Overview of Seanol

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SEANOL

A Cardio Wonder from the Sea

SEANOL, unique complex of marine complexes with many wonders of biological activities

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

Wonders of SEANOL

- Unprecedented vascular protection and rejuvenation
- Remarkable enhancement and protection of cognitive function
- Record-breaking efficacy can be realized: dramatic promotion of physiological action of various medicinal substances when applied together

TYPE 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.

Safety Features of SEANOL products

SEANOL products are manufactured from edible algae through food-compatible processes. So far several tens of thousands of people throughout the world have experienced SEANOL in various forms of product without side effects.
Several toxicity tests have been performed in GLP facilities and no adverse effect has been found in any of the test at effective human dose level (1~10mg/kg)

Examples of toxicity tests on SEANOL products

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

Test Type	SEANOL Content	*NOAEL (mg/kg)
Acute toxicity on rat	Type II, 65%	>2000
Acute toxicity on rat	Type I, 20%	>2000
Acute toxicity on dog	Type II, 65%	>1000
4-week chronic toxicity on rat	Type I, 20%	>2000
13-week chronic toxicity on rat	Type II, 65%	>1000
13-week chronic toxicity on dog	Type II, 65%	>111

*NOAEL: Non Observed Adverse Effects Level

Discoveries on physiological actions of SEANOL

Various physiological activities of SEANOL have been evaluated in vitro, in vivo and clinically as individual compounds (SN_1~SN_{14}) and complex form (SEANOL, Type I~IV), revealing its wonders in many well-being areas.

Summary of discovered physiological activities of SEANOL

Physiological Activities	Measurement method	Test type	Test Sample
Antioxidant activity	Free Radical Scavenging (DPPH)	t	SN_i/SEANOL(I~IV)
	Reducing Power (FRAP)	t	"
	Reducing Power (FRAP)	v	SEANOL(I)
	Peroxynitrite Scavenging	t	SN_i/SEANOL(I,II)
	Inhibition of LDL oxidation	t	"
Vasodilation	ACE inhibition	t	SN_i/SEANOL(I,II)
	Blood Pressure in SHR	v	SN_{i-k}
	Blood Pressure in renovascular surgery-induced hypertension	v	SEANOL(IV)
Fibrinolysis Promotion	Antiplasmin inhibition	t	SN_i
Heart Protection	Protection from Reperfusion Injury	v	SEANOL(I)
Anti-inflammation	Hyaluronidase assay	t	SN_i
	Phospholipase A2 assay	t	SN_i
	Lipoxygenase assay		
	LPS-induced PGE2 in macrophage	t	SN_i/SEANOL(III)
Arthritis treatment	Measurement of sGAG	t	SEANOL(III)
	Collagenase-induced Osteoarthirtis 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 Reductae	t	SEANOL(I,II)
Anti-Obesity	DGAT inhibition	t	SN_i/SEANOL(I,II)
	Body fat/Muscle	c	SEANOL(I)
Brain Function	bAPP down regulation	t	SEANOL(II)
	AChE inhibition	t	SN_i
	Memory Enhancement	v	SN_i
	MMSE	c	SEANOL(I)

* t = in vitro, v = in vivo, c = clinical
* SN_i : Individual compounds in SEANOL

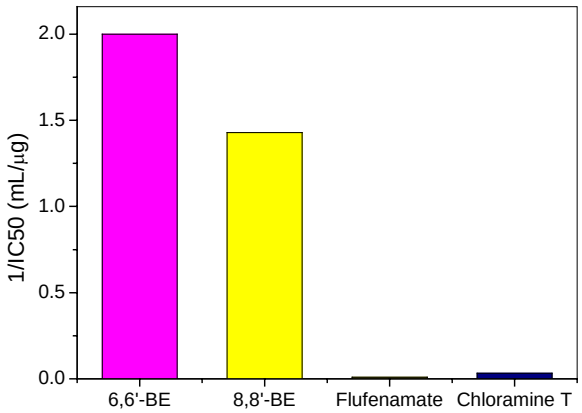
Unprecedented Cardiovascular protection and rejuvenation by SEANOL

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. Therefore multiple protections from different kinds of risk factors will greatly enhance the efficacy of a treatment. Multiple features of SEANOL for cardiovascular protection have been discovered in vitro.

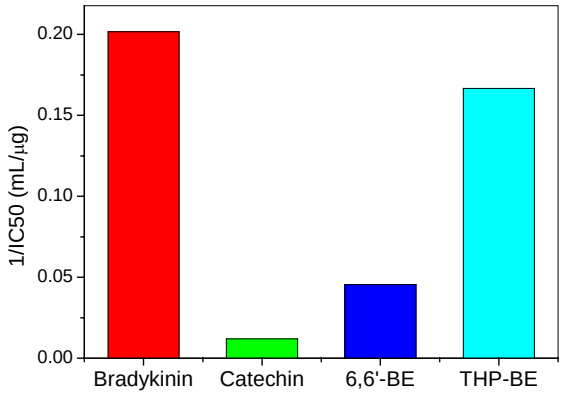
In vitro features of cardiovascular protection by SEANOL
- Promotion of Fibrinolysis by inhibition of antiplasmin
- ACE inhibition
- Multiple modes of antioxidative protection

* Promotion of dissolution of intravascular blood-clot via antiplasmin inhibition

Chronic inflammatory intravascular injuries due to aging and contamination of blood cause excessive coagulation to increase the blood viscosity which retards the blood circulation. A fibrinolytic enzyme called "plasmin" which is supposed to break down the blood clot is rapidly blocked by a protein called antiplasmin. SEANOL compounds, natural potent inhibitors of the antiplasmin are capable of efficient promotion of plasmin which 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 Chlroamine T. (figure1)



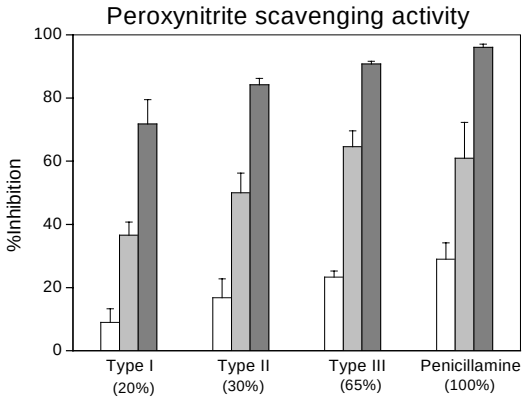
SEANOL tannins are potent natural ACE inhibitors

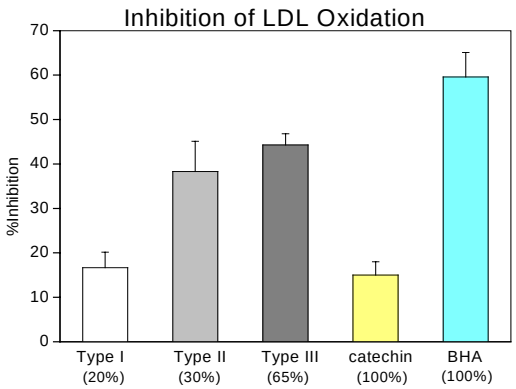


Angiotensin-converting enzyme (ACE), which is responsible for conversion of angiotensin I to angiotensin II and degradation of bradykinin, is a key component in the renin-angiotensin-aldosterone system. Angiotensin II regulates cellular proliferation, inflammation, and endothelial function, and is therefore important in the pathogenesis of atherosclerosis and its complications.
Upon aging or due to various vascular risk factors tend to increase the ACE level resulting in excessive vasoconstriction and hypertension. Current hypotensive drug block the action of ACE or its product angiotensin II. SEANOL compounds are capable of suppression of ACE and thus promotion of effective vasodilation. (Fig. 2) They are much more potent than a natural hypotensive substance catechin existing in green tea. Especially, one of the compounds in SEANOL, THP-BE is comparable to physiological vasodilative hormone called bradykinin.

Multiple antioxidant profiles of SEANOL

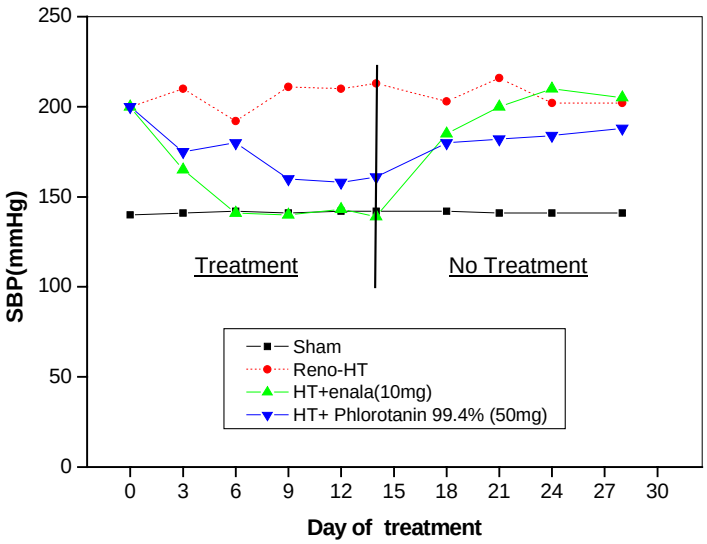
SEANOL' antioxidant activities against various reactive oxygen species which are known to attack endothelial cells causing endothelial dysfunction have been confirmed to be highly potent in physiologically relevant concentrations. Effective dose of SEANOL for free radical scavenging is 10~20 μg/mL range which belongs to most potent families of natural antioxidants. SEANOL itself and its individual compounds showed potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite. Even though antioxidant properties of SEANOL are only one of its health-beneficial features, they can contribute to its perfection in protection of vascular system together with other potent activities.





