

PC- Ecklonia Cava Extract



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I. EXECUTIVE SUMMARY

PC- Ecklonia Cava Extract (PC- ECE) 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 PC- ECE are available for review.

An extensive battery of scientific tests (in-vitro, in-vivo animal model tests, and human clinical studies) supports the PC- ECE polyphenol/phlorotannin platform. Specifically, PC- ECE 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 PC- ECE 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 from green tea, resveratrol, ECGC, and tocopherol) that are hydrophilic (water-soluble), PC- ECE’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, as confirmed by extensive NIH/NIA animal model tests on PC- ECE's phlorotannins for memory improvement in models mimicking Alzheimer's disease.

In addition, the hydrophobic content in PC- ECE 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, PC- ECE's ORAC scores for anti-oxidation potential (8,300) are significantly higher than most known land-based polyphenols.

Depending upon the medical application examined, PC- ECE's potency in-vivo tends to be from 100X-1000X 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. PC- ECE is currently protected by 4 patent applications, with additional patent applications expected over 2007.

Pilot human clinical trials (double-blinded, placebo-controlled Phase I) on PC- ECE 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 PC- ECE-based beverage evidenced an average 2.4kg weight loss, with a 15% reduction in visceral fat (confirmed through CAT-scans), as compared with placebo.

New placebo-controlled, double blind formal clinical studies (N=400+) are nearing completion in Hong Kong with type 2 diabetes patients (i.e., normalization of blood glucose levels for more than 80% of the diabetic population).

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 PC- ECE 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 PC- ECE in 2007.

Development of a **PC- ECE** -based “anti-aging” formulation for introduction in late-2007 is being explored. One potential formulation may combine **PC- ECE** with various HGH-promoters.

II. INTRODUCTON

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, etc.

Dr. Haengwoo Lee, a Ph.D. in Biochemistry, has spent much of the past 14 years and more than \$30MM 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 ‘PC- ECE’ in nutraceutical formulations.

“PC- ECE” is a trade name for standardized natural complexes of unique marine molecules that originate as second metabolites from specific brown algae. PC- ECE 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

PC- ECE is molecularly distinct from land-based polyphenols. Under HPLC analysis, there are 13 active peak fractions (including dieckol, 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.*

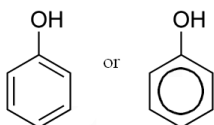
PC- ECE is further distinguished by having hydrophobic content, unlike the exclusive hydrophilic content characterizing virtually all land-based polyphenols (catechins, resveratrol, ECGC, tocopherol, etc.). This split hydrophobic chemistry allows PC- ECE to pass through the blood-brain barrier and serves as a positive attribute for improving mental acuity and memory. These benefits have been confirmed by extensive NIH/NIA animal model tests on PC- ECE’s polyphenol/phlorotannins testing for both memory improvement and as a chemo-protective compound against beta amyloid plaque deposition in the brain. In addition, the hydrophobic content in PC- ECE allows these polyphenols to remain in the mammalian metabolism up to 12 hours (unlike the typical 30-minute half-life of the hydrophilic, or water-soluble polyphenols available from all land-based sources).

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

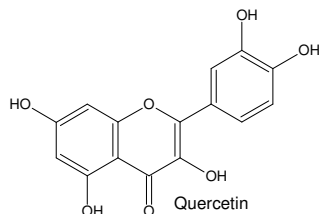
III. PC- ECE ORIGINS & STRUCTURE

PC- ECE 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:



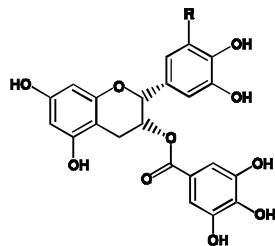
Polyphenols are phytochemicals (plant made) with multiple interconnected phenol rings. Flavonoids have a typical three-ring structure as follows:



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

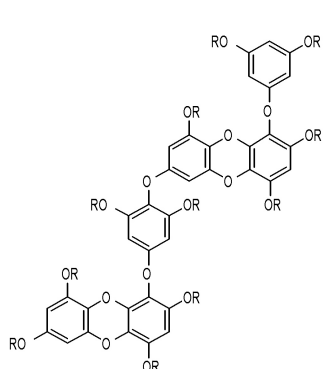
QuickTime™ and a Graphics decompressor are needed to see this picture.

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

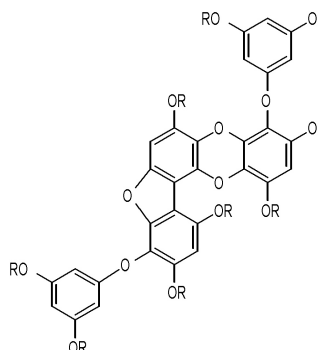


The power of any of these antioxidants rests in large part upon their ability to capture stray electrons from free radicals. The more rings in a phenol structure, the larger the

capacity to absorb electrons. The phenol structures of two of PC- ECE's more than 13 active fractions (dieckol and PFF) that are particularly important are provided below¹:



[dieckol]



[phlorofucofuroeckol (PFF)]

The ten patented PC- ECE 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 PC- ECE 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.² As a result PC- ECE polyphenols are much more powerful than resveratrol and even the extremely powerful green tea catechins. PC- ECE also has much more power than catechin to prevent oxidation of your neurons and LDL cholesterol (the first step in vascular disease).³

Type of PC- ECE

PC- ECE naturally occurs as high-molecular weight tannin (HMST, Mw > 2,000 dalton) and low-molecular one (LMST, Mw = 400-1000 dalton). PC- ECE 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

Safety Features of

PC- ECE products are

edible algae through food-compatible processes. So far several tens of thousands of

PC- ECE products

manufactured from

¹ *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

² Brunswick Laboratories ORAC Analysis, 05-0222, 02-04-05

³ Dr. Robert Rowen, *New Antioxidant Fights Heart Disease, Lowers Cholesterol, and Beats Viagra*. Second Opinion Newsletter, Vol XVI, No. 9, September 2006.

people throughout the world have experienced PC- ECE in various forms of product without side effect. 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).

Test Type	PC- ECE 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

Toxicity

No statistically significant serious adverse events were noted in any of the six prior supporting clinical studies of PC- ECE on various indications. The only adverse event noted in the fibromyalgia (“FMS”) clinical study (N=36) was a tendency for increased diarrhea among study subjects with a pre-existing condition of diarrhea (N=6 out of 36 study subjects).

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 PC- ECE as a safe food substance. No adverse effects were noted in these supporting pre-clinical studies.

Discoveries on physiological actions of PC- ECE

Various physiological activities of PC- ECE have been evaluated in vitro, in vivo and clinically as individual compounds (SN₁~SN₁₄) and complex form (PC- ECE, Type I~IV), revealing many of its health benefits.

Summary of PC- ECE physiological activities

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

- t = in vitro, v = in vivo, c = clinical
- SN_i: Individual compounds in PC- ECE

IV. PC- ECE HEALTH BENEFITS

1. CARDIOVASCULAR

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

1. 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);
2. Strong anti-plasmin inhibition effect (i.e., homogenizes blood flows, thereby lowering blood pressure and increasing arterial blood flow);
3. Strong elastase agonist effect, thereby increasing the flexibility of the vascular system and helping normalize blood flows and blood pressure;
4. 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 of hypertensive cardiovascular patients (reduction of blood pressure and increase of brachial artery FMD (+43%) and NMD (+59%) in CAD patients (11 of 39 patients, the others being healthy normals). 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 8-weeks of PC- ECE consumption (bar format, approximately 2.4gm/day of PC- ECE), with an even larger 59% increase in NMD at the brachial artery. The clinicians’ conclusion was that their cardiovascular risk profile had been substantially reduced in the CAD patients over this two-month study.

Similar cardiovascular benefits were observed in a series of randomized, placebo-controlled clinical studies on the favorable energy and mental acuity benefits of a PC-ECE-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 PC- ECE-based energy beverage by professional drivers.

