

The Science - Reference Guide

Please review the Reference Guide for studies and citations used in the creation of this document.

Please note this document presents a collection of statements, research and studies from around the world about the benefits of these ingredients. This information is provided for informational purposes only. These statements were variously made over several decades of time. This document does not intend to provide medical advice, nor does it intend to replace the advice of your personal physician or your own personal research into the ingredients. The FDA has not evaluated any statement made in this document. The information herein is not intended to diagnose any disease, nor is it intended to prescribe any preparation that claims to diagnose, treat, cure or prevent any disease.

Reference Guide

Ecklonia Cava

1. "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).
2. "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).
3. 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.
4. 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.
5. 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.
6. 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.
7. 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.

8. 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.
9. Cases S, Smith SJ, Zheng YW, Myers HM, Lear SR, Sande E, Novak S, Collins C, Welch CB, Lusi 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.
10. Chapman VJ, Chapman DJ. (1980). *Seaweeds and their uses*. London: Chapman & Hall.
11. "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).
12. 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.
13. 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.
14. 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)
15. Glombitza, K.W., Gerstberger, G. Phlorotannins With Dibenzodioxin Structural Elements From The Brown Alga *Eisenia Arborea*. *Phytochemistry* 24: 543-551 (1985)
16. 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
17. 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.
18. 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.
19. 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.
20. 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.
21. Henderson, W.R., E.Y. Chi. 1985. Ultrastructural Characterization And Morphometric Analysis Of Human Eosinophil Degranulation. *J. Cell Sci.* 73:33-48.
 22. 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.
 23. 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.
 24. 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.
 25. 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.
 26. 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.
 27. 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
 28. 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.
 29. 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*
 30. Kay, A.B. 1997. T Cells As Orchestrators Of The Asthmatic Response. *Ciba Found. Symp.* 206:56-67.
 31. 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.
 32. 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.
 33. 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*.

34. 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
35. 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.
36. Mcever, R.P. 1991. Selectins: Novel Receptors That Mediate Leukocyte Adhesion During Inflammation. *Thromb. Haemost.* 65:223-228.
37. 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.
38. 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).
39. Roche, W.R., R. Beasley, J.H. Williams, S.T. Holgate. 1989. Subepithelial Fibrosis In The Bronchi Of Asthmatics. *Lance* 1:520-524.
40. 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.
41. Sheehan, D.C., B.B. Hrapchak. 1980. Connective Tissue/Muscle Fiber Stains. In *Theory And Practice Of Histotechnology*. Battelle Press, Columbus, OH. 180-201.
42. 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)
43. 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.
44. 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.
45. 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)
46. 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.
47. 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
48. 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.

49. 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.
50. 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.* 103:779-78
51. 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.

Humic Acid

1. *National Institutes of Allergy and Infectious Diseases (NIAID), under the auspices of the National Institutes of Health, August 2001 - January 2002*
2. *Meeta Patnaik, M.D., Senior Research Scientist
Hun-Chi Lin, PhD, Director, Clinical Trials
Specialty Laboratories, Santa Monica, CA, August 1998*
3. *Research team at USC School of Medicine, January, 1998.*
4. *Jim A. Turpin Ph.D., Manager Retrovirus Research Laboratory
Tracy Loftus, Supervisor Retrovirus Research Laboratory
Southern Research Institute, September, 2000*
5. *van Rensburg CE, Department of Pharmacology, University of Pretoria, Pretoria, South Africa; Dekker J, Enerkom (Pty) Ltd, Pretoria, South Africa; Weis R, Smith TL, Janse van Rensburg E, Schneider J.*
6. *Schneider J, Weis R, Manner C, Kary B, Werner A, Seubert BJ, Riede UN.
Abteilung Virologie, Institut für Medizinische Mikrobiologie und Hygiene der Universität, Freiburg, Germany.*
7. *Edward Karamov PhD, Director of Immunochemistry Group, Ivanovsky Inst. of Virology, Moscow, Russia*
8. *National Institutes of Allergy and Infectious Diseases (NIAID), under the auspices of the National Institutes of Health, August 2001 - January 2002*
9. *Lu FJ, Tseng SN, Li ML, Shih SR.
Department of Biochemistry, College of Medicine, National Taiwan University, Taipei.*
10. Seffner, W. "Effects of humic acid on the availability of iodine in the food, investigated with the histometric assessment of the thyroid gland". Conference Paper Mengen- und spurenelemente-15 Arbelstagund, 1995.
11. Bernacci, F. et al. "In vivo and in vitro mutagenicity studies on natural humic acid". Conference paper 37, Riunione scientifica, October 1991.
12. Gau, R. et al. "Induction of oxidative stress by humic acid through increasing intracellular iron; a possible mechanism leading to atherothrombotic vascular

