Oryza

ORYZA OIL & FAT CHEMICAL CO., LTD.

ORYZA TOCOTRIENOL®

Cholesterol-Lowering Effect
Anti-Atherosclerosis Effect
Biological Antioxidant

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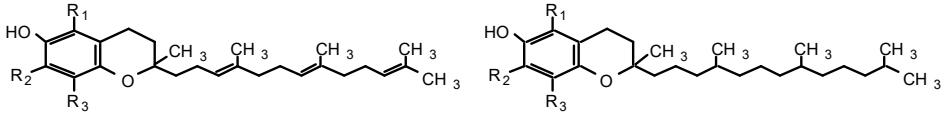
ORYZA TOCOTRIENOL®

Super Vitamin E from Rice

Rice bran oil has been widely used as cooking oil in the Southeast Asia. It is rich in health promoting substances such as γ-oryzanol, sterols, squalene, tocopherols and tocotrienols. Diet with high consumption of rice bran oil among the Asians has lower incidences of hyperlipidemia & cardiovascular complaints. Rice bran oil is rich in γ-oryzanol, sterols, tocopherols which are renowned health promoting substances with cholesterol lowering effects. Recent findings discovered that rice tocotrienols is highly beneficial for cardiovascular health, prevention against carcinogenesis and potent antioxidant.

1. Tocotrienols

Tocotrienols are members of the Vitamin E family. It differs from tocopherols in that they have an isoprenoid instead of a phytyl side chain. There are four tocopherols isomers (α, β, γ and δ) and four corresponding tocotrienols isomers.



	R_1	R_2	R_3
α-tocotrienol	CH_3	CH_3	CH_3
β-tocotrienol	CH_3	H	CH_3
γ-tocotrienol	H	CH_3	CH_3
δ-tocotrienol	H	H	CH_3

	R_1	R_2	R_3
α-tocopherol	CH_3	CH_3	CH_3
β-tocopherol	CH_3	H	CH_3
γ-tocopherol	H	CH_3	CH_3
δ-tocopherol	H	H	CH_3

Structures of Tocotrienols and Tocopherols

Tocotrienols are powerful lipid soluble antioxidants with excellent radical scavenging effects. Research indicates that the antioxidant activity of d-α-tocotrienol is 40-60x more potent than conventional d-α-tocopherol. Rice bran & rice germ oil are nature's richest source of tocotrienols which are not found in other vegetable oil such as soybean oil, safflower oil, corn oil, canola oil & cottonseed oil. Other sources include wheat, oat & barley.

2. Oryza Tocotrienols

Rice bran or rice germ oil is rich in tocotrienols especially γ-tocotrienol with potent biological effect against carcinogenesis. Recent findings revealed that tocotrienols is highly preventive against elevated blood cholesterol level which normally responsible for major cardiovascular diseases. Qureshi *et al*. reported that novel tocotrienol-rich fraction TRF_{25} from rice bran oil significantly lowered total cholesterol and LDL-cholesterol by 12% and 16% respectively.

Oryza Oil & Fat Chemical Co., Ltd. specializes in the manufacturing of rice bran and rice germ oil has successfully commissioned the extraction of rice tocotrienols, ORYZA TOCOTRIENOL® of various concentrations. ORYZA TOCOTRIENOL® contains natural blend of tocotrienols and tocopherols from rice bran oil distillate. It contains significant amount of α- and γ-tocotrienol with health promoting effects.

3. Absorption and Distribution of Tocotrienols

Several studies reported that tocotrienols are widely distributed in the skin than other organs in the human body. Ikeda *et al*. reported that α-tocotrienol and γ-tocotrienol were detected slightly in the liver, kidney and plasma, while substantial amount of these tocotrienols were detected in the skin of both rats and mice. This suggests that skin is a unique tissue in respect to its ability to discriminate between various vitamin E analogues.(1)

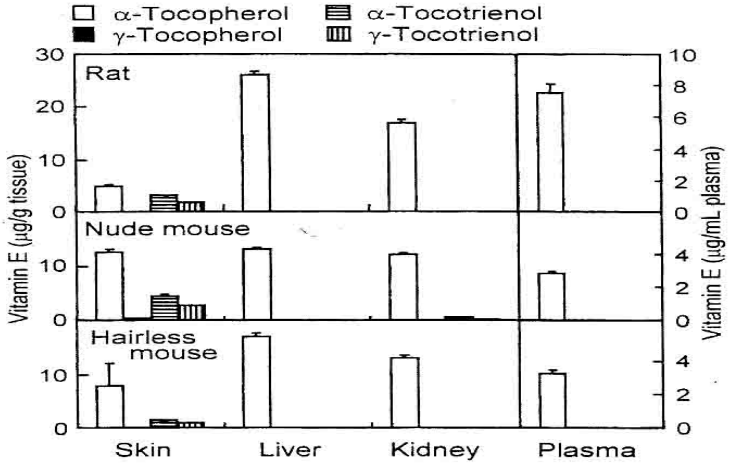


Fig. 1. Concentrations of α-tocopherol, γ-tocopherol, α-tocotrienol and γ-tocotrienol in the skin, liver, kidney and plasma of rats, nude mice and hairless mice. Values are means±SE. $n=6$. Rats were fed the diet for 8 wk, and both nude mice and hairless mice were fed the diet for 4 wk. The animals were killed after fasting for 24 h.

Meanwhile, Podda *et al*. also reported that the skin contained nearly 15% tocotrienols against 1% γ-tocopherol. The unique distribution of tocotrienols in skin suggested that they might have superior protection against environment stressors. Subsequently, Traber *et al*. reported that topically applied α- and γ-tocotrienols penetrate into the skin of hairless mice. Packer *et al*. revealed that tocotrienols penetrate rapidly through skin and efficiently combat oxidative stress induced by UV or ozone.(2)

4. Functions of Tocotrienols

4.1 Cholesterol Lowering Effect

Hypercholesterolemia (or elevated blood cholesterol level) remain to be one of the major risk factors of coronary heart disease, the leading cause of death in the United States. Tocotrienols are being increasingly recognized to have an important role in the prevention of atherosclerosis.

i. Response of hypercholesterolemic Subjects to Administration of Tocotrienols

The cholesterol-suppressive actions of tocotrienols were assessed in hypercholesterolemic subjects after acclimation to the American Heart Association Step 1 dietary regimen for 4 and 8 weeks, respectively. The 4-week dietary regimen alone elicited a 5% decrease ($P<0.05$) in the cholesterol level of 36 subjects. Subjects continuing on the dietary regimen for another 4-week period experienced an additional 2% decrease in their cholesterol levels. Dietary assessment based on unanticipated recalls of 24-hour food intake records suggest that significant reductions in energy and fat, predominantly in saturated fat intakes are responsible. The subjects experienced significant tocotrienols-mediated decreases in cholesterol. The group of subjects on a blend of tocols containing 40mg α-tocopherol, 48mg α-tocotrienol, 112mg γ-tocotrienol, and 60mg δ-tocotrienol/day for 4-week experienced a 10% decrease in cholesterol ($P<0.05$). Dietary assessments showed no further change in energy and fat intakes. α-tocopherol attenuates the cholesterol-suppressive action of the tocotrienols. The second group of subjects, acclimated to the dietary regimen for 8 weeks, received 200mg of γ-tocotrienol/day for 4-week. The cholesterol-suppressive potency of this α-tocopherol free preparation was calculated to be equivalent to that of the mixture of tocotrienols (220mg) used in prior study. Cholesterol of the 16 subjects in the second group decreased 13% ($P<0.05$) during the 4-week trial. Plasma apolipoprotein B and *ex vivo* generation of thromboxane B_2 were similarly responsive to the tocotrienol preparations, whereas neither preparation had an impact on high density lipoprotein cholesterol and apolipoprotein A-1 levels. [3]

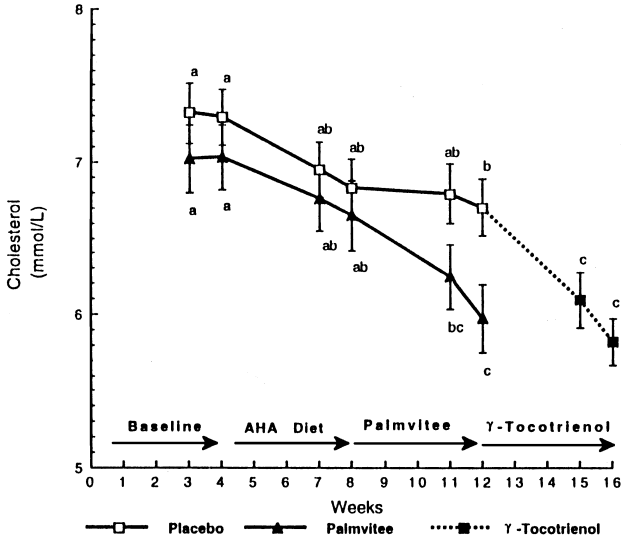


Fig. 2. Time-dependent impacts of American Heart Association Step 1 Diet (AHA) dietary regimen, Palmvitee and γ-Tocotrienol on serum cholesterol levels of hypercholesterolemic adult subjects. Differences between values on each plotted line which do not share a letter are significant ($P<0.05$).