Unprecedented Cardiovascular protection and rejuvenation by PC- ECE

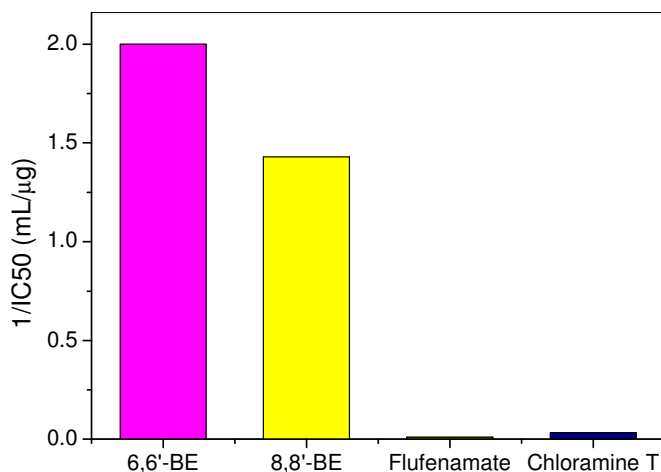
The cardiovascular system is exposed to various kinds of risk factors such as free radicals, inflammation, excessive coagulation, hypertension, etc. It is generally known that by doubling the kinds of risk factors, resulting impact tends to be quadrupled. Therefore multiple protections from different kinds of risk factors will greatly enhance the efficacy of a treatment. PC- ECE 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

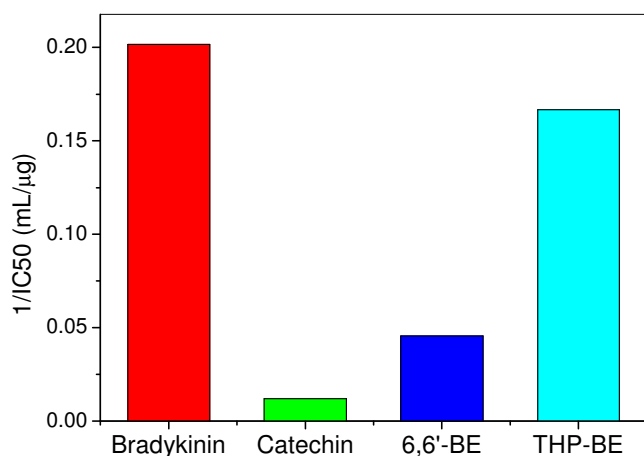
circulation. A fibrinolytic enzyme called “plasmin” that is supposed to break down the blood clot is rapidly blocked by a protein called anti-plasmin. PC- ECE compounds, natural potent inhibitors of the anti-plasmin are capable of efficient promotion of plasmin that performs fibrinolysis. PC- ECE compounds 6,6'-BE and 8,8'-BE show remarkable activity which is 40-200 times greater than synthetic compounds Flufenamate or Chloramine T.



PC- ECE tannins are potent natural ACE inhibitors

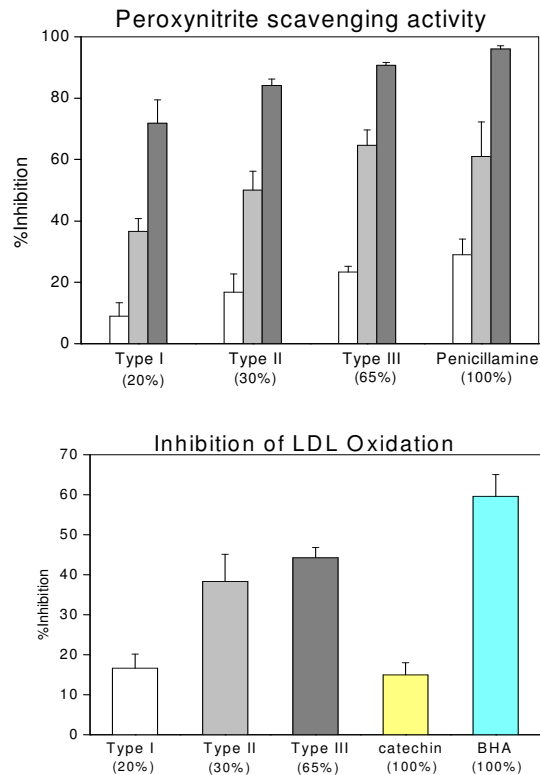
Angiotensin-converting enzyme (ACE), which is responsible for conversion of angiotensin I to angiotensin II and degradation of bradykinin, is a key component in the renin-angiotensin-aldosterone system. Angiotensin II regulates cellular proliferation, inflammation, and endothelial function, and is therefore 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. PC- ECE compounds suppress ACE and thus promote effective vasodilation. These compounds are much more potent than the natural hypotensive catechins found in green tea. The PC- ECE compound THP-BE has physiological vaso-dilative impact similar to the hormone called bradykinin.



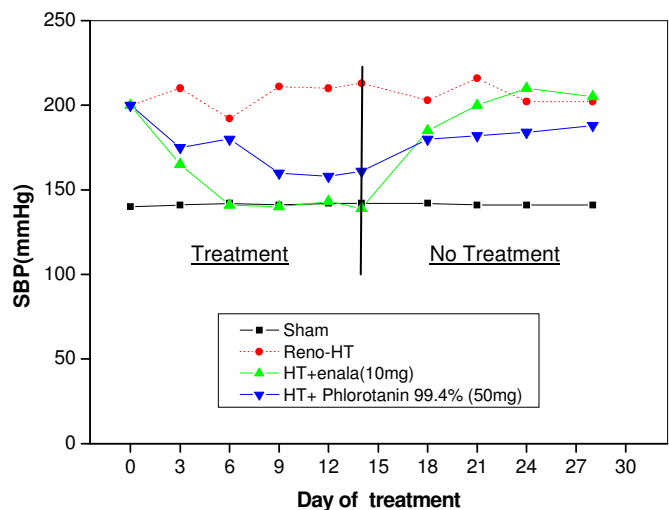
PC- ECE - Multiple antioxidant profiles

PC- ECE'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 PC- ECE for free radical scavenging is 10~20 µg/mL range. PC- ECE compounds showed potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite. PC- ECE's inhibition of LDL oxidation was significantly higher than catechin. The free-radical scavenging activity of PC- ECE is better than the well-known antioxidants such as catechin, tocopherol and butylhydroxyanisole (BHA) and *t*-butylhydroxytoluene (BHT).⁴



Effective cardiovascular protection by PC- ECE clearly demonstrated in renovascular hypertensive rat study.

The remarkable effect of PC- ECE 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

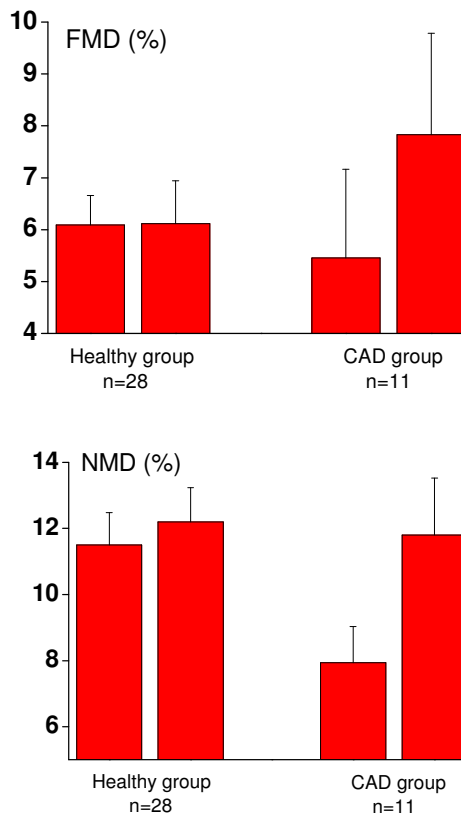


⁴ K. Kang, Y. Park, H.J. Hwang, S.H. Kim, J.G. Lee, H-C Shin. *Antioxidative Properties of Brown Algae Polyphenolics and Their Perspectives as Chemopreventive Agents Against Vascular Risk Factors*. Archives of Pharmacal Research Vol 26, No. 4, 286-293, 2003

140mmHg, respectively. Upon cessation of treatment, SBP increased again in both cases. Although PC- ECE 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.⁵

PC- ECE’s cardiovascular rejuvenation has been confirmed in human studies.

A clinical study using PC- ECE 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 PC- ECE, 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 PC- ECE’s ability to help restoration of vascular integrity by reversing atherosclerosis.



In the study, subjects were advised to ingest three bars containing SEAONL per day at any time of day for six weeks. The bars were ingested freely. Each bar contained 0.33% of PC- ECE-SL (100 mg/30g). Additional cardiovascular improvements included: reduction in LDL, increase in HDL, and reduction in triglyceride levels.

age		55.6 ±1.2
sex	male	n=17

⁵ 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 Pharmacogn. 37(3): 200-205 (2006)

	Female	n=22
height (cm)		163.4 ±7.6
weight(kg)		65.3 ±5.59
BMI (kg/m ²)		24.4 ±1.7
Disease history	11 of the testees had >50% narrowing in coronary artery	

Baseline data:

Lipid profile before and after:

	Before	6 weeks later	Difference	% Change
Total cholesterol	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	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)

Vasodilatory 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*

¹FMD: flow mediated dilation

²NMD: nitroglycerin mediated dilation

³CAD: 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 PC- ECE. As noted in the table below, PC- ECE 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. 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 PC- ECE 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. PC- ECE 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 PC- ECE on diabetic mouse tissue pathogenesis, it was shown that PC- ECE inhibited NF-kB expression in heart aortic vessel valves, kidney's, liver and pancreas. PC- ECE 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.

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

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

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

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

QuickTime™ and a
TIFF (LZW) decompressor
are needed to see this picture.

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

Note: LSL is PC- ECE solution used in research

Reduction of fat cell distribution after PC- ECE 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 PC- ECE.

The Effects of PC- ECE 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 PC- ECE treated mouse pancreas, very little reactive activity of NF-kB is seen in the islet and beta cells are normal (arrows).

PC- ECE 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 PC- ECE 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.