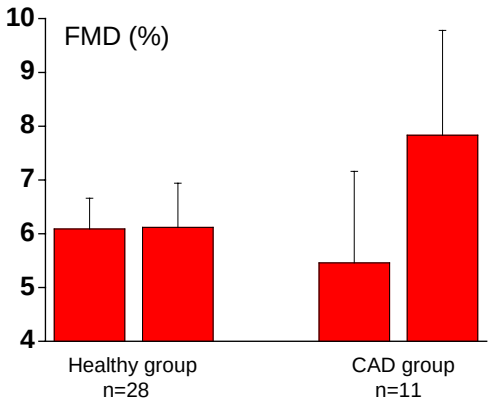
Effective cardiovascular protection by SEANOL has been clearly demonstrated in renovascular hypertensive rat study.

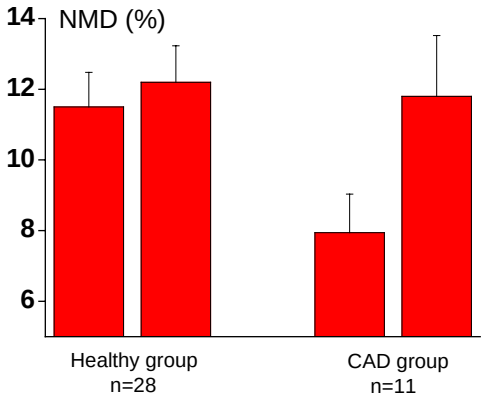
The remarkable effect of SEANOL on vasodilation was clearly demonstrated in the renovascular-clipping induced hypertensive rats. Renovascular clipping surgery which is known to increase the ACE activity via rennin-angiotensin-aldosterone system increased the systolic blood pressure (SBP) from 140 up 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. 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.



SEANOL's cardiovascular rejuvenation has been confirmed in two 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 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.

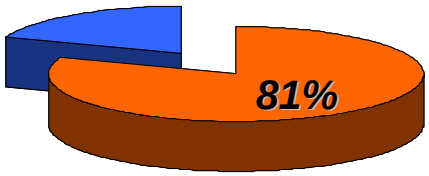
SEANOL's remarkable rejuvenating effect was again confirmed in its effect on erectile function which indicates the healthy state of cardiovascular function.

Clinical Condition

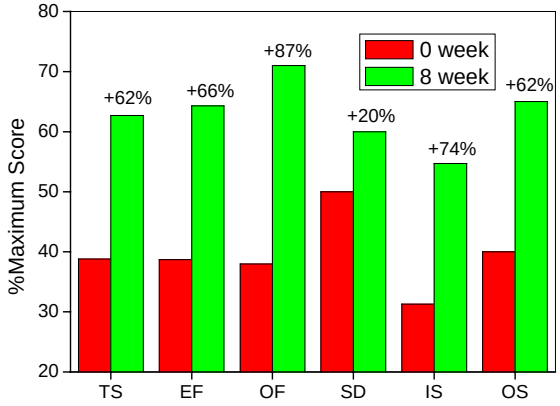
- 8 week, n=31, Average age: 52.7 ± 7.7
- Disease history

- None 14
- Diabetes 4
- Hypertension : 5
- Impotence treatment experience : 5
- Important operation history : 2

- Disease period: more than 6 months
- Test period : 8 Week
- 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 ± 13.1 to 47.0 ± 14.5 with 62% of improvement. When the IIEF scores were grouped into five separate domains, mean IIEF scores at 8th week were significantly greater than those at 0 week for all domains (all $p<0.01$). The degree of improvement was great in the following order: OF (87%), IS (74%), EF (66%), OS(62%), and SD(20%). Scores on key questions 3 (asking frequency of penetration) and 4 (asking frequency 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%) which is of psychological nature, great improvements were reported in the domains directly related with erection which is of physical nature and dependent on normal vascular function of the penile artery. This implies that the 8-week oral



administration of the brown-algae polyphenolics significantly improved the function of penile artery which physically controls erection. It is also noteworthy that great increase of the score in orgasmic function (87%), intercourse satisfaction (74%) and overall satisfaction (62%) as well as erectile function (66%) in comparison with the results for sildenafil reported by Marks et al (Marks, et al., 1999) (27%, 44%, 39% and 66%, respectively), indicates 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 the sexual function as well as the penile artery.

Since no side effect was reported, it is very promising to use SEANOL as a chemopreventive agent for the general protection of vascular system as well as improvement of erectile function.

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SEANOL-AL

For Allergies

I. Allergy, flu and SARS

- Due to increasing release of various pollutants from modern environments, more and more population is exposed to allergen and troubled by allergic reactions.
- 15~20 % of population in civilized society is estimated to be troubled by various allergies.
- Current treatment using anti-histamine agents have limited efficacy with many side effects.
- No specific treatment is available for ever-threatening virus-related diseases such as flu and SARS.
- Currently, maintenance of strong immune system is known to be the best strategy against these viruses.

II. SEANOL-AL FEATURES

- Patent to be filed in May, 2004 (assigned to H. W. Lee)
- An optimal combination of natural antiinflamatory and anti-allergic actions using SEANOL
- Dramatically relieves allergic reactions without any drowsiness, dizziness and other side effect of anti-histamine drugs.
- Immune-boosting power against cold and flu
- Its effectiveness has been demonstrated by allergen-induced murine asthma model by Dr. Chi, Dpt. of ???, U of Washington.
- Its immune-boosting power together with its amazing anti-allergic effect and reduction of hyper reactive allergic consequeses in the respiratory system is promising life-saving treatment of flu and SARS.

Effect of KLS (Re-named SEANOL-AL) on Allergen-induced murine asthma model (Summary)

By Dr. Emil Chi, Chairman, Dpt. of Histopathology Univ. of Washington

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. We have tested a healthy supplement product (KLS) 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 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.

KLS 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, KLS reduced the airway mucus plugging, and sub-epithelial fibrosis in the OVA-sensitized/ challenged mice. The reduced BAL fluid eosinophil indicated that KLS, an allergy nature product, is effective in improving the asthmatic lung structures. 12 days of feeding, KLS demonstrated no pathological alterations in the liver, kidney, spleen, or small intestine.

- 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

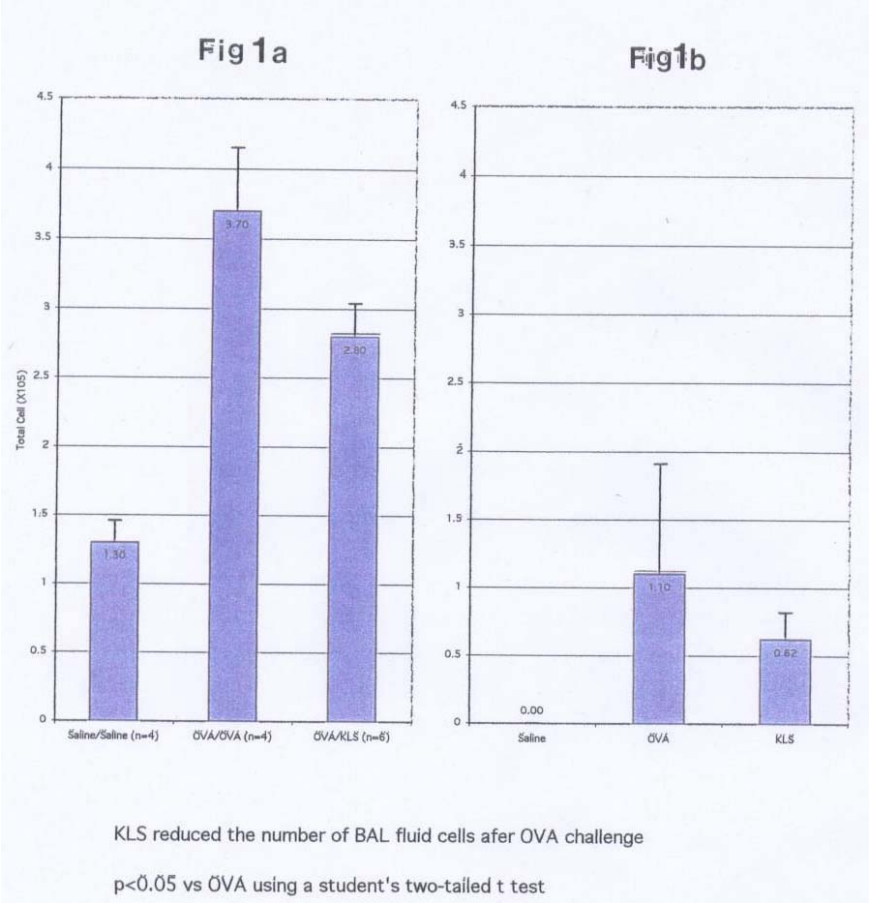


Fig. 1
KLS reduce the number of eosinophils in BAL fluid after OVA challenge. BAL fluid was obtained on day 62 from saline-treated mice (sal/ sal; n=4) and OVA treated mice (OVA/ OVA; n=4) or fed with 25 mg KLS per day for 12 days (OVA/ KLS; n=6).