Qureshi A.A. *et al*., *Lipids* **30**, 1171-1177 (1995)

ii. Lowering of Serum cholesterol in Hypercholesterolemic humans by tocotrienols

A double-blind, crossover, 8-week study was conducted to evaluate the effects of tocotrienol-rich fraction (TRF) on serum lipids of hypercholesterolemic human (serum cholesterol 6.21-8.02 mmol/L). During the initial 4-week, serum cholesterol level decreases significantly, serum total cholesterol (-15%), LDL cholesterol (-8%), Apo B (-10%), thromboxane (-25%), platelet factor 4 (-16%), and glucose (-12%). Meanwhile, serum cholesterol concentration of 7 hypercholesterolemic subjects (>7.84mmol/L) decreased 31% during a 4-week period were given 200mg γ-tocotrienol/day. The result indicated that γ-tocotrienol may be the most potent cholesterol inhibitor among tocotrienols isomers.(4)

Qureshi A.A. *et al*., *Am J Clin Nutr*., 53, 1021S-6S (1991)

iii. Novel tocotrienols of rice bran modulate cardiovascular disease risk parameters of hypercholesterolemic humans

Tocotrienols inhibits cholesterol synthesis by post-transcriptional suppression of β-hydroxy-β-methtylglutaryl-coenzyme A reductase activity. A double-blind, 12-week study was investigating the effect of novel rice bran tocotrienol-rich fraction TRF_{25} on hypercholesterolemic human subjects (serum total cholesterol >5.69mmol/L). After acclimation to an alcohol free regimen (baseline) participants were assigned to the National Cholesterol Education Program (NCEP) Step-1 diet (saturated fat <19%, total fat <30% of total calories and cholesterol <7.76mmol/L) and were evaluated after 4 weeks duration; one group of 21 participants was continued on the NCEP Step-1 diet for 4 weeks receiving 200mg TRF_{25} dissolved in 1.0gm corn oil (TRF_{25} group). Serum total cholesterol and LDL-cholesterol levels of all the participants decreased 5% and 8% respectively, during the 4-week NCEP Step-1 diet. Placebo group continuing on the NCEP Step-1 diet for an additional 4-week experienced additional but modest decreases in serum total cholesterol (2%) and LDL-cholesterol (3%), yielding significant ($P<0.05$) decreases when compared with baseline values. These responses confirm the cholesterol-lowering action of a low fat, low cholesterol diet. Participants receiving TRF_{25} had 12% and 16% reductions ($P<0.05$) in total cholesterol and LDL-cholesterol levels respectively during the 4-week experimental phase; during the 2 phases (NCEP Step-1 diet plus treatment) the serum total cholesterol and LDL-cholesterol levels of these participants were decreased ($P<0.05$) by 17% and 24%, respectively. TRF_{25}-mediated decreases in Apo B, Lp(a), platelet factor 4 and thromboxane B_2 (15%, 17%, 14% & 31% respectively) were significant ($P<0.05$). There was no change in the levels of HDL-cholesterol and apolipoprotein A-1 by this treatment. The treatments also resulted in remarkable increases in the levels of LDL-bound antioxidants, especially tocotrienols, which have substantially greater antioxidant activity than conventional vitamin E.(5)

Qureshi A.A. et al., ***J Nutr. Biochem***. **8**: 290-298, (1997)

iv. Hypocholesterolemic and antioxidant effect of rice bran oil non-saponifiables in hypercholesterolemic subjects

50 hypercholesterolemic subjects (27F, 23M; 49-83 yr; cholesterol > 5.6mmol/L) received a daily allotment of 3.1g rice bran non-saponifiable (RBN) or placebo (oil) capsules for 12 months in random, blind fashion. In the RBN group, serum total cholesterol decreased 14.1% and low density lipoprotein (LDL) cholesterol fell 20.6% ($p<0.05$); placebo value were stable. High-density lipoprotein (HDL) /cholesterol levels rose ($p<0.025$) and triglycerides/HDL values fell ($p<0.05$). None of these changes were seen in a previous palm tocol study. RBN use also led to a safer levels of thiobarbituric acid-reactive substances (TBARS), an indicator of peroxidation ($p<.02$). Placebo TBARS did not change. With addendum, serum α-tocopherol levels rose to twice pre-study baseline values ($P<.01$) and remained stable. Encapsulated rice bran non-saponifiables afforded a safe means to improve serum cholesterol, LDL, HDL, triglyceride, TBARS, and antioxidant risk factors. Hence, both atherosclerotic and thrombogenic risk factors improved with this RBN supplement.(6)

Table 1. Effect of daily addendum of Palm Tocotrienols or Rice Bran Non-saponifiables (RBN) upon serum lipids in hypercholesterolemic subjects (mmol/L)

	Palm tocotrienols (n=25)			RBN		
	Baseline	3yr	*p*	Start	12mo	*p*
Cholesterol	6.05±0.03	6.18±0.33	n. s.	6.18±0.33	5.31±0.20	< 0.05
LDL cholesterol	4.24±0.03	4.28±0.37	n. s.	4.28±0.37	3.40±0.18	< 0.05
HDL/cholesterol	0.17±0.01	0.17±0.02	n. s.	0.17±0.02	0.24±0.02	< 0.05
Triglyceride[a]/HDL	2.70±0.58	2.16±0.35	n. s.	2.16±0.35	1.21±0.21	< 0.05
	Palm placebo (n=25)			RBN placebo		
	Baseline	3yr	*p*	Start	12mo	*p*
Cholesterol	5.90±0.16	5.70±0.21	n. s.	5.70±0.21	6.06±0.32	n. s.
LDL cholesterol	4.19±0.14	3.95±0.18	n. s.	3.95±0.18	4.05±0.31	n. s.
HDL/cholesterol	0.20±0.14	0.21±0.06	n. s.	0.21±0.06	0.22±0.01	n. s.
Triglyceride[a]/HDL	1.80±0.35	1.54±0.31	n. s.	1.54±0.31	1.55±0.20	n. s.

Watkins T.R. *et al*., *Environmental & Nutritional Interactions*, **3**:115-122, 1999

v. Dose-dependent suppression of serum cholesterol by tocotrienol-rich fraction (TRF_{25}) of rice bran in hypercholesterolemic humans.