PC- ECE 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:

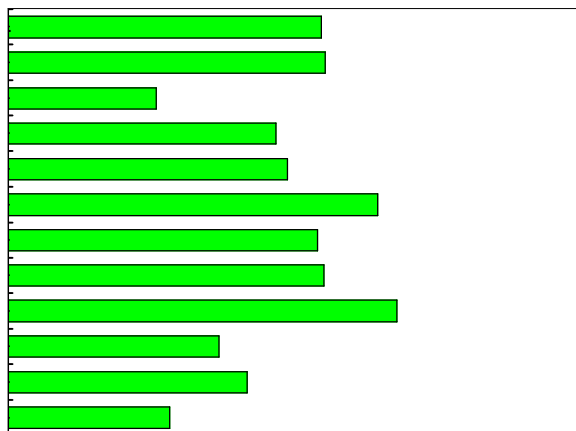
- Efficient fat loss + muscle gain;
- Promotion of energy expenditure through inhibition of triglyceride synthesis in fat tissues;

- 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.

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



Weight Reduction Effect with PC- ECE 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 PC- ECE-SL (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

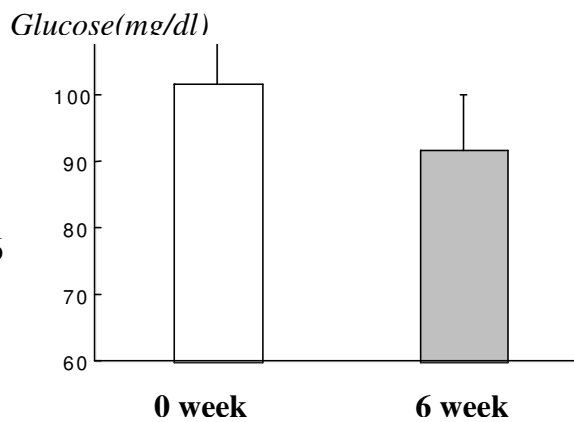
*p<0.01, ** <0.001

Recently a double blind, randomize, placebo-controlled 12-week clinical trial designed to evaluate the long-term safety and effectiveness of a PC- ECE-based drink in the improvement of body fat and metabolic syndromes was completed. Some of the trial results included:

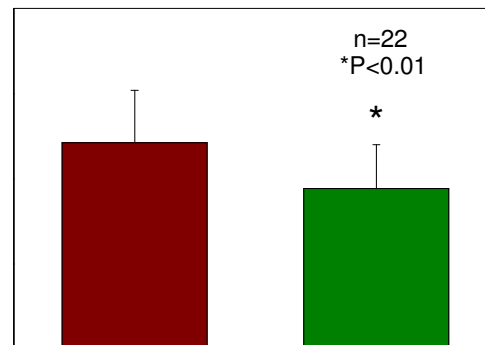
- Significant reduction in visceral fat vs. placebo;
- Significant decrease in total and LDL cholesterol vs. placebo;
- Increase in HDL cholesterol and decrease in blood glucose.

Additional Clinical study results:

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



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



3. ERECTILE DYSFUNCTION

PC- ECE'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.

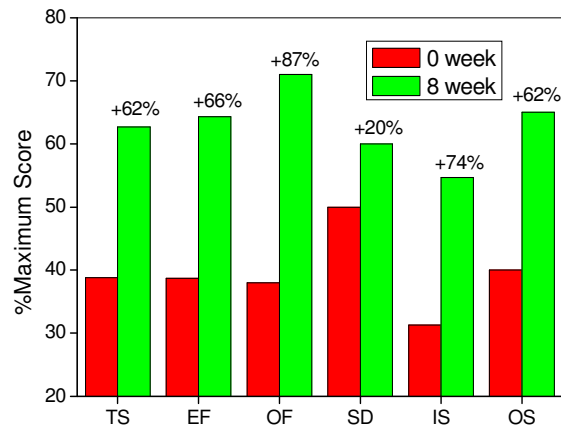
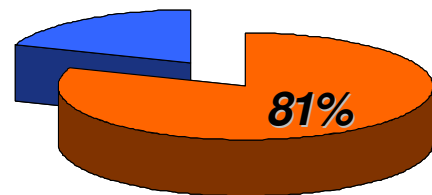
Vasodilation and Erectile function

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 PC- ECE on ACE and resulting vasodilation is thought to play an important role in inducing successful erectile function. A clinical study of PC- ECE'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 ± 7.7; 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 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 PC- ECE 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 PC- ECE 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 PC- ECE 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, PC- ECE is a promising chemo-preventive agent for general protection of the vascular system as well as improvement of erectile function.

4. NEUROLOGICAL

PC- ECE 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.

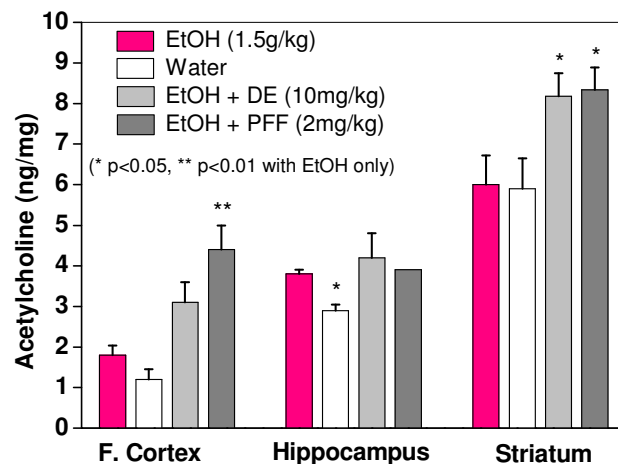
A human study of PC- ECE's impact on Alzheimer's disease is planned for China in 2007. This commitment is based upon three research findings:

1. The NIH's National Institute on Aging ("NIA") laboratories in Baltimore have spent nearly two years examining a predecessor PC- ECE compound in removing induced beta-amyloid plaques in rats, with very favorable outcomes;
2. The NIA laboratories have conducted rat water-maze studies, in which the predecessor PC- ECE compound established a noted improvement in rat water maze performance, as compared to controls;
3. Anecdotal PC- ECE 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 PC- ECE daily dosing.

Studies of PC- ECE 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.

Enhancement of Acetylcholine Level in mice brain by two PC- ECE 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.⁶

Acetylcholinesterase inhibitory activities of two phlorotannin compounds DE and PFF in PC- ECE

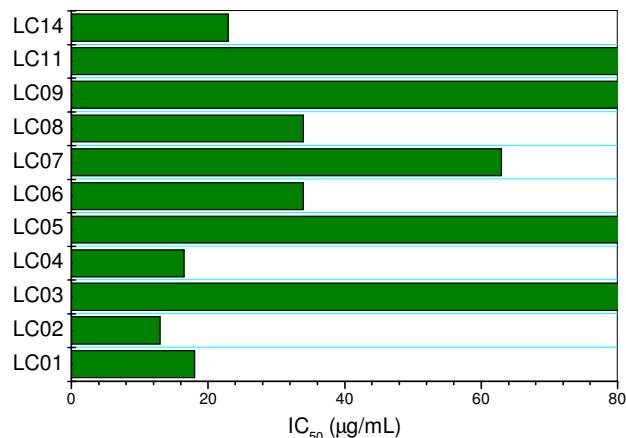
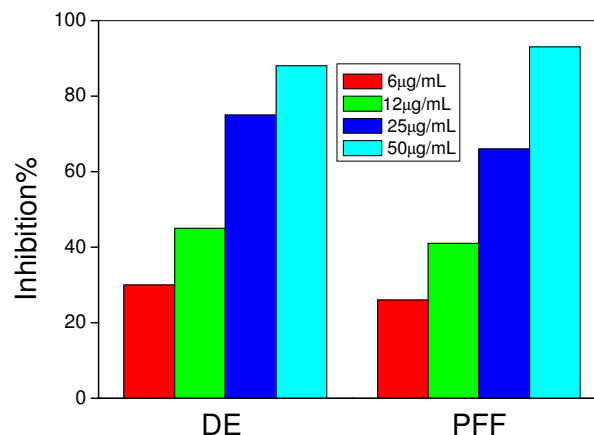
A large body of evidence is available that the neurotransmitter acetylcholine is crucial to learning and memory. Recently it was shown by applying PET imaging technique to conscious monkeys that a cholinesterase inhibitor drug, which has been used to improve cognition of patients in the early stage of Alzheimer's disease, did increase the brain level of acetylcholine and subsequently induced cognitive improvement in aged monkeys. Mild acetylcholinesterase inhibitory activity of the PC- ECE compounds Dieckol (DE) and Phlorofurofukoekol (PFF) is thought to be involved in up-regulation of neurotransmitter acetylcholine which 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. PC- ECE 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. The different peaks or compounds of PC- ECE (including DE and PPF) were analyzed separately for acetylcholinesterase inhibitory potency. As shown below all of the peaks exhibit acetylcholinesterase inhibitory properties with several possessing exceptional inhibitory properties.

