Ecklonia Cava Extract - Super Antioxidant

Ecklonia Cava Extract (ECE) is a standardized complex of marine molecules that originate from a *brown algae* species, Ecklonia Cava. ECE represents a category of polyphenols called phlorotannins. Their polyphenolic structure endows them with biological activities not found in land-based plants.

ECE naturally occurs as high-molecular weight tannin (Mw> 2,000 Dalton) and low-molecular weight tannin (Mw=400-1000 Dalton). ECE can be classified into four types depending on the ratio of high molecular weight and low molecular weight tannins. Various physiological activities of ECE have been evaluated in vitro, in vivo and clinically as individual compounds (ECE1-ECE14) and complex forms (ECE, Type I-IV).

Millions on Research

Dr. Haengwoo Lee and his team of M.D.'s and Ph.D.'s have spent over thirty million dollars on research, from in vitro to animal and human studies in Korea and some at the University of Washington. ECE is impressive therapeutic agent in a wide array of clinical applications.

SUPER ANTIOXIDANT

The power of an antioxidant is determined by its structure, which is made up of rings. These rings capture stray electrons from free radicals. Most flavonoids have three interconnected rings. ECE has up to eight interconnected rings, making its free-radical scavenging ability 10-100 times more powerful than other polyphenols. It is substantially more powerful than green tea catechins which have only four rings.

Multiple Antioxidant Profiles of ECE

ECE's antioxidant activities against various reactive oxygen species have been confirmed to be highly potent in physiologically relevant concentrations. The effective dose of ECE for free radical scavenging is in the 10-20 μg/mL range which belongs to most potent families of natural antioxidants. ECE has demonstrated potent reducing power and radical scavenging activities against DPPH radical, oxidized LDL and peroxynitrite.

Much Longer Half-Life

ECE is a unique polyphenol that has a very long half-life in the body. This is because ECE is a marine-based polyphenol which is 40% fat-soluble. All other polyphenols are derived from land-based plants and are water-soluble. The

half-life of ECE is up to 12 hours, compared to 30 minutes for water-soluble, land-based polyphenols. ECE also has the ability to cross the blood-brain barrier.

The Research of Martin Pall, Ph.D.

Peroxynitrite is the most notorious of the free radicals incriminated by Martin Pall, Ph.D.'s groundbreaking research on multiple *chemical sensitivity*, *fibromyalgia*, *chronic fatigue syndrome*, *posttraumatic stress disorder*, *Gulf War syndrome* and fourteen other conditions. Peroxynitrite plays a main role in Dr. Pall's mechanism, along with NF-kappaB and other inflammatory mediators. ECE also reduces tissue specific NF-kappaB. Peroxynitrate is a central reactive oxidant, which appears to play a major role in many disease processes.

FIBROMYALGIA

ECE: Phase I Clinical Trial Results (Preliminary)

In an 8-week, double-blinded, placebo-controlled study of established fibromyalgia patients, ECE was used as an adjunct therapy to the patients' current standard of physician care. The results established the general safety of ECE. ECE *cut the time it took the participants to fall asleep by 47 minutes*; it *increased total nighttime sleep by 1.6 hours*; it *improved soundness of sleep* by 80%; it *boosted their energy levels* by 71%; it gave them 2 1/4 more good days per week; it helped *reduce their pain* by 31%; and their *general condition improved* by 39%. Interestingly, these improvements were achieved at all doses. Patients given the placebo had no improvement during the study.

BRAIN FUNCTION: MEMORY, RELAXATION, ALERTNESS

Acetylcholine & Memory

Memory is dependent on the neurotransmitter acetylcholine (ACh). In an animal study, ECE increased rodent ACh by 140% in brain regions responsible for *learning and memory* in seven days. *Memory enhancement* increased by 100-200% at an oral dose as low as 0.2-1mg/kg.

With regard to mechanism, it is thought that the mild acetylcholinesterase inhibitory activity of two phlorotannin compounds found in ECE, dieckol (DE) and phlorofurofucoeckol (PFF), may be involved in the up-regulation of acetylcholine.

