

# ***SEANOL<sup>®</sup> Science***



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*“We have an adaptogen with protean effects on many systems. There are cardiovascular health benefits [scavenging of lipids, cholesterol and free radicals, anti-plasmin inhibition, elastase agonist effects, and down-regulation of the DGAT enzyme], diabetic benefits and anti-inflammatory properties [inhibition of NF-kB, COX and LOX]. The neurological effects, including long half-life lipophilic antioxidation, increased trans-cranial blood flow, neurotransmitters, alpha brain waves, parasympathetic/sympathetic ratios, inhibition of beta-amyloid formation and increased acetylcholine [decreased acetylcholinesterase] are particularly relevant to brain repair, regeneration and preservation. This is an almost ‘too good to be true’ nutraceutical. It is easy to get the interest of doctors with this broad range of healing applications.” Dr. Ken Wolkoff, November 2007*

## **I. EXECUTIVE SUMMARY**

SEANOL is a unique brown algae-based polyphenol/phlorotannin complex that is the result of more than 14 years and \$35MM of focused developmental funding and research. The general scientific literature includes several hundred articles and abstracts on the positive mammalian benefits of polyphenols. This abundance of health promoting metabolic effects has made polyphenols as a scientific category the crux of many nutraceutical formulations as well as the focus of many “life-extension” research studies. A number of scientific articles on SEANOL are available for review.

An extensive battery of scientific tests (in-vitro, in-vivo animal model tests, and human clinical studies) supports the SEANOL polyphenol/phlorotannin platform. Specifically, SEANOL has been proven to provide:

- a) Strong anti-oxidant scavenging of lipids, calcium and cholesterol as well as ‘free radicals’ from the cardiovascular system (thereby lowering risk of stroke and cardiovascular events, lowering cholesterol levels, and reducing vasculitis based neuropathy);
- b) Strong anti-plasmin inhibition effect (i.e., thins the blood and homogenizes blood flows, thereby lowering blood pressure);
- c) Strong elastase agonist effect (thereby increasing the flexibility of the vascular system and helping to normalize blood flows and blood pressure);
- d) Significant anti-inflammatory effects by inhibition of the NF-kB inflammatory pathway which also serves to normalize blood glucose levels;
- e) Significant analgesic effects by inhibiting the expression of the COX enzymes for arthritis (comparable to the COX-inhibitors), as well as for neuropathic and FMS/CFS pain;
- f) Down-regulation (by 60%) of the DGAT enzyme responsible for lipid (fat) metabolism (thereby assisting in weight management);
- g) Significant increase in trans-cranial blood flow along with significant increases in alpha brain waves and parasympathetic nerve response (thereby increasing alertness and focus for mental activity);
- h) 40% Inhibition of beta-amyloid brain plaque formation in mammals, combined with a 40% increase in acetylcholine and a 60%-80% reduction in AchE, thereby improving memory as well as memory disorders;
- i) Anti-tumor effects (currently tested only for dermatologic cancers);
- j) Improved production of HGH, GABA, noripenepherine and serotonin levels (as studied in mice, and anecdotally validated with various FMS patients).

The efficacy of SEANOL is further reinforced by virtue of the fact that these sea-based polyphenol/phlorotannin extracts include peak fractions as ‘hydrophobic’ (i.e., water-insoluble) compounds. Unlike virtually all of the land-based polyphenols (including catechins and ECGC) that are hydrophilic (water-soluble), SEANOL’s hydrophobic chemistry allows the polyphenols to pass through the blood-brain barrier. This serves as a positive attribute for improving mental acuity and memory.

In addition, the hydrophobic content in SEANOL allows the polyphenols to remain in the mammalian metabolism up to 12 hours (unlike the 30-minute half-life of the hydrophilic, or water-soluble land-based polyphenol sources). Lastly, SEANOL's ORAC scores for anti-oxidation potential (8,300) are significantly higher than most known land-based polyphenols.

Depending upon the medical application examined, SEANOL's potency in-vivo tends to be from 10X-100X more than a similar quantity of land-based polyphenols, resulting both from its higher anti-oxidant potential as well as its 24X improved half-life. SEANOL is currently protected by 4 patent applications, with additional patent applications expected.

Pilot human clinical trials (double-blinded, placebo-controlled Phase I) on SEANOL capsule products have established a high degree of safety and efficacy in the following medical indications:

- a) Hypertensive cardiovascular patients (reduction of blood pressure);
- b) Analgesia in osteoarthritic patients (comparable to the COX-2 inhibitors);
- c) Weight loss in both obese and normal patients;
- d) Erectile dysfunction amongst males with ED (comparable to Viagra, used as a positive control);
- e) Analgesia in neuropathic pain patients (i.e., neuralgia, 40% neuropathy reduction);
- f) Major multi-symptom management (i.e., reduction in pain [-31%], fatigue [-56%], sleep disorders [-62%]) for fibromyalgia patients).

A recently completed double blind, placebo-controlled three-month clinical study for weight loss with clinically obese patients using a SEANOL-based beverage evidenced an average 2.4kg weight loss, with a 15% reduction in visceral fat (confirmed through CAT-scans), as compared with placebo.

Prior open-label studies on confirmed AD patients with mild-to-moderate Alzheimer's (N=150) have indicated the ability to allow up to 60% of such patients to reassume unassisted living following 3 months of daily SEANOL dosing, due to dramatic improvements in memory and the ability to maintain life functions. AD remains a key target area for formal clinical development with SEANOL.

## II. INTRODUCTION

Hundreds of research articles and abstracts attesting to the powerful metabolic benefits of bioflavonoid compounds such as the catechins from green tea, resveratrol from grapes, tocopherol, etc. have been generated over the past decade. As powerful anti-oxidants with lipid, cholesterol and free radical scavenging properties, these bioflavonoids have been well documented for their metabolic benefits, including:

- Reduction of cardiovascular risk due to increased blood flow, reduced cholesterol deposition, reduced vascular inflammation, and reduced blood pressure;
- Anti-cancer effects;
- Anti-aging effects.

Dr. Haengwoo Lee, a Ph.D. in Biochemistry, has spent much of the past 14 years and more than \$35MM of public and private funding, in establishing and explicating the particular anti-oxidant metabolic benefits of a new class of polyphenols/phlorotannins extracted from marine algae, most notably Ecklonia cava. These extracts now serve as the basis for purified grades of algae-based anti-oxidants and are classified as ‘SEANOL’ in nutraceutical formulations.

“SEANOL” is a trade name for standardized natural complexes of unique marine molecules that originate as second metabolites from specific brown algae. SEANOL molecules with their chemical structures derived from dibenzo-p-dioxin skeleton represents a unique category of polyphenol often called phlorotannins. Their unique polyphenolic structures endow them with wonders of biological activities that are not found in terrestrial plants.

SEANOL is molecularly distinct from land-based polyphenols. Under HPLC analysis, there are 13 active peak fractions (including eckol, dieckol, phlorofucofuroeckol, fucosterol, etc.) of these polyphenol/phlorotannins that serve to provide anti-oxidant effects metabolically. The method of extraction and purification of these polyphenols has been patented by Dr. Lee, as well as these polyphenols’ principal therapeutic metabolic benefits through additional patent applications.

SEANOL is further distinguished by having hydrophobic content, unlike the exclusive hydrophilic content characterizing virtually all land-based polyphenols (catechins, ECGC, tocopherol, etc.). This split hydrophobic chemistry also allows SEANOL to pass through the blood-brain barrier and serves as a positive attribute for improving mental acuity and memory. These benefits have been noted in NIH/NIA animal model studies testing SEANOL’s polyphenol/phlorotannins for both memory improvement and as a chemo-protective compound against beta amyloid plaque deposition in the brain. In addition, the hydrophobic content in SEANOL allows these polyphenols to remain in the

mammalian metabolism up to 12 hours<sup>1</sup> (unlike the typical 30-minute half-life of the hydrophilic, or water-soluble polyphenols available from all land-based sources).

Lastly, SEANOL's ORAC score (more than 8,300)<sup>2</sup> for anti-oxidation potential is significantly higher than most known land-based polyphenols (including catechins). Depending upon the medical application examined, the anti-oxidant metabolic potency of SEANOL and is believed to be from 10X-100X stronger than a similar quantity of land-based polyphenols.

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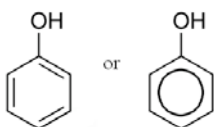
<sup>1</sup> SEANOL half-life is an estimate based on in vivo experimental data of hypertensive effect during and after treatment (Kor. J. Pharmacogn. 2006, 37(3): 200-205). In the study, SEANOL was compared with enalapril (half life= 27~36 hours). The finding that SEANOL showed a more persistent effect than enalapril at 7 and 14 days after cessation of treatment indicates that SEANOL's half-life is at least higher than enalapril.

<sup>2</sup> Brunswick Laboratories ORAC Analysis, 05-0222, 02-04-05.

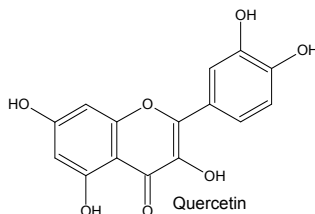
### III. SEANOL ORIGINS & STRUCTURE

SEANOL is a polyphenol extract from the **Ecklonia cava marine brown algae** grown off the **coasts of Korea and Japan**. The patented extraction process produces a complex polyphenol/phlorotannin compound possessing potent anti-oxidant and anti-inflammatory properties.

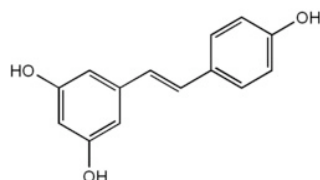
Flavonoids and related compounds are called polyphenols. Phenol is a simple ring chemical:



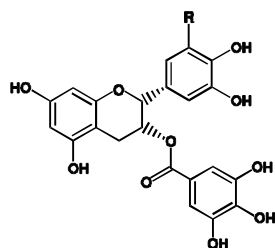
Polyphenols are phytochemicals (plant made) with multiple interconnected phenol rings. Flavonoids have a typical three-ring structure as follows:



Resveratrol has several analogues, but all share a 2-ring structure:

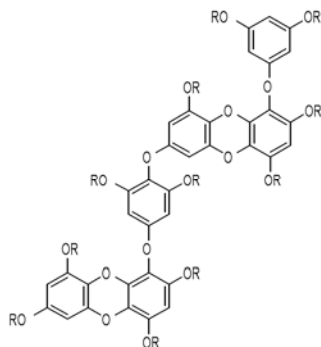


Catechins from green tea have 4 rings (corresponding to their 4 peaks under high-pressure liquid chromatographic ('HPLC) analysis):

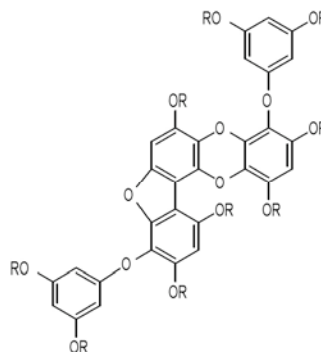


The power of any of these antioxidants rests in large part upon their ability to capture stray electrons from free radicals. The more rings in a phenol structure, the larger the

capacity to absorb electrons. The phenol structures of two of SEANOL's more than 13 active fractions (dieckol and PFF) that are particularly important are provided below<sup>3</sup>:



[dieckol]



[phlorofucofuroeckol (PFF)]

The ten patented SEANOL phenol structures such as dieckol and PFF are much more complex than those of the well-known anti-oxidants referenced above. This complex structure makes the SEANOL molecules extremely potent electron (free radical) absorbing mechanisms. When combined with their much longer in-vivo effect, these polyphenols surpass land-based polyphenols' free radical scavenging ability by 10-100X.<sup>4</sup> As a result SEANOL polyphenols are much more powerful than resveratrol and even the extremely powerful green tea catechins. SEANOL also has much more power than catechin to prevent oxidation of your neurons and LDL cholesterol (the first step in vascular disease).<sup>5</sup>

#### Types of SEANOL

SEANOL naturally occurs as high-molecular weight tannin (HMST, Mw > 2,000 dalton) and low-molecular one (LMST, Mw = 400-1000 dalton). SEANOL can be classified into four types depending on the ratio of HMST and LMST.

Class	LMST content(%)
Type I	< 40
Type II	41~60
Type III	61~80
Type IV	81~100

<sup>3</sup> *Improvement of Memory by Dieckol and Phlorofucofuroeckol in Ethanol-Treated Mice: Possible Involvement of the Inhibition of Acetylcholinesterase*, Chang-Seon Myung, and et. al., Arch Pharm Res, Vol. 28, No 6, 691-698, p.693, 2005

<sup>4</sup> see footnote 2

<sup>5</sup> Dr. Robert Rowen, *New Antioxidant Fights Heart Disease, Lowers Cholesterol, and Beats Viagra*. Second Opinion Newsletter, Vol. XVI, No. 9, September 2006.



### Safety Features of SEANOL products

SEANOL products are manufactured from edible algae through food-compatible processes. Tens of thousands of people have experienced SEANOL in various forms without side effect. Several toxicity tests have been performed in GLP facilities and no adverse effect has been found in any tests at effective human dose levels (1~10mg/kg).