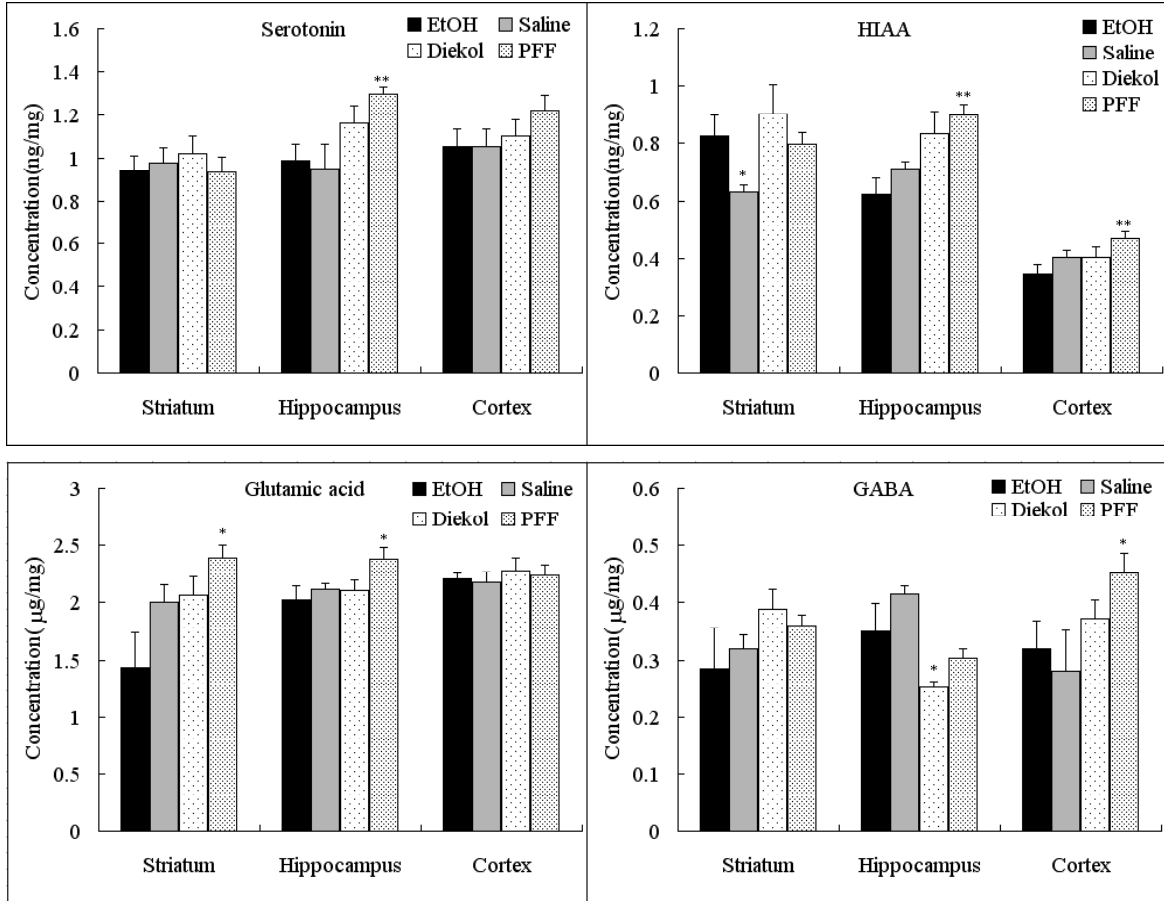
Neurotransmitter stimulation by DE and PPF in PC- ECE

The beneficial effects of PC- ECE compounds on neurotransmitter levels have been demonstrated in a mouse study. There were significant



⁶ C-S Myung, H-C Shin, H.Y. Bao, S.J. Yeo, B.H. Lee, J.S. Kang. *Improvement of Memory by Dieckol and Phlorofucofuroeckol in Ethanol-Treated Mice: Possible Involvement of the Inhibition of Acetylcholinesterase.* Archives of Pharmacal Research Vol 28, No 6, 691-698, 2005

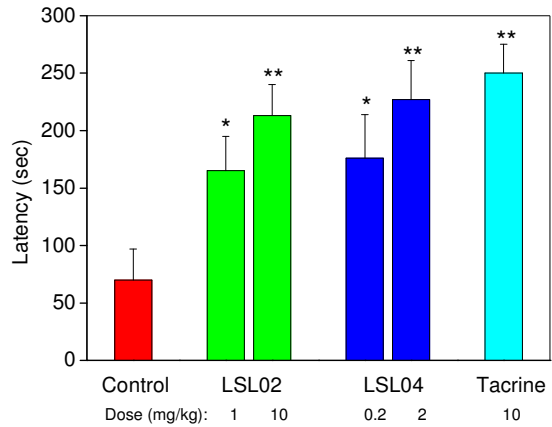
increases in serotonin and GABA levels observed in the study.



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

Memory Enhancement in mice by DE and PFF in PC- ECE

The beneficial effect of the PC- ECE 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 especially, 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.

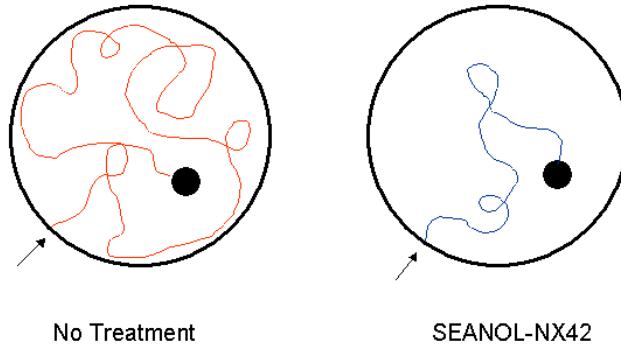


Resistance of Learning deficit induced by stress in water-maze test

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

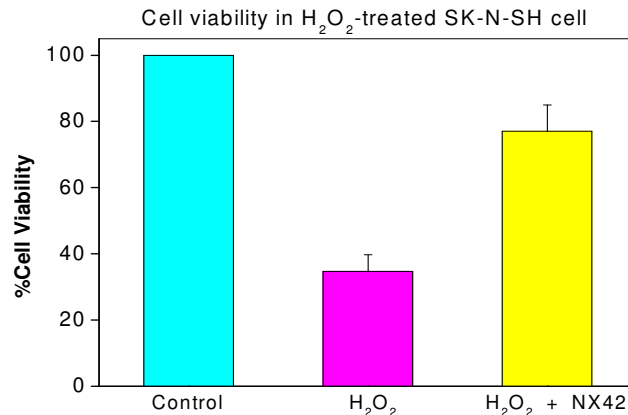
Morris water maze test after 5-day learning

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



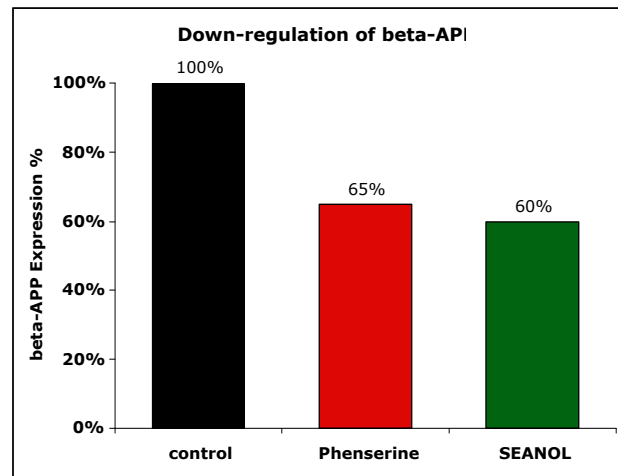
Neuroprotective Effects of PC-ECE

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



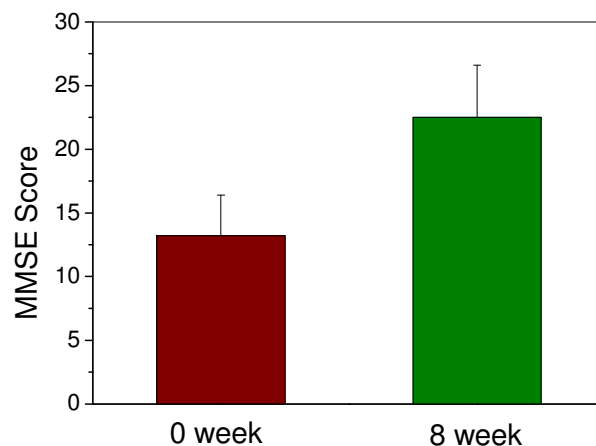
- PC- ECE compounds are both powerful antioxidants and anti-inflammatory agents capable of scavenging free radicals and suppressing excessive inflammatory reactions.
- Fucoidan in PC- ECE has recently been found to protect neuronal cells from ischemia induced inflammatory reactions that often occur in the aged and highly-stressed brain.

PC- ECE 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, PC- ECE 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. PC- ECE was shown to have similar beta-APP down regulating effect as Phenserine (Axonyx), an acetylcholinesterase inhibitor drug currently in Phase III testing.



Recovery of Cognitive Function Amongst Dementia Patients

After 8 weeks of oral PC- ECE dosing, substantial improvement in cognitive function was noted amongst light to moderate dementia patients (n=171). Dementia symptoms stopped or improved for 80% of patients. Cognitive function improvement was measured by MMSE (Mini Mental State Examination).