Increased Blood Flow

ECE crosses the blood-brain barrier and significantly *improves blood flow*, which is likely another way ECE *improves memory*. More specifically, Dr. Lee's group found that ECE can increase the velocity of blood flow in the carotid artery from an average of 36.68 cm/sec. to 40.09 cm/sec., while the placebo showed no improvement.

Relaxation & Alpha-Waves

An EEG study on brain waves of healthy middle age volunteers found that ECE compounds *increase alpha-waves*. Alpha-waves are an indicator of *relaxation*.

Alertness

Prevented sleepiness in bus drivers and in high school students during daytime activities. This is likely due to increased *blood flow* and *oxygen delivery*.

Neuroprotective Effects

ECE demonstrated powerful neuroprotective effects owing to several features of its components. ECE compounds are both *powerful antioxidants* and *anti-inflammatory agents* capable of scavenging free radicals and suppressing excessive inflammatory reactions. Fucoidan in ECE has recently been found to protect neuronal cells from ischemia-induced inflammatory reactions which often occur in the aged and highly stressed brain. ECE compounds also neutralize the neurotoxic free-radical peroxynitrite.

Enhancement of Acetylcholine Levels in Mice

After 7 days oral administration of two ECE compounds (DE 10mg/kg and PFF 2mg/kg), mice under ethanol-induced cognitive impairment showed substantial enhancement of acetylcholine in three brain regions related to memory formation, as compared with non-treated mice, 140% enhancement was observed in the frontal cortex that is crucial in *long-term memory* and *associative thinking*.

Resistance of Stress-Induced Learning Deficit in Mice

In a 5-day study, ECE treated mice showed significant resistance to electric shock treatment-induced learning deficiency, as compared to non-treated mice whose learning process was significantly retarded during the test period.

Memory Enhancement in Mice

The beneficial effects of ECE compounds on memory enhancement were further demonstrated by measuring the latency time avoiding the previously experienced electric shock treatment in mice as passive-avoidance memory testing. After 7 days oral administration of two ECE compounds DE and PFF (as low as 1 and 0.2mg/kg), mice under ethanol-induced cognitive impairment showed 130-140% improvement, especially in the PFF group.

Beta-Amyloid Deposition Inhibition in Rats

Researchers at the National Institute of Health's aging research labs in Baltimore studied ECE in rats and found it to *inhibit beta-amyloid deposition in the brain*. Beta-amyloid is the same substance that accumulates in Alzheimer's disease. The rats also learned maze challenges faster, which demonstrated improvement in short-term memory.

ARTHRITIS, INFLAMMATION, NEURALGIA

Dr. Lee and colleagues found ECE to naturally s*uppress inflammatory responses* and *neutralize inflammatory damage* caused by reactive oxygen species. The optimal combination of ECE's natural anti-inflammatory and tissue-protective properties appears to enable dramatic improvement in both *arthritis* and *neuralgia*. In a human trial, ECE significantly *reduced pain* in a group of knee arthritis patients compared with placebo.

Comparable to CelebrexÆ

ECE's ability to treat *arthritis* was found to be comparable to CelebrexÆ, the prescription drug that reduces inflammatory cox enzymes.

The influence of ECE in lipopolysaccharide (LPS)-induced generation of prostaglandin E2 (PGE2) using RAW 246.7 cells was studied. While PGE2 was barely detectable in non-stimulated cells, more than one hundred times the amount of PGE2 was detected in the stimulated cells. ECE, celecoxib (CelebrexÆ) and aspirin all showed significant inhibition of PGE2 generation in the concentration range tested. ECE showed inhibition of 61%, 85%, 92% and 99% at concentrations of 10, 30, 60 and 100 µg/mL, showing similar activity to celecoxib which showed 65%, 79%, 85% and 96%.

Cartilage Protecting Activities

As demonstrated above, ECE compared almost identically to celecoxib in the ability to reduce PGE2 by slowing down the lipoxygenase (LOX) system. ECE

compounds have more than double the ability of resveratrol to inhibit LOX. These results were demonstrated in a study on rabbit cartilage cells. Those cells treated with ECE had up to an 80% reduction in degeneration.