Qureshi *et al*. prompted further study into the cholesterol lowering effect of rice bran tocotrienols. Results revealed that a daily dose of tocotrienol-rich fraction (TRF_{25}) of rice bran in hypercholesterolemic subjects produces maximum decreases of 20%, 25%, 14% (P<0.05) and 12%, respectively, in serum total cholesterol, LDL-cholesterol, apolipoprotein B' and triglycerides compared with the baseline values.(7)

Table 2. Effect of AHA Step-1 diet and different of TRF_{25} on serum lipid parameters in hypercholesterolemic human subjects

Treatments	otal cholesterol (mmol/l)	LDL-cholesterol (mmol/l)	polipoprotein B (g/l)	Triglycerides (mmol/l)	HDL-cholesterol (mmol/l)	polipoprotein B (g/l)
Baseline	6.79±0.45[a,b] (100.00)[c]	5.95±0.48[a] (100.00)	0.85±0.11[a] (100.00)	2.85±0.86[a] (100.00)	0.79±0.16[a] (100.00)	1.10±0.16[a] (100.00)
AHA Step-1 diet	6.50±0.32[a] (95.71)	5.66±0.42[a] (95.04)	0.81±0.10[a] (95.33)	2.73±0.83[a] (95.72)	0.82±0.16[a,b] (103.89)	1.12±0.16[a,b] (102.19)
AHA Step-1 diet +TRF_{25} 25 m	6.12±0.39[b] (90.12)	5.28±0.44[b] (88.72)	0.79±0.01[a,b] (94.31)	2.71±0.83[a] (95.01)	0.84±0.15[a,b,c] (107.16)	1.12±0.17[a,b] (102.32)
AHA Step-1 diet +TRF_{25} 50 m	5.66±0.46[c] (83.44)	4.72±0.48[c] (79.33)	0.76±0.02[a,b] (89.79)	2.52±0.81[a] (88.30)	0.90±0.14[b,c] (115.12)	1.22±0.17[a,b] (111.11)
AHA Step-1 diet +TRF_{25} 100	5.46±0.51[c] (80.42)	4.49±0.54[c] (75.39)	0.73±0.06[b] (86.27)	2.51±0.81[a] (88.20)	0.93±0.12[b,c] (118.76)	1.25±0.18[b,c] (113.78)
AHA Step-1 diet +TRF_{25} 200	5.52±0.47[c] (81.25)	4.55±0.50[c] (76.50)	0.74±0.04[b] (87.49)	2.53±0.82[a] (88.83)	0.91±0.12[b,c] (115.52)	1.25±0.18[b,c] (113.43)

Superscripted letters a-c : values in a row not sharing a common superscript letter are significantly different

[a] Time of drawing blood was 08:00 h. The subjects were fasted for 12 h before samples were taken.

[b] Data expressed as means±SD (standard deviation) ; n=18 per group.

[c] Percentage with respect to baseline values are in parentheses.

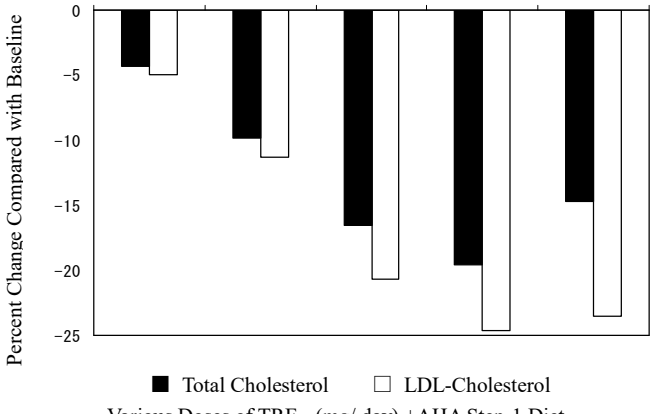


Fig. 3 The dose dependent decreases of TRF_{25} plus AHA Step-1 Diet on the concentrations of serum total cholesterol and LDL-cholesterol as compared to their respective baseline values.

Qureshi A.A. *et al*., *Atherosclerosis*, **161**, 199-207 (2002)

4.2 Prevents atherosclerosis

Epidemiological studies have linked the dietary intake of vitamin E and other anti-oxidants with a reduced risk of coronary heart disease[18] and ischemic stroke[19] and with a decrease in carotid artery thickness[20].

vi. Antioxidant Effects of Tocotrienols in Patients with Hyperlipidemia and Carotid Stenosis

The effect of γ-tocotrienol enriched fraction in patients with carotid atherosclerosis. Serum lipids, fatty acid peroxides, platelet aggregation, and carotid artery stenosis were measured over an 18-month period in 50 patients with cerebrovascular disease. Bilateral duplex ultrasonography revealed apparent carotid atherosclerotic regression in 7 and in 2 of the 25 tocotrienol patients, while none of the control group exhibited regression and 10 of 25 showed progression. Serum thiobarbituric acid reactive substances, an *ex vivo* indicator of maximal platelet peroxidation, decreased in the treatment group from 1.08±0.70 to 0.80±0.55um/L ($p<0.05$) after 12 months, and in the control group there is slight increase.[8]

Table 3. Comparison of change in carotid stenosis in groups receiving tocotrienols or placebo for six and twelve months[a]

	Antioxidant	Placebo
Six months		
Marked regression	1	0
Regression	5	0
No change	18	20
Progression	1	2
Marked progression	0	3
Total number	25	25
Twelve months		
Marked regression	1	0
Regression	6	0
No change	16	15
Progression	2	6
Marked progression	0	4
Total number	25	25

[a]Data expressed as number of subjects per category.

Tomeo A.C. et al., *Lipids*, Vol.30, no 12 (1995)

4.3 Anti-carcinogenesis

Tocotrienols being a potent antioxidant with 40-60x higher potency than conventional d-α-tocopherol is preventive against peroxidation of unsaturated lipids, particularly in cell biomembrane. *in vitro* and *in vivo* experimental studies have suggested that tocotrienols may possess anticancer properties. Guthrie *et al*. suggested that tocotrienols are effective inhibitor of both estrogen receptor-negative and -positive cells. Meanwhile, Nesaretnam *et al*. found that tocotrienol-rich-fraction (TRF) inhibited growth of MDA-MB-435 estrogen-receptor -negative human breast cancer cells.

vii. Effect of Tocotrienols on the Growth of a Human Breast Cancer Cell Line in Culture

The effect of tocotrienol-rich fraction (TRF) and α-tocopherol (α-T) on the proliferation, growth and plating efficiency (PE) of MDA-MB-435 estrogen-receptor-negative human breast cancer cells was compared. TRF inhibited the proliferation of these cells by 50% at 180μg/mL, whereas α-T had no effect at concentration up to 1000μg/mL. Similarly, TRF demonstrated inhibitory effect on cell growth and PE of MDA-MB-435 estrogen -receptor-negative human breast cancer cells, whereas α-T had no effect. These results

suggest that the inhibition is due to the presence of tocotrienols in TRF rather than α-T.[9]

Nesaretnam K. *et al*., *Lipids* **30**, 1139-1143 (1995)

viii. Inhibition of Proliferation of Estrogen Receptor-Negative MDA-MB-435 and –Positive MCF-7 Human Breast Cancer Cells by Tocotrienols and Tamoxifen, alone and in combination

Further experiments were prompted to investigate the effects of tocotrienol-rich fraction with estrogen receptor-positive MCF-7 cells. Results showed that tocotrienols inhibited the proliferation of estrogen receptor-positive MCF-7 cells. The IC_{50} for TRF, α-tocopherol, α-, γ-, and δ-tocotrienols were 4, 125, 6, 2 and 2μg/mL, respectively. Tamoxifen, a widely used synthetic antiestrogen was tested in combination with TRF, α-tocopherol and the individual tocotrienols at ratio 1:1. It was found that 1:1 combination of γ- or δ-tocotrienol with tamoxifen showed a synergistic inhibitory effect on the proliferative rate and growth of the cells. Results suggest that tocotrienols are effective inhibitors of both estrogen receptor-negative and –positive cells and that combinations with tamoxifen should be considered as a possible improvement in breast cancer therapy.[10]

Table 4. Inhibition of proliferation MDA-MB-435 cells by TRF and its components, with and without tamoxifen[a]

Inhibitor	IC_{50} (μg/ml)
α-Tocopherol	> 1000
TRF	180 ± 3
α-Tocotrienol	90 ± 3
γ-Tocotrienol	30 ± 2
δ-Tocotrienol	90 ± 3
Tamoxifen	90 ± 4
TRF + Tamoxifen	3.9 ± 0.2
α-Tocotrienol + Tamoxifen	1.5 ± 0.05
γ-Tocotrienol + Tamoxifen	1.9 ± 0.02
δ-Tocotrienol + Tamoxifen	5.9 ± 0.1

[a] Estrogen receptor-negative MDA-MB-435 human breast cancer cells were cultured with or without various concentrations of the test compounds. The concentration required to inhibit cell proliferation by 50% was determined, as measured by the incorporation of [^{3}H]thymidine into DNA. The experiments were done in triplicate, and the results are averages of three experiments. Values are given as average ± SEM.