Test type (Name of sample)	NOAEL <sup>a</sup>	Estimated NOAEL for SEANOL <sup>b</sup>
Chromosomal Aberration test <sup>1</sup> (98% phlorotannin)	negative <sup>c</sup>	negative <sup>c</sup>
Micronucleus test <sup>1</sup> (98% phlorotannin)	negative <sup>c</sup>	negative <sup>c</sup>
Ames test <sup>1</sup> (98% phlorotannin)	negative <sup>c</sup>	negative <sup>c</sup>
Acute toxicity on rat <sup>1</sup> (62% phlorotannin)	>2g/kg	> 12.4g/kg
Acute toxicity on dog <sup>1</sup> (62% phlorotannin)	>2g/kg	> 12.4g/kg
2-week repeated on dog <sup>2</sup> (62% phlorotannin)	>1g/kg	> 6.2g/kg
4-week sub-acute toxicity on rat <sup>2</sup> (20% phlorotannin)	>2g/kg	> 4g/kg
13-week chronic toxicity on rat <sup>2</sup> (62% phlorotannin)	111mg/kg (male), 333mg/kg (female)	> 0.69g/kg (male) > 2.1 g/kg (female)
13-week chronic toxicity on dog <sup>2</sup> (62% phlorotannin)	>1g/kg	> 6.2g/kg
Intravenous toxicity in mice <sup>3</sup> (98% phlorotannin), Tested up to 40mg/kg/day, 5 consecutive days	negative <sup>c</sup>	negative <sup>c</sup>

a. NOAEL: Non-Observed Adverse Effect Level

b. By accounting for the phlorotannin content in the sample used for a study, estimated NOAEL for SEANOL is calculated by multiplication of the ratio of phlorotannin content in the study to that of SEANOL (10%). It is assumed that chemicals other than phlorotannin extracted from *E. cava* do not significantly influence the toxicity

c. No toxicity

### Toxicity

No statistically significant serious adverse events were noted in any of the supporting clinical studies of SEANOL. The only adverse event noted in the fibromyalgia (“FMS”) clinical study (N=36) was a tendency for increased diarrhea amongst some study subjects with a pre-existing condition of diarrhea (N=6). The magnesium or aloe vera present in Fibronol<sup>®</sup> have been hypothesized as the primary contributing factors to this noted event.

Several mouse and rat studies for toxicity have been conducted in Korea, Japan and the US, principally for the Korean FDA, in order to register SEANOL as a safe food substance. No adverse effects were noted in these supporting pre-clinical studies.<sup>6</sup>

<sup>6</sup> *Evaluation of Toxicity of SEANOL™*, Hyeon-Cheol Shin, Ph.D, LiveChem Inc., Seoul, Korea, June 2007

### Health benefits arising from physiological actions of SEANOL

Physiological activities of SEANOL have been evaluated in vitro, in vivo and clinically as individual compounds (SN<sub>1</sub>~SN<sub>14</sub>) and complex forms (SEANOL, Type I~IV).

Physiological Activities	Measurement method	Test	Test Sample
Antioxidant activity	Free Radical Scavenging (DPPH)	t	SN <sub>i</sub> /SEANOL (I~IV)
	Reducing Power (FRAP)	t	“
	Reducing Power (FRAP)	v	SEANOL (I)
	Peroxyntirite Scavenging	t	SN <sub>i</sub> /SEANOL (I, II)
	Inhibition of LDL oxidation	t	“
Vasodilatation	ACE inhibition	t	SN <sub>i</sub> /SEANOL (I, II)
	Blood Pressure in SHR	v	SN <sub>i-k</sub>
	Blood Pressure in renovascular surgery-induced hypertension	v	SEANOL (IV)
Fibrinolysis Promotion	Antiplasmin inhibition	t	SN <sub>i</sub>
Heart Protection	Protection from Reperfusion Injury	v	SEANOL (I)
Anti-inflammation	Hyaluronidase assay	t	SN <sub>i</sub>
	Phospholipase A2 assay	t	SN <sub>i</sub>
	Lipoxygenase assay		
	LPS-induced PGE2 in macrophage	t	SN <sub>i</sub> /SEANOL (III)
Arthritis treatment	Measurement of sGAG	t	SEANOL (III)
	Collagenase-induced Osteoarthritis Model	v	SEANOL (III)
	ISK, VAS, etc	c	SEANOL (I)
Erectile Function	IIEF	c	SEANOL (I)
Cholesterol Lowering	Blood test	c	SEANOL (I)
	Blood test	v	SEANOL (I, III)
Protection from high glucose	Inhibition of Aldose Reductase	t	SEANOL (I, II)
Anti-Obesity	DGAT inhibition	t	SN <sub>i</sub> /SEANOL (I, II)
	Body fat/Muscle	c	SEANOL (I)
Brain Function	bAPP down regulation	t	SEANOL (II)
	AChE inhibition	t	SN <sub>i</sub>
	Memory Enhancement	v	SN <sub>i</sub>
	MMSE	c	SEANOL (I)

- t = in vitro, v = in vivo, c = clinical; SN<sub>i</sub> = Individual SEANOL compounds

## IV. SEANOL HEALTH BENEFITS

### 1. CARDIOVASCULAR

Following 14 years of in-vitro, in-vivo and clinical tests, SEANOL has been proven to provide the following cardiovascular metabolic benefits:

- a. Uniquely strong anti-oxidant scavenging of lipids, calcium, and cholesterol as well as 'free radicals' from the cardiovascular system (thereby lowering risk of stroke and cardiovascular events, lowering cholesterol levels, and reducing vasculitis-caused neuropathy);
- b. Strong anti-plasmin inhibition effect (i.e., homogenizes blood flows, thereby lowering blood pressure and increasing arterial blood flow);
- c. Strong elastase agonist effect, thereby increasing the flexibility of the vascular system and helping normalize blood flows and blood pressure;
- d. Significant anti-inflammatory effect, by inhibition of the Nf-kB inflammatory pathway, which also serves to normalize blood glucose levels and lead to statistically significant re-establishment of insulin sensitivity in the pancreas.

In a study including hypertensive cardiovascular patients, there were significant increases in brachial artery FMD and NMD amongst the CAD patients. This study was an open-label study of 11 confirmed CAD patients and 28 normal healthy patients (control), conducted at Yonsei University Medical School. The CAD patient group experienced a significant 43% increase in FMD at the brachial artery over six weeks of SEANOL consumption, with an even larger 49% increase in NMD at the brachial artery. The clinicians' conclusion was that their cardiovascular risk profile had been substantially reduced in the CAD patients.<sup>7</sup>

Similar cardiovascular benefits were observed in a series of randomized, placebo-controlled clinical studies on the favorable energy and mental acuity benefits of a SEANOL-based, non-caffeine "energy" beverage. In these studies (N=50), trans-cranial blood flow velocity increased 7.5%-9% in neck peak and average blood flow within 40 minutes of consumption. The studies also established a notable 30% reduction in drowsiness one-hour following consumption of the trial SEANOL-based energy beverage by professional drivers.<sup>8</sup>

#### **Unprecedented Cardiovascular protection and rejuvenation by SEANOL**

The cardiovascular system is exposed to various kinds of risk factors such as free radicals, inflammation, excessive coagulation, hypertension, etc. It is generally known that by doubling the kinds of risk factors, resulting impact tends to be quadrupled.

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<sup>7</sup> *Effect of Mo'bar on hemopoiesis, Endothelial function, Endocrinological profile, and Daily activities in Adults*, Yangsoo Jang, Cardiology Division, College of Medicine, Yonsei University, Seoul, Korea, November 2001.

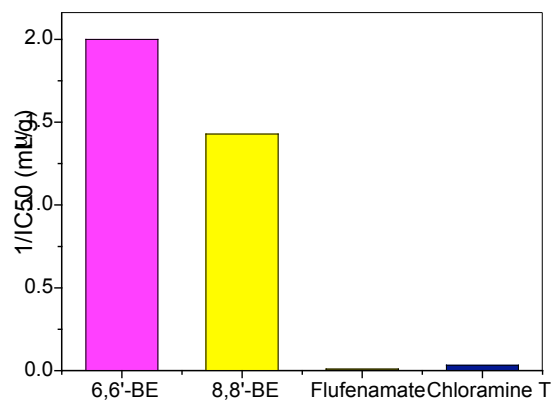
<sup>8</sup> *Summary of SEANOL-based Beverage Metrics*, Hyeon-Cheol Shin, Ph.D, LiveChem Inc., Seoul, Korea, June 2006. [Internal studies]

Therefore multiple protections from different kinds of risk factors will greatly enhance the efficacy of a treatment. SEANOL offers **multiple features of cardiovascular protection** that have been discovered in vitro, including:

- **Promotion of fibrinolysis by inhibition of anti-plasmin**
- **ACE inhibition**
- **Multiple modes of anti-oxidative protection**

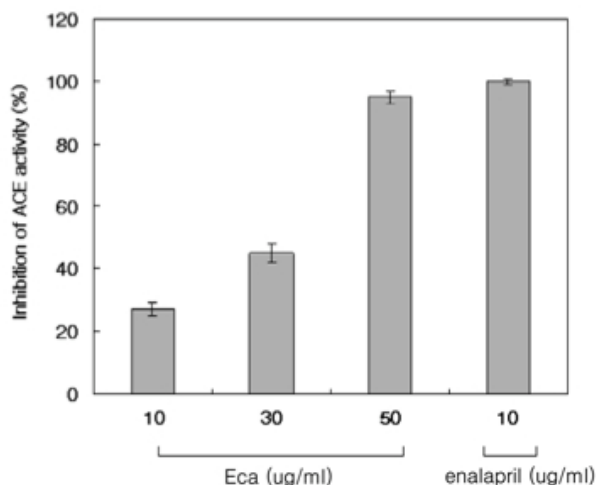
#### **Anti-plasmin inhibition promotes dissolution of intravascular blood-clot**

**Chronic inflammatory intravascular injuries due to aging** and contamination of blood cause **excessive coagulation** that increases blood viscosity thereby retarding blood circulation. A fibrinolytic enzyme called “plasmin” that is supposed to break down the blood clot is rapidly blocked by a protein called anti-plasmin. SEANOL compounds, natural potent inhibitors of the anti-plasmin are capable of efficient promotion of plasmin that performs fibrinolysis. SEANOL compounds 6,6'-BE and 8,8'-BE show remarkable activity which is 40-200 times greater than synthetic compounds Flufenamate or Chloramine T.



#### **SEANOL tannins are potent natural ACE inhibitors**

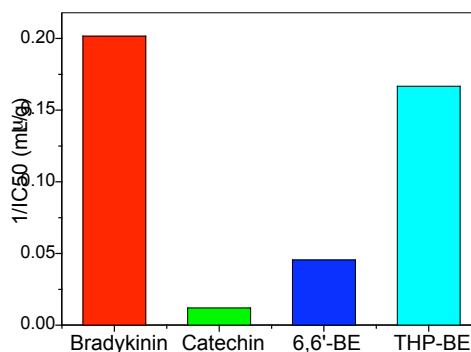
Angiotensin-converting enzyme (ACE), which is responsible for conversion of angiotensin I to angiotensin II and degradation of bradykinin, is a key component in the renin-angiotensin-aldosterone system. Angiotensin II regulates cellular proliferation, inflammation, and endothelial function, and is therefore important in the pathogenesis of atherosclerosis and its complications. **Aging and other vascular risk factors tend to increase the ACE level** resulting in excessive **vasoconstriction and hypertension**. Current hypotensive drugs block the action of ACE or its product angiotensin II. SEANOL compounds suppress ACE and thus promote effective vasodilation.<sup>9,10</sup>



<sup>9</sup> J-H Hong, B-S Son, B-K Kim, H-Y Chee, K-S Song, B-H Lee, H-C Shin, K-B Lee, *Antihypertensive Effect of Ecklonia cava Extract*, Korean Journal Pharmacognosy v. 37(3): 200-205, 2006 (Kor; Eng; 23 ref).

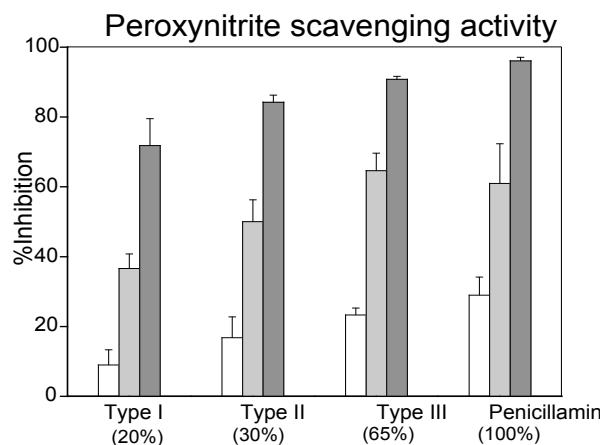
<sup>10</sup> S.K. Hyun, et. al., *Angiotensin-converting enzyme I inhibitory activity of phlorotannins from Ecklonia stolonifera*, Fisheries Science 72, 1292-1299, 2006

SEANOL compounds are much more potent than the natural hypotensive catechins found in green tea. The SEANOL compound THP-BE has physiological vaso-dilative impact similar to the bradykinin hormone.



### SEANOL - Multiple antioxidant profiles

SEANOL's antioxidant activities against various reactive oxygen species that are known to attack endothelial cells causing endothelial dysfunction have been confirmed to be highly potent in physiologically relevant concentrations. Effective dose of SEANOL for free radical scavenging is 10~20 µg/mL range. SEANOL compounds showed potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite. SEANOL's inhibition of LDL oxidation was significantly higher than catechin.



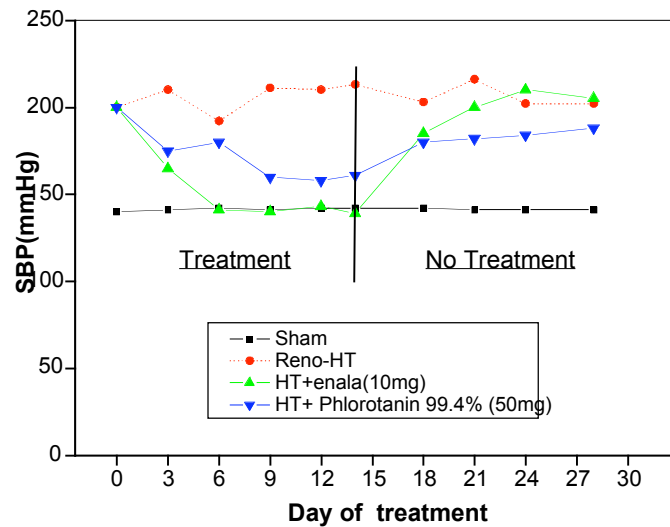
The free-radical scavenging activity of SEANOL is better than the well-known antioxidants such as catechin, tocopherol and butylhydroxyanisole (BHA) and *t*-butylhydroxytoluene (BHT).<sup>11</sup>

### Effective cardiovascular protection by SEANOL clearly demonstrated in renovascular hypertensive rat study.

The remarkable effect of SEANOL on vasodilation was clearly demonstrated in the renovascular-clipping induced hypertensive rats. Renovascular clipping surgery that is known to increase the ACE activity via rennin-angiotensin-aldosterone system increased the systolic blood pressure (SBP) from 140 up to over 200mmHg after 4 weeks. Upon oral administration of phlorotannin (99.4%, 50mg/kg) or enalapril (commercial hypotensive drug, 10mg/kg) SBP dropped to as low as 160 and 140mmHg, respectively.