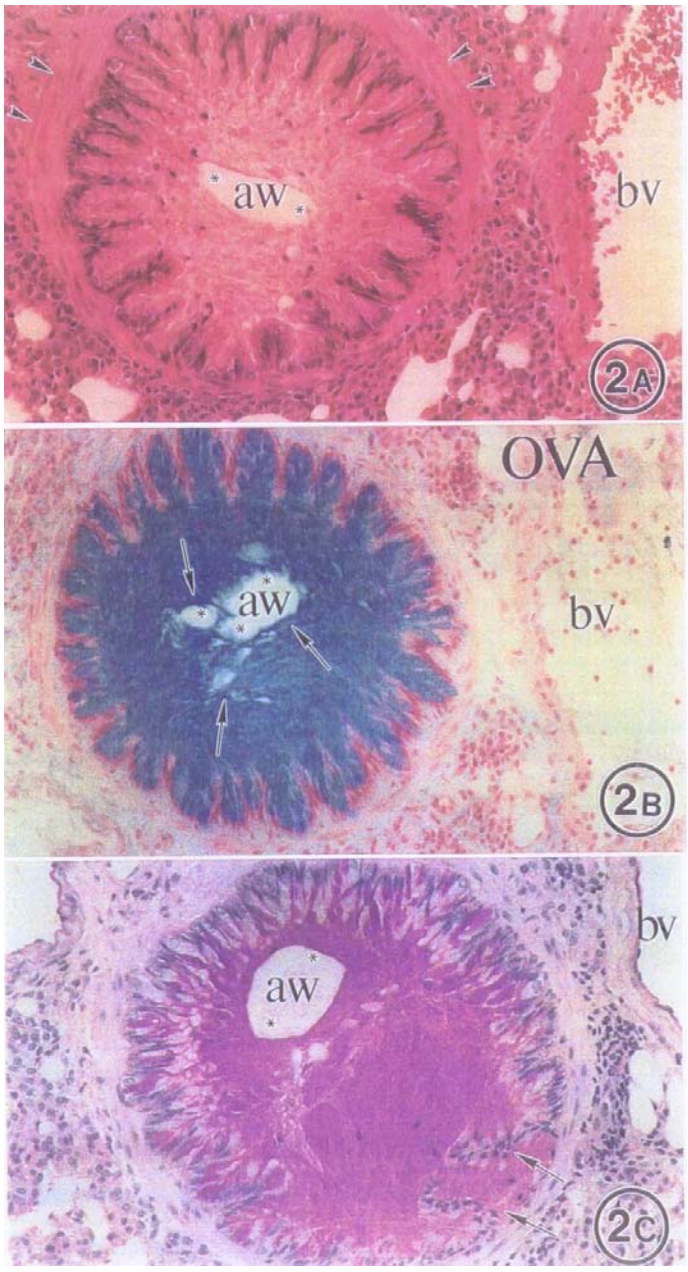


Fig. 2
Airway inflammation in OVA treated mice. Lung tissues of OVA-treated mice (OVA, A, B, C).
A) In the OVA immunized/ challenged mice, a dense inflammatory cell infiltrate around the airway (aw) and blood vessels (bv) is observed. Eosinophil and mononuclear cells are the predominant cells in the 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 seria 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
Airway collagen accumulation and fibrosis in OVA-treated mice. Lung tissue was obtained from OVA-sensitized/ challenged mice.
A) Stained with PAS for basement membrane underneath of epithial cells (arrowheads). The basement membrane is shown in the airway epithelial layer and slightly thickened. There are many newly released mucus grands in the epithelial cell surfaces (arrows). X150
B) An extensive collagen deposition (arrows) is shown in the lung interstitium surrounding the airway (aw) and around the blood vessels in OVA-treated mice (arrows). The collagen deposition is found within the airway tissue of the cellular infiltration and the inner layer of the smooth muscle cell layer (arrowheads). X150