Table 5. Incidence of ACF in each group

Group (treatment)	No. of rats	ACF/colon	Large ACF/colon (over 4 crypts)
1(AOM alone)	8	62.7±14.9	8.5±3.6
2(AOM + 0.038%α-tocopherol)	6	33.9±6.9#	1.8±1.7#
3(AOM + 0.005%ORYZA TOCOTRIENOL)	4	50.3±13.9#	3.4±1.3#
4(AOM + 0.025%ORYZA TOCOTRIENOL)	9	48.4±13.9#	2.5±1.5#
5(AOM + 0.1%ORYZA TOCOTRIENOL)	8	41.3±12.2#	1.5±1.4#
6(0.1%ORYZA TOCOTRIENOL)	4	0	0
7(basal diet)	4	0	0

Significantly different from group 1 by Student's or Welth's t-test

Guthrie *et al*., *J. Nutr*. 127: 544S-548S,1997

ix. Tocotrienols Inhibit the Growth of Human Breast Cancer Cells Irrespective of Estrogen Receptor Status

Antiproliferative effect of tocotrienols were investigated on the growth of both

estrogen-responsive (ER+) MCF7 human breast cancer cells and estrogen –unresponsive (ER-) MDA-MB-231 human breast cancer cell, and effect were compared with α-tocopherol (α-T). TRF inhibited growth of MCF7 cells in both the presence and absence of estradiol with a nonlinear dose-response but such that complete suppression of growth was achieved at 8μg/mL. Separation of TRF into individual tocotrienols revealed that all fractions could inhibit growth of both ER+ & ER- cells and of ER+ cells in both the presence and absence of estradiol. Nevertheless, γ- fraction were the most inhibitory. In contrast, α-T had no inhibitory effect on MCF7 cell growth in all conditions. Results demonstrated that tocotrienols can exert direct inhibitory effects on the growth of breast cancer cells. (11)

Nesaretnam K. *et al*., *Lipids*, Vol **33**, no. 5 (1998)

4.4 Antioxidative effect

Vitamin E is renowned for its potent antioxidant activities and has been regarded as the most important lipid soluble antioxidant in the human blood plasma and circulating lipoproteins. Serbinova *et al*. reported that d-α-tocotrienol possesses 40-60 times higher antioxidant activity as compared to conventional d-α-tocopherol. Meanwhile, Suarna *et al*. reported that dietary tocotrienols effectively reacted against peroxyl radicals in rat and human lipoproteins.

Similarly, Kamat *et al*. demonstrated that TRF was significantly more effective than α-tocopherol against lipid peroxidation and protein oxidation in rat brain mitochondria.

x. Tocotrienols as potent inhibitors of lipids peroxidation and protei oxidation in rat brain mitochondria

Tocotrienol-rich fraction was found to significantly inhibit oxidative damage *in vitro* to both lipids and proteins in rat brain mitochondria induced by ascorbate-Fe^{2+}, the free radical initiator azobis (2-amidopropane) dihydrochloride (AAPH) and photosensitization. The inhibitory effect was both time- and concentration-dependent. Nevertheless, the inhibitory effect seems to be mainly due to γ-tocotrienol. Tocotrienols are capable of protecting the brain against oxidative damage and thereby from the ensuing adverse alterations.(12)

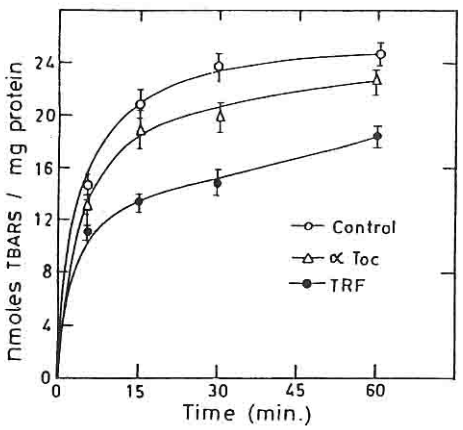


Fig. 4. Ascorbate-Fe^{2+}-induced lipid peroxidation in rat brain mitochondria as a function of time with and without TRF, as assessed by TBARS. The concentration used was 5 μM and values are mean ± SE from 5 experiments.

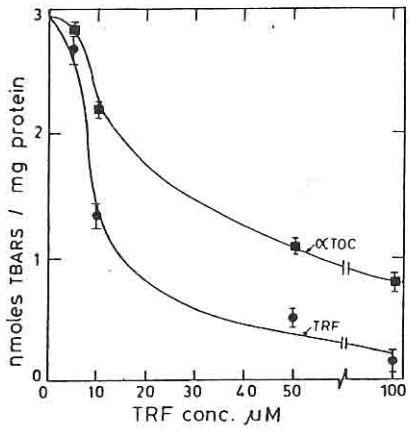


Fig. 5. AAPH-induced lipid peroxidation in rat brain mitochondria as a function of concentration of TRF and α-tocopherol. Peroxidation was assessed by TBARS and incubation was carried out for 5 min.

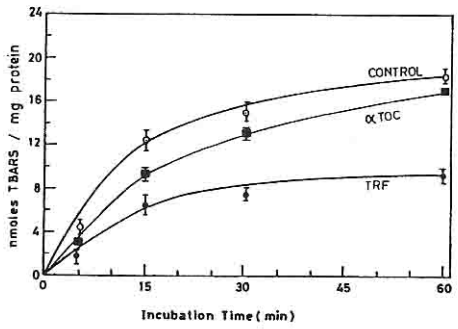


Fig. 6. The photosensitisation-induced lipid peroxidation in rat brain mitochondria and its prevention by TRF as a function of time. TRF was used at a concentration of 50 μM.

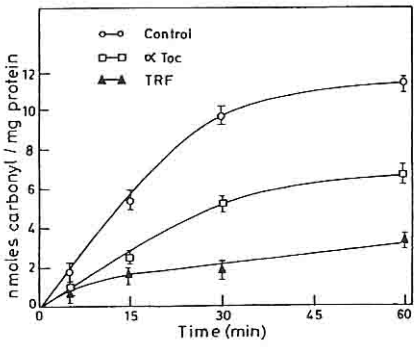


Fig. 7. Protein oxidation of brain mitochondria and inhibition by a-tocopherol and TRF as a function of time. Oxidative damage was induced by the ascorbate-Fe^{2+} system. The concentration of TRF was 5 μM.