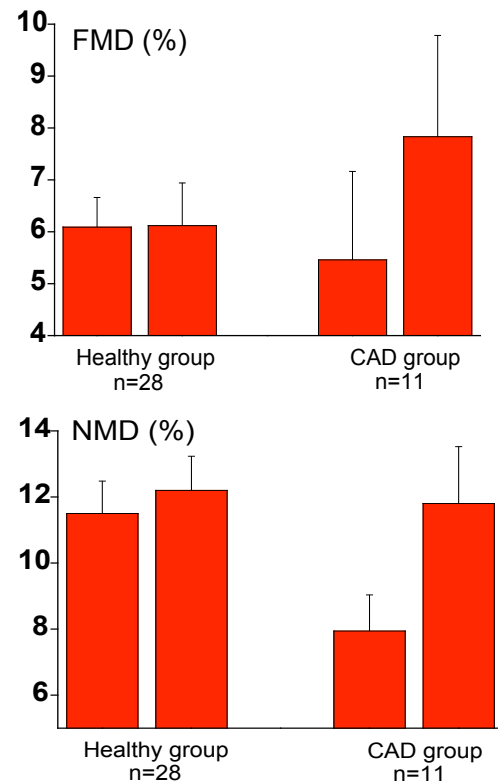
<sup>11</sup> K. Kang, Y. Park, H.J. Hwang, S.H. Kim, J.G. Lee, H-C Shin. *Antioxidative Properties of Brown Algae Polyphenolics and Their Perspectives as Chemopreventive Agents Against Vascular Risk Factors*. Archives of Pharmacal Research Vol. 26, No. 4, 286-293, 2003

Upon cessation of treatment, SBP increased again in both cases. Although SEANOL showed similar pattern to the drug, it showed slower rebounding of blood pressure during no treatment period, which indicates its potential as a vascular protector upon prolonged ingestion.<sup>12</sup>



SEANOL's **cardiovascular rejuvenation** has been confirmed in human studies.

A clinical study using SEANOL was conducted confirming its **capacity to regenerate vascular endothelium and recover plasticity of blood vessel after 6-week treatment** by measuring FMD (flow-mediated dilation) & NMD (Nitroglycerin-mediated dilation) of normal and CAD group with narrowed coronary artery by 50+%. FMD indicates NO releasing ability of endothelial cells to expand blood vessel by detecting shear stress caused by incoming blood flow. In other words, someone whose endothelium is damaged gives a low FMD value compared with healthy one. **After a 6-week treatment with SEANOL, clinical data showed that FMD, the endothelium-dependent dilation was greatly enhanced in CAD (coronary artery disease) group, indicating its remarkable activity of inducing recovery of endothelial cells.** NMD, the endothelium-independent dilation, which represents the vascular plasticity, also showed remarkable improvement in CAD group, again supporting SEANOL's ability to help restoration of vascular integrity by **reversing atherosclerosis**.



In the study, subjects were advised to ingest three bars containing SEANOL per day at any time of day for six weeks. The bars were ingested freely. Each bar contained 0.33% of SEANOL-SL (100 mg/30g). As noted in the following tables, additional cardiovascular improvements included: reduction in LDL, increase in HDL, and reduction in triglyceride levels.<sup>13</sup>

<sup>12</sup> see footnote 8

<sup>13</sup> see footnote 7

**Baseline data:****Lipid profile before and after:**

	Before	6 weeks later	Difference	% Change
Total cholesterol (mg/dL)	228.3±6.95	224.0±6.08	-4.3	- 1.9%
LDL cholesterol (mg/dL)	141.1±6.24	135.2±5.64*	-5.9	- 4.2%
HDL cholesterol (mg/dL)	46.5±1.83	50.7±2.04**	+4.2	+ 9.0%
Atherogenic index <sup>1</sup>	3.91±0.15	3.42±0.14*	-0.49	- 12.5%
Triglycerides (mg/dL)	215.1±23.5	195.4±25.3*	-19.7	- 9.2%

<sup>1</sup>Atherogenic index = (total cholesterol - HDL cholesterol)/HDL cholesterol

\*p<0.05, \*\*p<0.01(compared with initial values)

**Vasodilatory function before and after:**

	Non CAD (n=28)		<sup>3</sup> CAD patients (n=11)	
	Week 0	Week 6	Week 0	Week 6
<sup>1</sup> FMD(%)	6.09±0.57	6.12±0.82	5.46±1.70	7.83±1.95*
<sup>2</sup> NMD(%)	11.5±0.98	12.2±1.03	7.94±1.09	11.8±1.72*

<sup>1</sup>FMD: flow mediated dilation

<sup>2</sup>NMD: nitroglycerin mediated dilation

<sup>3</sup>CAD: coronary artery disease

\*p<0.05

**Improvement of lipid metabolism with dietary supplement**

In another study, subjects were advised to ingest 6 capsules daily (3 capsules 2 hours before lunch, 3 capsules 2 hours after dinner) for eight weeks. Each capsule contained 100mg of SEANOL. As noted in the table below, SEANOL improved all of the cholesterol measures along with reducing triglyceride levels.

N=21	Week 0	8 week	Difference	% Change
Total Cholesterol (mg/dL)	258.26 ± 28.11	233.43 ± 32.08*	-24.83	-10
LDL Cholesterol (mg/dL)	171.13 ± 28.02	141.78 ± 34.43*	-29.35	-17
HDL Cholesterol (mg/dL)	48.52 ± 12.77	50.09 ± 13.16	+1.57	+3
TG (mg/dL)	197.74 ± 132.04	179.2 ± 112.69*	-18.54	-9
Artherogenic Index	4.32 ± 0.45	3.66±0.34*	-0.66	- 15.2%

\*p<0.01 based on Week 0 data.



## 2. ENDURANCE, ATHLETICS & ALERTNESS

The benefits of SEANOL are also applicable to endurance and athletic activities. A recently completed placebo-controlled study of a SEANOL-based beverage (EntroPower®, 2 cans/day, 720mg SEANOL/can, no caffeine) amongst cyclists (n=40) showed significant improvement in key endurance parameters including VO<sub>2</sub>max capacity, heart rate levels and time to exhaustion.<sup>14</sup> Some of the study results included:

- a. *VO<sub>2</sub>max capacity*: SEANOL group experienced with a 10.2% increase in capacity that was significantly higher than the 6% increase amongst placebo;
- b. *Heart Rate*: SEANOL group experienced a 19% decline in resting heart rate that was significantly lower than the 10% decline amongst placebo;
- c. *Time to Exhaustion*: SEANOL group experienced a 9.9% improvement in time to exhaustion that was significantly higher than the 4.3% increase amongst placebo.

A series of randomized, placebo-controlled clinical studies on the favorable energy and mental acuity benefits of a similar SEANOL-based beverage noted increases in alpha and alpha/beta brain waves as measured by EEG (with positive implications for mental acuity), together with improved neck arterial (cranial) blood flow as measured by EKG. These studies also noted SEANOL induced increases in para-sympathetic nerve response and reduction in sympathetic nerve response (ECG measured). The studies results<sup>15</sup> included:

- a. *Trans-Cranial Blood Flow*: a 7.5-9% increase in peak and average neck blood flow, within 40 minutes of consumption;
- b. *Alpha/Beta Brain Waves*: a favorable 6-17% increase in beta and alpha brain waves, with a 13% increase in alpha/beta ratios, as measured against placebo;
- c. *Sympathetic and Para-Sympathetic Nerve Balance*: a 7% decrease in sympathetic nerve balance and an 11% increase in parasympathetic nerve balance;

In another set of studies amongst professional drivers and students a notable reduction in drowsiness one-hour following consumption of the trial SEANOL-based energy beverage. The drivers experienced a one-day 29% reduction in overall drowsiness with SEANOL (vs. placebo), with a marked 48% reduction in drowsiness while driving. Students experienced an 11% reduction in drowsiness while studying (vs. placebo).

The same SEANOL-based beverage has recently been given to ‘average/middle of the pack’ racehorses in South Korea. The only change in the horses’ diet and training was the introduction of the beverage for a period of time leading up to a race. The horses’ race performances were improved compared to their prior results with most of the horses moving from past middle place finishes to being race winners. Recently several of these horses set track records for the 1,000, 1,200, 1,400, and 1,600-meter distances.

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<sup>14</sup> *SEANOL for Endurance Athletes*, Sekyu Kwon M.D., Seonje Lee M.D., Mirae Medical Foundation, Korea, July 18, 2007.

<sup>15</sup> see footnote 8



### 3. WEIGHT MANAGEMENT & DIABETES

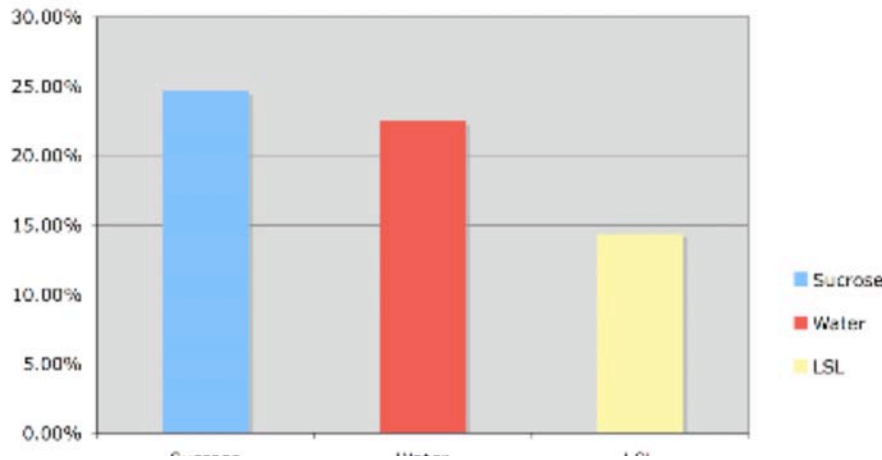
Obese Americans now exceeds 60MM with over 65% of those over 20 years old deemed significantly overweight by the Center for Disease Control (CDC) (i.e., over 130MM people). The CDC recently defined obesity as the number one health risk to Americans, contributing significantly to more than 30 chronic, life-threatening diseases, including diabetes, CVD, CHD and stroke.

The Type 2 diabetic population of 20MM Americans has 90% of its members classified as clinically obese. The US has a resident population of more than 60MM adults with CHD or CVD, roughly corresponding with the 60MM obese adults.

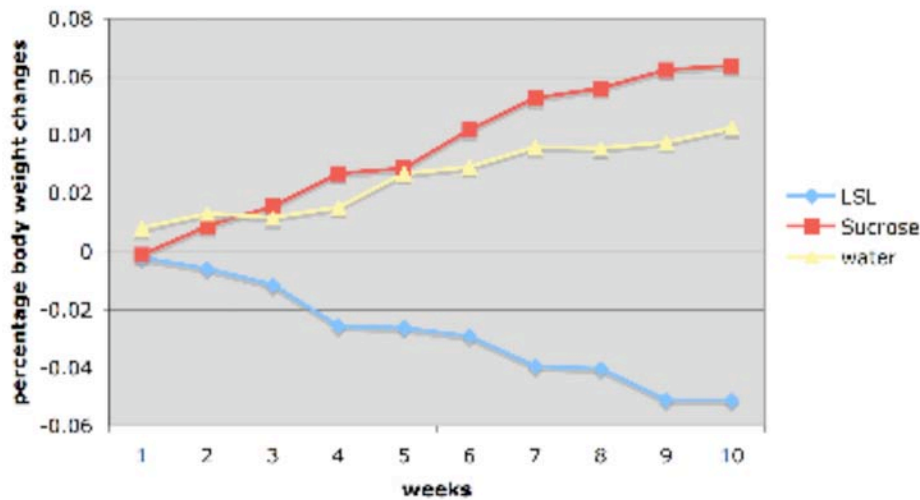
The health benefits of SEANOL include significant anti-inflammatory effects that arise from inhibition of the Nf-kB inflammatory pathway, which also serves to normalize blood glucose levels and lead to statistically significant re-establishment of insulin sensitivity in the pancreas. SEANOL also down-regulates (by up to 60%) the DGAT enzyme responsible for lipid (fat) metabolism, thereby assisting in fat/weight loss. In a study of the effect of SEANOL on diabetic mouse tissue pathogenesis<sup>16</sup>, it was shown that SEANOL inhibited NF-kB expression in heart aortic vessel valves, kidney's, liver and pancreas. SEANOL induced a reduction of the number of fat cells in tissues and in association with blood vessels, which indicates that the liver, muscle and fat tissues were involved in glucose homeostasis in weight reduction. There was also a significant reduction in the amount of adipose cells in skeletal muscle. The following charts and images illustrate some of these results.

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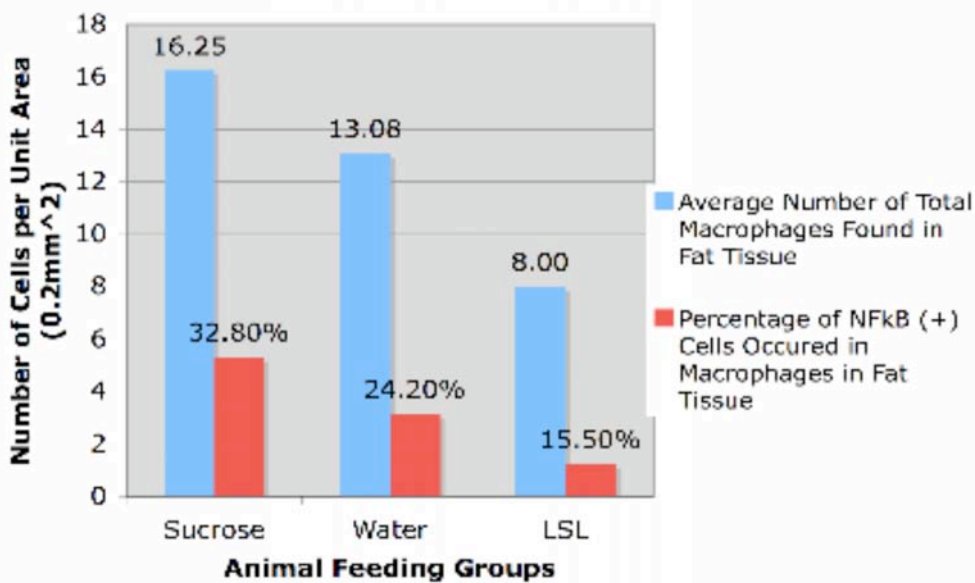
<sup>16</sup> *The Beneficial Effects of Feeding SEANOL-Based Drink "X2" In a Fat Mouse Model Study*, Emil Chi Ph.D., Department of Pathology, University of Washington, November 2004.