Additionally, a series of randomized, placebo-controlled clinical studies on the favorable energy and mental acuity benefits of a PC- ECE-based, non-caffeine “energy” beverage

have been completed. In these studies (N=50), 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 PC- ECE induced increases in para-sympathetic nerve response and reduction in sympathetic nerve response (ECG measured). In addition, these studies have established a notable reduction in drowsiness one-hour following consumption of the trial PC- ECE-based energy beverage. The studys' results included:

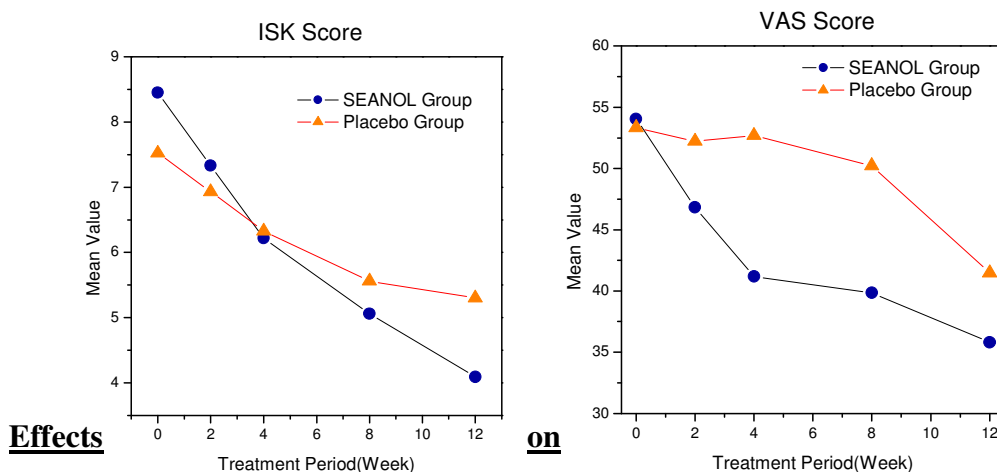
- Trans-Cranial Blood Flow: a 7.5-9% increase in peak and average neck blood flow, within 40 minutes of consumption;
- Alpha/Beta Brain Waves: a favorable 6-17% increase in beta and alpha brain waves, with a 13% increase in alpha/beta ratios, as measured against placebo;
- Sympathetic and Para-Sympathetic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

5. NEURALGIA & ARTHRITIS

PC- ECE 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 PC- ECE'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 PC- ECE Phase I-a study among FMS patients.

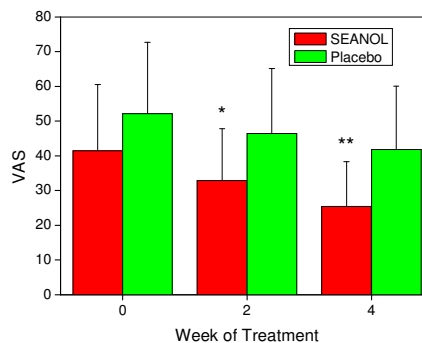
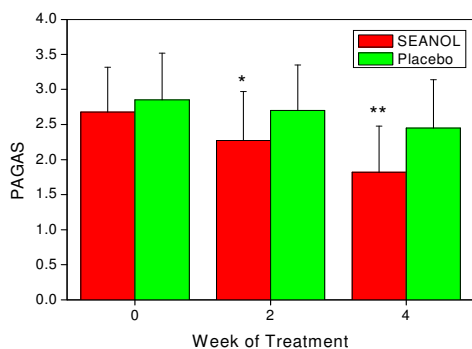
PC- ECE was tested for efficacy amongst patients with osteoarthritic knee conditions. The results below demonstrate the potential benefits of PC- ECE to this population.

- PC- ECE 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)



Neuralgia

	Total	PC- ECE (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

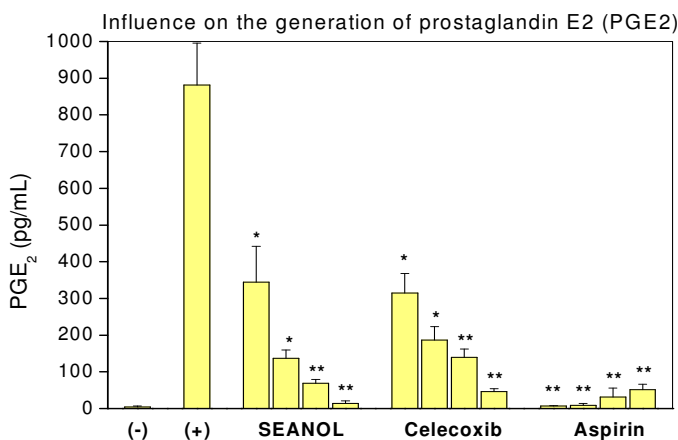


PAGAS: Patient's Global Assessment Scale; *p<0.05, **p<0.01

Anti-inflammatory activities of PC- ECE

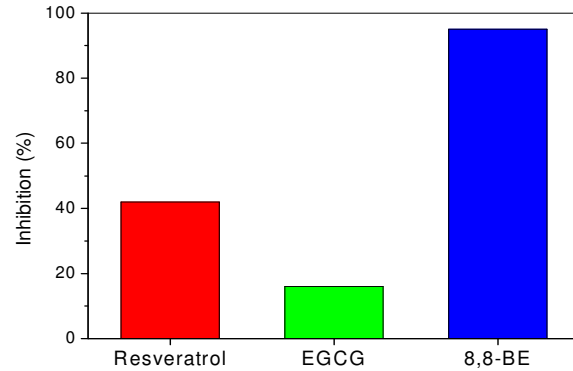
The influence of PC- ECE in LPS-induced generation of PGE₂ using RAW 246.7 cells was studied. While PGE₂ was barely detectable in non-stimulated cells, more than hundred-fold PGE₂ was detected in the stimulated cells. PC- ECE, celecoxib and aspirin all showed significant inhibition of PGE₂ generation

in the concentration range tested (10~100 µg/mL). PC- ECE showed inhibition of 61%, 85%, 92% and 99% at concentration of 10, 30, 60 and 100 µg/mL, respectively, showing similar activity to celecoxib that showed 65%, 79%, 85% and 96%, respectively.⁷



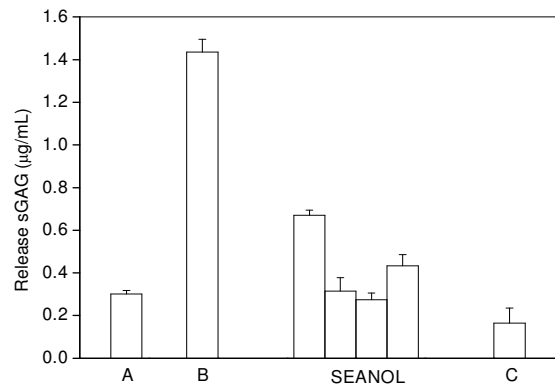
⁷ H-C Shin, H.J. Hwang, K.J. Kang, B.H. Lee, *An Antioxidative and Anti-inflammatory Agent for Potential Treatment of Osteoarthritis from Ecklonia Cava*, Arch Pharm Res Vol 29, No 2, 165-171, 2006.

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 PC- ECE 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 PC- ECE

Rabbit articular cartilage explant culture was treated with recombinant human interleukin 1 α (rhIL-1 α) 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 α for 60h, the amount of released glycosaminoglycan into the culture medium increased significantly compared to the vehicle group ($1.44 \pm 0.06 \mu\text{g}/\text{mg}$ vs. $0.30 \pm 0.01 \mu\text{g}/\text{mg}$). $10 \mu\text{M}$ ($3.2 \mu\text{g}/\text{mL}$) diclofenac that is known as a selective COX-2 inhibitor was used as a positive control. PC- ECE significantly interfered with the rhIL-1 α -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 $\mu\text{g}/\text{mL}$ concentration, respectively. In the figure, (A) no rhIL-1 α , (B) rhIL-1 α , (C) rhIL-1 α + diclofenac ($10 \mu\text{M}$), For VENTOL, rhIL-1 α + 1, 3, 10 and 30 $\mu\text{g}/\text{mL}$ (from left to right)



A clinical study of patients with neuropathic pain (N=40, randomized, double-blinded, placebo-controlled) established that PC- ECE has a highly favorable impact on neuropathic pain (79% positive response, average neuropathy reduction over 4 weeks of 40%), which is also a common FMS symptom. Standard prescription medications for neuropathic pain typically tend to have a low rate of response in effecting a significant decrease in neuropathic pain.

6. FIBROMYALGIA/CHRONIC FATIGUE SYNDROME

PC- ECE based capsule product (PC- ECE) provided major multi-symptom management (i.e., reduction in pain, fatigue, sleep disorders) for fibromyalgia patients. From a mechanism of action perspective among fibromyalgia (FMS) patients, the research conducted on PC- ECE 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 PC- ECE-based PC- ECE 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).

Notably, in contrast the advanced (Phase III) clinical studies on FMS that major pharma have 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, PC- ECE'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.