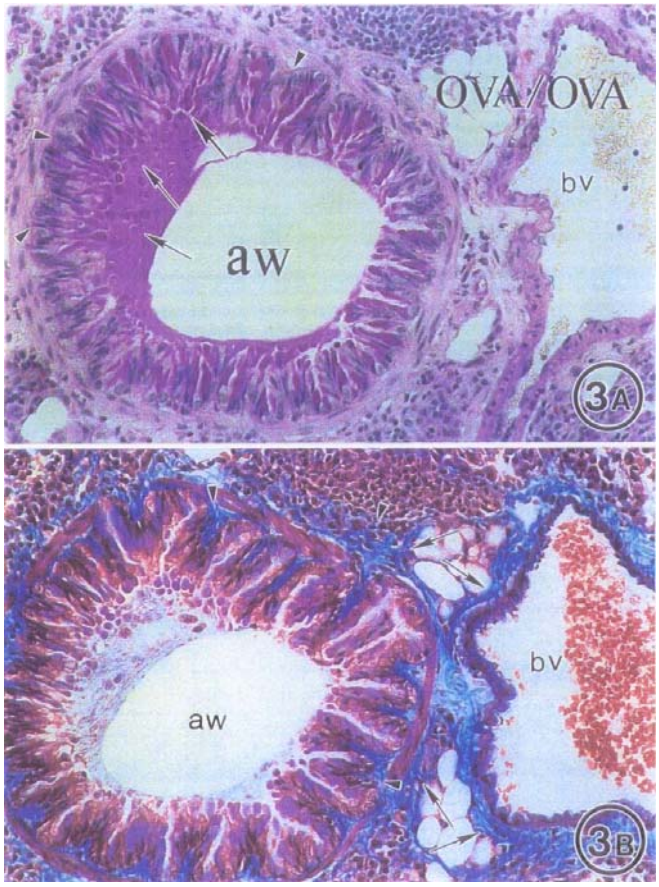
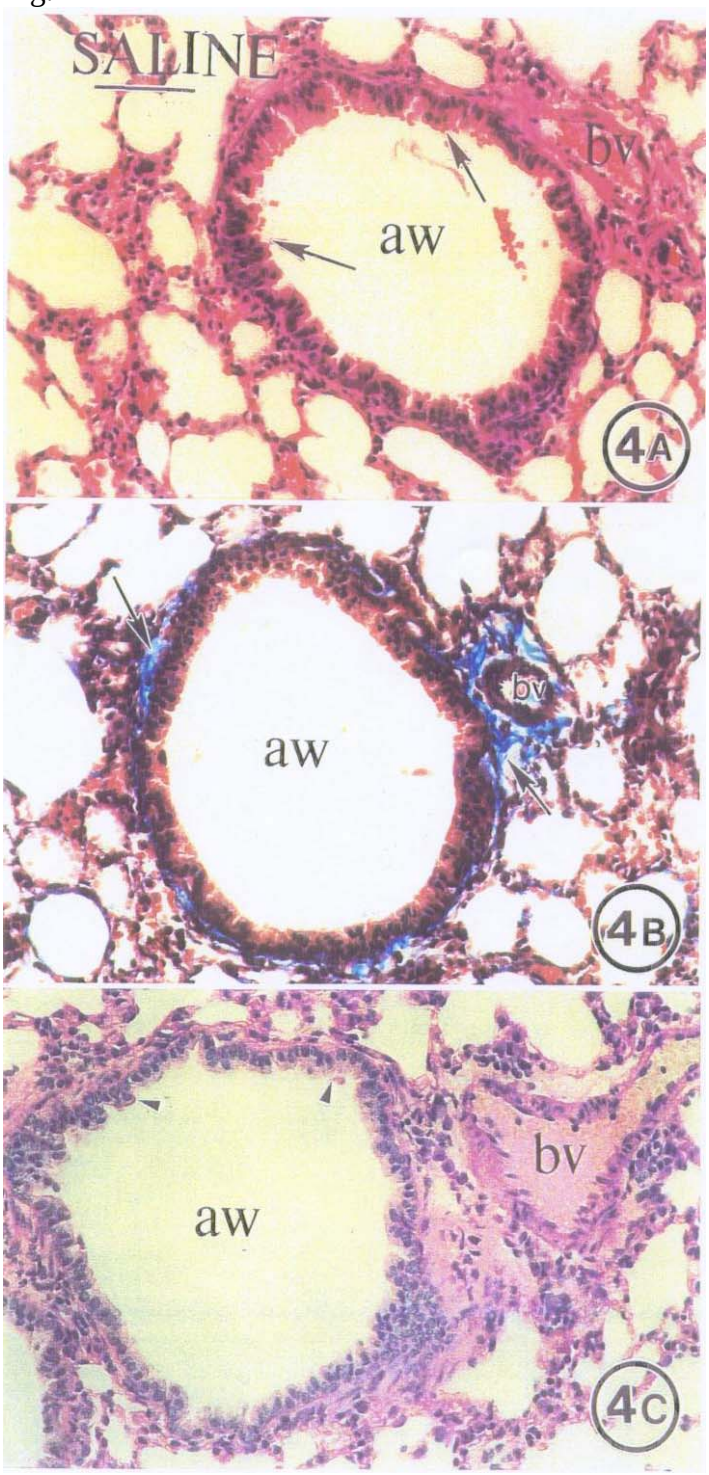
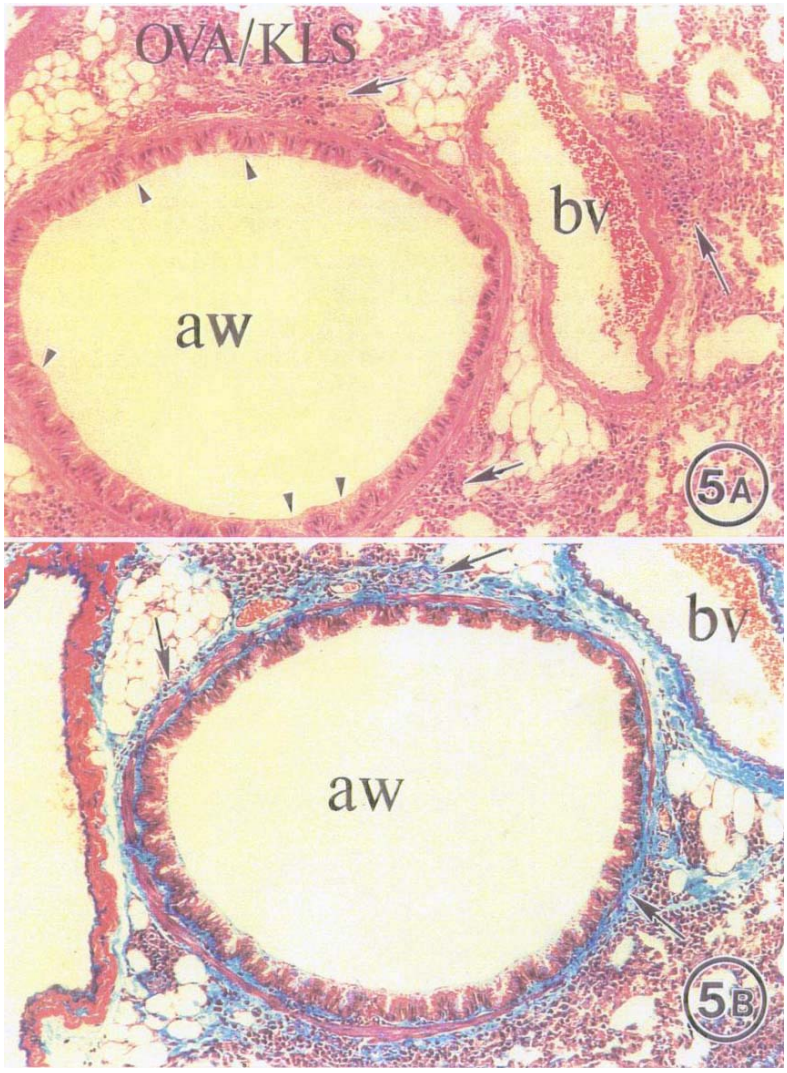


Fig. 4



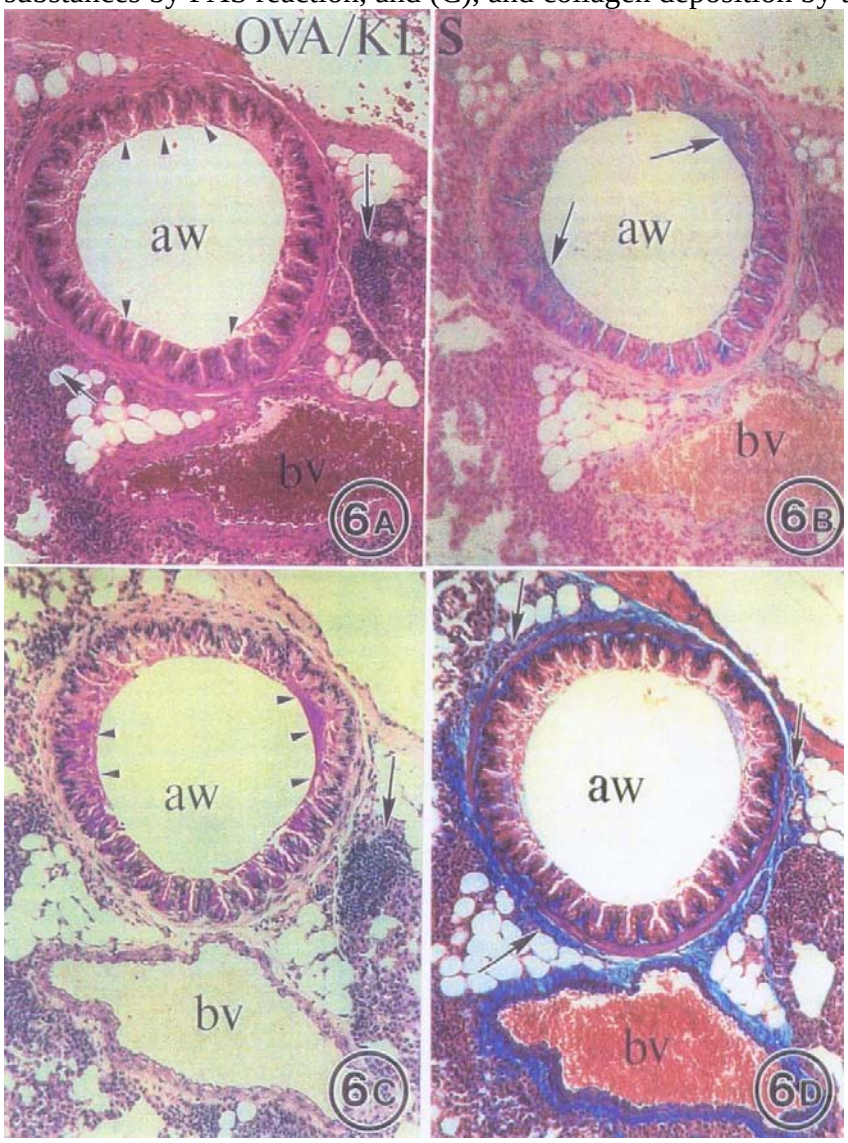
A) Saline-treated mice were obtained at day 62 stained with hematoxylin and eosin. Little mucus (arrows) is observed in the airway (aw) of the control mice. X150
B) Lung tissue was obtained from saline treated mice stained with Masson's trichrome techniques, little collagen (arrows) is observed in the lung interstitium around the airway (aw) in control mice. Few collagen bundles is seen surrounding the blood vessel (bv). X150
C) In control mouse lung tissue sections stained with PAS show little mucus carbohydrate substance in the airway lumen and the mucus containing epithelial cells (arrowheads). X150