Percentage of **NF-kB** positive cells in the pancreas of each treatment group

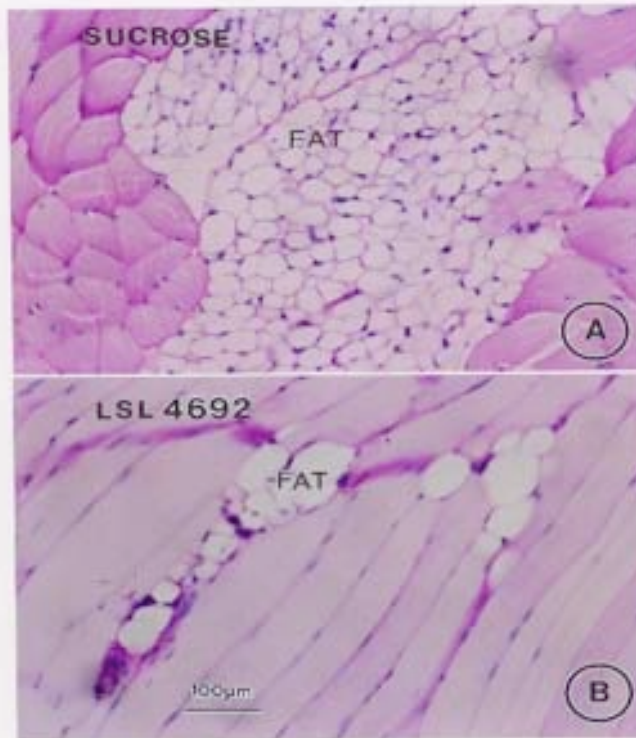


Percentage of **body weight** change in treatment of diabetic mouse



Percentage of **NF-kB(+)** macrophage in fat tissue

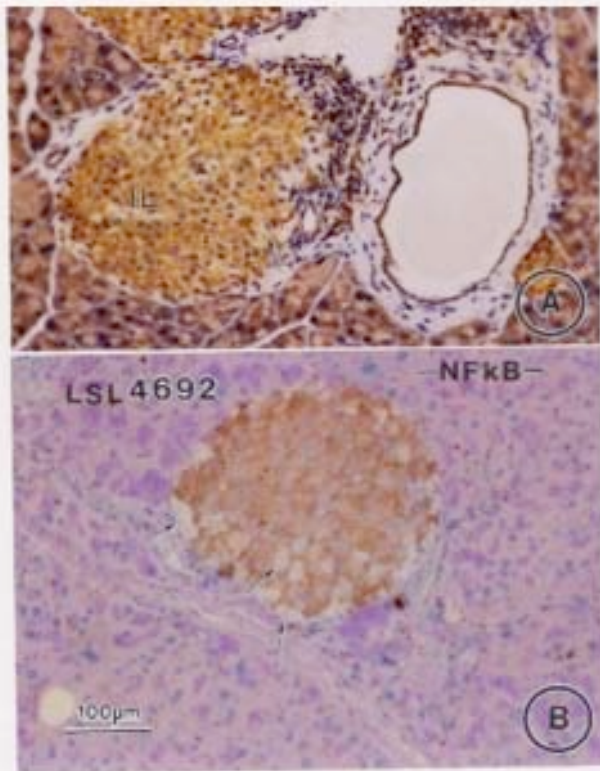
Note: LSL is SEANOL solution used in research



**Reduction of fat cell distribution after SEANOL treatment (PAS stain):**

(A) Fat cell deposits in the intracellular muscle bundles in mouse fed with sucrose.

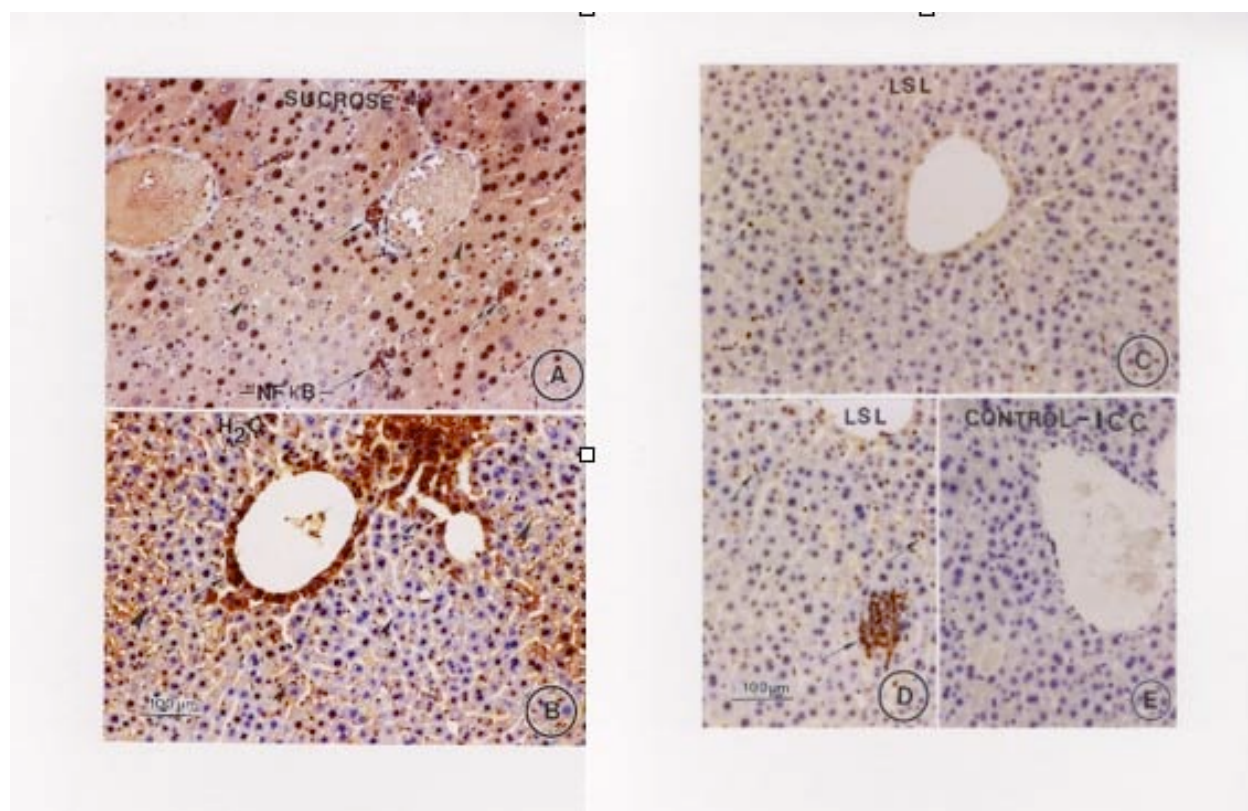
(B) A reduced number of intracellular fat cells shown in the skeletal muscle of mouse treated with SEANOL.



**The Effects of SEANOL Feeding in the Pancreas**

(A) In the sucrose feeding group, **NF-kB activation** is seen in islets (IL) and in the beta cells (arrows). **Also many cellular infiltrates** are seen in the vessel connective tissues (arrowheads).

(B) In the SEANOL treated mouse pancreas, **very little reactive activity of NF-kB is seen in the islet and beta cells are normal** (arrows).



### **SEANOL and NF-kB in diabetic mouse liver**

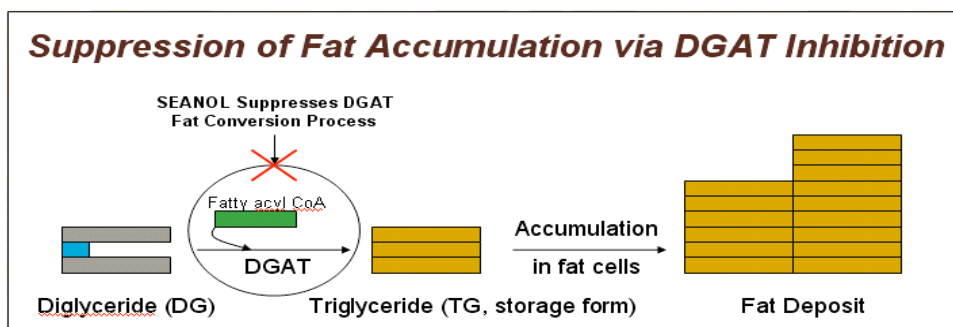
The sucrose feeding group (A) and the water feeding group (B) show increased hepatic NF-kB activity in the nuclei and Kupffer cells (arrows). In the water group, the predominant cellular activity is in the cellular infiltrate (arrows). In the SEANOL feeding group (C and D), there is very little activity observed in hepatic cells, except for a few small Kupffer cells (arrows). The immunocytochemistry staining control (E) shows no NF-kB activity.

SEANOL is an optimal combination of natural compounds capable of suppressing triglyceride (storage form of fat) synthesis, removing cholesterol, and providing overall cardiovascular protection. Some of the clinically proven benefits include:

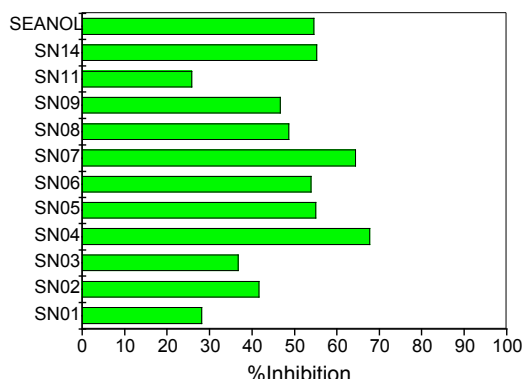
- **Efficient fat loss + muscle gain;**
- Promotion of energy expenditure through inhibition of triglyceride synthesis in fat tissues;
- **Provides additional cardiovascular protection for obese population that is prone to CVD and CHD** through lowering bad cholesterol and scavenging free radicals.

#### **Inhibition of DGAT - an important enzyme that synthesizes storage form of fat.**

DGAT (Acyl CoA:diacylglycerol acyltransferase) catalyzes the final step in triacylglycerol (TG) synthesis by using diacylglycerol and fatty acyl CoAs. Recently it is recognized as a novel and safe target for the treatment of obesity. DGAT is involved in intestinal fat absorption, lipoprotein assembly, regulation of plasma TG concentration, fat storage in adipocytes, and energy metabolism in muscle. DGAT knockout mouse has been shown to have obesity resistance upon high-fat diet and the mechanism of which was confirmed to be through energy expenditure.



SEANOL is composed of natural DGAT-inhibitory compounds that suppress the enzyme activity by 30-70% at 25ug/mL. SEANOL suppresses the DGAT activity over 50% at the same concentration.<sup>17,18</sup>



<sup>17</sup> United States Patent Application 20050101660, May 12, 2005, Haeng Woo Lee (Seoul, Korea).

<sup>18</sup> SEANOL-Obesity/DGAT Research Notes, Hyeon-Cheol Shin, Ph.D, LiveChem Inc., Seoul, Korea, 2005.



### Weight Reduction Effect with SEANOL Beverage

Subjects were told to drink 1 can of product per day at any time of the day for two weeks. Each can of beverage contained SEANOL (200 mg/180 mL) and flavor. At the end of the two-week period, the body fat levels were reduced over 7% on average with some weight loss and conversion to muscle.

Baseline data

	Before	2 weeks later	Difference	% Change
Weight (kg)	76.74±16.01	75.65±15.82	- 1.09*	- 1.42
Muscle (kg)	49.01±10.33	50.14±10.16	+ 1.13**	+ 2.31
Body fat (kg)	24.88±8.92	23.02±8.88	- 1.86**	- 7.48

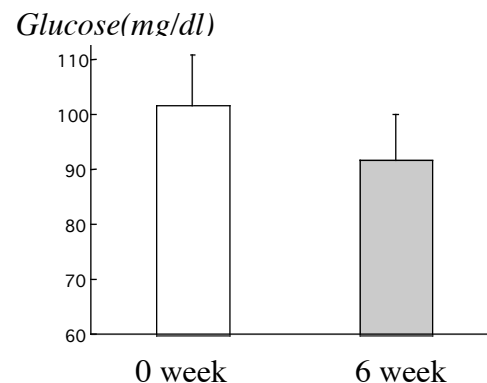
\*p<0.01, \*\* <0.001

Recently a double blind, randomize, placebo-controlled 12-week clinical trial designed to evaluate the long-term safety and effectiveness of a SEANOL-based drink in the improvement of body fat and metabolic syndromes was completed (n=117; placebo, single-dose, double-dose; dose = 720mg SEANOL in beverage form). Some of the trial results included:

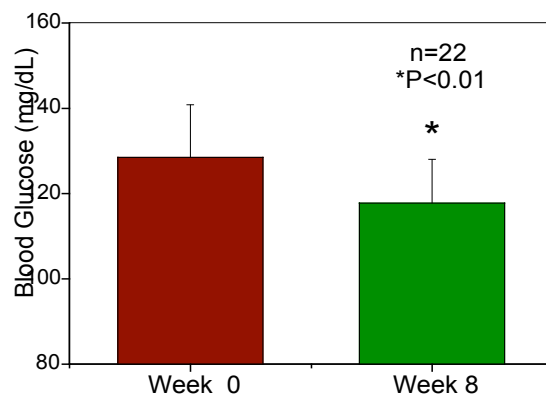
- Significant reduction in visceral fat vs. placebo;
- Significant decrease in total and LDL cholesterol vs. placebo;
- Increase in HDL cholesterol and decrease in blood glucose.