Rabbit Model

In an animal study, rabbit articular cartilage explant culture was treated with recombinant human interleukin 1 (rhIL-1) 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 for 60 hours, the amount of released glycosaminoglycan into the culture medium increased significantly compared to the vehicle group (1.44 ± 0.06μg/mg vs. 0.30 ± 0.01μg/mg). Diclofenac, which is known as a selective COX-2 inhibitor was used as a positive control at a dose of 10μM (3.2μg/mL). ECE significantly interfered with the rhIL-1-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 μg/mL concentration.

Neuropathy: 4-Week Clinical Trial

Researchers recently studied ECE on 40 patients with *neuropathy*. ECE reduced *nerve pain* by 40% in four weeks. Overall, 80% of the patients responded favorably.

Speculation about Neuropathy Mechanism

The strong lipid and cholesterol reducing potential of ECE supports *reduced vascular inflammation*. Increasingly, the scientific literature supports the notion that many forms of nerve pain or neuropathy are caused by nerve pressure, as exerted by swollen, inflamed blood vessels adjacent to the nerves.

ALLERGIES / ASTHMA

Overall, ECE appears to significantly *relieve allergic reactions* without drowsiness, dizziness and other side effects of anti-histamine drugs.

Allergic Inflammation: Mouse Model

Dr. Lee and his team found that ECE significantly *reduced allergic inflammation* in mice. Specifically, ECE reduced the migration of eosinophils to the lungs by 75%. Inflammatory white blood cells (CD4+4 T Cells, resultant cytokines Il-4, 5, 13) were reduced by 50%. Mucus plugs in the airways were

reduced by 75%. Airway epithelial hyperplasia reduced by 75%. Collagen-causing fibrosis in lung interstitium (fibrosis, airway remodeling) and smooth muscle cell thickness was reduced by 20% and 32%. These latter findings suggest that ECE compounds can prevent or reverse the progression of chronic lung disease such as asthma and Chronic Obstructive Pulmonary Disease (COPD).

5-Lipoxygenase (5-LOX)

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 ECE compounds (8,8-BE) significantly inhibits 5-LOX compared with other well-known natural medicinal compounds such as resveratrol and EGCG.

University of Washington Asthma Mouse Model

The efficacy of ECE for *asthma* was demonstrated in an allergen-induced murine asthma mouse model by Dr. Emil Chi, Chairman, Department of Histopathology, University of Washington.

The researchers tested an ECE product (KLS) in a mouse model of allergen-induced chronic lung inflammation and fibrosis. BALB/c mice, after intraperitoneal antigen sensitization on day 0 and day 14, were given weekly intranasal inhalations of antigen from day 14-60. The antigen-treated and challenged mice developed an extensive eosinophil and mononuclear cell inflammatory response, mucus cell hyperplasia and mucus occlusion of the airway.

KLS was found to be 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 antigen-sensitized / challenged mice. The reduced BAL fluid eosinophil indicated that KLS is effective in *improving the asthmatic lung structures*. No pathological alterations in the liver, kidney, spleen, or small intestine were found.

CARDIOVASCULAR BENEFITS

Coronary Artery Disease

ECE has been shown to *improve coronary artery disease* (CAD). Researchers found that ECE is even more potent at inhibiting the oxidation of LDL cholesterol than green tea catechins and appears to scrub the plaque off the endothelial lining. ECE also *reduces vascular inflammation* by preventing oxidation, which also directly effects inflammatory mediators such as inflammatory prostaglandins, etc.

Coronary Artery Disease: 6-Week Clinical Trial

A clinical trial using ECE was conducted confirming its capacity to regenerate vascular endothelium and recover plasticity of blood vessels after 6 weeks of treatment by measuring flow-mediated dilation (FMD) & nitroglycerin-mediated dilation (NMD) of normal and CAD patients with narrowed coronary arteries by 50+%. FMD indicates nitric oxide (NO) releasing ability of endothelial cells to expand blood vessels by detecting shear stress caused by incoming blood flow (low FMD value can indicate endothelium damage).