Fig. 5



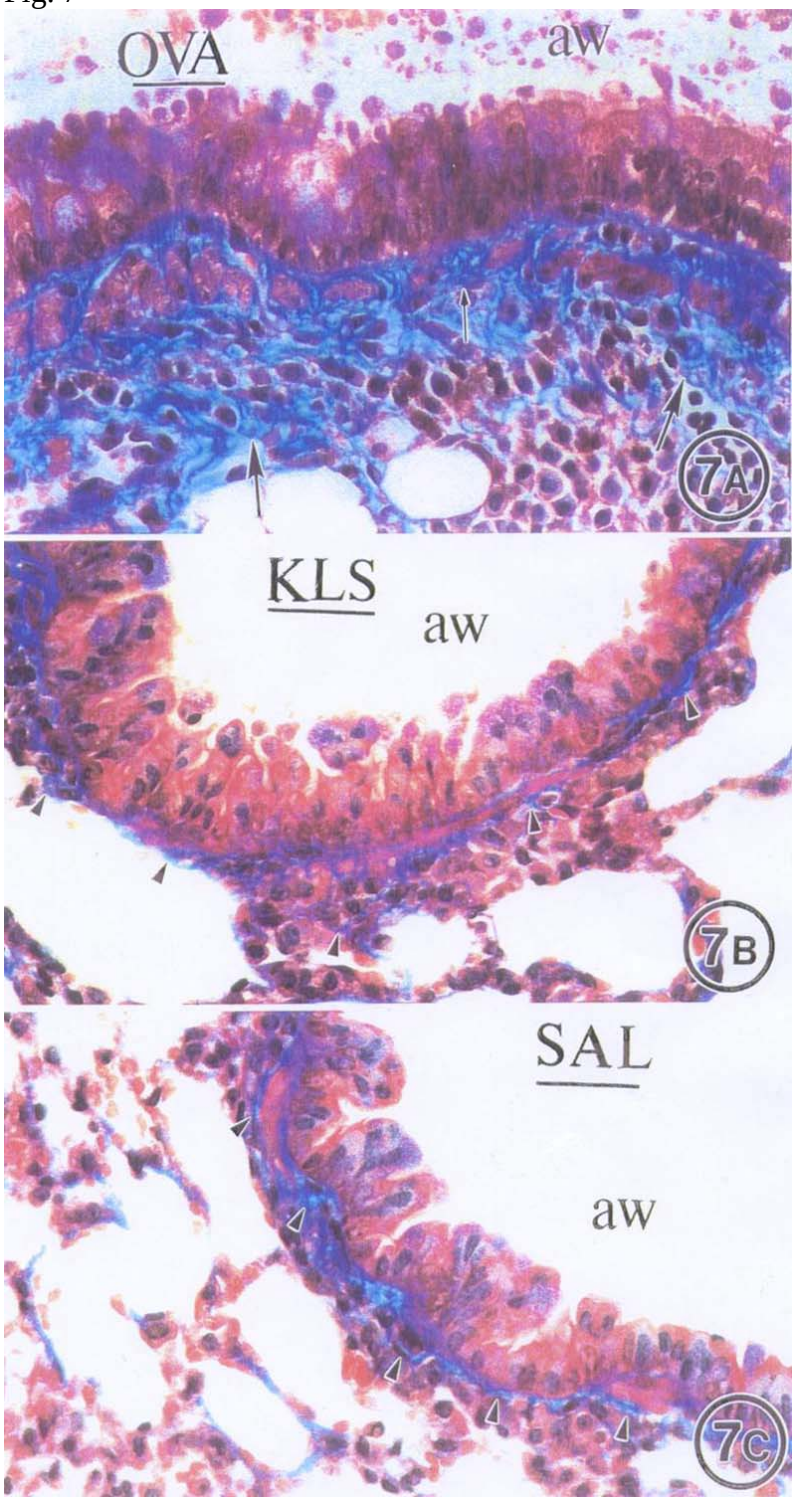
Effect of KLS on airway inflammation and remodeling in OVA treated mice. Lung tissue of OVA-sensitized/ challenged mice fed with KLS for 12 days at 25 mg per day was obtained. Stained with hematoxylin and eosin (A) and Masson,s trichrome (B). A) The inflammatory infiltration (arrows) of the lung interstitium around the airway (aw) and blood vessels (bv) is reduced by feeding KLS treatment in OVA-sensitized/ challenged mice. X100 B) A reduction in lung collagen deposition (arrows) around the airways (aw) and blood vessels (bv) is seen in the OVA-sensitized mice treated with KLS. X100

Fig. 6
KLS reduce 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 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).



A) 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
B) Mucus release (arrows) into the airways (aw) is decreased. X100
C) PAS positive carbohydrate substance (arrowheads) also reduced. X100
D) KLS inhibit some collagen deposition (arrows) in the interstitium of airway (aw) of the OVA-treated mice. X100

Fig. 7



KLS reduce collagen deposition in the lung interstitium of OVA-treated mice.
Lung tissue was obtained from OVA treated mice (A), lung tissue obtained from KLS treated OVA-sensitized/ challenged mice (B) and lung tissue from saline treated control (C).
A) In OVA-treated mice, more numerous and dense collagen bundle (arrows) are observed in the lung interstitium compared with animal treated with KLS.
B) Much less collagen bundle deposits and collagen are thin (arrowheads).
C) In saline control lung tissue, the collagen deposits are thin in various thickness is much less than the OVA-treated. All X150

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SEANOL-AR

For a Peaceful Body

I. Arthritis and Neuralgia

- Arthritis, a joint-related disease with pain and inflammation, is one of the most difficult-to-treat degenerative diseases.
- Around 12% of whole population and over 70% of age 60+ is affected with arthritis.
- High demand for effective agents without side effects of current drugs.
- Neuralgia, a painful symptom along the direction of peripheral nerves, is extremely difficult to treat due to its absence of clinical concreteness other than pain.
- In Asian countries, neuralgia treatment market is about the same as arthritis. However, no specific treatment is available yet.

FEATURES

- Patent Pending Product: Korean Patent Application# 10-2004-0028066 (Livechem, Inc)
  TITLE: "Compound for improving neuralgia containing dibenzo-p-dioxine derivatives extracted from marine plants and articles comprising thereof"

- An optimal combination using SEANOL's natural anti-inflammatory and tissue-protective activities enabling dramatic improvement in both arthritis and neuralgia.

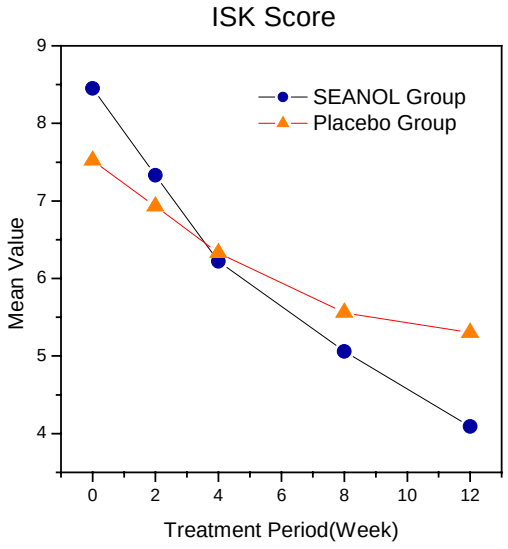
- The best and only agent which is truly effective in neuralgia

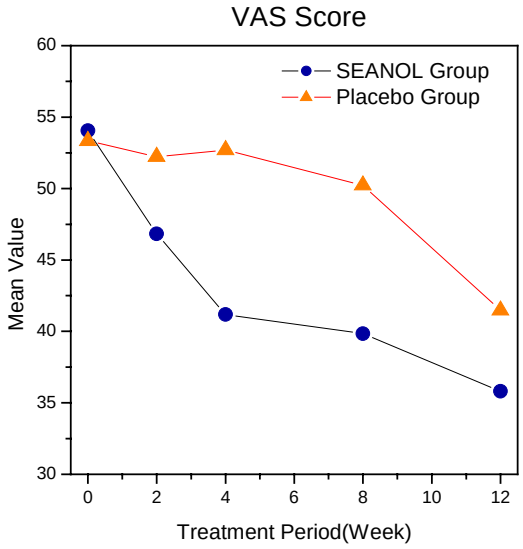
- Natural suppression of inflammatory responses

- Neutralization of Inflammatory damage caused by reactive oxygen species

* Effects on patients with osteoarthritic knee

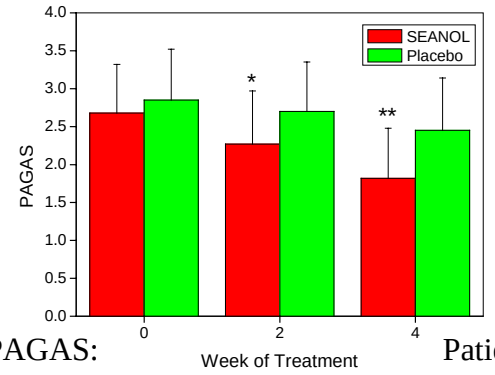
- SEANOL group (n=55); Placebo group (n=27)
- ISK: Index of Severity of knee Joint (1~5, 5 with most severe)
- VAS: Visual Analogue Scale of Pain (0~100mm, 100mm with highest pain)