### Additional Clinical study results:

Amongst a sample of pre-diabetic women, SEANOL induced substantial reductions in blood glucose measures. The fasting serum glucose levels amongst hyperlipidemic postmenopausal women (n=17, age=56 +/-10, open label, 1.8g SEANOL/day, p<0.01). College of Medicine, Yonsei University, Korea.



Amongst a sample of early phase diabetics, SEANOL induced a significant reduction in fasting serum glucose levels. (n=22, M/F=12/10, age=56 +/-10, open label, 4.8g SEANOL/day). Department of Internal Medicine, Korea University.



#### 4. ERECTILE DYSFUNCTION

SEANOL's remarkable rejuvenating effects were confirmed in its effect on erectile function that indicates the healthy state of cardiovascular function. Phlorotannins are known to be potent antioxidants and anti-inflammatory agents. Together with their ACE inhibitory activity that is also beneficial to vascular homeostasis, these agents with long-term ingestion can contribute to a healthier vascular system, including those components necessary to erectile function.

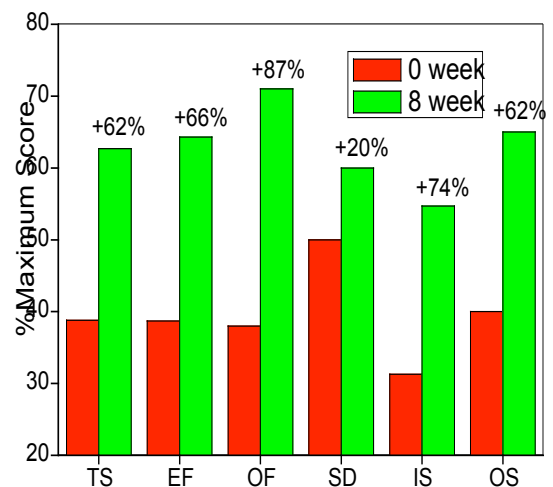
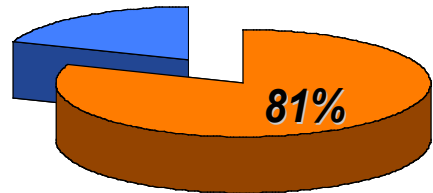
##### Vasodilation and Erectile function

It has been reported that vasculogenic ED patients have elevated level of angiotensin II during the whole course of erection process. The demonstrated action of SEANOL on ACE inhibition and resulting vasodilation is thought to play an important role in inducing successful erectile function. A clinical study of SEANOL's impact amongst ED patients showed results that were comparable or better than results achieved from Viagra that was used as a positive control.

**Clinical Study:** 8 week study, n=31, average age:  $52.7 \pm 7.7$ , 2.4g SEANOL/day;

**Evaluation:** International Index of Erectile Function (IIEF) score

Population with 25+% improvement in IIEF score was as high as 81%. Total IIEF score significantly increased from  $29.1 \pm 13.1$  to  $47.0 \pm 14.5$  with 62% of improvement. When the IIEF scores were grouped into five separate domains, mean IIEF scores at Week 8 were significantly greater than those at Week 0 for all domains (all  $p < 0.01$ ). The degree of improvement was greatest in the following order: Orgasmic Function (87%), Intercourse Satisfaction (74%), Erectile Function (66%), Overall Satisfaction (62%), and Sexual Desire (20%). Scores on key Questions 3 (frequency of penetration) and 4 (frequency of maintaining an erection after penetration), which directly indicate the ability to achieve and maintain an erection sufficient for sexual activity, were improved up to 74% and 77%, respectively ( $p < 0.01$ ). It is very important to note that despite the marginal improvement in sexual desire (20%) that is of psychological nature, great improvements were reported in the domains directly related with erection that is of physical nature and dependent on normal vascular function of the penile artery. This implies that the 8-week oral administration of the SEANOL polyphenols significantly improved the function of the penile artery that physically controls erection.



It is also noteworthy that the scores for orgasmic function (87%), intercourse satisfaction (74%) and overall satisfaction (62%) as well as erectile function (66%) are at or above levels achieved by sildenafil (Viagra) reported by Marks et al (1999) [27%, 44%, 39% and 66%, respectively]. These results demonstrate that SEANOL significantly contributed to the normalization of the general vascular conditions around the sexual organ. In other words, it strongly indicates that the long-term administration of SEANOL significantly contributed to the neutralization of oxidative risk factors, thereby improving peripheral blood circulation around muscles and nerves involved in sexual function as well as in the penile artery. Since no side effect was reported, SEANOL is a promising chemo-preventive agent for general protection of the vascular system as well as improvement of erectile function.<sup>19</sup>

## 5. NEUROLOGICAL

SEANOL has been shown to inhibit the formation of beta-amyloid brain plaque formation as well as improve short-term memory in mammals, thereby improving overall memory function.

1. The NIH's National Institute on Aging ("NIA") laboratories in Baltimore have examined a predecessor SEANOL compound in removing induced beta-amyloid plaques in rats, with very favorable outcomes;<sup>20</sup>
2. The NIA laboratories have conducted rat water-maze studies, in which the predecessor SEANOL compound established a noted improvement in rat water maze performance, as compared to controls;<sup>21</sup>
3. Anecdotal SEANOL studies on nearly 300 mild-to-moderate AD patients at the Seoul-and-Hong Kong based Mirae Medical Institute, in which nearly 60% of the diagnosed AD patients were able to resume unassisted living following three months of SEANOL daily dosing.

Studies of SEANOL have shown that it can increase levels of acetylcholine and inhibit acetylcholinesterase. Acetylcholine is a chemical neurotransmitter that sends signals between nerve cells. Acetylcholine is a primary neurotransmitter in the brain, and is associated with memory and cognition. Inhibition of its breakdown has been shown to improve memory and cognition.

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<sup>19</sup> see footnote 11

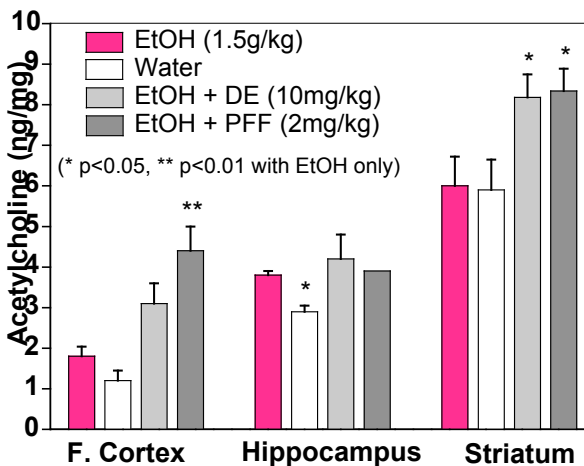
<sup>20</sup> Unpublished research findings, Prof. Bongho Lee (Hanbat National University, Korea); visiting scholar, National Institute of Aging, National Institute of Health, 2004.

<sup>21</sup> see footnote 19



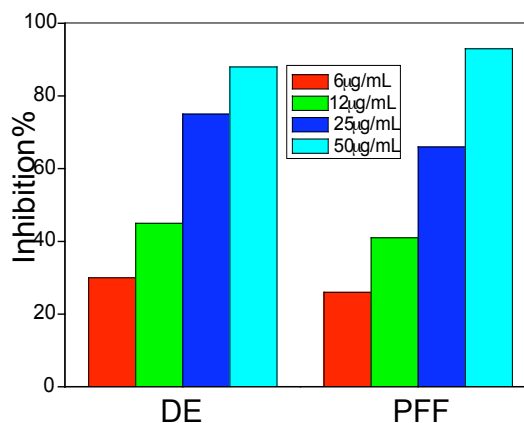
### Enhancement of Acetylcholine Level in mice brain by two SEANOL compounds

Upon 7-day oral administration of DE (10mg/kg) and PFF (2mg/kg), respectively, mice under ethanol-induced cognitive impairment condition showed substantial enhancement of acetylcholine in three brain regions related with memory formation compared with no-treatment case. Especially, 140% of enhancement was observed in frontal cortex that is crucial in long-term memory and associative thinking.<sup>22</sup>



### Acetylcholinesterase inhibitory activities of two phlorotannin compounds DE and PFF in SEANOL

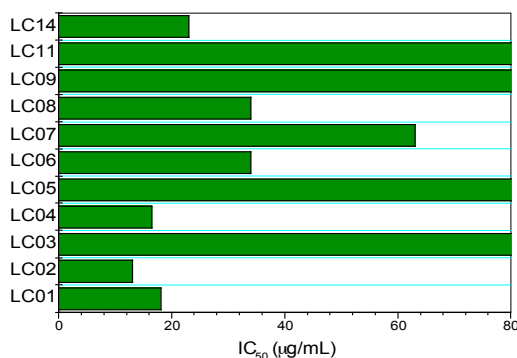
A large body of evidence is available that the neurotransmitter acetylcholine is crucial to learning and memory. Recently it was shown by applying PET imaging technique to conscious monkeys that a cholinesterase inhibitor drug, which has been used to improve cognition of patients in the early stage of Alzheimer's disease, did increase the brain level of acetylcholine and subsequently induced cognitive improvement in aged monkeys. Mild acetylcholinesterase inhibitory activity of the SEANOL compounds Dieckol (DE) and Phlorofurofukoeckol (PFF) is thought to be involved in up-regulation of neurotransmitter acetylcholine that plays crucial roles in memory and learning.



Acetylcholinesterase is an enzyme that degrades acetylcholine in the brain and other tissues of the body. Acetylcholinesterase lowers acetylcholine levels and is often targeted for inhibition by drugs seeking to treat Alzheimer's disease. SEANOL selectively inhibits acetylcholinesterase, the enzyme primarily responsible for degrading acetylcholine, thus increasing the availability of this beneficial neurotransmitter and potentially increasing memory and learning capacity without negative side effects.

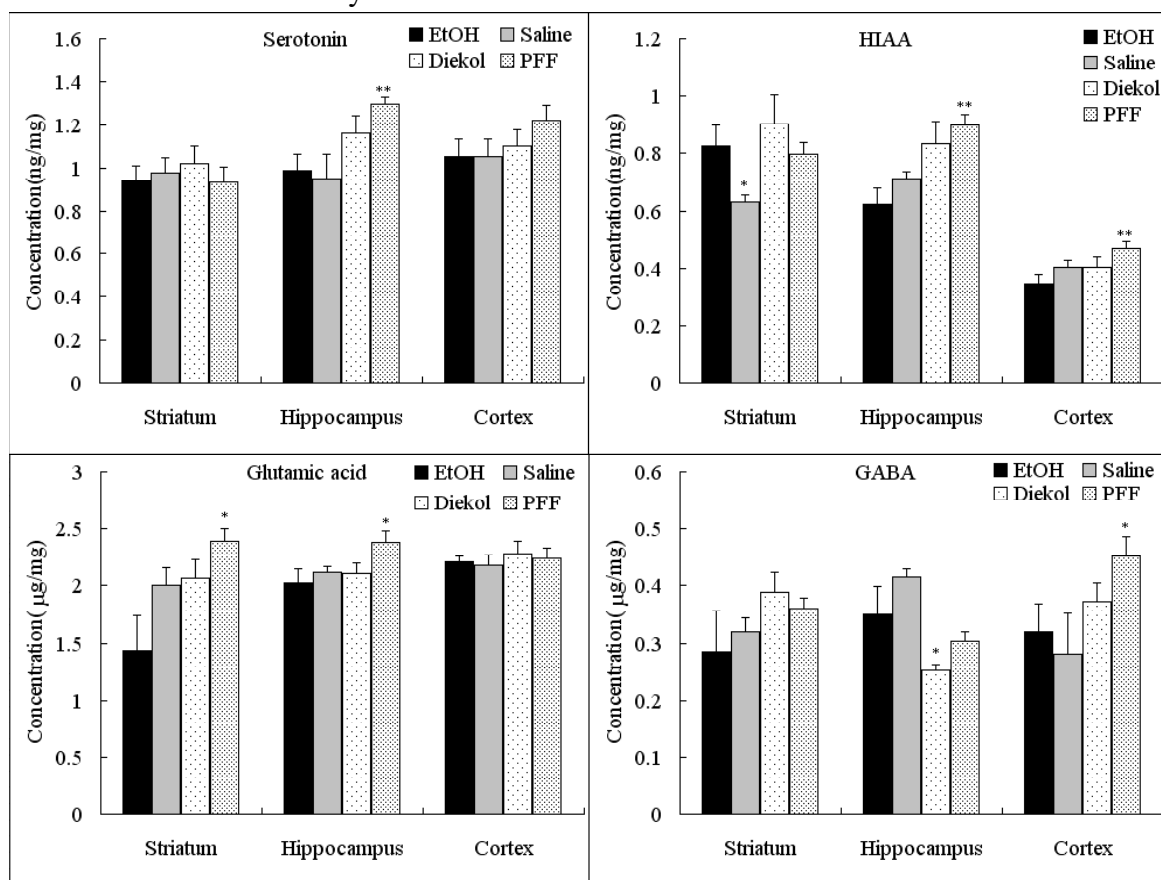
<sup>22</sup> see footnote 3

The different peaks or compounds of SEANOL (including DE and PPF) were analyzed separately for acetylcholinesterase inhibitory potency. As shown in the following table all of the peaks exhibit acetylcholinesterase inhibitory properties with several possessing exceptional inhibitory properties.