7. CANCER

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

Chemoprevention of UVB-induced Skin Carcinogenesis by PC- ECE 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 PC- ECE on UVB radiation-induced skin carcinogenesis on SKH-1 mice.
2. Protocol: SKH-1 hairless mice (N=48) were treated orally or topically with PC- ECE and irradiated with UVB three times (160mJ/cm²) per week for 26 weeks.
3. Summary of Results - In both dietary and topical treatment of PC- ECE
 - 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

Chemoprevention and Support Program, Division of Hematology and Oncology, Dept. of Internal Medicine, College of Medicine and Public Health, Ohio State University

The results of this study provide evidence that PC- ECE 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.⁸

Another outcome of the study was the finding that PC- ECE 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 PC- ECE significantly inhibited the production of iNOS by 48-78% depending upon dosage level and delivery method (dietary or topical).⁹

8. ALLERGIES

⁸ 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).

⁹ 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.

PC- ECE 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 by allergen-induced murine asthma model by Dr. Chi, Dept. of Histopathology, University of Washington.

Effect of PC- ECE 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. PC- ECE (“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 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.

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

Summary of results:

- 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

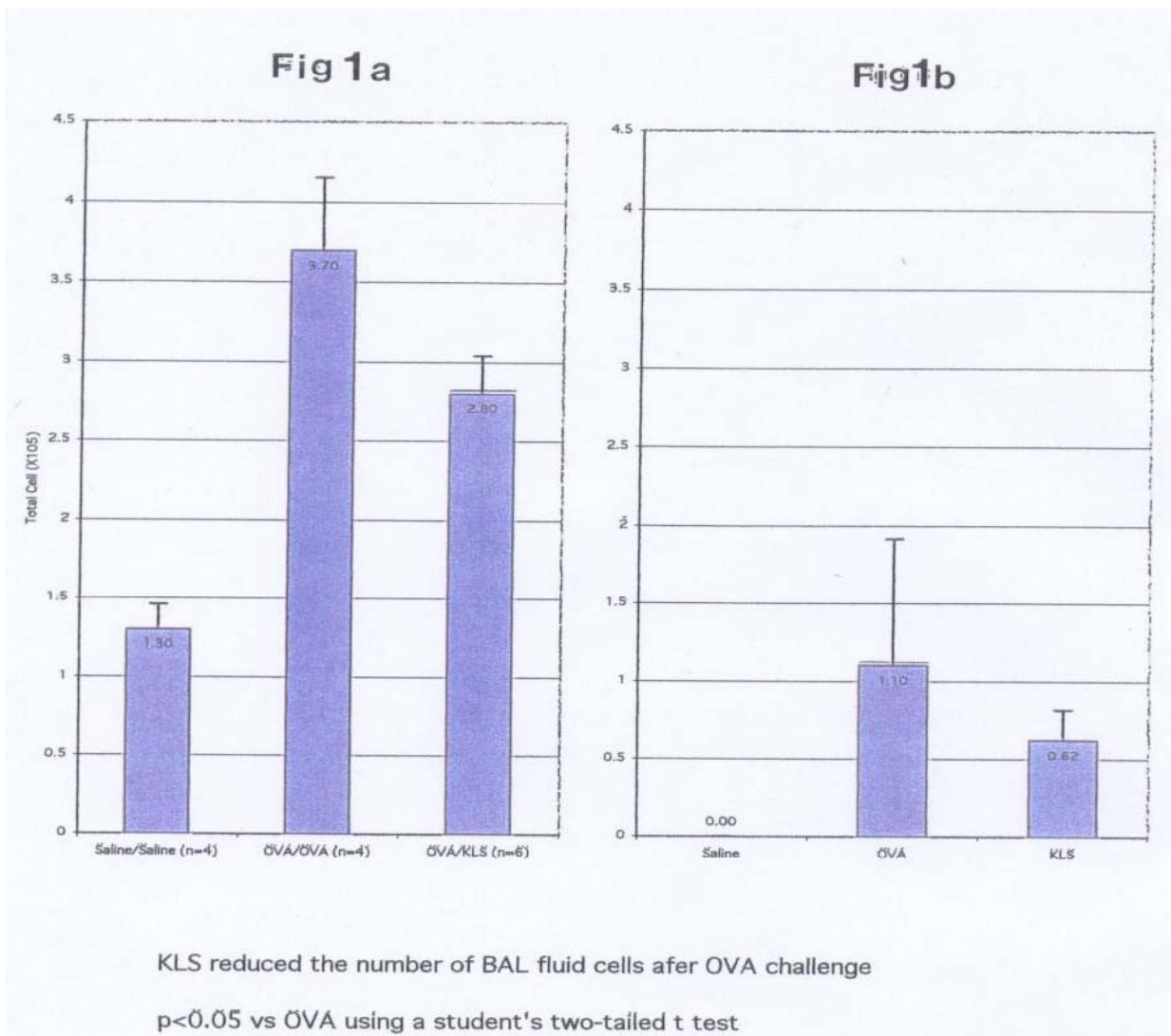


Fig. 1
 PC- ECE (KLS) reduced the number of eosinophils in BAL fluid after OVA challenge. BAL fluid was obtained on day 62 from saline-treated mice (sal/ sal; n=4) and OVA treated mice (OVA/ OVA; n=4) or fed with 25 mg KLS per day for 12 days (OVA/ KLS; n=6).

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

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.