- disorder in blackfoot disease". *Biochem Biophys Res Commun*, 2001; Vol 283; Issue 4: 743-49.
13. Iubitskaia , NS . "Sodium humate in the treatment of osteoarthritis patients." *Vopr Kurortol Fizioter Lech Fiz Kult*, 1999; Issue 5, 22-24.
 14. Schiller, F. "Results of an oriented clinical trial of ammonium humate for the local treatment of herpesvirus hominis (HVH) infections". *Dermatol Monatsschr*, 1979, Vol. 165; Issue 7; 505-09.
 15. Riede, U.N. "Humate induced activation of human granulocytes. *Virchows Arch B Cell Pathol Incl Mol Pathol*, 1991; Issue 1: 27-34.
 16. Herzig, I. "The effect of sodium humate on cadmium deposition in the organs of chickens". *Vet Med*, 1994, Vol 39; Issue 4; 175-85.
 17. Hampi, I, et al. "Pharmacokinetics of sodium humate in chickens". *Vet Med*, 1994; Vol 39, Issue 6; 305-313.
 18. Schneider, J, et al. "Inhibition of HIV-1 in cell culture by synthetic humate analogues derived from hydroquinone; mechanism of inhibition". *Virology*, 1996; Vol 218, Issue 2, 389-95.
 19. Thiel, KD, et al. "In vitro studies of the antiviral activity of ammonium humate against herpes simplex virus type 1 and type 2". *Zentralbl Bakteriol*, 1977; Vol. 239, Issue 3, 304-321.
 20. Laub, R. "The chemically induced inhibition of HSV infection". Laub BioChem Corp., August 1998.
 21. Laub, R. "The chemically induced inhibition of HIV-1 replication". Laub BioChem Corp., January 1995.

Aloe Vera

1. Devaraj, S., Patel, S., Jialal, R., Jialal, I. *Aloe supplements enhance bioavailability of vitamin C and B12 in older adults*. The FASEB Journal: Experimental Biology 2007® Abstracts 8.1-701.35. Washington, DC; April 28-May 2, 2007.
2. Vinson, J.A., Al Kharrat, H. & Andreoli, L. *Effect of Aloe vera preparations on the human bioavailability of Vitamins C and E*. *Phytomedicine*. 2005; 12: 760-765.
3. Davis, Robert H, Ph.D. "Aloe Vera: A Scientific Approach". Vantage Press, New York, 1st Edition.1997. 35,36,109-111.
4. Radmilo, Anicic, "Aloe", Aloe Vera Community of Canada. February 20, 2007, http://www.Aloeveracanada.ca/about_av.html
5. Tizard, Ian Dr. "Research Reveals Aloe's Effects on Inflammation". Texas A&M University. Consultant for Carrington Laboratories. International Aloe Science Council. 1996-2002. <http://www.iasc.org/articles.html>.
6. Unlisted Author, "The Wonders of Aloe Vera: The Natural Healer." April 2007, <http://www.Aloeverabenefits.com/index.html>
7. Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M, Toida T, Hayasawa H, Takase M, Inagaki M, Higuchi R (2006). "Identification of five

- phytosterols from *Aloe vera* gel as anti-diabetic compounds". *Biol. Pharm. Bull.* 29 (7): 1418–22.
8. Food And Drug Administration,, HHS (2002). "Status of certain additional over-the-counter drug category II and III active ingredients. Final rule". *Fed Regist* 67 (90): 31125
 9. Rajasekaran S et al. "Mineral Contents of Aloe Vera leaf gel and their role on streptozotocin-induced diabetic rats." *Biol Trace Elem Res.* 108(1-3):185-95, 2005.www.humanapress.com
 10. Rajasekaran S et al. "Beneficial effects of Aloe Vera leaf gel extract on lipid profile status in rats with streptozotocin diabetes." *Clin Exp Pharmacol Physiol.* 33(3):232-7, 2006.
 11. Lim BO et al. "Efficacy of dietary Aloe Vera supplementation on hepatic cholesterol and oxidative status in aged rats." *J Nutr Sci Vitaminol* (Tokyo). 49(4):292-6, 2003