After 6 weeks of treatment with ECE, clinical data showed that FMD, the endothelium-dependent dilation, was greatly enhanced in the CAD 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 the CAD group, again supporting ECE's ability to support restoration of *vascular integrity* by reversing *atherosclerosis*.

Cholesterol: 6-Week ClinicalTrial

Researchers gave 39 adults (average age 55.6) low dose (100 mg) ECE compounds for six weeks. Their average cholesterol dropped from 228 to 224. LDL dropped from 141 to 135. HDL rose from 46.5 to 50.7 (highly significant). *Triglycerides* fell from 215 to 195, and the atherogenic index dropped 12.5%.

Some of the parameters from the above study show very mild changes, which in themselves, may not be statistically significant. However, all parameters went in a health-positive direction, so taken together, the changes in *LDL*, *HDL*, *triglycerides*, *blood pressure* and *antioxidant protection* are very significant. Also, endothelial cells were protected against oxidative damage, and were able to produce significantly more NO, which dilates blood vessels. Dramatic increases in *blood flow* were also found at this low dose.

Hypertension: 4-Week Animal Study

The remarkable effect of ECE on vasodilation was clearly demonstrated in renovascular clipping induced hypertensive rats. Renovascular clipping surgery is known to increase ACE activity via the renin-angiotensin-aldosterone system, which increased systolic blood pressure (SBP) from 140 to over 200 mm Hg after 4 weeks. Upon oral administration of phlorotannin (99.4%, 50 mg/kg) or enalapril (commercial hypotensive drug, 10 mg/kg) SBP dropped to as low as 160 and 140 mm Hg. Upon cessation of treatment, SBP increased again in both cases. Although ECE showed a similar pattern to the drugs, it also showed a slower rebounding of blood pressure during the no treatment period, which indicates its potential as a vascular protector with prolonged oral administration.

ACE Inhibition

Angiotensin-converting enzyme (ACE), is responsible for conversion of angiotensin I to angiotensin II and degradation of bradykinin, and 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 or various vascular risk factors tend to increase ACE levels resulting in excessive vasoconstriction and hypertension. Current hypotensive drugs block the action of ACE or its by-product angiotensin II.

ECE tannins have been found to be potent natural ACE inhibitors, demonstrating more than 15 times the power to inhibit ACE as the most powerful land-based polyphenols, including the natural hypotensive substance catechin found in green tea. One of the compounds found in ECE, THP-BE is comparable to the physiological vasodilative hormone bradykinin.

Antiplasmin Inhibition

Plasmin (a fibrinolytic enzyme that breaks down blood clots) is rapidly blocked by a protein called antiplasmin. ECE compounds are natural potent inhibitors of anti-plasmin, capable of efficient promotion of plasmin that performs fibrinolysis. ECE compounds have shown remarkable activity which is 40-200 times greater than synthetic compounds Flufenamate and Chloramine T. One study on ECE compounds found a small but significant rise in prothrombin time and a fall in fibrinogen levels.

ERECTILE FUNCTION

Nitric Oxide

ECE can regenerate the vascular endothelium, the cells critical to the inner lining of the blood vessels. They generate the chemical nitric oxide (NO), which keeps the arterial walls relaxed and dilated. After a six-week study of ECE, flow mediated dilation and NO mediated dilation increased by 60% and 50%. In another study, coronary artery disease patients were given ECE for six weeks. Blood flow controlled by NO increased 50-60%. These results confirm that ECE can rejuvenate damaged endothelial cells to produce NO. This effect was further confirmed in a study on *erectile dysfunction* (see below). Interestingly, ViagraÆ works by increasing NO in the penile artery.

ECE v.ViagraÆ: 8-Week Clinical Trial

Scientists studied 31 men with *erectile dysfunction* (ED) for over six months. They compared eight weeks of ECE use to ViagraÆ. They looked at orgasmic function (OF), intercourse satisfaction (IS), overall satisfaction (OS), and erectile function (EF). Over those eight weeks, ECE scored 87%, 74%, 62%, and 66%. ViagraÆ scored 27%, 44%, 39%, and 66%. No adverse effects were reported with ECE:

Population with 25+% Improvement in IIEF (International Index of Erectile Function) 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 the 8th week were significantly greater than those at week 0 for all domains (all $p<0.01$). The *degree of improvement was significant* in the following order: OF (87%), IS (74%), EF (66%), and OS (62%). Scores on key questions (asking frequency of penetration and 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%) 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.