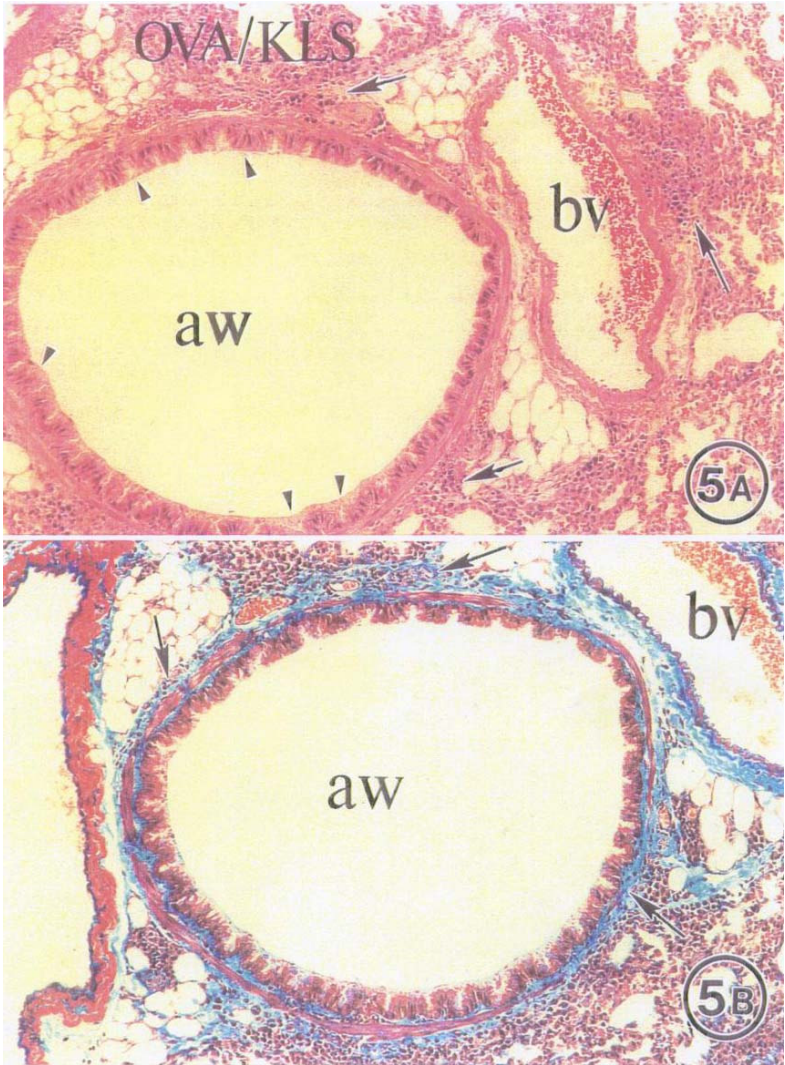


Fig. 3

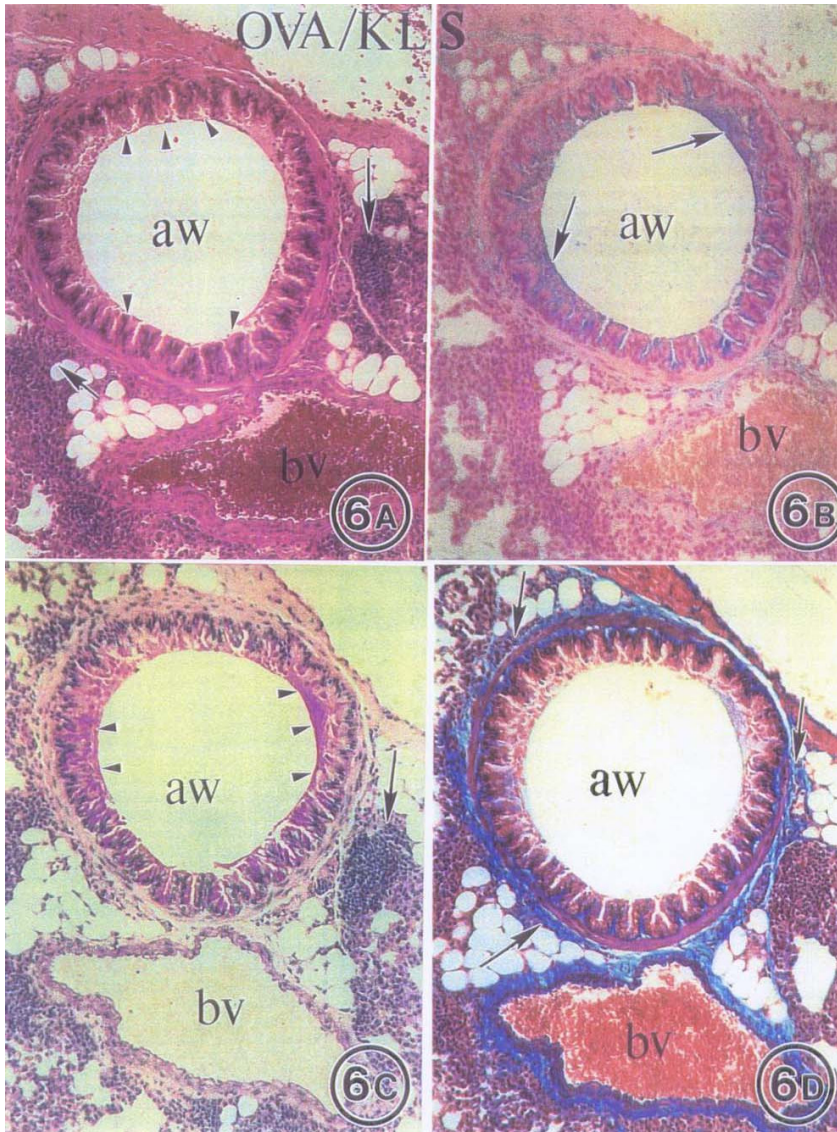
Effect of PC- ECE (KLS) on airway inflammation and remodeling in OVA treated mice. Lung tissue of OVA-sensitized/ challenged mice fed with KLS for 12 days at 25 mg per day was obtained. Stained with hematoxylin and eosin (A) and Masson's trichrome (B).

A) The inflammatory infiltration (arrows) of the lung interstitium around the airway (aw) and blood vessels (bv) is reduced by feeding PC- ECE (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 PC- ECE (KLS). X100

Fig. 6

PC- ECE (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).



A) PC- ECE (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) PC- ECE (KLS) inhibits some collagen deposition (arrows) in the interstitium of airway (aw) of the OVA-treated mice. X100

V. CONCLUSION

PC- ECE is a potent new polyphenol/phlorotannin compound extracted from brown algae. PC- ECE 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, on the one hand, and passing the blood-brain barrier, on the other.

Extensive pre-clinical and clinical research has been conducted on these specific compounds over the past 14 years. On the basis of this research, PC- ECE appears to be safe polyphenols with an unusual degree of potential efficacy in medical indications ranging from: CAD/CHD, type 2 diabetes (story still unfolding), AD (more to come), erectile dysfunction, FMS/CFS, sleep disorders (from the FMS clinical study), neuropathy, vasculitis, osteoarthritis, and even potentially certain cancers.

In the short term, PC- ECE-based nutraceuticals may represent a uniquely valuable new tool for physicians to offer their patient base as an alternative supplement in augmenting their current standard of care. It is exciting to consider that the algae-based polyphenol nutraceuticals may represent a unique and more potent “weapon” in the physician’s tool-kit to reduce a number of primary risk factors in indications having a high prevalence in North America.

References:

References:

- "Composition For Prevention And Improvement Of Dementia And Promotion Of Memory, And Healthy Assistance Foodstuffs Containing The Composition" Korean Patent Application# 10-2003-88177 (Assigned To Haengwoo Lee).
- "Compound For Improving Hypertension Containing Inhibitors Of Angiotensin Converting Enzyme Activity Extracted From Marin Plants And Articles Comprising Thereof", Korean Patent Application 10-2004-24347 (Livechem, Inc).
- "Compound For Improving Neuralgia Containing Dibenzo-P-Dioxine Derivatives Extracted From Marine Plants And Articles Comprising Thereof". Korean Patent Application 10-2004-0028066 (Livechem, Inc).
- Ahn MJ, Yoon KD, Min SY, Lee JS, Kim JH, Kim TG, Kim SH, Kim NG, Huh H, Kim J. Inhibition of HIV-1 reverse transcriptase and protease by phlorotannins from the brown alga *Ecklonia cava*. *Biol Pharm Bull*. 2004 Apr;27(4):544-7.
- Aikawa, T., S. Shimura, H. Sasaki, M. Ebina, And T. Takishima. 1992. Marked Goblet Cell Hyperplasia With Mucus Accumulation In The Airways Of Patients Who Died Of Severe Acute Asthma Attack. *Chest* 101:916-921.
- Athukorala Y, Kim KN, Jeon YJ. Antiproliferative and antioxidant properties of an enzymatic hydrolysate from brown alga, *Ecklonia cava*. *Food Chem Toxicol*. 2006 Jul;44(7):1065-74. Epub 2006 Mar 3.
- Becker AJ, Uckert S, Stief CG, Scheller F, Knapp WH, Hartmann U, Jonas U. Plasma levels of angiotensin II during different penile conditions in the cavernous and systemic blood of healthy men and patients with erectile dysfunction. *Urology*. 2001 Nov;58(5):805-10.
- Becker AJ, Uckert S, Stief CG, Truss MC, Machtens S, Scheller F, Knapp WH, Hartmann U, Jonas U. Possible role of bradykinin and angiotensin II in the regulation of penile erection and detumescence. *Urology*. 2001 Jan;57(1):193-8.
- Cases S, Smith SJ, Zheng YW, Myers HM, Lear SR, Sande E, Novak S, Collins C, Welch CB, Lusic AJ, Erickson SK, Farese RV Jr. Identification of a gene encoding an acyl CoA:diacylglycerol acyltransferase, a key enzyme in triacylglycerol synthesis. *Proc Natl Acad Sci U S A*. 1998 Oct 27;95(22):13018-23.
- Chapman VJ, Chapman DJ. (1980). *Seaweeds and their uses*. London: Chapman & Hall.
- De Angelis L, Marfella MA, Siniscalchi M, Marino L, Nappo F, Giugliano F, De Lucia D, Giugliano D. Erectile and endothelial dysfunction in Type II diabetes: a possible link. *Diabetologia*. 2001 Sep;44(9):1155-60.
- Djukanovic, R., J.W. Wilson, K.M. Britten, S.J. Wilson, A.F. Walls, W.R. Roche, P.H. Howarth, S.T. Holgate. 1990. Quantitation Of Mast Cells And Eosinophils In The Bronchial Mucosal Of Symptomatic Atopic Asthmatics And Healthy Control Subjects Using Immunohistochemistry. *Am.Rev.Respir.Dis*. 142:863-871.
- Dorrance AM, Lewis RW, Mills TM. "Captopril Treatment Reverses Erectile Dysfunction In Male Stroke Prone Spontaneously Hypertensive Rats." *Int J Impot Res*. 2002 Dec;14(6):494-7
- Fukuyama Y, Kodama M, Miura I, Kinzyo Z, Mori H, Nakayama Y, Takahashi M. Anti-plasmin inhibitor. VI. Structure of phlorofucofuroeckol A, a novel phlorotannin with both dibenzo-1,4-dioxin and dibenzofuran elements, from *Ecklonia kurome* Okamura. *Chem Pharm Bull (Tokyo)*. 1990 Jan;38(1):133-5.
- Fukuyama, Y., Kodama, M., Miura, I., Kinzyo, Z., Kido, M., Mori, H., Nakayama, Y., Takahashi, M. Structure Of An Anti-Plasmin Inhibitor, Eckol, Isolated From The Brown Alga *Ecklonia Kurome* Okamura And Inhibitory Activities Of Its Derivatives On Plasmin Inhibitors. *Chem. Pharm. Bull*. 37: 349-353 (1989)
- Glombitza, K.W., Gerstberger, G. Phlorotannins With Dibenzodioxin Structural Elements From The Brown Alga *Eisenia Arborea*. *Phytochemistry* 24: 543-551 (1985)
- Grunig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson DD, Locksley RM, Corry DB. Requirement for IL-13 independently of IL-4 in experimental asthma. *Science*. 1998 Dec 18;282(5397):2261-3.
- Hamed EA, Meki AR, Gaafar AA, Hamed SA. Role Of Some Vasoactive Mediators In Patients With Erectile Dysfunction: Their Relationship With Angiotensin-Converting Enzyme And Growth Hormone. *Int J Impot Res*. 2003 Dec;15(6):418-25.
- Henderson, W.R., E.Y. Chi. 1985. Ultrastructural Characterization And Morphometric Analysis Of Human Eosinophil Degranulation. *J. Cell Sci*. 73:33-48.