Kamat J.P. *et al*., *Neuroscience Letters* 195 (1995) 179-182

xi. Free Radical Recycling and Intramembrane Mobility in the antioxidant properties of α-tocopherol and α-tocotrienol

α-tocotrienol was compared to α-tocopherol in Fe^{2+}+ascorbate and Fe^{2-}+NADPH induced lipid peroxidation in rat liver microsomal membrane. Results clearly indicated that d-α-tocotrienol possesses **40-60 times higher antioxidant activity** and **6.5 times** better protection of cytochrome P-450 against oxidative damage. ESR studies were performed of recycling efficiency of the chromanols from their chromanoxyl radicals to clarify the mechanisms responsible for the higher antioxidant activity. It was concluded that the higher antioxidant potency of d-α-tocotrienol was due to (i) its higher recycling efficiency from chromanoxyl radicals, (ii) its uniform distribution in membrane bilayer & (iii) its stronger disordering of membrane lipids which makes interaction which makes interaction of chromanols with lipids radicals more efficients.(13)

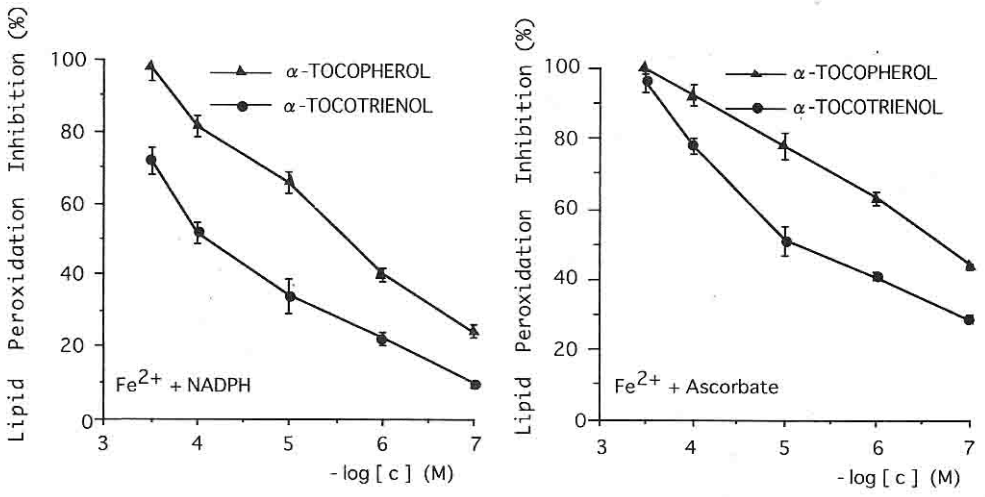


Fig. 8. Inhibition of lipid peroxidation in rat liver microsomes by alpha-tocopherol and alpha-tocotrienol. Microsomal suspensions were preincubated with chromanols for 15 min at 25°C after which lipid peroxidation-inducing system was added. The reaction was stopped after 5 min. Other conditions as in Methods.

Serbinova E *et al*., *Free Rad. Bio. Med*. **10**, 263-75 (1991)

xii. **Comparative antioxidant activity of tocotrienols and other natural lipid-soluble antioxidants in a homogenous system, and in rat and human lipoproteins.**
The antioxidant activity of tocotrienols toward peroxyl radicals was compared with that of other natural lipid-soluble antioxidants in 3 different systems by measuring the temporal disappearance of antioxidants and the formation of lipid hydroperoxides. Dietary supplementation of tocotrienol-rich preparation in rats and human resulted in a dose-dependent appearance of α- and γ-tocotrienols in plasma and all circulating lipoproteins, respectively. Exposure of such enriched rat plasma to aqueous peroxyl radicals resulted in simultaneous consumption of the α- and then γ-isomers of vitamin E. Hence, dietary tocotrienols become incorporated into circulating human lipoproteins where they react with peroxyl radicals as efficiently as the corresponding tocopherol isomers.[14]

Suarna C *et al.*, *Biochimica et Biophysica Acta*, **1166**, 163-70 (1993)

xiii. **Efficacy of Topically Applied Tocopherols and Tocotrienols in protection of murine skin from oxidative damage induced by UV-Irradiation**
Efficacy of various form of vitamin E in protection of skin from UV-light induced oxidative stress was assessed. TRF treatment increased mouse skin vitamin E content. Vitamin E concentrations were significantly higher in irradiated TRF-treated skin than the non-irradiated PEG-treated skin (control) ($p<.01$). UV-irradiation of skin destroys its antioxidants; however, prior application of TRF to mouse skin results in preservation of vitamin E. [15]

Weber C. *et al.*, *Free Rad. Bio. Med*., **22**, 761-9 (1997)

xiv. Penetration and distribution of α-tocopherol, α- or γ-tocotrienols applied individually onto murine skin

Distribution of various form of vitamin E into skin layers was compared. The largest fraction of skin vitamin E following topical application was found in the deeper subcutaneous layers, PD (40±15%) and D (36±15%). Hence, applied vitamin E penetrate rapidly through the skin.[16]

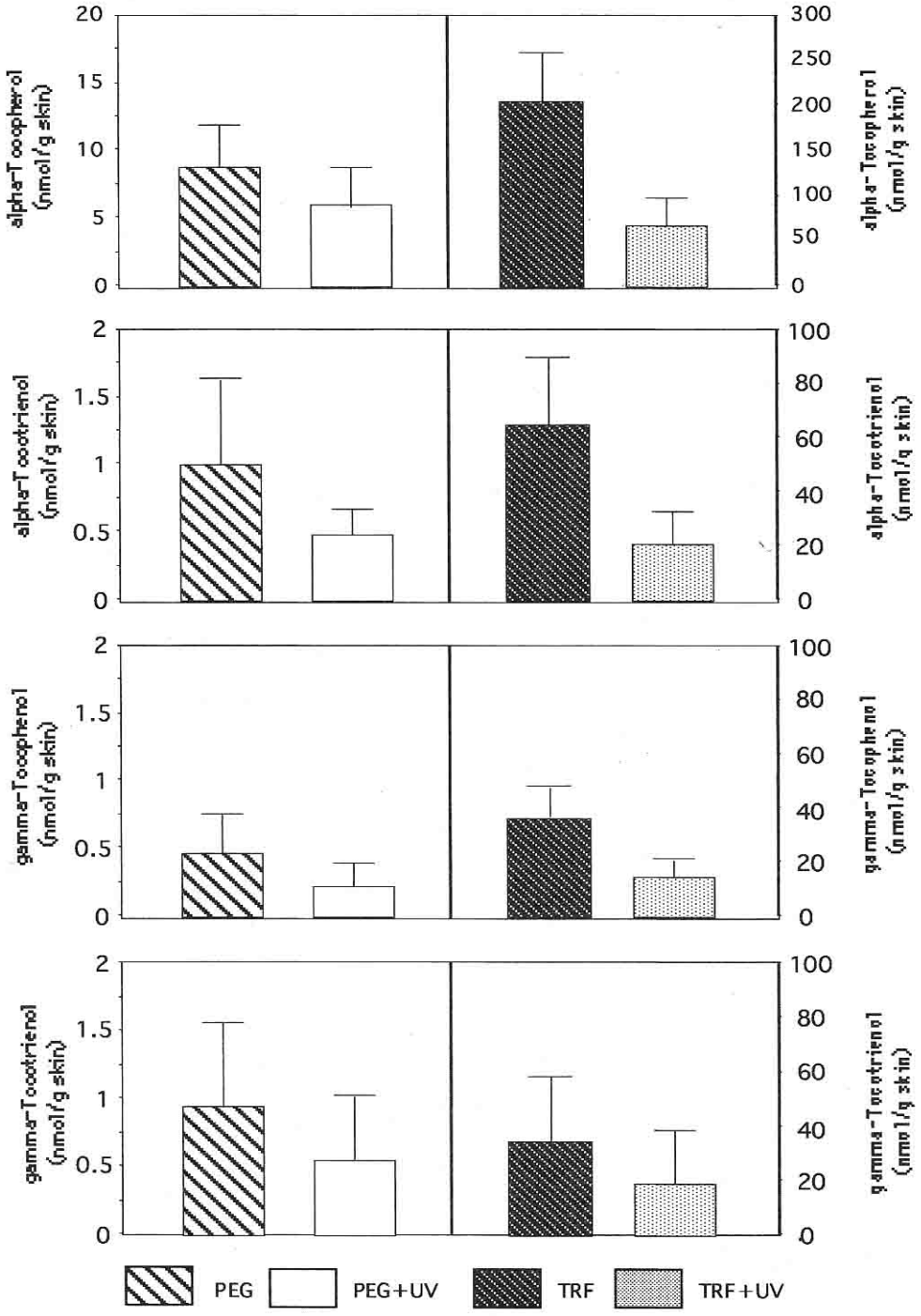


Fig. 9. α-tocopherol, α-tocotrienol, γ-tocopherol and γ-tocotrienol contents of murine skin.

Traber M. G. *et al*. *Asia Pacific J. Clin. Nutr*., **6(1)**, 63-67 (1997)

4.5. Recovery Enhancement from strenuous exercise & fatigue

Hirahara *et al.* reported that serum lactic acid was lower in rats loaded with tocotrienol after 30 minutes strenuous exercise as compared to group loaded with α-tocopherol. Tocotrienols is beneficial in promoting physical recovery from strenuous exercise.

