US008278351B2

(12) **United States Patent**
Sampalis

(10) **Patent No.: US 8,278,351 B2**
(45) **Date of Patent: *Oct. 2, 2012**

(54) **NATURAL MARINE SOURCE PHOSPHOLIPIDS COMPRISING POLYUNSATURATED FATTY ACIDS AND THEIR APPLICATIONS**

(75) Inventor: **Fontini Sampalis**, Laval (CA)

(73) Assignee: **Neptune Technologies & Bioressources, Inc.**, Laval QC (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **13/189,714**

(22) Filed: **Jul. 25, 2011**

(65) **Prior Publication Data**

US 2012/0028922 A1 Feb. 2, 2012

Related U.S. Application Data

(63) Continuation of application No. 10/485,094, filed as application No. PCT/CA02/01185 on Jul. 29, 2002, now Pat. No. 8,030,348.

(60) Provisional application No. 60/307,842, filed on Jul. 27, 2001.

(51) **Int. Cl.**
A61K 31/215 (2006.01)
A61K 31/661 (2006.01)

(52) **U.S. Cl.** **514/506**; 514/75

(58) **Field of Classification Search** 514/506, 514/75

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,331,695	A	5/1982	Zosel
4,915,876	A	4/1990	Lindsay
4,963,527	A	10/1990	Bombardelli et al.
5,006,281	A	4/1991	Rubin et al.
5,434,183	A	7/1995	Larsson-Backstrom
6,055,936	A	5/2000	Collin
6,265,450	B1	7/2001	Asami et al.
6,521,768	B2	2/2003	Beaudoin
6,713,447	B2	3/2004	Beaudoin
7,572,464	B2	8/2009	Chandler
2011/0104297	A1	5/2011	Bruheim

FOREIGN PATENT DOCUMENTS

AU	671329	B	8/1996
CA	1098900	A	4/1981
CA	2115571	A1	12/1993
CA	2 251 265	A1	4/2000
CA	2 362 663	A1	6/2001
EP	0 275 005	A2	7/1988
EP	0 209 037	B1	2/1990
EP	0 507 363	B1	5/1993
EP	0 275 224	B1	7/1993
EP	0 732 378	A2	9/1996
EP	0 773 283	B1	7/1999
ES	2 088 750	B1	3/1997
JP	51-76467		7/1976
JP	53-112195		9/1978
JP	55-23949	A	2/1980
JP	59-196032	A	11/1984
JP	60-03507	A	2/1985
JP	60-153779	A	8/1985
JP	S6323819		7/1986
JP	63-295698		12/1988
JP	64-50890	A	2/1989
JP	02-167055		6/1990
JP	2-215351	A	8/1990
JP	4-57853	A	2/1992
JP	04-273817		9/1992
JP	06-237703		8/1994
JP	8-198754	A	8/1996
JP	8-302382	A	11/1996
JP	2909508	B2	6/1999
JP	2000-60432	A	2/2000
KR	2002037140		5/2002
NO	147365	B	12/1982
WO	WO 84/01715	A1	5/1984
WO	WO 92/21335	A1	12/1992
WO	WO 96/37200	A1	11/1996
WO	WO 97/39759	A2	10/1997
WO	WO 99/64547	A1	12/1999
WO	WO 00/23546	*	4/2000
WO	WO 00/23546	A1	4/2000
WO	WO 00/44862	A1	8/2000
WO	WO 02/092540		11/2002
WO	WO 02/102394		12/2002