Also noteworthy, was a significant increase in the *orgasmic function* score (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), which indicates that ECE significantly contributed to the normalization of the general vascular conditions around the sexual organ.

These results strongly indicate that the long-term administration of ECE significantly contributes to the neutralization of oxidative risk factors, thereby improving peripheral blood circulation around muscles and nerves involved in sexual function as well as the penile artery. No adverse effects were reported.

Vasodilation & Erectile Function

It has been reported that vasculogenic ED patients have elevated levels of angiotensin II for the duration of the erection process. The demonstrated action of ECE on ACE and resulting vasodilation is thought to play an important role in inducing *successful erectile function*.

Long-Term Improvement Via Vascular Protection

As discussed, ECE phlorotanins have potent *antioxidant* and *anti-inflammatory* effects. Together with ECE's ACE inhibitory activity, which is also beneficial to vascular homeostasis, these activities, upon long-term oral administration, may all contribute to supporting a healthy vascular system, including the penile artery.

WEIGHT LOSS

DGAT Inhibition

Diacylglycerol acetyl transferase (DGAT) is the enzyme involved in the final step of triglyceride synthesis. Triglycerides are circulating fat bodies that ultimately wind up in the fat cells, and are almost always elevated in diabetes. They also have emerged as a major risk factor in vascular disease.

Dr. Lee found that ECE compounds inhibited DGAT more than 50%. In genetically caused obese laboratory rats, ECE *reduced body fat* and increased physical activity. In another study, ECE caused leanness and fat-resistance in animals given a high fat diet.

ECE Beverage: 2-Week Clinical Trial

In a human study, 141 young adults were given a beverage containing ECE at 200 mg daily. In two weeks their average weight dropped nearly 2.5 pounds, *muscle mass increased* by nearly 2.5 pounds, and body fat dropped by 4 pounds, or 7.48%. ECE stimulates the body *to burn fat* by *increasing muscle mass*.

OBESITY

Obesity & Cardiovascular Disease

As discussed, ECE contains an optimal combination of natural compounds capable of suppressing triglyceride synthesis, while promoting cholesterol removal and cardiovascular protection. ECE provides additional cardiovascular protection for obese patients prone to CVD and CHD through lowering LDL cholesterol and scavenging free radicals.

DGAT Inhibition & Obesity

DGAT inhibition has recently been 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 mice have been shown to have *obesity resistance* with a high-fat diet, the mechanism of which was confirmed to be through energy expenditure.

DIABETES

Aldose Reductase Inhibition

When blood sugar levels become elevated, aldose reductase is the enzyme that converts excess glucose into the sugar alcohol sorbitol. Sorbitol can build up in critical cells and cause damage. Recent research found that animals deficient in aldose reductase were protected from the retinal complications of diabetes. ECE compounds have been found to be potent aldose reductase inhibitors, which may be of benefit for patients with *metabolic syndrome*, syndrome X, or *diabetes*.

Reduced Fat in Liver & Pancreas

A mouse study showed that ECE *reversed fat deposition in liver and pancreas cells*. Furthermore, this same study showed that ECE served to markedly inhibit NF-kappaB inflammation in the pancreas. A recent Harvard (Joslin School of Diabetes) mouse study directly implicates excessive fat deposition in the mouse pancreas as turning on the NF-kappaB inflammation pathway, resulting in full-blown type II diabetes and insulin insensitivity in the mice.

SAFETY

ECE is manufactured from edible algae through food-compatible processes. Tens of thousands of people throughout the world have experienced ECE in

various forms of product without adverse effects. To date, Dr. Lee's team has not found toxicity at any level. Several toxicity tests have been performed and no adverse effects have been found at the effective human dose level of 1-10 mg/kg.

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