4.6 Protection against oxidative damage

Experimental study found that ORYZA TOCOTRIENOL® effectively inhibited H_2O_2 & t-BHP induced oxidative cell death in keratinocyte (HaCaT).

<Materials & Method>

Preparations of cells and sample:

HaCaT cells were cleansed twice with buffer solution. Samples of ORYZA TOCOTRIENOL®, 200μg/mL were prepared and added to 50μL of buffer solution.

50μL of H_2O_2 (20mmol/L) & 50μL of t-BHP (1.8mmol/L) was used to induce reaction.

Treatment and assays:

HaCaT cells were incubated in H_2O_2 for 2 hours prior to buffer rinse.

Similar procedures were carried out for HaCaT cells incubated in t-BHP solution. Cell viability was analysed by NR assay.

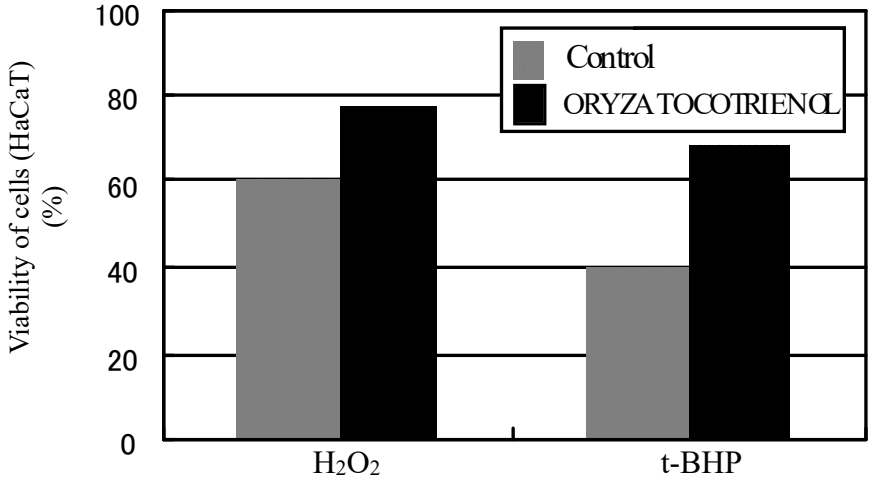


Fig.10. Protective effect of ORYZA TOCOTRIENOL® for cell damage

4.7 Promotion of skin collagen cells growth

The effect of ORYZA TOCOTRIENOL® on human dermal fibroblasts (NHDF) proliferation was examined. MTT assay revealed that 123% fibroblasts proliferation rate was observed at concentration of 0.025% ORYZA TOCOTRIENOL® (as illustrated in Fig. 10)

<Materials & Method>

NHDF cells ($2x10^4$cells/well) were suspended in 1% FBS-DMEM medium followed by incubation in 96-well plate. The medium was replaced by 1% FBS-DMEM containing ORYZA TOCOTRIENOL® after 24 hours incubation. Cells were further cultured for 48 hours and fibroblasts proliferation rate was evaluated by MTT assay.

Similar experiments were carried out 3 times and fibroblasts proliferation rate was estimated. Proliferation Index was determined to be more than 105% reproducibility.

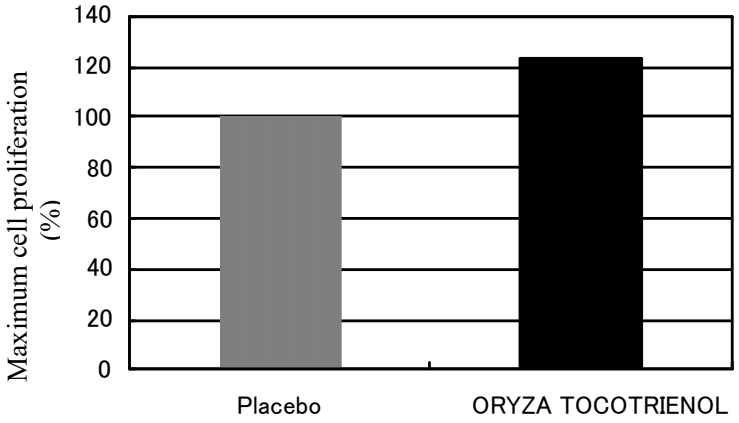


Fig.11. Cell activating effect of ORYZA TOCOTRIENOL®

4.8 Skin rejuvenating effect

The effect of ORYZA TOCOTRIENOL® on the production of hyaluronic acid was examined. Experiment revealed that hyaluronic acid production increased in the presence of ORYZA TOCOTRIENOL® at concentration >0.0031% as illustrated in Fig 12. Results indicated that ORYZA TOCOTRIENOL® rejuvenate skin effectively and suitable for cosmetics applications.

<Materials & Methods>

ORYZA TOCOTRIENOL® (50%) was diluted 1/10 with 99.5% ethanol. The first dilution was further diluted to different concentrations for hyaluronic acid production and human fibroblasts proliferation analysis. Normal human dermal fibroblasts was cultured followed by medium replacement with DMEM containing 0.5% fetal bovine serum (FBS) and ORYZA

TOCOTRIENOL® and subsequently culture for 48 hours. Supernatant layer was obtained and hyaluronic acid was measured with ELISA. Anti-keratan sulphate (mouse) was used as the primary antibody while peroxidase-labelled anti-mouse IgG_1 as secondary antibody. After colour development with ABTS solution, absorbance at wavelength 405nm was measured. Meanwhile, protein in cells was measured according to Lowry's method. The amount of hyaluronic acid per unit of protein was calculated as hyaluronic acid production. DMEM containing 5% FBS was used as positive control.

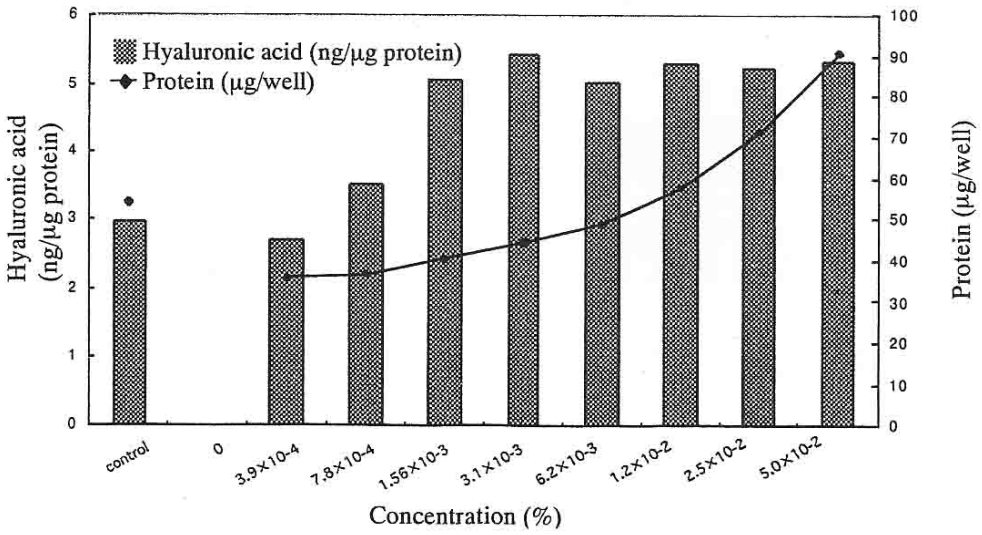
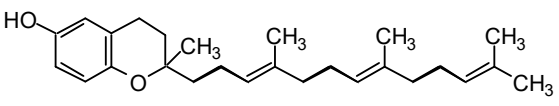


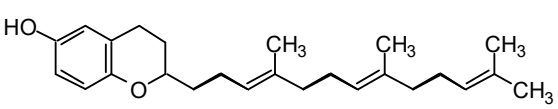
Fig.12. Hyaluronic acid production on normal human dermal fibroblasts of ORYZA TOCOTRIENOL®