OTHER PUBLICATIONS

Medina et al., "^{13}C Nuclear magnetic resonance monitoring of free fatty acid release after fish thermal processing" *J. Amer. Oil Chem. Soc.* 71(5): 479-482 (1994).
Grit et al., "Hydrolysis of Phosphatidylcholine in Aqueous Liposome Dispersions" *Int. J. Pharmaceutics* 50: 1-6 (1989).
Herman and Groves, "The Influence of Free Fatty Acid Formation on the pH of Phospholipid-Stabilized Triglyceride Emulsions" *Pharmaceutical Research* 10(5): 774-776 (1993).
Singh and Heldman, *Introduction to Food Engineering* (3rd ed.), New York, NY: Academic Press, 2008 (pp. 222-227).
Heldman and Lund, *Handbook of Food Engineering*, New York, NY: Marcel Dekker, 1992 (pp. 247-259). Hughes et al., "Determination of Carryover and Contamination for Mass Spectrometry-Based Chromatographic Assay" *The AAPS Journal 2007*; 9 (3) Article 42, pp. E353-E360.
Elliott et al., Current Trends in Quantitative Proteomics. *J. Mass. Spectrom.*, 44 (12): 1637-1660 (2009).
Gigliotti et al. "Extraction and Characterisation of Lipids from Antarctic Krill (*Euphausia superba*)" Food Chemistry 125(3): 1028-1036 (Apr. 2011).
Kassis et al., "Characterization of Lipids and Antioxidant Capacity of Novel Nutraceutical Egg Products Developed with Omega-2-Rich Oils" J Sci Food Agr 92(1): 66-73 (2012).
O'Doherty et al., "Role of Luminal Lecithin in Intestinal Fat Absorption" Lipids 8: 249-55 (1973).
Mattson et al. "The Digestion and Absorption of Triglycerides" J Biol Chem 239:2772-7 (1964).

(Continued)

Primary Examiner — James D Anderson
Assistant Examiner — Gregg Polansky
(74) *Attorney, Agent, or Firm* — Cooley LLP

(57) **ABSTRACT**

A phospholipid extract from a marine or aquatic biomass possesses therapeutic properties. The phospholipid extract comprises a variety of phospholipids, fatty acid, metals and a novel flavonoid.

OTHER PUBLICATIONS

Tso et al., "Evidence for Separate Pathways of Chylomicron and Very Low-Density Lipoprotein Assembly and Transport by Rat Small Intestine" *Am J Physiol* 247: G599-G610 (1984).

Carnielli et al. "Intestinal absorption of long-chain polyunsaturated fatty acids in preterm infants fed breast milk or formula" Am J Clin Nutr 67:97-103 (1998).

Bottino et al., "Resistance of Certain Longchain Polyunsaturated Fatty Acids of Marine Oils to Pancreatic Lipase Hydrolysis" Lipids 2, 489-93 (1967).

Hernell et al., "Does the Bile Salt-Stimulated Lipase of Human Milk Have a Role in the Use of the Milk Long-Chain Polyunsaturated Fatty Acids?" J Pediatr Gastroenterol Nutr 16: 426-31 (1993).

Morgan et al. "Fatty Acid Balance Studies in Term Infants Fed Formula Milk Containing Long-Chain Polyunsaturated Fatty Acids" Acta Paediatr 87: 136-42 (1998).

Simopoulos, "Omega-3 Fatty Acids in Inflammation and Autoimmune Diseases" J Am Coll Nutr 21(6): 495-505 (2002).

Hong et al., "Novel Docosatrienes and 17S-resolvings Generated from Docosahexaenoic Acid in Murine Brain, Human Blood, and Glial Cells. Autacoids in Anti-Inflammation" J Biol Chem 278(17): 14677-87 (2003).

Tou et al., "Krill for Human Consumption: Nutritional Value and Potential Health Benefits" Nutr Rev 65(2): 63-77 (2007).

Bunea et al., "Evaluation of the Effects of Neptune Krill Oil on the Clinical Course of Hyperlipidemia" Altern Med Rev 9: 420-28 (2004).

Bridges et al., "Determination of Digestibility, Tissue Deposition, and Metabolism of the Omega-3 Fatty Acid Content of Krill Protein Concentrate in Growing Rats" J Agric Food Chem 58: 2830-7 (2010).

Ulven et al., "Metabolic Effects of Krill Oil are Essentially Similar to Those of Fish Oil But at Lower Dose of EPA and DHA, in Health Volunteers" Lipids 46: 37-46 (2011).

Sampalis et al., "Evaluation of the Effects of Neptune Krill Oil™ on the Management of Premenstrual Syndrome and Dysmenorrheal" Altern Med Rev 8: 171-9 (2003).

Nutritioinal Labeling and Education Act (NLEA) Requirements (Aug. 1994-Feb. 1995), U.S. Food and Drug Administration (available at http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm114098.htm).

GRAS Notice for Aker Biomarine Antarctic AS, Dec. 14, 2010.

St. Jean, "Krill oil production according to the Beaudoin patent," Notebook page, Neptune Technologies & Bioresources.