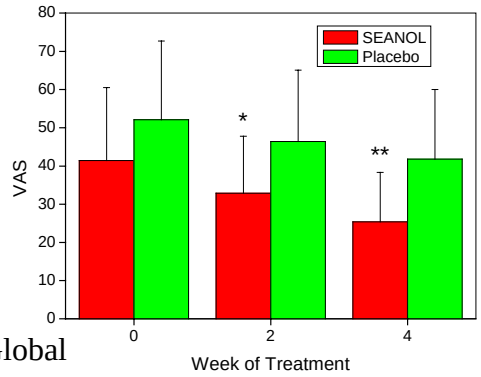




*** Effects on Neuralgia**

	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

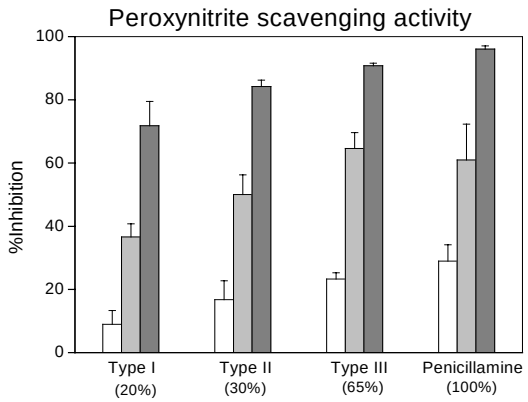


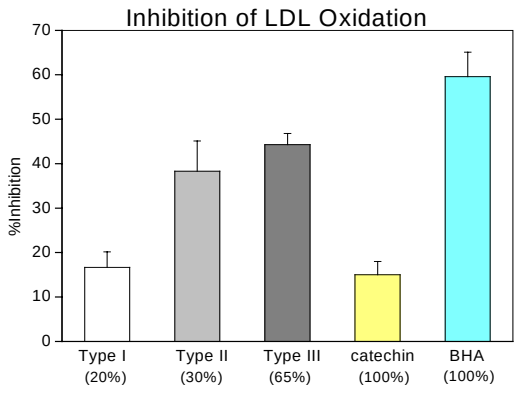


PAGAS: Patient's Global Assessment Scale
*p<0.05; **p<0.01

*** Multiple antioxidant profiles of SEANOL**

SEANOL' antioxidant activities against various reactive oxygen species which 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 which belongs to most potent families of natural antioxidants. SEANOL itself and its individual compounds showed potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite. Even though antioxidant properties of SEANOL are only one of its health-beneficial features, they can contribute to its perfection in protection

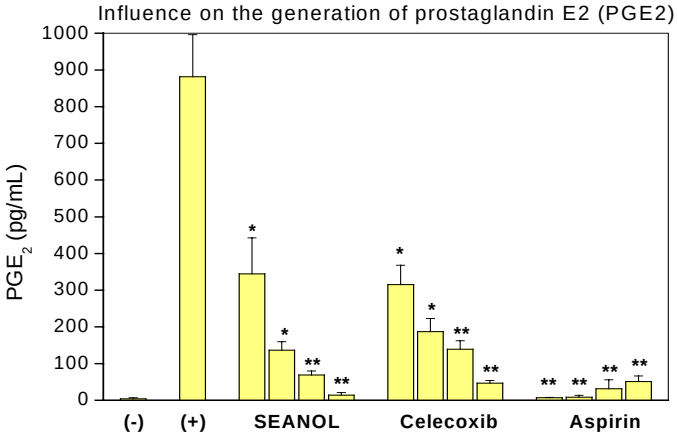




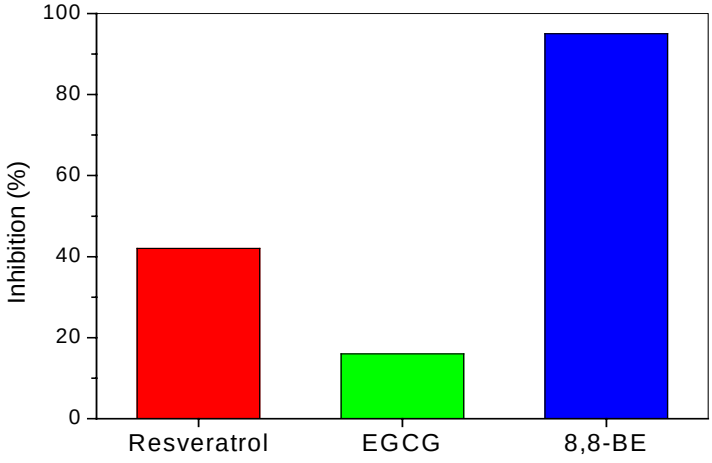
of cartilage together with antiinflamatory activities.

*** Antiinflamatory activities of SEANOL**

The influence of SEANOL in LPS-induced generation of PGE_2 using RAW 246.7 cells was studied. While PGE_2 was barely detectable in non-stimulated cells, more than hundred-fold PGE_2 was detected in the stimulated cells. SENAOL, celecoxib and aspirin all showed significant inhibition of PGE_2 generation in the concentration range tested (10~100 μg/mL). SEANOL showed inhibition of 61%, 85%, 92% and 99% at concentration of 10, 30, 60 and 100 μg/mL, respectively, showing similar activity to celecoxib which showed 65%, 79%, 85% and 96%, respectively.

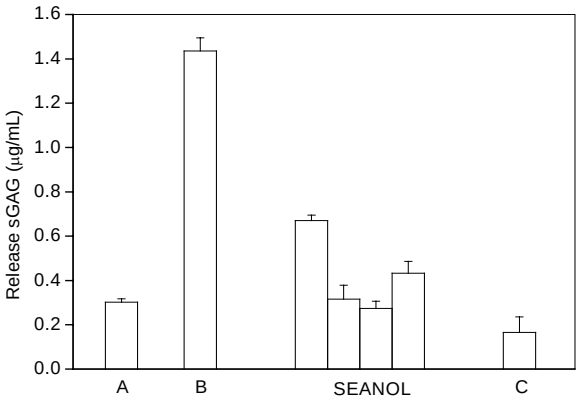


Lipoxygenases (LOXs) are involved in the biosynthesis of various bioregulators, which are closely related to pathogenesis of allergies, atherosclerosis and some cancers. 5-Lipoxygenase (5-LOX) catalyzes the first step in the oxygenation of arachidonic acid, thus leading to the production of biologically active compounds such as leukotrienes and 5-hydroxyeicosatetraenoic acid. The peptidoleukotrienes (leukitriene 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..



*** Cartilage protecting activities of SEANOL**

Rabbit articular cartilage explant culture was treated with recombinant human interleukin 1α (rhIL-1α) 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-1α for 60h, the amount of released glycosaminoglycan into the culture medium increased significantly compare to the vehicle group (1.44 ± 0.06μg/mg vs. 0.30 ± 0.01μg/mg). 10μM (3.2μg/mL) diclofenac which is known as a selective COX-2 inhibitor was used as a positive control. SEANOL significantly interfered with the rhIL-1α-mediated degradation of proteoglycan in all concentrations tested ($p < 0.001$). It showed 53%, 79%, 81% and 70% of inhibition at 1, 3, 10 an 30 μg/mL concentration, respectively. In the figure, (A) no rhIL-1α, (B) rhIL-1α, (C) rhIL-1α + diclofenac (10μM), For VENTOL, rhIL-1α + 1, 3, 10 and 30μg/mL (from left to right)

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NECTAR

For A Healthy Liver

I. Hangover, Liver function and fatigue

- Asian market eagerly demands effective drink to help overcome hangover due to typical heavy-drinking culture in this area.
- Keeping strong liver function is crucial not only for prevention of hepatic diseases but also for energetic life without fatigue. Beverage type of such product will help people with convenient maintenance of liver function.

II. Key Features of NECTAR

- Patent Pending Product: Korean Patent Application# 10-2003-19591 (Assigned to Livechem, Inc)
  TITLE: "COMPOSITION OF NEUTRCEUTICAL FOOD FOR THE IMPROVEMENT OF LIVER FUNCTION AND PREVENTION OF HEPATIC DISEASE"

- A drink with optimal combination of 15 food-based Chinese herbal extracts for liver and Plant-Extract Vinegar (oak or bamboo)

- Dramatic reduction of bad consequences from heavy drinking: headache, uneasy stomach, etc.