### Neurotransmitter stimulation by DE and PPF in SEANOL

The beneficial effects of SEANOL compounds on neurotransmitter levels have been demonstrated in a mouse study. There were significant increases in serotonin and GABA levels observed in the study.<sup>23</sup>

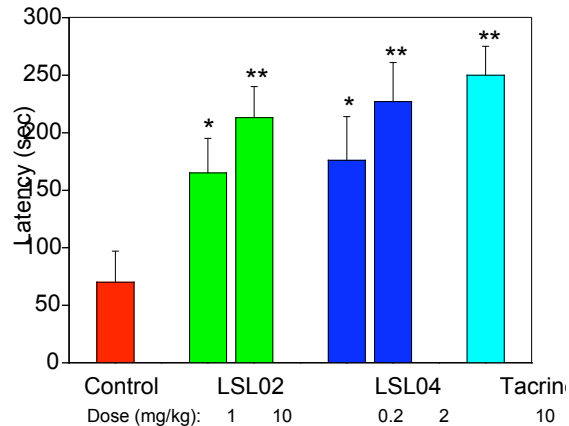


*Effects of diekol and PPF on the serotonergic/GABAergic neurotransmitter in ethanol treated mice. Values represent mean  $\pm$  S.E. (ug/mg tissue) of 6-10 mice. \*  $p < 0.05$ , \*\*  $p < 0.01$  when compared to ethanol-treated mice.*

<sup>23</sup> see footnote 21

## Memory Enhancement in mice by DE and PFF in SEANOL

The beneficial effect of the SEANOL compounds on **cognitive behavior** has been further demonstrated by measuring the latency time avoiding the previously experienced electric shock in mouse passive-avoidance memory test. Upon 7-day oral administration of DE and PFF as low as 1 and 0.2mg/kg, respectively, **mice under ethanol-induced cognitive impairment condition showed 130~140% improvement**. PFF showed comparable magnitude of effect at the dose as low as one fifth of tacrine, which is a current prescription drug for AD patients.<sup>24</sup>

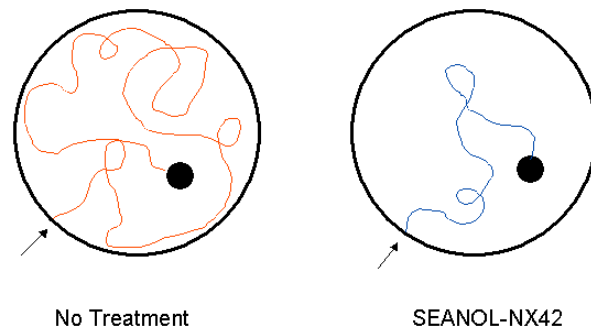


## Resistance of Learning deficit induced by stress in water-maze test

Learning trial for 5 consecutive days revealed that electric-shock treatment during learning period significantly retarded the learning process in mice. However, SEANOL treated mice showed significant resistance to learning deficiency observed in non-treated ones.

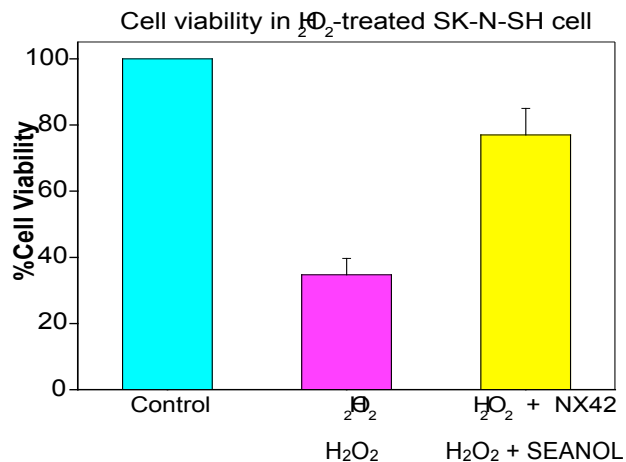
### Morris water maze test after 5-day learning

- 5-week old ICR mice)
- Exposure to 15 electric shock during learning period



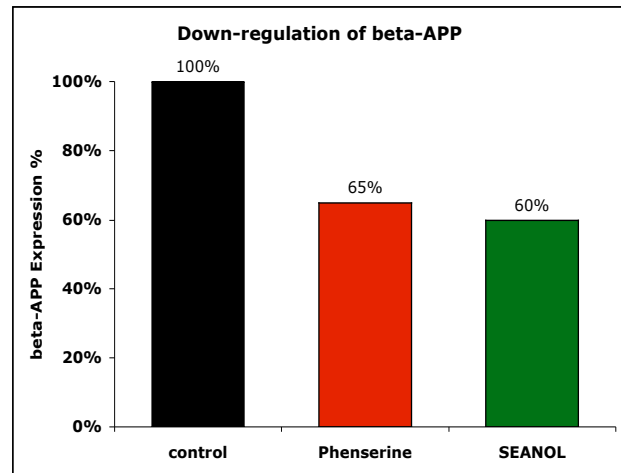
## Neuroprotective Effects of SEANOL

Neuronal cells in human brain are under constant attack by deleterious substances such as free radicals and malfunctioning amyloid proteins. SEANOL also shows powerful neuro-protective effect owing to several features of its components.



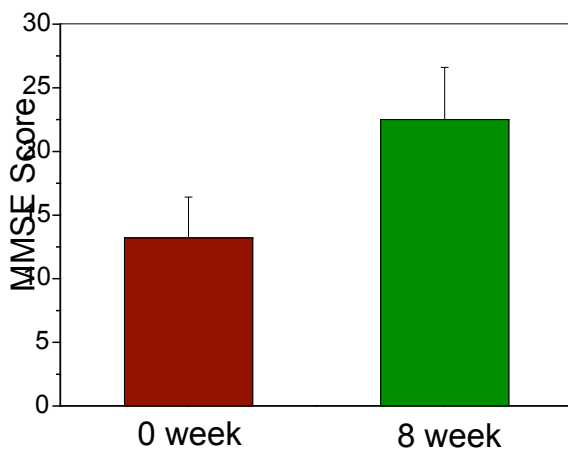
<sup>24</sup> see footnote 18

SEANOL also has been shown to have the ability to inhibit the formation of the beta-amyloid precursor protein (beta-APP), a large protein that is the source of the neurotoxic peptide, beta amyloid. By inhibiting the formation of beta-APP, SEANOL can decrease the presence of the soluble beta amyloid protein that is potentially deposited in the brain as amyloid plaques, apparently causing eventual neuronal cell death. SEANOL was shown to have similar beta-APP down regulating effect as Phenserine (Axonyx), an acetylcholinesterase inhibitor drug currently in Phase III testing.<sup>25</sup>



### Recovery of Cognitive Function Amongst Dementia Patients

After 8 weeks of oral SEANOL dosing (4.8g/day), substantial improvement in cognitive function was noted amongst light to moderate dementia patients (n=17). Dementia symptoms stopped or improved for 80% of patients. Cognitive function improvement was measured by MMSE (Mini Mental State Examination). Open label study was done at Mirae Medical Foundation, Seoul, Korea.



A series of randomized, placebo-controlled clinical studies on the favorable energy and mental acuity benefits of a SEANOL-based, non-caffeine “energy” beverage have been completed. In these studies (N=50, one can 720mg SEANOL in beverage form), notable improvements in EEG measurement of alpha and alpha/beta brain wave increases are noted (with positive implications for mental acuity), together with improved neck arterial (cranial) blood flow as measured by EKG. These studies also noted SEANOL induced increases in para-sympathetic nerve response and reduction in sympathetic nerve response (ECG measured). In addition, these studies have established a notable reduction

<sup>25</sup> see footnote 17

in drowsiness one-hour following consumption of the trial SEANOL-based energy beverage. The studies results<sup>26</sup> included:

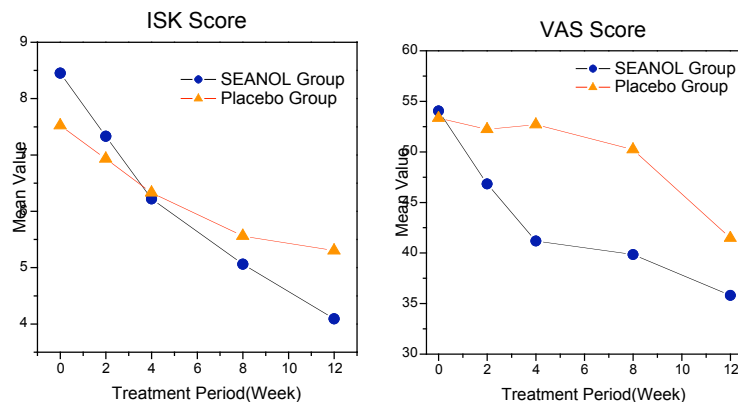
- a. Trans-Cranial Blood Flow: a 7.5-9% increase in peak and average neck blood flow, within 40 minutes of consumption;
- b. Alpha/Beta Brain Waves: a favorable 6-17% increase in beta and alpha brain waves, with a 13% increase in alpha/beta ratios, as measured against placebo;
- c. Sympathetic and Para-Sympathetic Nerve Balance: a 7% decrease in sympathetic nerve balance and an 11% increase in parasympathetic nerve balance;
- d. Driver and Student Drowsiness: Professional drivers experienced a one-day 29% reduction in overall drowsiness with SEANOL (vs. placebo), with a marked 48% reduction in drowsiness while driving. Students experienced an 11% reduction in drowsiness while studying (vs. placebo).

## 6. NEURALGIA & ARTHRITIS

SEANOL has demonstrated significant analgesic effects in inhibiting the expression of the COX enzymes for arthritis, as well as for neuropathic and FMS/CFS pain. Clinical studies show that SEANOL's impact on neuralgia for osteoarthritic patients is comparable to the COX-2 inhibitors (used as a positive control) that also is reinforced by the 30% reduction in pain found in the SEANOL study among FMS patients.

SEANOL was tested for efficacy in a 12-week study amongst patients (n=82, SEANOL group=55, placebo group=27) with osteoarthritic knee conditions. The dosing was 600 mg SEANOL/day. The results below demonstrate the potential benefits of SEANOL to this population:

- ISK: Index of Severity of knee Joint (1~5, 5 with most severe)
- VAS: Visual Analogue Scale of Pain (0~100mm, 100mm with highest pain)

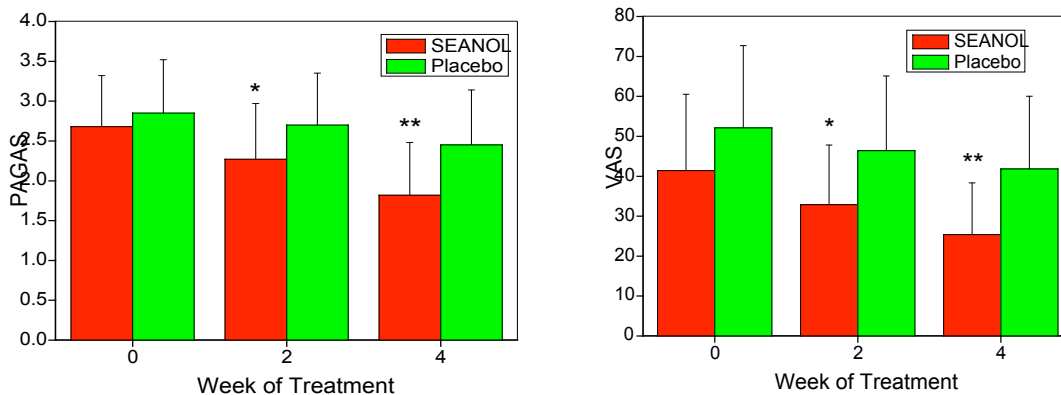


<sup>26</sup> see footnote 8

A 4-week clinical study of patients with **neuropathic pain** (N=40, randomized, double-blinded, placebo-controlled) established that SEANOL capsule product (Fibronol) has a **highly favorable impact on neuropathic pain (79% positive response, average neuropathy reduction over 4 weeks of 40%)**. Active product dosing was 2g of SEANOL/day. Patient's global assessment (PaGAs) and Visual analog scale of pain (VAS) were measured at baseline, 2 weeks and 4 weeks.<sup>27</sup> **Standard prescription medications for neuropathic pain typically tend to have a low rate of response in effecting a significant decrease in neuropathic pain.**

### Anthropometric parameters at baseline

	Total	SEANOL (n=22)	Placebo (n=20)
Age	55.9 ± 11.1	54.7 ± 10.9	57.2 ± 11.5
Sex (M:F)	24:18 (57%:43%)	12:10 (55%:45%)	12:8 (60%:40%)
Height (cm)	165.9 ± 7.9	165.6 ± 8.2	166.2 ± 7.7
Weight (kg)	59.7 ± 9.2	59.6 ± 9.6	59.8 ± 9.0



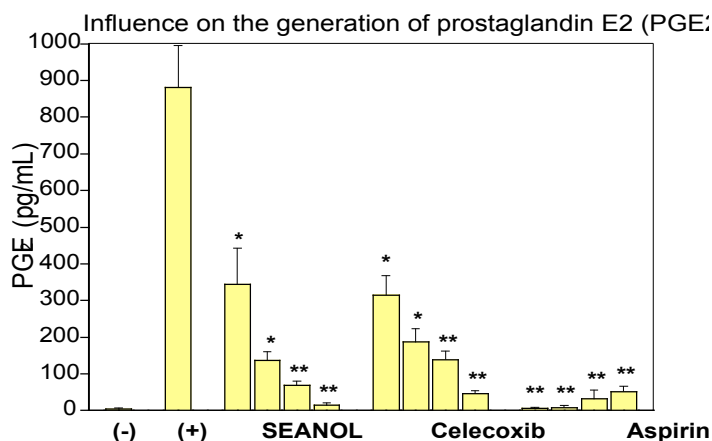
PAGAS/VAS assessment scales: \*p<0.05, \*\*p<0.01

### Anti-inflammatory activities of SEANOL

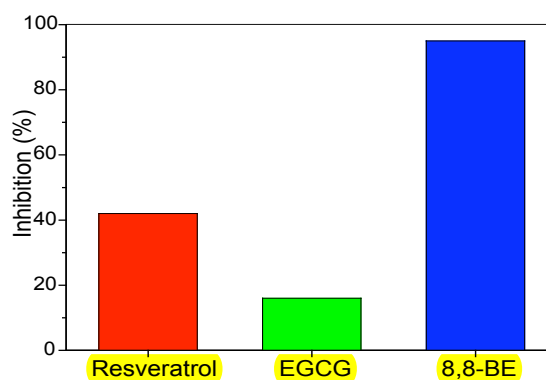
The influence of SEANOL in LPS-induced generation of **PGE<sub>2</sub> using** RAW 246.7 cells was studied. While PGE<sub>2</sub> was barely detectable in non-stimulated cells, more than hundred-fold PGE<sub>2</sub> was detected in the stimulated cells. **SEANOL, celecoxib and aspirin all showed significant inhibition of PGE<sub>2</sub> generation in the concentration range tested**

<sup>27</sup> *Evaluation of FIBRONOL on the Relief Effects on Neuralgic Pain*, Sekyu Kwon M.D., Seonje Lee M.D., Mirae Medical Foundation, Seoul, Korea, September 30, 2005.