4.9 Novel Tocotrienols from Rice Bran

In 2000 Qureshi *et al*. reported that two novel tocotrienols were isolated from rice bran. Their structures were established as desmethyl tocotrienol and didesmethyl tocotrienol. These tocotrienols significantly lowered serum total and LDL cholesterol levels and inhibited HMG-CoA reductase activity in chickens. They had much greater *in vitro* antioxidant activities and greater suppression against B16 melanoma cell proliferation compared with α-tocopherol. Results indicated that the number and position of methyl substituent in tocotrienols affect their hypocholesterolemic, antioxidant, and antitumor properties.(17)



Desmethyl–tocotrienol



Didesmethyl–tocotrienol

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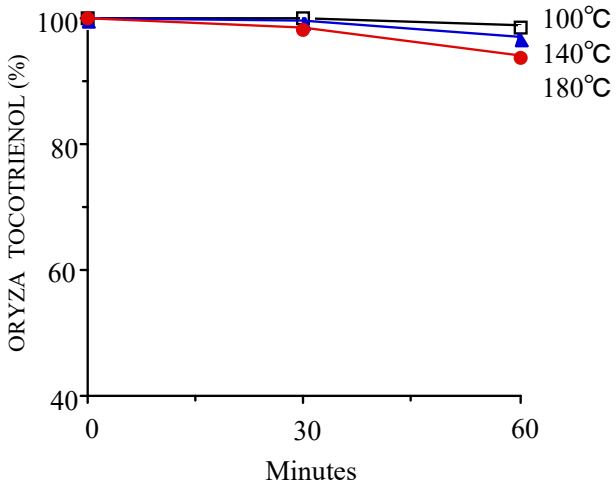
18 Rimm E.B. *et al.*, *N. Engl. J. Med*., **328**, 1450-1456 (1993)
19 Mason J.E. *et al*., *New Engl. J. Med*., **23(Nov.)** (1995)
20 Kritchevsky S.B. *et al*., *ARIC Study, Circulation*., **87(3)**, (1993)

5. Stability of ORYZA TOCOTRIENOL®

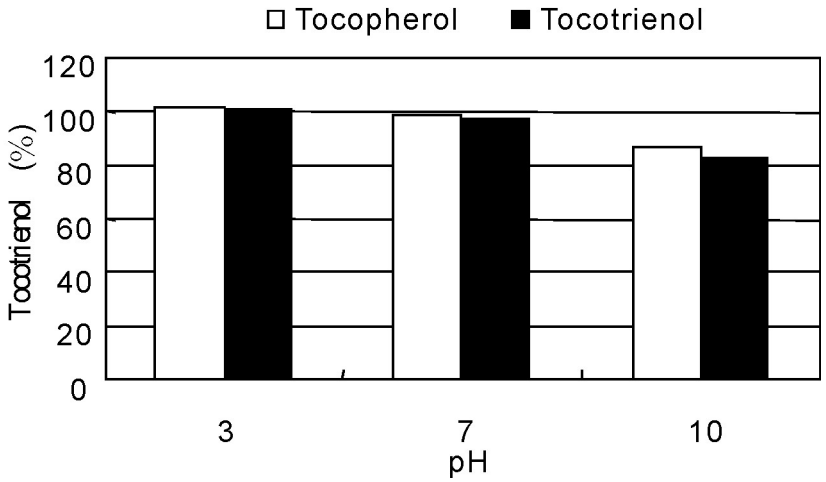
5.1 Thermal Stability

ORYZA TOCOTRIENOL® is highly stable 100°C, the conventional temperature applied during food processing.



5.2 Stability of ORYZA TOCOTRIENOL® -L8 in different pH

2% solution of ORYZA TOCOTRIENOL® -L8 was adjusted pH from 3 to 10 and kept at room temperature for 7 days. Tocotrienol and tocopherol were stable under pH 3 and 7. Approx. 20% of tocotrienol and tocopherol were decreased at pH10.



6. Recommended Daily Dosage

Daily dose of 25mg – 60mg total tocotrienols is recommended as nutritional supplements. Hence, different standards of ORYZA TOCOTRIENOL® offer different range of dosage recommendations:

Description	Aspect	Recommended daily dosage
Oryza Tocotrienol®	oil	160mg – 380mg
Oryza Tocotrienol®-90	oil	42mg − 100mg
Oryza Tocomix-P15CD	powder	320mg − 750mg
Oryza Tocomix-P27CD	powder	140mg – 330mg
Oryza Tocotrienol®-L10	emulsion	420mg − 1000mg

7. Safety Profile

7.1 Acute Toxicity (LD50)

No abnormalities or toxic effects observed in ICR mice after administration of ORYZA TOCOTRIENOL® 5000mg/kg. Similarly, no adverse reaction or toxic effects reported in human after daily dose of 240mg for 18-24 months. LD_{50} (in mouse) is deduced to be >5000mg/kg.

7.2 Patch Test

The patch test was carried out according to the SIMPLE PATCH-TESTS technique. Twenty volunteers, among which 13 were women aged from 22 to 61 years old and 7 were men aged from 22 to 54 years old, took part in the test.

0.025 mL of ORYZA TOCOTRIENOL®-90 was applied to healthy skin in the dorsal

area and maintained in place by an adhesive material of type Finn CHAMBERS on film SCANPOR whose cavity measures 1 cm in diameter. The patches were removed 48 hrs after the application and the degree of erythema was evaluated.

As a result, no reactions of irritation were observed under the standard conditions of the application of ORYZA TOCOTRIENOL®-90 to the normal skin.

7.3 Solvents/Residual Agricultural Chemicals

ORYZA TOCOTRIENOL® and ORYZA TOCOTRIENOL®-90 was examined for 498 agricultural chemical residues, according to the food hygiene regulation and pesticide legislation. All items were below the detection limits.

Test trustee: Masis Co., LTD
"Oriza Tocotrienol"
Date of issue of the report: August 24, 2007 Contract No. : 13952
"Oriza Tocotrienol-90"
Date of issue of the report: December 25, 2007 Contract No. : 16468

8. Applications

Applications	Examples
Nutraceuticals	Health supplements in soft capsules, tablet, and hard capsules
Foods	Candy, Gum, Cake, Cookies, Wafer, Drink, Margarine etc
Cosmetics	Moisturizer, Cream, Exfoliating agent, Lotion, Body care products, lipstick etc

9. Packaging

Product Description	Weight / unit	Packaging
Oryza Tocotrienol®	5kg & 15kg	Interior: Can Exterior: Carboard with nitrogen filling
Oryza Tocotrienol®-90	1kg	Interior: Can Exterior: Carboard with nitrogen filling
Oryza Tocomix-P15CD	5kg	Interior: Polyvinylidene coating bag Exterior: Cardboard box
Oryza Tocomix-P27CD		
Oryza Tocotrienol®-L10	5kg	Interior: A double layered plastic bag Exterior: Cardboard box

10. Storage

Exposure to air, heat, metallic ions and alkaline & acidic conditions may affect the quality of ORYZA TOCOTRIENOL®.
Store at cool, dry, dark place and avoid places with high humidity.

Oryza Tocomix-P15 is highly hygroscopic, do not break seal when is not required.

11. Expression of ORYZA TOCOTRIENOL®

11.1 Food Application

Description	Expression
Tocotrienol®	Rice oil extract (containing tocotrienols)
Tocotrienol®-90	Tocotrienol or Rice oil extract (containing tocotrienols)
Tocotrienol®-L10	Rice oil extract (containing tocotrienols) and Glycerin and Glycerin esters of fatty acids
Tocomix- P15CD, P27CD,	Rice oil extract (containing tocotrienols) and Cyclodextrin and Acacia gum

11.2 Cosmetic Application

ORYZA TOCOTRIENOL®,

Expression	Rice Bran Oil, Tocotrienol, Tocopherol
INCI Name	Oryza Sativa (rice) Bran Oil (and) Tocotrienols (and) Tocopherol

ORYZA TOCOTRIENOL®-90

Expression	Tocotrienols, Tocopherol, Rice Bran Oil
INCI Name	Tocotrienols (and) Tocopherol (and) Oryza Sativa (rice) Bran Oil

ORYZA TOCOTRIENOL®-L10

Expression	Glycerin, water, polyglyceryl-10 Oleate, Rice Bran Oil, Tocotrienols, Tocopherol
INCI Name	Glycerin (and) Water (and) Polyglyceryl-10 Oleate (and) Oryza Sativa (rice) Bran Oil (and) Tocotrienols (and) Tocopherol

PRODUCT STANDARD

PRODUCT NAME
ORYZA TOCOTRIENOL®
(FOOD)

This product is mixture of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It contains minimum of 16.0 % total tocotrienols (α, β, γ, δ) .