Winther et al., Elucidation of Phosphatidylcholine Composition in Krill Oil Extracted from *Euphausia superba Lipids* 46(1): 25-36 (2011).

U.S. Appl. No. 60/307,842, filed Jul. 27, 2001, Sampalis.

U.S. Appl. No. 60/298,383, filed Jun. 18, 2001, Sampalis.

"Neptune Technologies IPO Warmly Received in Cool Financial Climate," Extract from Canadian Corporate Newswire, (Jun. 7, 2001).

Araki et al., "Positional Distribution of Fatty Acids in Glycerolipids of the Marine Red Alga, *Porphyra yezoensis*," Plant Cell Physiol. 28(5):761-766 (1987).

Aureli et al., "Aging brain: effect of acetyl-L-carnitine treatment on rat brain energy and phospholipid metabolism. A study by ^{31}P and ^{1}H NMR spectroscopy," Brain Research 526(1):108-112 (1990).

Barak et al., "Inositol Treatment of Alzheimer's Disease: A Double Blind, Cross-Over Placebo Controlled Trial," Prog. Neuro-Psychopharmacol. Biol. Psychiat. 20:729-735 (1996).

Barkai et al., "Reduced Myo-Inositol Levels in Cerebrospinal Fluid from Patients with Affective Disorder," Biol. Psychiatry 13:65-72 (1978).

Basile et al., "Antibacterial activity of pure flavonoids isolated from mosses," Phytochemistry 52(8):1479-1482 (1999).

Bast and Haenen, "Interplay between lipoic acid and glutathione in the protection against microsomal lipid peroxidation," Biochem. Biophys. Acta. 963:558-561 (1988).

Bell and Dick, "Molecular Species Composition of the Major Diacyl

Benjamin et al., "Double-blind, placebo-controlled, crossover trial of inositol treatment for panic disorder," Am. J. Psychiatry 15:1084-1086 (1995).

Berkow, R., "Generalized Cardiovascular Disorders," The Merck Manual of Diagnosis and Therapy, Chapter 24, Merck Research Laboratories, Rahway, NJ, USA: pp. 409-431 (1992).

Birchall and Chappell, "Aluminium, Chemical Physiology, and Alzheimer's Disease," Lancet 29:1008-1010 (1988).

Bowyer et al., "The Determination of the Fatty Acid Composition of Serum Lipids Separated by Thin-Layer Chromatography; and a Comparison with Column Chromatography," Biochim. Biophys. Acta 70:423-431 (1963).

Burgess et al., "Long-chain polyunsaturated fatty acids in children with attention-deficit hyperactivity disorder," Am. J. Clin. Nutr. 71(suppl):3275-3305 (2000).

Caprioli et al., "Age-Dependent Deficits in Radial Maze Performance in the Rat: Effect of Chronic Treatment with Acetyl-L-Carnitine," Prog. Neuro-Psychopharmacol. Biol, Psychiat. 14(3):359-369 (1990).

Carell et al., "A Novel Procedure for the Synthesis of Libraries Containing Small Organic Molecules," Angew. Chem. Int. Ed. Engl. 33(20):2059-2061 (1994).

Carell et al., "A Solution-Phase Screening Procedure for the Isolation of Active Compounds from a Library of Molecules," Angew. Chem. Int. Ed. Engl. 33(20):2061-2064 (1994).

Cenacchi et al., "Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration," Aging Clin. Exp. Res. 5:123-133 (1993).

Chandrasekar et al., "Tissue Specific Regulation of Transforming Growth Factor Beta by Omega-3 Lipid-Rich Krill Oil in Autoimmune Murine Lupus," Nutr. Res. 16(3):489-503 (1996).

Château et al., "Dimethyl sulfoxide-induced apoptosis in human leukemic U937 cells," Anal. Cell. Pathol. 10:75-84 (1996).

Cheng et al., "Huperzine A, a novel promising acetylcholinesterase inhibitor," NeuroReport 8:97-101 (1996).

Christensen et al., "Lymphatic absorption of n-3 polyunsaturated fatty acids from marine oils with different intramolecular fatty acid distributions," Biochim. Biophys. Acta 1215:198-204 (1994).