- Henderson, W.R., Jr., D.B. Lewis, R.K. Albert, Y. Zhang, W.J.E. Lamm, G.K.S. Chiang, F. Jones, P. Eriksen, Y. Tien, M. Jonas, E.Y. Chi. 1996. *The Importance Of Leukotrienes In Airway Inflammation In A Mouse Model Of Asthma*. *J. Exp. Med.* 184:1483-1494.
- Henderson, W.R., Jr., E.Y. Chi, C.R. Maliszewski. 2000. *Soluble Interleukin-4 Receptor (Sil-4R) Inhibits Airway Inflammation Following Allergen Challenge In A Mouse Model Of Asthma*. *J. Immunol.* 164:1086-1095.
- Hoppe HA. (1979). *Marine algae and their products and constituents in pharmacy*. In: *Marine Algae in Pharmaceutical Science*. Hoppe HA, Levring T, Tanaka Y, eds. Berlin & New York: Walter de Gruyter.
- Hoshino, M., Y. Nakamura, J.J. Sim. 1998. *Expression Of Growth Factors And Remodeling Of The Airway Wall In Bronchial Asthma*. *Thorax* 53:21-27.
- Kang K, Park Y, Hwang HJ, Kim SH, Lee JG, Shin HC. *Antioxidative properties of brown algae polyphenolics and their perspectives as chemopreventive agents against vascular risk factors*. *Arch Pharm Res.* 2003 Apr;26(4):286-93.
- Kang KA, Lee KH, Chae S, Koh YS, Yoo BS, Kim JH, Ham YM, Baik JS, Lee NH, Hyun JW. *Triphlorethol-A from Ecklonia cava protects V79-4 lung fibroblast against hydrogen peroxide induced cell damage*. *Free Radic Res.* 2005 Aug;39(8):883-92.
- Kang KA, Lee KH, Chae S, Zhang R, Jung MS, Ham YM, Baik JS, Lee NH, Hyun JW. *Cytoprotective effect of phloroglucinol on oxidative stress induced cell damage via catalase activation*. *J Cell Biochem.* 2006 Feb 15;97(3):609-20.
- Kang KA, Lee KH, Chae S, Zhang R, Jung MS, Lee Y, Kim SY, Kim HS, Joo HG, Park JW, Ham YM, Lee NH, Hyun JW. *Eckol isolated from Ecklonia cava attenuates oxidative stress induced cell damage in lung fibroblast cells*. *FEBS Lett.* 2005 Nov 21;579(28):6295-304. Epub 2005 Oct 19.
- Kang KA, Zhang R, Lee KH, Chae S, Kim BJ, Kwak YS, Park JW, Lee NH, Hyun JW. *Protective effect of triphlorethol-A from Ecklonia cava against ionizing radiation in vitro*. *J Radiat Res (Tokyo).* 2006 Mar;47(1):61-8.
- Kang, K., Park, Y., Hwang, H. J., Kim, S. H., Lee, J. G., Shin, H.-C. (2003). *Antioxidative Properties Of Brown Algae Polyphenolics And Their Perspectives As Chemopreventive Agents Against Vascular Risk Factors*. *Arch. Pharm. Res.* 26: 286-293
- Kang, K.J., Hwang, H.J., Hong, D.H., Park, Y.J., Kim, S.H., Lee, B.H., Shin, H.C. *Anti-Oxidant And Anti-Inflammatory Activities Of Ventol, A Phlorotannin-Rich Natural Agent Derived From Ecklonia Cava, And Its Effect On Proteoglycan Degradation In Cartilage Explant Culture*. Submitted To *Molecular Pathology And Pharmacology*
- Kay, A.B. 1997. *T Cells As Orchestrators Of The Asthmatic Response*. *Ciba Found. Symp.* 206:56-67.
- Kim MM, Ta QV, Mendis E, Rajapakse N, Jung WK, Byun HG, Jeon YJ, Kim SK. *Phlorotannins in Ecklonia cava extract inhibit matrix metalloproteinase activity*. *Life Sci.* 2006 Sep 5;79(15):1436-43. Epub 2006 May 7.
- Krug, N., J. Madden, A.E. Redington, P. Lackie, R. Djukanovic, U. Schauer, S.T. Holgate, A.J. Frew, P.H. Howarth. 1996. *T-Cell Cytokine Profile Evaluated At The Single Cell Level In Bal And Blood In Allergic Asthma*. *Am. J. Respir. Cell Mol. Biol.* 14:319-326.
- Lee, B.H., Stein, S. *Improvement Of Learning Behavior Of Mice By An Antiacetylcholinesterase And Neuroprotective Agent Nx42, A Laminariales-Alga Extract*. Presented To The *Pharm. Soc. Kor., Spring Conference (2004)*; Manuscript Submitted To *Korean Journal Of Food Science And Technology*.
- Lee, S.H., Han, S.B., Baik, J.Y. *The Influence Of VNP Intake On The Symptoms Of Osteoarthritis Of The Knee Joint*. Clinical Report By Department Of Orthopedic Surgery, Anam Hospital, Korea University Medical Center
- Mcever, R.P. 1991. *Selectins: Novel Receptors That Mediate Leukocyte Adhesion During Inflammation*. *Thromb. Haemost.* 65:223-228.
- Myung CS, Shin HC, Bao HY, Yeo SJ, Lee BH, Kang JS. *Improvement of memory by dieckol and phlorofucofuroeckol in ethanol-treated mice: possible involvement of the inhibition of acetylcholinesterase*. *Arch Pharm Res.* 2005 Jun;28(6):691-8.
- Nakamura, T., Nagayama, K., Uchida, K., Tanaka, R. *Antioxidant Activity Of Phlorotannins Isolated From The Brown Alga Eisenia Bicyclis*. *Fisheries Sci.* 62: 923-926 (1996).
- Roche, W.R., R. Beasley, J.H. Williams, S.T. Holgate. 1989. *Subepithelial Fibrosis In The Bronchi Of Asthmatics*. *Lance* 1:520-524.

- Ruehl ML, Orozco JA, Stoker MB, Mcdonagh PF, Coull BM, Ritter LS. Protective Effects Of Inhibiting Both Blood And Vascular Selectins After Stroke And Reperfusion. *Neurol Res.* 2002 Apr;24(3):226-32.
- Sheehan, D.C., B.B. Hrapchak. 1980. Connective Tissue/Muscle Fiber Stains. In *Theory And Practice Of Histotechnology*. Battelle Press, Columbus, OH. 180-201.
- Shibata, T., Fujimoto, K., Nagayama, K., Yamaguchi, K., Nakamura, T. Inhibitory Activity Of Brown Algal Phlorotannins Against Hyaluronidase. *Int. J. Food Sci. Tech.* 37: 703-709 (2002)
- Shibata, T., Nagayama, K., Tanaka, R., Yamaguchi, K., Nakamura, T. Inhibitory Effects Of Brown Algal Phlorotannins On Secretory Phospholipase A2S, Lipoxygenases And Cyclooxygenases. *J. Appl. Phycol.* 15: 61-66 (2003)
- Shin HC, Hwang HJ, Kang KJ, Lee BH. An antioxidative and antiinflammatory agent for potential treatment of osteoarthritis from *Ecklonia cava*. *Arch Pharm Res.* 2006 Feb;29(2):165-71.
- Smith SJ, Cases S, Jensen DR, Chen HC, Sande E, Tow B, Sanan DA, Raber J, Eckel RH, Farese RV Jr. Obesity resistance and multiple mechanisms of triglyceride synthesis in mice lacking Dgat. *Nat Genet.* 2000 May;25(1):87-90.
- Temann UA, Prasad B, Gallup MW, Basbaum C, Ho SB, Flavell RA, Rankin JA. A novel role for murine IL-4 in vivo: induction of MUC5AC gene expression and mucin hypersecretion. *Am J Respir Cell Mol Biol.* 1997 Apr;16(4):471-8.
- Tsukada H, Nishiyama S, Fukumoto D, Ohba H, Sato K, Kakiuchi T. Effects of acute acetylcholinesterase inhibition on the cerebral cholinergic neuronal system and cognitive function: Functional imaging of the conscious monkey brain using animal PET in combination with microdialysis. *Synapse.* 2004 Apr;52(1):1-10.
- Uhm CS, Kim KB, Lim JH, Pee DH, Kim YH, Kim H, Eun BL, Tockgo YC. Effective treatment with fucoidin for perinatal hypoxic-ischemic encephalopathy in rats. *Neurosci Lett.* 2003 Dec 15;353(1):21-4.
- Virag R, Floresco J, Richard C. Impairment Of Shear-Stress-Mediated Vasodilation Of Cavernous Arteries In Erectile Dysfunction. *Int J Impot Res.* 2004 Jan;16(1):39-42
- Wills-Karp, M., J. Luyimbazi, X. Xu, B. Schofield, T.Y. Neben, C.L. Karp, D.D. Donaldson. 1998. Interleukin-13: Central Mediator Of Allergic Asthma. *Science* 282:2258-2261.
- Zhu, Z., R.J. Homer, Z. Wang, Q. Chen, G.P. Geba, J. Wang, Y. Zhang, J.A. Elias. 1999. Pulmonary Expression Of Interleukin-13 Causes Inflammation, Mucus Hypersecretion, Subepithelial Fibrosis, Physiologic Abnormalities, And Eotaxin Production. *J. Clin. Invest.* 103:779-788.