPHA LIPOIC ACID-L1	The product is the liquid of α-lipoic acid for foods. It is suitable for dough.	Soft gel capsule, candy,chewing gum, cookies, chocolate, jelly, *etc*.
ALPHA LIPOIC ACID-PC, PC80	The product is the powder of α-lipoic acid for cosmetics.	Face care (milk, cream, *etc*.) Body care (body cream, soap *etc*.) Makeup (lipstick, foundation, *etc*.)
ALPHA LIPOIC ACID-WSPC7	The product is water-soluble powder for cosmetics. It is suitable for toners and conditioning lotions.	Face care (lotion, milk, cream, *etc*.) Body care (body lotion, body cream, soap *etc*.) Makeup (lipstick, foundation, *etc*.)
ALPHA LIPOIC ACID-LC1	The product is liquid of α-lipoic acid for cosmetics. It is suitable for cosmetics.	Makeup (lipstick, *etc*.)

13. Packaging

ALPHA LIPOIC ACID-P, P80, WSP7 (Powder, Food Grade)
ALPHA LIPOIC ACID-PC, PC80, WSPC7 (Powder, Cosmetic Grade)
5kg Interior packaging : aluminum-coated plastic bag
Exterior packaging : cardboard box

ALPHA LIPOIC ACID-L1 (Liquid, Food Grade)
ALPHA LIPOIC ACID-LC 1(Liquid, Cosmetic Grade)
5kg Interior packaging : cubic polyethylene container
Exterior packaging : cardboard box

14. Storage

Store in cool, dry place. Avoid humidity. In particular, ALPHA LIPOIC ACID-L1,and ALPHA LIPOIC ACID-LC1 is stored under 5℃.

15. Expression of the indication ALPHA LIPOIC ACID

＜Food＞

ALPHA LIPOIC ACID-P, P80, WSP8, L1

Example : α-Lipoic Acid , Thioctic Acid

If you have multiple representation, please select bellow one.

ALPHA LIPOIC ACID-P	ALPHA LIPOIC ACID-P80	ALPHA LIPOIC ACID -WSP7	ALPHA LIPOIC ACID -L1
α-Lipoic Acid or Thioctic Acid	Thioctic acid, vegetable oil & Fat	Thioctic acid, Cyclodextrin	Thioctic acid, Glycerin ester of fatty acid, propylene glycol ester of fatty acid, glycerin, ethanol

＜Cosmetic＞

	ALPHA LIPOIC ACID-PC	ALPHA LIPOIC ACID -WSPC7	ALPHA LIPOIC ACID -LC1
INCIName	Thioctic acid	Cyclodextrin Thioctic acid	Polyglyceryl-10 Myristate Propylene Glycol Caprylate Glycerin Thioctic acid Alcohol

*Please refer to your nation's standard.

Precaution for use in Japan: Please follow below composition rates of thioctic acid not to exceed the values (November, 2007).

Component	The maximum amount in 100 g (g)		
	Washable cosmetics not applied to mucosa	Non-washable cosmetics not applied to mucosa	Cosmetics applied to mucosa
Thioctic acid	0.01	0.01	Prohibition of mixing

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-P

(FOOD)

This product guarantees minimum of 98.0 % α-lipoic acid (thioctic acid, 1,2-dithiolane-6-pentanoic acid).

1.Appearance	Light yellowish or yellowish crystalline powder. It has no smell or slightly unique smell. Soluble in chloroform and ethanol. Slightly soluble in water.	
2.Certification Test	The maximum absorbance wave length: 331～335 nm. The minimum absorbance wavelength: 278～283 nm.	
3.Content of α-Lipoic Acid	Min. 98.0 %	(HPLC)
4.Melting Point	60~63℃	(The Japanese Standards for Food Additives)
5.Loss on Drying	Max. 0.5 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)
6.Ignition Residue	Max. 0.1 %	(The Japanese Standards for Food Additives)
Purity Test		
(1)6,8-Epitrithiooctanoic acid	Max. 0.1 %	(HPLC)
(2)Polymer	Max. 2.0 %	(Precipitation Method)
(3)Heavy Metals (as Pb)	Max. 10 ppm	(Sodium Sulfide Colorimetric Method)
(4)Arsenic (as As_2O_3)	Max. 1 ppm	(Standard Methods of Analysis in Food Safety Regulation)
Standard Plate Counts	Max. 1×10^3 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Composition	Ingredient	Content
	Thioctic Acid	100 %

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-P80

(FOOD)

This product contain minimum of 80.0 % α-lipoic acid (thioctic acid, 1,2-dithiolane-6-pentanoic acid).