Church et al., "Spectrophotometric Assay Using o-Phthaldialdehyde for Determination of Proteolysis in Milk and Isolated Milk Proteins," J. Dairy Sci. 66:1219-1227 (1983).

Cohen et al., "Brain Choline Uptake and Cognitive Function in Middle Age," Biol. Psych . 41:90S, Abstract No. 307 (1997).

Cohen et al., "Inositol has behavioral effects with adaptation after chronic administration," J. Neural Transm. 104:299-305 (1997).

Colodny and Hoffman, "Inositol—Clinical Applications for Exogenous Use," Altern. Med. Rev. 3(6):432-447 (1998).

Crook et al., "Effects of phosphatidylserine in age-associated memory impairment," Neurology 41:644-649 (1991).

Dawson et al., "8 Lipids and long-chain fatty acids," pp. 181-184, in Data for Biochemical Research, 3rd Edition (1986).

Delwaide et al., "Double-blind randomized controlled study of phosphatidylserine in senile demented patients," Acta Neurol. Scand . 73:136-140 (1986).

Deutch, "Menstrual pain in Danish women correlated with low n-3 polyunsaturated fatty acid intake," Eur. J. Clin. Nutr. 49(7):508-516 (1995).

Devasagayam et al., "Prevention of Singlet Oxygen-Induced DNA Damage by Lipoate," Chem.-Biol. Interactions 86:79-92 (1993).

Edwards et al., "Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients," J. Affect. Disord. 48(2-3):149-155 (1998).

Estiarte et al., "Free-air CO_2 enrichment of wheat: leaf flavonoid concentration throughout the growth cycle," Physiologia Plantarum 105(3):423-433 (1999).

Folch et al., "A Simple Method for the Isolation and Purification of Total Lipides from Animal Tissues," J. Biol. Chem. 226:497-509 (1957).