(10~100  $\mu\text{g/mL}$ ). SEANOL showed inhibition of 61%, 85%, 92% and 99% at concentration of 10, 30, 60 and 100  $\mu\text{g/mL}$ , respectively, showing similar activity to celecoxib that showed 65%, 79%, 85% and 96%, respectively.<sup>28</sup>



Lipoxygenases (LOXs) are involved in the biosynthesis of various bioregulators, which are closely related to pathogenesis of allergies, atherosclerosis and some cancers. 5-Lipoxygenase (5-LOX) catalyzes the first step in the oxygenation of arachidonic acid, thus leading to the production of biologically active compounds such as leukotrienes and 5-hydroxyeicosatetraenoic acid. The peptidoleukotrienes (leukotriene C4, leukotriene D4 and leukotriene E4) are powerful spasmogens, which have been implicated in inflammatory and allergic responses. Therefore, inhibition of 5-LOX is a medicinal target for the treatment of inflammatory diseases. One of the SEANOL compounds (8,8-BE) is an excellent inhibitor of 5-LOX compared with other well-known natural medicinal compounds such as resveratrol and EGCG.<sup>29</sup>



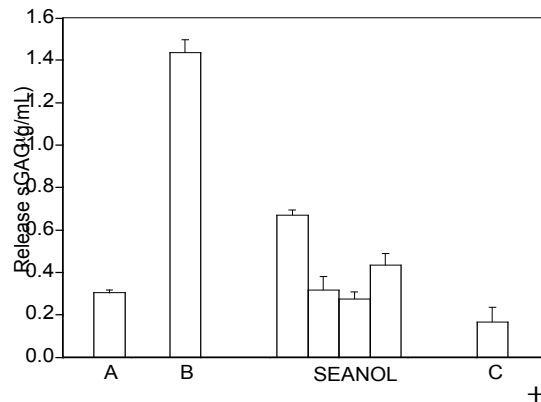
### Cartilage protecting activities of SEANOL

Rabbit articular cartilage explant culture was treated with recombinant human interleukin 1 $\alpha$  (rhIL-1 $\alpha$ ) to induce proteoglycan degradation. The amount of glycosaminoglycan released into the medium was measured as an index of proteoglycan degradation. When the rabbit cartilage explants were treated with rhIL-1 $\alpha$  for 60h, the amount of released glycosaminoglycan into the culture medium increased significantly compared to the vehicle group ( $1.44 \pm 0.06 \mu\text{g/mg}$  vs.  $0.30 \pm 0.01 \mu\text{g/mg}$ ).

<sup>28</sup> H-C Shin, H.J. Hwang, K.J. Kang, B.H. Lee, *An Antioxidative and Anti-inflammatory Agent for Potential Treatment of Osteoarthritis from Ecklonia Cava*, Arch Pharm Res Vol 29, No 2, 165-171, 2006.

<sup>29</sup> Toshiyuki Shibata, et al, *Inhibitory effects of brown algal phlorotannins on secretory phospholipase A<sub>2</sub>s, lipoxygenases and cyclooxygenases*, Journal of Applied of Phycology 15, 61-66, 2003.

10 $\mu$ M (3.2 $\mu$ g/mL) diclofenac that is known as a selective COX-2 inhibitor was used as a positive control. SEANOL significantly interfered with the rhIL-1 $\alpha$ -mediated degradation of proteoglycan in all concentrations tested ( $p < 0.001$ ). It showed 53%, 79%, 81% and 70% of inhibition at 1, 3, 10 and 30  $\mu$ g/mL concentration, respectively. In the figure, (A) no rhIL-1 $\alpha$ , (B) rhIL-1 $\alpha$ , (C) rhIL-1 $\alpha$  + diclofenac (10 $\mu$ M), For VENTOL (SEANOL), rhIL-1 $\alpha$  1, 3, 10 and 30 $\mu$ g/mL (from left to right)



## 7. FIBROMYALGIA

SEANOL based capsule product (Fibronol<sup>®</sup>) provided major multi-symptom management (i.e., reduction in pain, fatigue, sleep disorders) for fibromyalgia (FMS) patients. From a mechanism of action perspective among FMS patients, the research conducted on SEANOL demonstrates anecdotally that it promotes increased serotonin and HGH production, and it is hypothesized that it also serves to down-regulate ‘Substance-P’ leading to reduced nociception (amplification of pain sensations).

In an important pilot fibromyalgia clinical study (n=36), the SEANOL-based Fibronol product evidenced the following clinical outcomes: 71% increase in energy, 56% increase in sleep quantity, 80% improvement in the quality of sleep, 45 min faster to sleep, 30% reduction in pain, 39% improvement in Global Impact (functions of daily life).<sup>30</sup>

Notably, the advanced (Phase III) clinical studies sponsored by major pharmaceutical companies that have been organized and conducted for their developmental fibromyalgia compounds have virtually all been unable to achieve statistical significance from placebo or ‘p-values’ in outcomes (typical ‘p-values’ have ranged from 0.4-0.6). In direct contrast to these results, Fibronol’s typical ‘p-values’ in primary clinical outcomes with confirmed FMS patients were <0.001 in value (the only exception in ‘p-value’ was <0.024, for “mean time to sleep”) in this small (n=36) Phase I clinical study.

## 8. CANCER

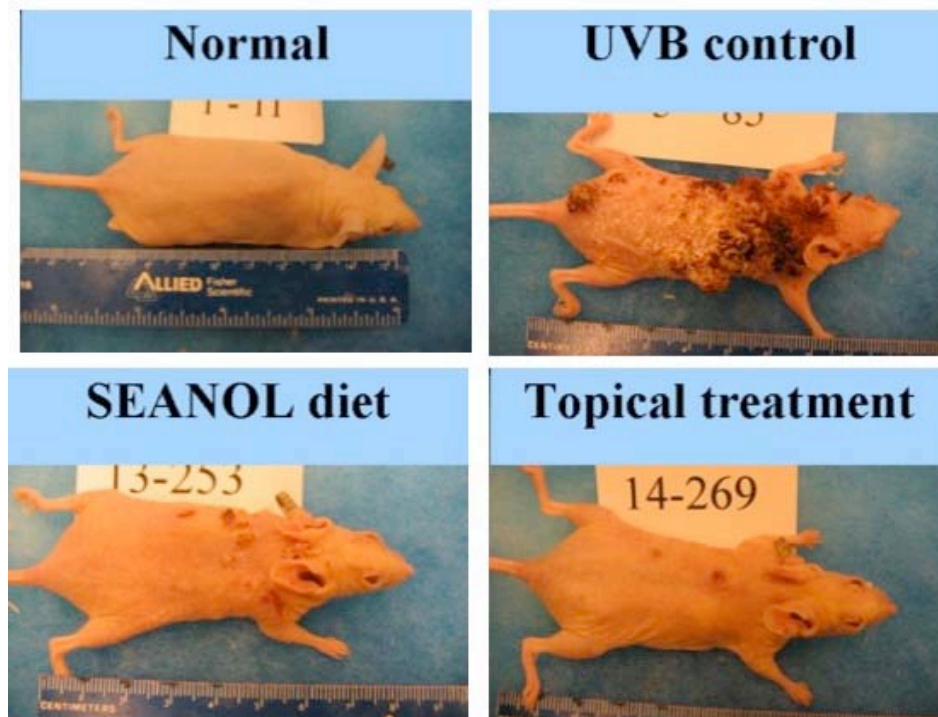
SEANOL anti-tumor effects currently tested only for dermatologic cancers in mice. No clinical studies of the anti-cancer potential of SEANOL have been conducted to date, although a single murine dermatological cancer study performed on SEANOL is summarized below:

<sup>30</sup> Fibronol Phase 1-a Clinical Study Abstract, Craig Palmer Ph.D, Fibronol LLC, November 2005, unpublished study



### Chemoprevention of UVB-induced Skin Carcinogenesis by SEANOL on SKH-1 Mice

1. Purpose of the Study: Chronic exposure of solar ultraviolet B (UVB) radiation to skin induces oxidative stress, which plays a crucial role in the induction of **non-melanoma skin cancer**. In this study, the research investigated the effect of oral feeding and topical application of SEANOL on **UVB radiation-induced skin carcinogenesis** on SKH-1 mice.
2. Protocol: SKH-1 hairless mice (N=48) were **treated orally or topically with SEANOL** and irradiated with UVB three times (160mJ/cm<sup>2</sup>) per week for 26 weeks.
3. **Summary of Results - In both dietary and topical treatment of SEANOL**
  - **Significantly reduced tumor multiplicity by ~50%**
  - **Significantly decreased PGE2 levels by 50~80%**
  - **Significant down-regulation of inflammatory genes (COX2 and iNOS)** was also observed through RT-PCR, Western Blot, etc
  - Regulation of other genes are in question



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The results of this study provide evidence that SEANOL possesses excellent anti-photo carcinogenesis effect, which may be associated with the prevention of UVB-mediated oxidative stress, an inflammation pathway in the skin. The study also indicates potential for chemoprevention of other types of cancer.<sup>31</sup>

Another outcome of the study was the finding that SEANOL affords strong protection against UVB-induced iNOS suppression and inflammatory damage in the skin. Chronic exposure to UVB induced substantial increase in iNOS expression together with severe damage in the skin. However SEANOL significantly inhibited the production of iNOS by 48-78% depending upon dosage level and delivery method (dietary or topical).<sup>32</sup>

## 9. ALLERGIES

SEANOL has been shown to dramatically relieve allergic reactions without any drowsiness, dizziness and other side effect of anti-histamine drugs. Its effectiveness has been demonstrated in an allergen-induced murine asthma model.

### Effect of SEANOL on Allergen-induced murine asthma model

Airway infiltration and remodeling in chronic asthma is characterized by eosinophils, mucus cell hyperplasia with mucus hypersecretion accumulation of mononuclear cells in airway interstitium and sub-epithelial fibrosis of the airway wall. SEANOL ("KLS" in test results) was tested in a mouse model of allergen induced chronic lung inflammation and fibrosis. BALB/c mice, after I.P. OVA sensitization on day 0 and day 14, gave intranasal (i.n.) inhalation of OVA weekly about day 14-60. The OVA-treated and challenged mice developed an extensive eosinophil and mononuclear cell inflammatory response, mucus cell hyperplasia and mucus occlusion of the airway. A striking feature of this inflammatory response was the widespread deposition of collagen beneath the airway epithelial cell layer and also in the lung interstitium in the sites of leukocytic infiltration that was not observed in the saline-treated control mice.

SEANOL was tested and found effective in reducing allergic reaction in inflammation. By feeding at a concentration of 5.4 mg/ml in the drinking water for 12 days, SEANOL reduced the airway mucus plugging, and sub-epithelial fibrosis in the OVA-sensitized/ challenged mice. The reduced BAL fluid eosinophil indicated that SEANOL is effective in improving the asthmatic lung structures. After 12 days of feeding, SEANOL demonstrated no pathological alterations in the liver, kidney, spleen, or small intestine.

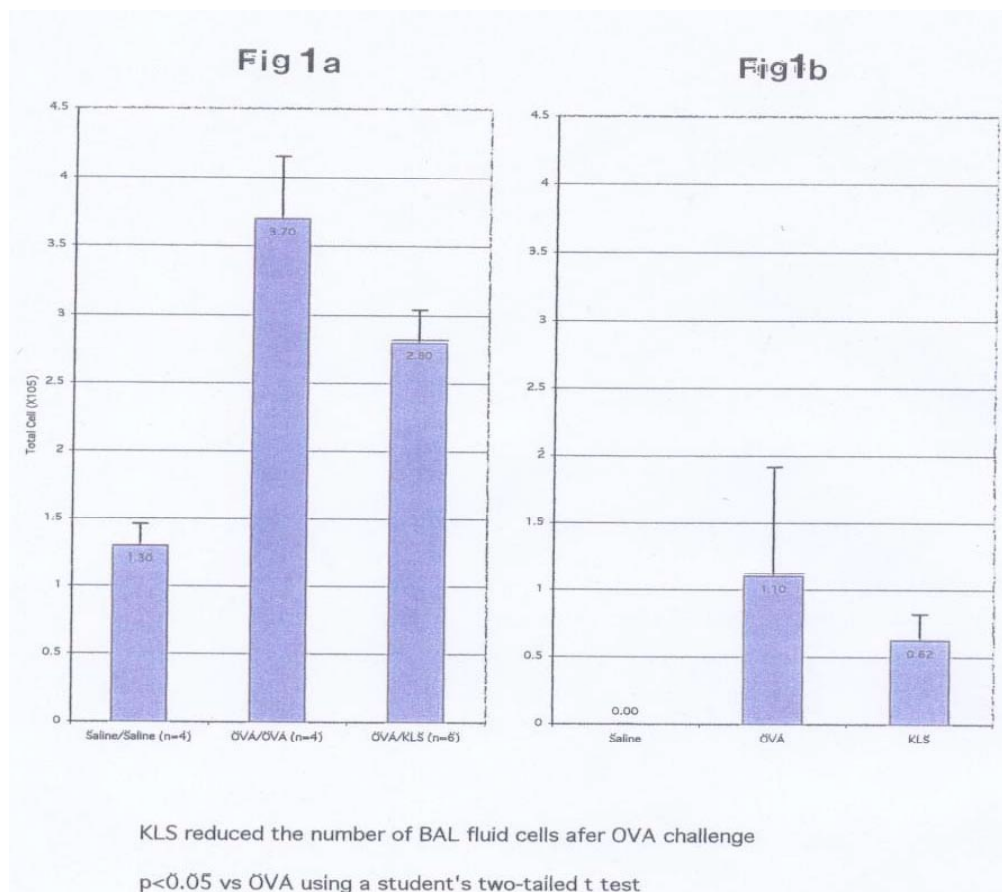
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<sup>31</sup> H. Hwang, T. Chen, R. Nines, H-C Shin, G. Stoner. *Photochemoprevention of UVB – induced skin carcinogenesis in SKH-1 mice by brown algae polyphenols*. International Journal of Cancer: 119, 2742-2749 (2006).