Appearance	Slight yellowish or yellowish powder. It has no smell or slightly unique smell.	
Certification Test	The maximum absorbance wave length: 331～335 nm. The minimum absorbance wavelength: 278～283 nm.	
Content of α-Lipoic Acid	Min. 80.0%	(HPLC)
Loss on Drying	Max. 0.5 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)
Ignition Residue	Max. 0.1 %	(The Japanese Standards for Food Additives)
Purity Test		
(1)6,8-Epitrithiooctanoic acid	Max. 0.1 %	(HPLC)
(2)Heavy Metals (as Pb)	Max. 10 ppm	(Sodium Sulfide Colorimetric Method)
(3)Arsenic (as As_2O_3)	Max. 1 ppm	(Standard Methods of Analysis in Food Safety Regulation)
Standard Plate Counts	Max. 1×10^3 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Residual Solvents			
(1)Ethanol	Max. 0.1 %		(GC)
(2)Other Solvents			
Acetone	Not detected	(Less than 1 ppm)	(GCMS)
Cyclohexane	Not detected	(Less than 1 ppm)	(GCMS)
Dichloromethane	Not detected	(Less than 1 ppm)	(GCMS)
Ethyl acetate	Not detected	(Less than 1 ppm)	(GCMS)
Hexane	Not detected	(Less than 1 ppm)	(GCMS)
MTBE	Not detected	(Less than 1 ppm)	(GCMS)
Toluene	Not detected	(Less than 1 ppm)	(GCMS)

Composition

Ingredient	Content
Thioctic Acid	80%
Vegetable Oils & Fats	20%
	100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-WSP7

(FOOD)

This product guarantees a minimum of 7.0 % α-lipoic acid (thioctic acid, 1,2-dithiolane- 6-pentanoic acid). This product is water-soluble.

Appearance	Slight yellowish or yellowish powder. It has no smell or slightly unique smell.		
Certification Test	The maximum absorbance wave length: 331～335 nm. The minimum absorbance wavelength: 278～283 nm.		
Content of α-Lipoic Acid	Min. 7.0%	(HPLC)	
Loss on Drying	Max. 9.0 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)	
Ignition Residue	Max. 0.1 0%	(The Japanese Standards for Food Additives)	
Purity Test			
(1)Heavy Metals (as Pb)	Max. 10 ppm	(Sodium Sulfide Colorimetric Method)	
(2)Arsenic (as As_2O_3)	Max. 1 ppm	(Standard Methods of Analysis in Food Safety Regulation)	
Standard Plate Counts	Max. 1×10^3 cfu/g	(Analysis for Hygienic Chemists)	
Moulds and Yeasts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists)	
Coliforms	Negative	(Analysis for Hygienic Chemists)	
Residual Solvents			
(1)Ethanol	Max. 0.1 %		(GC)
(2)Other Solvents			
Acetone	Not detected	(Less than 1 ppm)	(GCMS)
Cyclohexane	Not detected	(Less than 1 ppm)	(GCMS)
Dichloromethane	Not detected	(Less than 1 ppm)	(GCMS)
Ethyl acetate	Not detected	(Less than 1 ppm)	(GCMS)
Hexane	Not detected	(Less than 1 ppm)	(GCMS)
MTBE	Not detected	(Less than 1 ppm)	(GCMS)
Toluene	Not detected	(Less than 1 ppm)	(GCMS)

Composition

Ingredient	Content
Thioctic Acid	7%
Cyclodextrin	93%
	100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-L1

(FOOD)

This product is water-soluble liquid which emulsified α-lipoic acid (thioctic acid 1,2-dithiolane-6-pentanoic acid) to soluble. It contains minimum of 10.0 % α-lipoic acid.