Gadaleta et al., "Mitochondrial DNA Transcription and Translation

Ghirardi et al., "Effect of Acetyl-L-Carnitine Chronic Treatment on Discrimination Models in Aged Rats," Physiol. Behav. 44(6):769-773 (1988).
Gill et al., "Calcium signalling mechanisms in endoplasmic reticulum activated by inositol 1,4,5-triphosphate and GTP," Cell Calcium 10:363-374 (1989).
Hanahan and Thompson, "Complex Lipids," Ann. Rev. Biochem. 32:215-240 (1963).
Henderson et al., "Lipid Composition of the Pineal Organ from Rainbow Trout (*Oncorhynchus mykiss*)," Lipids 29(5):311-317 (1994).
Hosokawa et al., "Conversion to Docosahexaenoic Acid-Containing Phosphatidylserine from Squid Skin Lecithin by Phospholipase D-Mediated Transphosphatidylation," J. Agric. Food Chem. 48(10):4550-4554 (2000).
Houghten et al., "The Use of Synthetic Peptide Combinatorial Libraries for the Identification of Bioactive Peptides," BioTechniques 13(3):412-421 (1992).
Ikeda et al., "Effects of Long-Term Feeding of Marine Oils with Different Positional Distribution of Eicosapentaenoic and Docosahexaenoic Acids on Lipid Metabolism, Eicosanoid Production, and Platelet Aggregation in Hypercholesterolemic Rats," Lipids 33(9):897-904 (1998).
Imperato et al., "Acetyl-L-carnitine enhances acetylcholine release in the striatum and hippocampus of awake freely moving rats,"Neurosci. Lett. 107(1-3):251-255 (1989).
Kagan et al., "Dihydrolipoic Acid-A Universal Antioxidant Both in the Membrane and in the Aqueous Phase. Reduction of Peroxyl, Ascorbyl and chromanoxyl Radicals," Biochem. Pharmacol 44:1637-1649 (1992).
Kalmijn et al., "Polyunsaturated Fatty Acids, Antioxidants, and Cognitive Function in Very Old Men," Am. J. Epidemiol. 145(1):33-41 (1997).
Kalmijn et al., "Dietary Fat Intake and the Risk of Incident Dementia in the Rotterdam Study," Ann. Neurol. 42:776-782 (1997).
Kawakami et al., "The Rationale for E2020 as a Potent Acetylcholinesterase Inhibitor," Bioorg. Med. Chem. 4:1429-1446 (1996).
Kidd, "Phosphatidylcholine: A Superior Protectant Against Liver Damage," Alt. Med. Rev. 1:258-274 (1996).
Kitamura et al , "Inhibition of myo-inositol transport causes acute renal failure with selective medullary injury in the rat," Kidney Int. 53:146-153 (1998).
Knopman et al., "Long-term tacrine (Cognex) treatment: Effects on nursing home placement and mortality, tacrine study group" Neurology 47:166-167 (1996).
Kojima et al., "Different Changes in Expression and Function of Connexin 26 and Connexin 32 During DNA Synthesis and Redifferentiation in Primary Rat Hepatocytes Using a DMSO Culture System," Hepatology 26(3):585-597 (1997).
Kristensen et al., "Dietary supplementation with n-3 polyunsaturated fatty acids and human platelet function: a review with particular emphasis on implications for cardiovascular disease," J. Intern. Med. 225(Suppl. 1):141-150 (1989).
Lam, "Application of combinatorial library methods in cancer research and drug discovery," Anti-Cancer Drug Design 12:145-167 (1997).
Levine et al., "Double-blind, controlled trial of inositol treatment of depression," Am. J. Psychiatr. 152:792-794 (1995).
Levine et al., "Follow-up and Relapse Analysis of an Inositol Study of Depression," Isr. J. Psychiatry Relat. Sci. 32:14-21 (1995).
Levine et al., "Inositol treatment raises CSF inositol levels," Brain Res. 627:168-169 (1993).
Levine, "Controlled trials of inositol in psychiatry," Eur. Neuropsychopharmacol. 7:147-155 (1997).
Markham et al., "Luteolin 7-Glucuronide-3'-Mono(trans)ferulylglucoside and other Unusual Flavonoids in the Aquatic Liverwort Complex, *Riccia fluitans*," Phytochemistry 17:1601-1604 (1978).