- Therapeutic for hepatic diseases by improving liver function

III. Market Responses on anti-hangover test

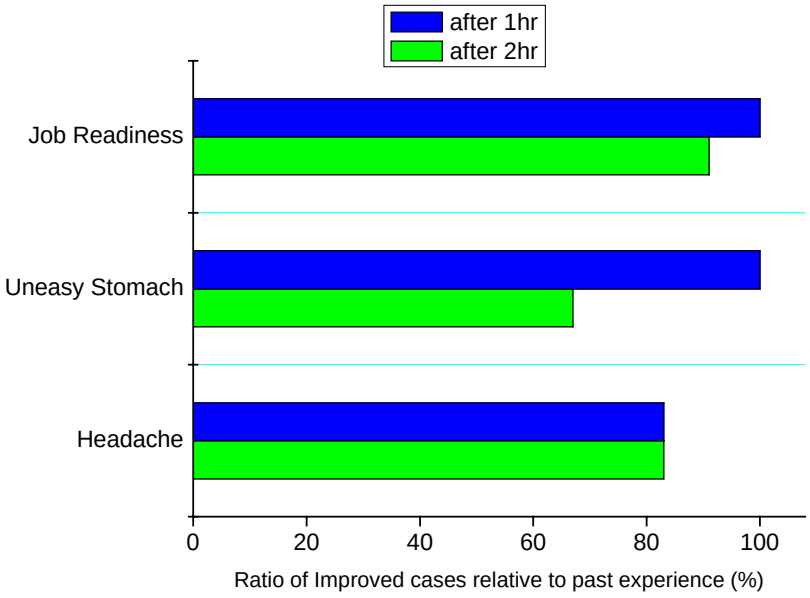
- Participants: Office workers of age of 30~50.
- Average quantity of drinking: 930mL of 22% liquor (v/v)

1. In case of taking NECTAR shortly before and after drinking

- Evaluation of four factors on the following morning

2. In case of taking NECTAR in the shortly before and after drinking

- Average quantity of drinking: 930mL of 22% liquor (v/v)
- Intake of NECTAR on the following morning before breakfast
- Evaluation of three factors 1 and 2hr after NECTAR intake



IV. Protection and Improvement of Liver Function

1. Acute Protection of liver from CCl_4-induced hepatotoxicity by oral administration of NECTAR (SD rat)

24hr after CCl_4-induced hepatotoxicity

Group	ALT(karmen/ml)	AST(karmen/ml)
Normal	14 ± 1	146 ± 5
Control	258 ± 2	469 ± 5

NECTAR	216 ± 3	422 ± 7

Normal group: 7 day treatment with saline + olive oil (i.p.)
Control group: 7 day treatment with saline + CCl4/olive oil (1:1, i.p.)
NECTAR group: 7 day treatment with NECTAR (150mg/kg) + CCl4/olive oil (1:1, i.p.)

2. Acute Improvement of liver function from CCl_4-induced hepatotoxicity by oral administration of NECTAR (SD rat)

24hr after CCl_4-induced hepatotoxicity

Group	ALT(karmen/ml)	AST(karmen/ml)
Normal	14 ± 1	175 ± 3
Control	232 ± 2	521 ± 8
NECTAR	193 ± 3	489 ± 7

Normal group: olive oil (i.p.) → saline (3hr later)
Control group: CCl4/olive oil (1:1, i.p.) → saline (3hr later)
NECTAR group: CCl4/olive oil (1:1, i.p.) → NECTAR (150mg/kg, 3hr later)

3. Improvement of liver function on chronic administration of NECTAR (human)

Liver biochemistry	Day 0	Day 20	Day 40
GPT(U/L)	110	60	37
GOT(U/L)	72	50	32
γ-GTP(U/L)	81	67	44

Normal range of G

SEANOL-SW

A Cardiovascular Product

I. Vascular Health and Erectile Function

- Any risk factors against blood flow into penile artery contribute to ED.
- Diseases leading to vascular damages such as diabetes, atherosclerosis, hypertension, etc account for about 70 percent of cases of ED.
- Critical factors necessary for successful erectile function are proper blood viscosity and efficient vasodilation.

II. FEATURES

- Patent Pending Product: Korean Patent Application# 10-2004-24347 (Assigned to Livechem, Inc); US Patent to be filed in 2004

  TITLE: *"Compound for improving hypertension containing inhibitors of angiotensin converting enzyme activity extracted from marin plants and articles comprising thereof"*

- An optimal combination of natural agents capable of promoting blood flow, vasodilation and vascular protection to realize both short-term effect and fundamental improvement.

- Remarkable improvements in orgasmic function and intercourse satisfaction in addition to erectile functions.

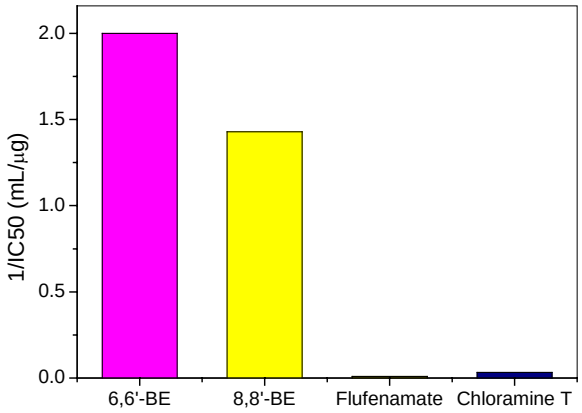
- Enhancement of blood flow via counterbalancing the excessive coagulation in the artery. It is composed of natural potent inhibitors of antiplasmin which blocks the fibrinolytic action of plasmin.

- Effective Vasodilation and vascular protection through ACE inhibition can help both erectile dysfunction and hypertensive population.

III. Scientific Reports

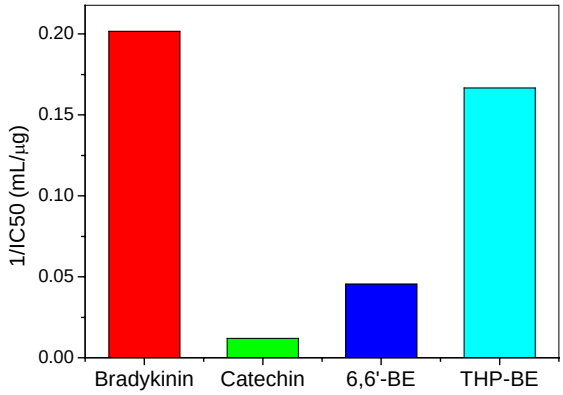
* Promotion of dissolution of intravascular blood-clot via antiplasmin inhibition

Chronic inflammatory intravascular injuries due to aging and contamination of blood cause excessive coagulation to increase the blood viscosity which retards the blood circulation. A fibrinolytic enzyme called "plasmin" which is supposed to break down the blood clot is rapidly blocked by a protein called antiplasmin. SEANOL compounds, natural potent inhibitors of the antiplasmin are capable of efficient promotion of plasmin which 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 Chlroamine T. (figure1)



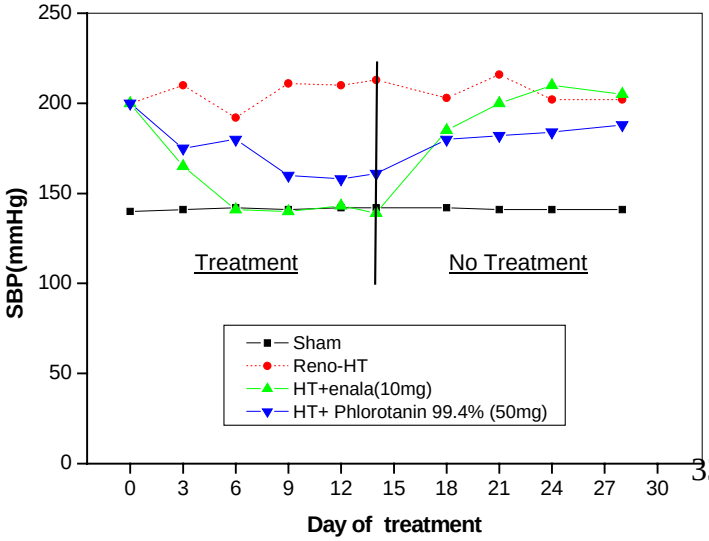
SEANOL compounds are potent natural ACE inhibitors

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.
Upon aging or due to various vascular risk factors tend to increase the ACE level resulting in excessive vasoconstriction and hypertension. Current hypotensive drug block the action of ACE or its product angiotensin II. SEANOL compounds are capable of suppression of ACE and thus promotion of effective vasodilation. (Fig. 2) They are much more potent than a natural hypotensive substance catechin existing in green tea. Especially, one of the compounds in SEANOL, THP-BE is comparable to physiological vasodilative hormone called bradykinin.



Effective vasodilation by SEANOL has been 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 which 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. 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.

Vasodilation and Erectile function

It has been reported that vasculogenic ED patients has elevated level of angiotensin II during the whole course of erection process. The demonstrated action of SEANOL on ACE and resulting vasodilation is thought to play an important role in inducing successful erectile function.

Long-term improvement via vascular protection

Phlorotannin are known to be potent antioxidants and anti-inflammatory agents. Together with their ACE inhibitory activity which is also beneficial to vascular homeostasis, these activities, upon long-term ingestion can all contribute to keeping healthy vascular system including penile artery.