Appearance	Slightly yellow or red-brown colored sticky liquid with slightly unique smell.	
Certification Test	0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.	
Content (HPLC)	Total tocopherols and tocotrienols Total tocotrienols	Min. 30.0 % Min. 16.0 %
Peroxide Value	Max. 10.0 meq/kg	(Japan Oil Chemists' Society)
Purity Test		
(1) Solubility	Dissolve 2.0g of this product in 20ml of ethanol, the solution should be clear.	
(2) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(3) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
Standard Plate Counts	Max. 1×10^2cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Negative	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Composition

Ingredients	Contents
Rice oil extract concentrate	100 %

PRODUCT STANDARD

PRODUCT NAME

ORYZA TOCOTRIENOL®-90

(FOOD)

This product is mixture of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It contains minimum of 60.0 % total tocotrienols (α, β, γ, δ) .

Appearance	Red-brown colored sticky liquid with slightly unique smell.
Certification Test	0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.

Content(HPLC)

Total tocopherols and tocotrienols	Min. 90.0 %
Total tocotrienols	Min. 60.0 %

Peroxide Value	Max. 10.0 meq/kg	(Japan Oil Chemists' Society)
Purity Test		
(1) Solubility	Dissolve 2.0g of this product in 20ml of ethanol, the solution should be clear.	
(2) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(3) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
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)

Composition

Ingredients	Contents
Rice oil extract	100 %

PRODUCT STANDARD

PRODUCT NAME
ORYZA TOCOMIX-P15CD
(FOOD)

This product is mixture powder of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It includes more than 8.0 % of total tocotrienols (α, β, γ, δ) .

Appearance	Yellowish colored powder with slightly unique smell.	
Certification Test	0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.	
Content(HPLC)	Total tocopherols and tocotrienols	Min. 15.0 %
	Total tocotrienols	Min. 8.0 %
Loss on drying	Max. 10.0 %	(Analysis for Hygienic Chemist, 1g, 105°C, 2h)
Purity Test		
(1) Heavy Metals (as Pb)	Max. 10ppm	(The Japanese Standard for Food Additives)
(2) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
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

Ingredients	Contents
Rice oil extract	30 %
Cyclodextrin	50 %
Acacia Gum	20 %
Total	100.0 %

PRODUCT STANDARD

PRODUCT NAME
ORYZA TOCOMIX-P27CD
(FOOD)

This product is mixture powder of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It includes more than 18.0 % of total tocotrienols (α, β, γ, δ) .

Appearance	Yellowish colored powder with slightly unique smell.	
Certification Test	0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.	
Content (HPLC)	Total tocopherols and tocotrienols	Min. 27.0 %
	Total tocotrienols	Min. 18.0 %
Loss on drying	Max. 10.0%	(Analysis for Hygienic Chemist, 1g, 105°C, 2h))
Purity Test		
(1) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(2) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
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

Ingredients	Contents
Rice oil extract	30 %
Cyclodextrin	50 %
Acacia Gum	20 %
Total	100 %

PRODUCT STANDARD

PRODUCT NAME
ORYZA TOCOTRIENOL®-L10

This product is water-soluble mixture of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It contains minimum of 7.0 % total tocotrienols (α, β, γ, δ) .

Appearance	Light brown colored sticky liquid with slightly unique smell.
Certification Test	0.15 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.

Content(HPLC)	Total tocopherols and tocotrienols	Min. 10.0 %
	Total tocotrienols	Min. 7.0 %

Purity Test

(1) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(2) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
Standard Plate Counts	Max. 1×10^3cfu/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

Ingredients	Contents
Glycerin	44 %
Purified water	28 %
Glycerin ester of fatty acid	16 %
Rice oil extract (contains tocotrienol)	12%
Total	100 %

PRODUCT STANDARD

PRODUCT NAME

ORYZA TOCOTRIENOL®

(COSMETIC)

This product is mixture of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It contains minimum of 16.0 % total tocotrienols (α, β, γ, δ) .

Appearance	Slightly yellow or red-brown colored sticky liquid with slightly unique smell.	
Certification Test	0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.	
Content (HPLC)		
	Total tocopherols and tocotrienols	Min. 30.0 %
	Total tocotrienols	Min. 16.0 %
Peroxide Value	Max. 10.0 meq/kg	(Japan Oil Chemists' Society)
Purity Test		
(1) Solubility	Dissolve 2.0g of this product in 20ml of ethanol, the solution should be clear.	
(2) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(3) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)
Standard Plate Counts	Max. 1×10^2cfu/g	(Analysis for Hygienic Chemists)
Moulds and Yeasts	Negative	(Analysis for Hygienic Chemists)
Coliforms	Negative	(Analysis for Hygienic Chemists)

Composition

Ingredients	Contents
Oryza Sativa (Rice) Bran Oil	70 %
Tocotrienols	16 %
Tocopherol	14 %
Total	100%

PRODUCT STANDARD

PRODUCT NAME

ORYZA TOCOTRIENOL®-90

(COSMETIC)

This product is mixture of tocotrienols extracted and concentrated from the rice bran and the rice germ of *Oryza sativa* Linne (*Gramineae*). It contains minimum of 60.0 % total tocotrienols (α, β, γ, δ) .

Appearance — Red-brown colored sticky liquid with slightly unique smell.

Certification Test — 0.01 g of this product is dissolved in 10 ml of ethanol, then 2 ml of nitric acid is added to the mixture. After incubation at 75℃ for 15 minutes, the solution shows red-orange color.

Content(HPLC)

Total tocopherols and tocotrienols	Min. 90.0 %
Total tocotrienols	Min. 60.0 %

Peroxide Value	Max. 10.0 meq/kg	(Japan Oil Chemists' Society)

Purity Test

(1) Solubility	Dissolve 2.0g of this product in 20ml of ethanol, the solution should be clear.	
(2) Heavy Metals (as Pb)	Max. 10ppm	(Sodium Sulfide Colorimetric Method)
(3) Arsenic (as As_2O_3)	Max. 1ppm	(Standard Methods of Analysis in Food Safety Regulation, The Third Method, Apparatus B)

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)

Composition

Ingredients	Contents
Tocotrienols	60 %
Tocopherol	30 %
Oryza Sativa (Rice) Bran oil	10 %
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：

ORYZA OIL & FAT CHEMICAL CO., LTD.
Headquarters:
No.1, Numata Kitagata-cho, Ichinomiya-city, Aichi-pref.,
493-8001 JAPAN
TEL : +81 (0) 586 86 5141
FAX : +81 (0) 586 86 6191
URL/ http: //www.oryza.co.jp/
E-mail : info@oryza.co.jp

適正製造規範 GMP JIHFS 一般社団法人 日本健康食品規格協会

ISO 22000 BUREAU VERITAS Certification

ISO 22716 BUREAU VERITAS Certification

Tokyo sales office:
5F Diamant-building 1-5 Kanda-suda-cho
Chiyoda-ku, Tokyo, 101-0041 JAPAN
TEL : +81-3-5209-9150　FAX : +81-3-5209-9151
E-mail: tokyo@oryza.co.jp

“The catalog was created based on academic data. For expressions of consumer products containing this product, follow the Health Promotion Law, Pharmaceutical Low, and other related laws and regulations.”

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ORYZA OIL & FAT CHEMICAL CO., LTD.