Mills et al., "Dietary N-6 and N-3 Fatty Acids and Salt-induced Hypertension in the Borderline Hypertensive Rat," Lipids 24(1):17-24 (1989).
Mohr et al., "Treatment of Alzheimer's Disease with Sabeluzole: Functional and Structural Correlates," Clin. Neuropharmacol. 20:338-345 (1997) (Abstract only).
Mori et al., "Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men," Am. J. Clin. Nutr. 71:1085-1094 (2000).
Navarra and Lipkowitz, pp. 134, 141-142 in Encyclopedia of Vitamins, Minerals and Supplements (1996).
Newberne et al., "Lipotropes, Immunocompetence, and Cancer," Cancer Res. 43(Suppl.):2426s-2434s (1983).
Paradies et al., "Carnitine-acylcarnitine translocase activity in cardiac mitochondria from aged rats: the effect of acetyl-L-carnitine," Mech. Aging Develop. 84(2):103-112 (1995).
Parthasarathy et al., "Biochemical and Molecular Properties of Lithium-Sensitive Myo-Inositol Monophosphatase," Life Sci. 54(16):1127-1142 (1994).
Prados et al., "Actin, Tropomyosin and α-Actinin as Markers of Differentiation in Human Rhabdomyosarcoma Cell Lines Induced with Dimethyl Sulfoxide," Cell. Mol. Biol. 39(5):525-536 (1993).
Prentice et al., "Nerve growth factor-induced changes in neural cell adhesion molecule (N-CAM) in PC12 cells," EMBO J. 6(7):1859-1863 (1987).
Raa and Hansen, "Isolation of astaxanthin from crayfish or shrimp waste for use as a coloring agent in fish feed," Chem. Abstracts 98:177859m (1983).
Rao et al., "Phytochemical Investigation on Leaves of *Rhynchosia densiflora*," Indian J. Nat. Prod. 14(1):20-22 (1998).
Rogers and Adelstein, "MaxEPA Fish Oil Enhances Cholesterol-induced Intimal Foam Cell Formation in Rabbits," Am. J. Pathol. 137(4):945-951 (1990).
Rogers et al., "The Efficacy and Safety of Donepezil in Patients with Alzheimer's Disease: Results of a US Multicentre, Randomized, Double-Blind, Placebo-Controlled Trial," Dementia 7:293-303 (1996) (Abstract only).
Sargent, "Fish oils and human diet," Br. J. Nutr. 78(Suppl. 1):S5-S13 (1997).
Saynor and Gillott, "Changes in Blood Lipids and Fibrinogen with a Note on Safety in a Long Term Study on the Effects of n-3 Fatty Acids in Subjects Receiving Fish Oil Supplements and Followed for Seven Years," Lipids 27(7):533-538 (1992).
Schneider et al., "Potential Role for Estrogen Replacement in the Treatment of Alzheimer's Dementia," Am. J. Med. 103(3A):46S-50S (1997).
Seidman et al., "Biologic Activity of Mitochondrial Metabolites on Aging and Age-Related Hearing Loss," Am. J. Otol. 21:161-167 (2000).
Seidman, "Polyunsaturated Phosphatidylcholine in NT Factor™ Improves Mitochondrial Function, Auditory Sensitivity and May Slow Some Aspects of the Aging Process," Anti-Aging Medical News, pp. 5, 16-19 (2001).
Serbinova et al., "Thioctic Acid Protects Against Ischemia-Reperfusion Injury in the Isolated Perfused Langendorff Heart," Free Rad. Res. Commun. 17:49-58 (1992).
Sharaf, "Isoscutellarein 8-O-(6"-trans-p-coumaroyl)-β-D-glucoside from *Stachys aegyptiaca*," Fitoterapia 69(4):355-357 (1998).
Simopoulos, "Omega-3 fatty acids in health and disease and in growth and development," Am. J. Clin. Nutr. 54:438-463 (1991).
Sjölander and Urbaniczky, "Integrated Fluid Handling System for Biomolecular Interaction Analysis," Anal. Chem. 63(29):2338-2345 (1991).
Stoll et al., "Omega-3 fatty acids and bipolar disorder: a review," Prostagland. Leukotrienes Essent. Fatty Acids 60(5&6):329-337 (1999).
Suzuki and Shibata, "The utilization of Antarctic krill for human food," Food Rev. Int. 6(1):119-147 (1990).
Suzuki et al., "α-Lipoic acid is a potent inhibitor of NF-κB activation