Appearance	Slight yellowish liquid with unique smell.	
Content of α-Lipoic Acid	Min. 10.0 %	(HPLC)
Purity Test		
(1)Heavy Metals (as Pb)	Max. 10 ppm	(Sodium Sulfide Colorimetric Method)
(2)Arsenic (as As_2O_3)	Max. 1 ppm	(Standard Methods of Analysis in Food Safety Regulation)
Standard Plate Counts	Max. 1×10^3 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)
Residual Solvents		
Solvents except Ethanol	Not detected	(Less than 0.1 ppm) (GCMS)

Composition

Ingredients	Contents
Glycerin Ester of Fatty Acid	50%
Propylene Glycol Ester of Fatty Acid	23%
Glycerin	15%
Thioctic Acid	10%
Ethanol	2%
Total	100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-PC

(COSMETIC)

This product guarantees a minimum of 98.0 % α-lipoic acid （thioctic acid, 1,2-dithiolane-6-pentanoic acid）.

Appearance	Light yellowish or yellowish crystalline powder. It has no smell or slightly unique smell. Soluble in chloroform and ethanol. Slightly soluble in water.	
Certification Test	The maximum absorbance wavelength: 331～335 nm. The minimum absorbance wave length: 278～283 nm.	
Content of α-Lipoic Acid	Min. 98.0 %	(HPLC)
Melting Point	60 ～ 63℃	
Loss on Drying	Max. 0.5 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)
Ignition Residue	Max. 0.1 %	
Purity Test		
(1)6,8-Epitrithiooctanoic acid	Max. 0.1 %	(HPLC)
(2)Polymer	Max. 2.0 %	(Precipitation Method)
(3)Heavy Metals (as Pb)	Max. 10 ppm	(The Second Method of The Japanese Standards of Quasi-Drug Ingredients)
(4)Arsenic (as As_2O_3)	Max. 1 ppm	(The Third Method of The Japanese Standards of Quasi-Drug Ingredients)
Standard Plate Counts	Max. 1 × 10^2 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Max. 1 × 10^2 cfu/g	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Residual Solvents			
(1)Ethanol	Max. 0.1 %		(GC)
(2)Other Solvents			
Acetone	Not detected	(Less than 1 ppm)	(GCMS)
Cyclohexane	Not detected	(Less than 1 ppm)	(GCMS)
Dichloromethane	Not detected	(Less than 1 ppm)	(GCMS)
Ethyl acetate	Not detected	(Less than 1 ppm)	(GCMS)
Hexane	Not detected	(Less than 1 ppm)	(GCMS)
MTBE	Not detected	(Less than 1 ppm)	(GCMS)
Toluene	Not detected	(Less than 1 ppm)	(GCMS)

Composition	Ingredient	Content
	Thioctic Acid	100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-PC80

(COSMETIC)

This product contains minimum of 80.0% α-lipoic acid (thioctic acid, 1,2-dithiolane-6-pentanoic acid).

Appearance	Slight yellowish or yellowish crystalline powder. It has no smell or slightly unique smell.	
Certification Test	The maximum absorbance wavelength: 331～335 nm. The minimum absorbance wave length: 278～283 nm.	
Content of α-Lipoic Acid	Min. 80.0%	(HPLC)
Loss on Drying	Max. 0.5 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)
Ignition Residue	Max. 0.1 %	
Purity Test		
(1)6,8-Epitrithiooctanoic acid	Max. 0.1 %	(HPLC)
(2)Heavy Metals (as Pb)	Max. 10 ppm	(The Second Method)
(3)Arsenic (as As_2O_3)	Max. 1 ppm	(The Third Method)
Standard Plate Counts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists of The Japanese Standards of Quasi-Drug Ingredients)
Moulds and Yeasts	Max. 1×10^2 cfu/g	(Analysis for Hygienic Chemists of The Japanese Standards of Quasi-Drug Ingredients)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Residual Solvents		
(1)Ethanol	Max. 0.1 %	(GC)
(2)Other Solvents		
Acetone	Not detected (Less than 1 ppm)	(GCMS)
Cyclohexane	Not detected (Less than 1 ppm)	(GCMS)
Dichloromethane	Not detected (Less than 1 ppm)	(GCMS)
Ethyl acetate	Not detected (Less than 1 ppm)	(GCMS)
Hexane	Not detected (Less than 1 ppm)	(GCMS)
MTBE	Not detected (Less than 1 ppm)	(GCMS)
Toluene	Not detected (Less than 1 ppm)	(GCMS)