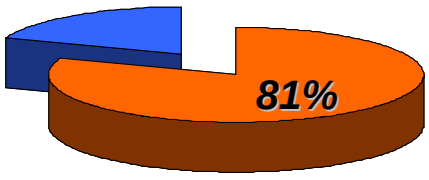
Clinical Test

Clinical Condition

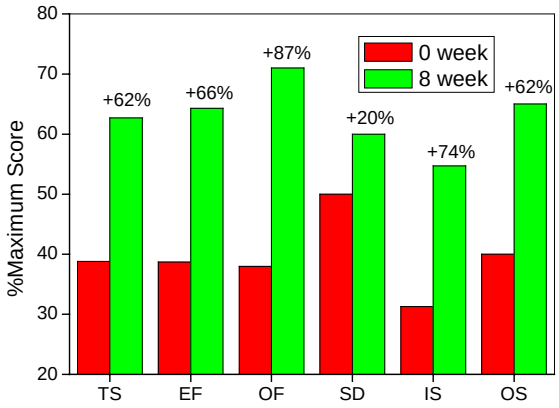
- 8 week, n=31, Average age: 52.7 ± 7.7
- Disease history

- None 14
- Diabetes 4
- Hypertension : 5
- Impotence treatment experience : 5
- Important operation history : 2

- Disease period: more than 6 months
- Test period : 8 Week



Population with 25+% Improvement in IIEF score was as high as 81%. Total IIEF score significantly increased from 29.1 ± 13.1 to 47.0 ± 14.5 with 62% of improvement. When the IIEF scores were grouped into five separate domains, mean IIEF scores at 8th week were significantly greater than those at 0 week for all domains (all $p<0.01$). The degree of improvement was great in the following order: OF (87%), IS (74%), EF (66%), OS(62%), and SD(20%). Scores on key questions 3 (asking frequency of penetration) and 4



(asking 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%) which is of psychological nature, great improvements were reported in the domains directly related with erection which is of physical nature and dependent on normal vascular function of the penile artery. This implies that the 8-week oral administration of the brown-algae polyphenolics significantly improved the function of penile artery which physically controls erection. It is also noteworthy that great increase of the score in orgasmic function (87%), intercourse satisfaction (74%) and overall satisfaction (62%) as well as erectile function (66%) in comparison with the results for sildenafil reported by Marks et al (Marks, et al., 1999) (27%, 44%, 39% and 66%, respectively), indicates 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 the sexual function as well as the penile artery.

Since no side effect was reported, it is very promising to use SEANOL as a chemo preventive agent for the general protection of vascular system as well as improvement of erectile function.

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Fukuyama, Y., Kodama, M., Miura, I., Kinzyo, Z., Kido, M., Mori, H., Nakayama, Y. and Takahashi, M.
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SEANOL-SL

For Obesity

I. Obesity and Cardiovascular diseases

- Obese Americans now exceeds 60MM. 65+ % of age of 20+ are 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.
- Type 2 diabetic population of 14MM Americans has 90% of its members listed as clinically obese
- For ages 55~65, 77+% of American men and 73+% of American women become significantly overweight (BMI =30+), with more than a third of such surviving men and 43% of women categorized as obese (BMI=40+).
- US has a resident population of more than 60MM adults with CHD or CVD, roughly corresponding with the 60MM obese adults.

II. KEY FEATURES of SEANOL-SL

- Patent Pending Product: US Patent Application# ???? (Assigned to TSDC); TITLE: "COMPOSITION FOR PREVENTION AND TREATMENT OF OBESITY, CARDIOVASCULAR AND CORONARY ARTERY DISEASE"

- An optimal combination of natural compounds capable of suppressing triglyceride (storage form of fat) synthesis, cholesterol removal and cardiovascular protection. Suitable for beverages and other applications.

- Characterized by efficient fat loss + muscle gain supported by good science and clinical data

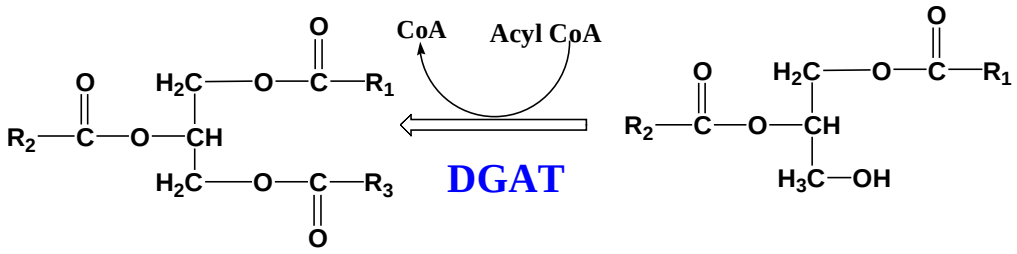
- Promotes energy expenditure through inhibition of triglyceride synthesis in fat tissues

- Provides additional cardiovascular protection for obese population which is prone to CVD and CHD through lowering bad cholesterol, scavenging free radicals.

III. Scientific Reports

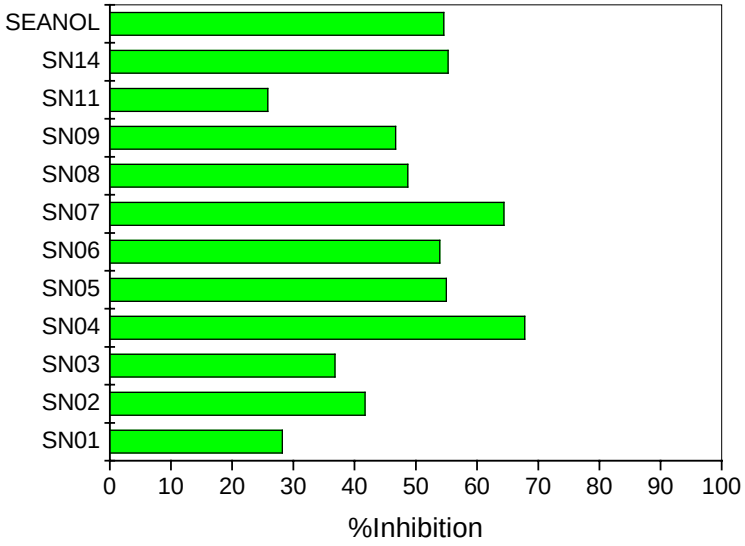
* Inhibition of DGAT, an important enzyme that synthesize storage form of fat.[1]

DGAT(Acyl CoA:diacylglycerol acyltransferase) catalyzes the final step in triacylglycerol (TG) synthesis by using diacylglycerol and fatty acyl CoAs (Figure). 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.[2]



triacylglycerol **diacylglycerol**

SEANOL is composed of natural DGAT-inhibitory compounds which suppress the enzyme activity by 30-70% at 25ug/mL. SEANOL suppresses the DGAT activity over 50% at the same concentration.



*** SLIMMING EFFECT USING BEVERAGE TYPE**

Subjects were told to drink 1 can of product per day at any time of the day for two weeks. Each can of beverage contain 0.11% of SEANOL-SL (200 mg/180 mL) and flavor.

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, **P<0.001

age		16.5 ±0.5 (16~17)
sex	Male	N= 64 (45.4%)
	female	N=77 (54.6%)
Height (cm)		168.9 ±7.6 (150 ~ 188)
Weight (kg)		76.7 ±16.0 (52.8 ~ 134.8)
BMI (kg/m2)		26.8 ±4.7 (20 ~ 46)
Muscle (kg)		49.0 ±10.3 (22.0 ~ 69.6)
Body fat (kg)		24.9 ±8.9 (10.8 ~ 61.5)

*** IMPROVEMENT OF CHOLESTEROL METABOLISM AND RECOVERY OF VASODILATORY FUNCTION (Bar type application)**

Subjects were advised to ingest three bars 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).

Baseline data

age		55.6 ±1.2
sex	male	n=17
	Female	n=22
height (cm)		163.4 ±7.6
weight(kg)		65.3 ±5.59
BMI (kg/m2)		24.4 ±1.7
Disease history		11 of the testees had >50% narrowing in coronary artery

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[1]	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%

[1] Atherogenic index = (total cholesterol - HDL cholesterol)/HDL cholesterol

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

Vasodilator function before and after

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

[1]FMD: flow mediated dilation
[2]NMD: nitroglycerin mediated dilation
[3]CAD: coronary artery disease
*p<0.05

*** IMPROVEMENT OF LIPID METABOLISM WITH DIETARY SUPPLEMENT**
Subjects were advised to ingest 6 capsules (3 capsules 2hr before lunch, 3 capsules 2hr after dinner) daily for eight weeks. Each capsule contains 100mg of SEANOL-SL

N=21	0 week	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 data on 0 week.

<REFERENCES>
1. Cases, et. al., *Proc. Natl. Acad. Sci. USA*, 95:13018–13023 (October 1998).
2. Smith SJ, Cases S, Jensen DR, et al. *Nat Genet* 25:87–90 (2000).