<sup>32</sup> H. Hwang, T. Chen, G. Stoner, K-B Lee, Y-C Yoo, H-C Shin. *Suppression of iNOS Expression by Phlorotannins in Chronic Exposure of Skin to UVB Radiation*. Laboratory Animal Research 2005; 21(4), 385-389.

**Summary of results:<sup>33</sup>**

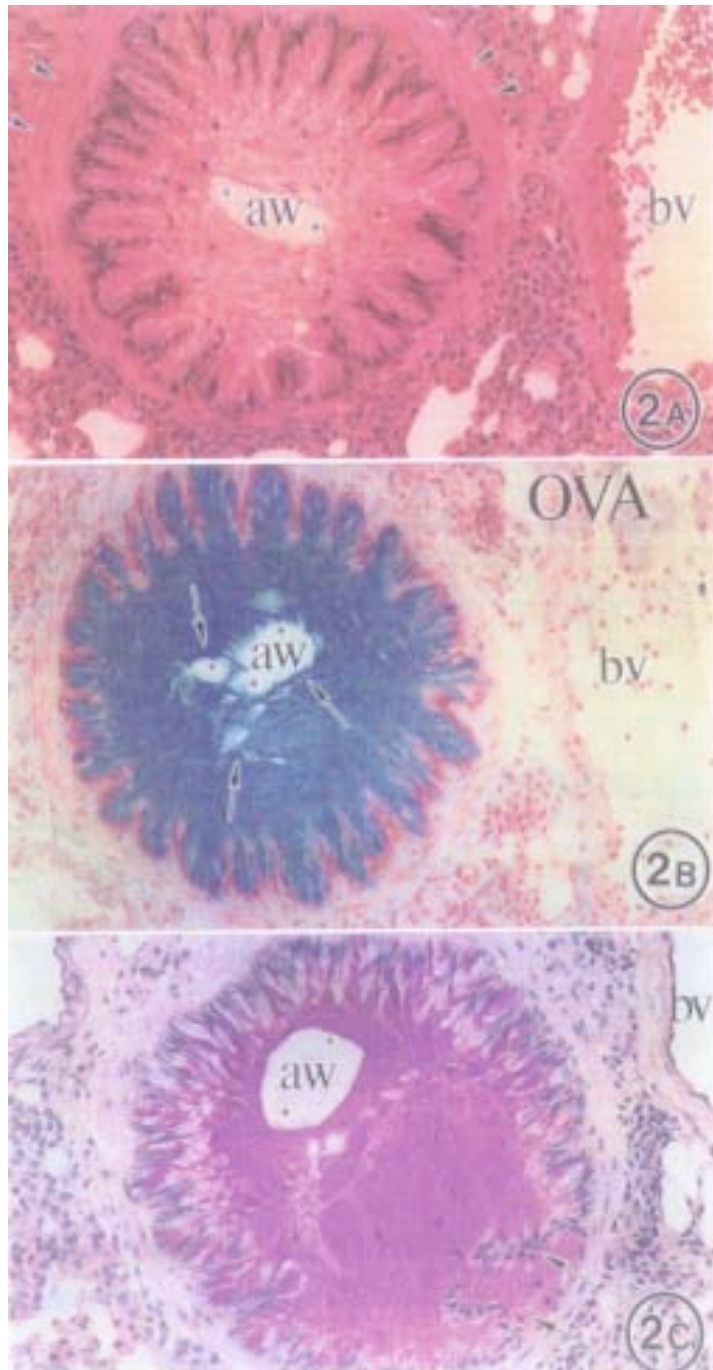
- Eosinophil migration in the lung reduced by 75%
- Cellular infiltration (CD4+4 T Cells, resultant cytokines IL-4, 5, 13) reduced by 50%
- Mucus plug in airways reduced by 75%
- Airway epithelial hyperplasia reduced by 75%
- Collagen in lung interstitium (fibrosis, airway remodeling) and smooth muscle cell thickness reduced by 20% and 32%, respectively



**Fig. 1**

SEANOL (KLS) reduced the number of eosinophils in BAL fluid after OVA challenge. BAL fluid was obtained on day 62 from saline-treated mice (sal/ sal; n=4) and OVA treated mice (OVA/ OVA; n=4) or fed with 25 mg KLS per day for 12 days (OVA/ KLS; n=6).

<sup>33</sup> *Effect of KLS (renamed SEANOL) on Allergen-induced murine asthma model (Summary)*, Dr. Emil Chi, Chairman, Dept. of Histopathology, University of Washington, 2005.



**Fig. 2**

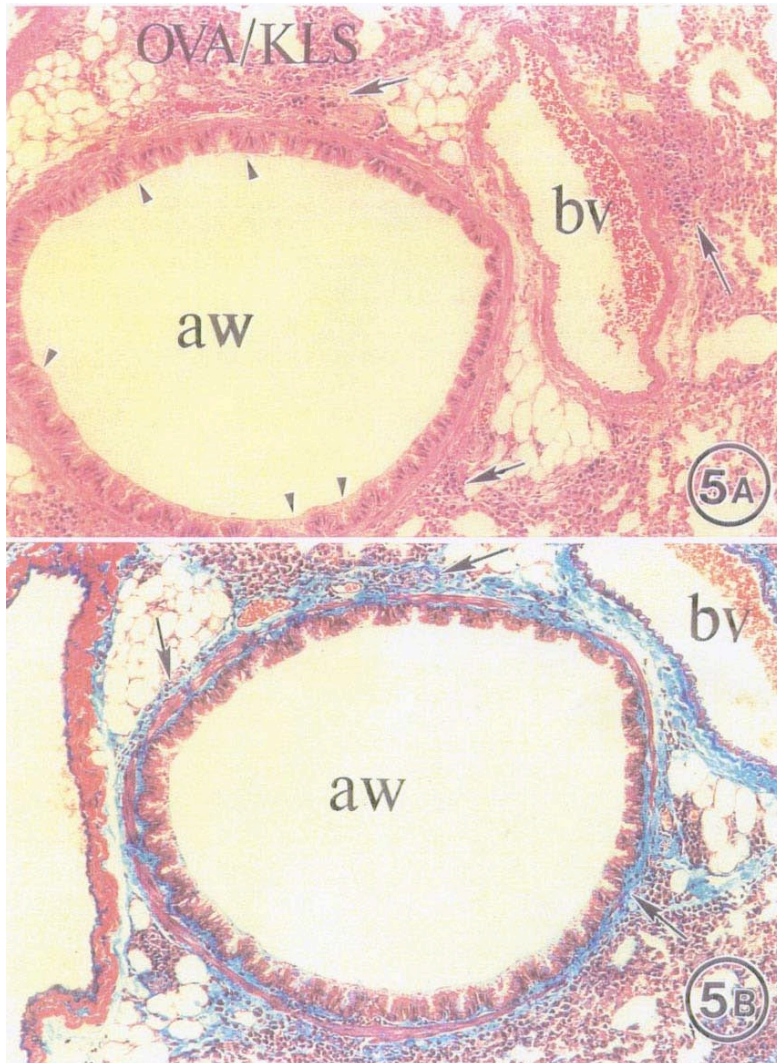
**Airway inflammation** in OVA treated mice. Lung tissues of OVA-treated mice (OVA, A, B, C).

A) In the OVA immunized/challenged mice, a **dense inflammatory cell infiltrate around the airway (aw) and blood vessels (bv)** is observed. Eosinophil and mononuclear cells are the predominant cells in the OVA treated mice. **Airway wall are thickened** (arrowheads). H&E stain, X150.

B) **Mucus occlusion** (arrows) of the airway (aw) lumen is observed in the OVA/OVA treated mice. Alcian blue with nuclear fast red counterstaining reveal the mucus prevent in the airway lumen. In this section, **the mucus substances occupied the major proportion of the space in the airway (\*)**. X150

C) PAS Staining of the serial section of (A) and (B) shows **the airway lumen is filled with carbohydrates; many mucus cells are slash off the airway (arrows)**. PAS stain, X150.





**Fig. 3**

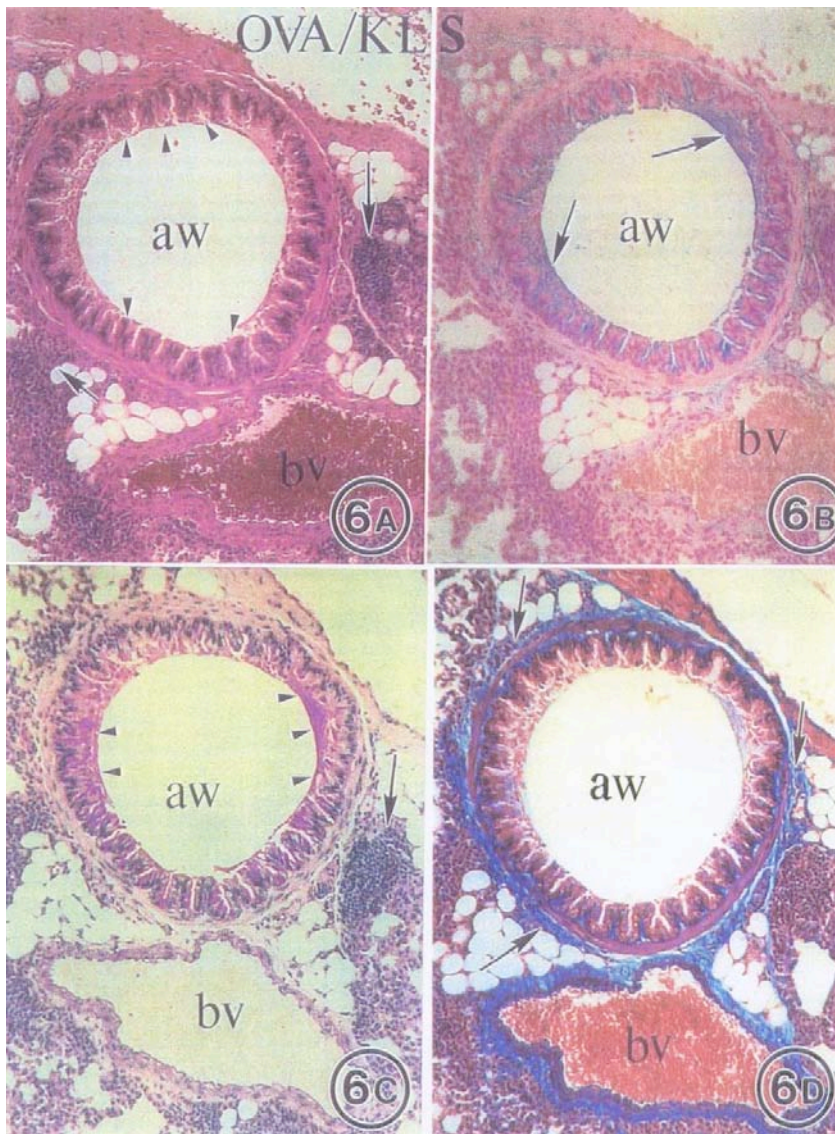
**Effect of SEANOL (KLS) on airway inflammation and remodeling in OVA treated mice.** Lung tissue of OVA-sensitized/ challenged mice fed with KLS for 12 days at 25 mg per day was obtained. Stained with hematoxylin and eosin (A) and Masson's trichrome (B).

5A) The **inflammatory infiltration** (arrows) of the lung interstitium around the airway (aw) and blood vessels (bv) **is reduced** by feeding SEANOL (KLS) treatment in OVA-sensitized/ challenged mice. X100

5B) **A reduction in lung collagen deposition** (arrows) around the airways (aw) and blood vessels (bv) is seen in the OVA-sensitized mice treated with SEANOL (KLS). X100

Fig. 6

**SEANOL (KLS) reduced airway inflammation and fibrosis** in OVA-treated mice. Lung tissue was obtained from OVA-sensitized/ challenged mice treated with KLS. The tissue was examined by a series section to illustrate various features of cell infiltration by hematoxylin and eosin staining (A). Mucus released by alcian blue staining (B), carbohydrate substances by PAS reaction, and (C), and collagen deposition by trichrome staining (D).



6A) **SEANOL (KLS) treatment decreased the cellular infiltrate (arrows) of the lung interstitium around the airway (aw).** Protein of the airways is free of mucus materials (arrowheads). X100

6B) Mucus release (arrows) into the airways (aw) is decreased. X100

6C) PAS positive carbohydrate substance (arrowheads) also reduced. X100

6D) SEANOL (KLS) inhibits some collagen deposition (arrows) in the interstitium of airway (aw) of the OVA-treated mice. X100

## V. CONCLUSION

SEANOL is a potent new polyphenol/phlorotannin compound extracted from brown algae. SEANOL is currently offered commercially in nutraceutical form only through selected sources. These polyphenols are chemically distinct from all land-based polyphenols, and possess a unique hydrophobic content, which has potential favorable metabolic effects both for longer metabolism and passing the blood-brain barrier.

Extensive pre-clinical and clinical research has been conducted on these specific compounds over the past 14 years. On the basis of this research, SEANOL is a safe polyphenol/phlorotannin compound with an unusual degree of potential efficacy in medical indications ranging from: CAD/CHD, diabetes, AD, erectile dysfunction, FMS/CFS, sleep disorders, neuropathy, vasculitis, osteoarthritis, and even potentially certain cancers.

In the short term, SEANOL-based nutraceuticals may represent a uniquely valuable new tool for physicians and others to offer to their patient and customer bases as an alternative supplement in augmenting their current standard of care. It is exciting to consider that SEANOL-based polyphenol nutraceuticals may represent a unique and more potent “weapon” in the physician and individual ‘tool-kits’ being applied to reduce a number of primary risk factors in indications having a high prevalence in North America and throughout the world.