Composition	Ingredient	Content
	Thioctic Acid	80%
	Hydrogenated Rapeseed Oil	20%
		100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-WSPC7

(COSMETIC)

This product guarantees a minimum of 7.0% α-lipoic acid (thioctic acid, 1,2-dithiolane- 6-pentanoic acid). This product is water-soluble.

Appearance	Slight yellowish or yellowish powder.	
	It has no smell or slightly unique smell.	
Certification Test	The maximum absorbance wavelength: 331～335 nm.	
	The minimum absorbance wave length: 278～283 nm.	
Content of α-Lipoic Acid	Min. 7.0%	(HPLC)
Loss on Drying	Max. 9.0 %	(1g, 40℃, reduced pressure, P_2O_5, 4 hours)
Ignition Residue	Max. 0.10 %	
Purity Test		
(1)Heavy Metals (as Pb)	Max. 10 ppm	(The Second Method of The Japanese Standards of Quasi-Drug Ingredients)
(2)Arsenic (as As_2O_3)	Max. 1 ppm	(The Third Method of The Japanese Standards of Quasi-Drug Ingredients)
Standard Plate Counts	Max. 1 × 10^2 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Negative	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Residual Solvents			
(1)Ethanol	Max. 0.1 %		(GC)
(2)Other Solvents			
Acetone	Not detected	(Less than 1 ppm)	(GCMS)
Cyclohexane	Not detected	(Less than 1 ppm)	(GCMS)
Dichloromethane	Not detected	(Less than 1 ppm)	(GCMS)
Ethyl acetate	Not detected	(Less than 1 ppm)	(GCMS)
Hexane	Not detected	(Less than 1 ppm)	(GCMS)
MTBE	Not detected	(Less than 1 ppm)	(GCMS)
Toluene	Not detected	(Less than 1 ppm)	(GCMS)

Composition

Ingredient	Content
Cyclodextrin	93%
Thioctic Acid	7%
	100%

PRODUCT STANDARD

PRODUCT NAME

ALPHA LIPOIC ACID-LC1

(COSMETIC)

This product is water-soluble liquid which emulsified α-lipoic acid (thioctic acid, 1,2-dithiolane-6-pentanoic acid) to soluble. It contains minimum of 10.0% α-lipoic acid..

Appearance	Slight yellowish liquid with aroma.	
Content of α-Lipoic Acid	Min.10.0%	(HPLC)
Purity Test		
(1)Heavy Metals (as Pb)	Max. 10 ppm	(The Second Method of The Japanese Standards of Quasi-Drug Ingredient)
(2)Arsenic (as As_2O_3)	Max. 1 ppm	(The Third Method of The Japanese Standards of Quasi-Drug Ingredient)
Standard Plate Counts	Max. 1 × 10^2 cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Max. 1 × 10^2 cfu/g	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)
Residual Solvents		
Solvents except Ethanol	Not detected (Less than 0.1 ppm)	(GCMS)

Composition

Ingredients	Contents
Polyglyceryl-10 Myristate	50 %
Propylene Glycol Caprylate	23 %
Glycerin	15 %
Thioctic Acid	10 %
Alcohol	2 %
Total	100 %

ORYZA OIL & FAT CHEMICAL CO., LTD. striving for the development of the new functional food materials to promote health and general well-being.

From product planning to OEM - For any additional information or assistance, please contact :

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