Szabo et al., "Surface plasmon resonance and its use in biomolecular interaction analysis (BIA)," Curr. Opin. Struct. Biol. 5:699-705 (1995).
Tokunaga et al., "Formation of Dimethyl Sulfide in Antarctic Krill," Bull Jpn. Soc. Sci. Fisheries 43(10):1209-1217 (1977).
Trubiani et al., "The c-myc gene regulates the polyamine pathway in DMSO-induced apoptosis," Cell Prolif. 32:119-129 (1999).
Vadnal et al., "Role of Inositol in the Treatment of Psychiatric Disorders. Basic and Clinical Aspects," CNS Drugs 7:6-16 (1997).
van Dyck et al., "The acetylcholine releaser linopirdine increases parietal regional cerebral blood flow in Alzheimer's disease," Psychopharmacology 132:217-226 (1997).
Wiegand and Anderson, "Phospholipid Molecular Species of Frog Rod Outer Segment Membranes," Exp. Eye Res. 37(2):159-173 (1983).
Yamaguchi et al., "Supercritical Carbon Dioxide Extraction of Oils from Antarctic Krill," J. Agric. Food Chem. 34:904-907 (1986).
Yarochkin et al., "Technochemical Characteristics of the Canned Food 'Natural Antarctic Krill Meat' and Its Food Value," Voprosy pitaniia Mar.-Apr.(2):69-72 (1985).
Yongmanitchai and Ward, "Positional distribution of fatty acids, and molecular species of polar lipids, in the diatom *Phaeodactylum tricornutum*," J. Gen. Microbiol. 139:465-472 (1993).
Youdim et al., "Essential fatty acids and the brain: possible health implications," Int. J. Devl. Neuroscience 18(4-5):383-399 (2000).
Fricke et al., "Lipid, Sterol and Fatty Acid Composition of Antarctic Krill," Lipids, 19(11):821-827 (1984).
Gordeev et al., "Fatty Acid Composition of the Main Phospholipids of the Antarctic Krill *Euphausia superba*," translated from Khimiya Prirodnykh Soedinenii, No. 2, 181-187 (1990).
Kuroda et al., "Comparison of Hypocholesterolemic Effect among Three Phospholipids Containing Different Fatty Acid and the Related Oils in Rats," Jpn. J. Nutr., 48(5):213-220 (1990).
Makuta et al., "Effects of EPA and Use in Health Foods," Japan Food Science 25(1):29-35 (1986).
Aker Biomarine's Corrected Request for Reexamination of Patent No. 8,030,348 (U.S. Appl. No. 95/001,774).
Declaration of Bjorn Ole Haugsgjerd, submitted in Aker Biomarine's Corrected Request for Reexamination of Patent No. 8,030,348 (U.S. Appl. No. 95/001,774).
Declaration of Thomas Gundersen, submitted in Aker Biomarine's Corrected Request for Reexamination of Patent No. 8,030,348 (U.S. Appl. No. 95/001,774).
Non Final Office Action issued in the Reexamination of Patent No. 8,030,348 (U.S. Appl. No. 95/001,774).
Aker Biomarine's Corrected Request for Reexamination of Patent No. 8,057,825 (U.S. Appl. No. 95/001,819).
Declaration of Nils Hoem, submitted in Aker Biomarine's Corrected Request for Reexamination of Patent No. 8,057,825 (U.S. Appl. No. 95/001,819).
Complaint filed by Neptune in *Neptune Technologies* v. *Aker Biomarine ASA, et al.*—Case 1:11-cv-00894-GMS.
Answer filed by Aker/Schiff in *Neptune Technologies* v. *Aker Biomarine ASA, et al.*—Case 1:11-cv-00894-GMS.
Complaint filed by Neptune in *Neptune Technologies* v. *Enzymotec Limited, et al.*—Case 1:11-cv-00895-GMS.
Answer filed by Enzymotec in *Neptune Technologies* v. *Enzymotec Limited, et al.*—Case 1:11-cv-00895-GMS.
Answer filed by Mercola in *Neptune Technologies* v. *Enzymotec Limited, et al.*—Case 1:11-cv-00895-GMS.
Request for Opposition of EP 1417211 submittted by Aker Biomarine (Feb. 29, 2008).
Request for Opposition of EP 1417211 submittted by Enzymotec Technologies (Feb. 29, 2008).
Decision of Board in Opposition of EP 1417211 (Dec. 30, 2009).
Aker Biomarine's Request for Oppostion of accepted application AU 2002322233 (Apr. 22, 2009).
Aker Biomarine's Submission of Experimental Report on Flavonoid Analysis by Professor Andersen (Feb. 29, 2008) in Opposition to EP 1417211.
Extract from an interview by the inventor, Fontini Sampalis (2005), www.dilesta.com/Tina.htm.
Sampalis et al., "Evaluation of the Effects of Neptune Krill Oil™ on the Management of Premenstrual Syndrome and Dysmenorrhea," Alternative Medicine Review 8(2), 171-178 (2003).
Extract from online KEGG database for Lucenin-2.
Levy et al., "The novel Flavonoid Chemistry and Phylogenetic Origin of *Phlox floridana*," Evolution 29:487-499 (Sep. 1975).
Bandyukov et al., "Natural Flavonoid C-Glycosides," Chemistry of Natural Compounds, vol. 17, No. 1 Jan.-Feb. 1981—Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 5-24 (Jan.-Feb. 1981).
Voirin et al., "Separation of Flavone C-Glycosides and Qualitative Analysis of *Passiflora incarnata* L. by Capillary Zone Electrophoresis," Phytochem. Anal. 11, 90-98 (2000).
Iwashina, "The Structure and Distribution of the Flavonoids in Plants," J. Plant Res. 113:287-299 (2000).
Jay, "C-Glycosylflavonoids," The Flavonoids: Advances in Research Since 1986, Ed. J.B. Harborne, Chapter 3 (1994), ISBN 0 412 480700 (1993), pp. 57-93.
Webpage www.naturalnutritionals.com/kril4.html, 2005, downloaded Jan. 23, 2008.
Definition of "aglycon," IUPAC Compendium of Chemical Terminology, 2nd Edition, ISBN 0865426848 (1997).
Enzymotec's Submission of a Letter from Igal Gozlan of the Tami-IMI Institute of Research and Development to Enzymotec Ltd. (Jan. 14, 2008) in Opposition to EP 1417211.
Pages from www.seakrill.com with publications (computer translations from Spanish to English) (Sep. 1997 and Oct. 1999).

* cited by examiner

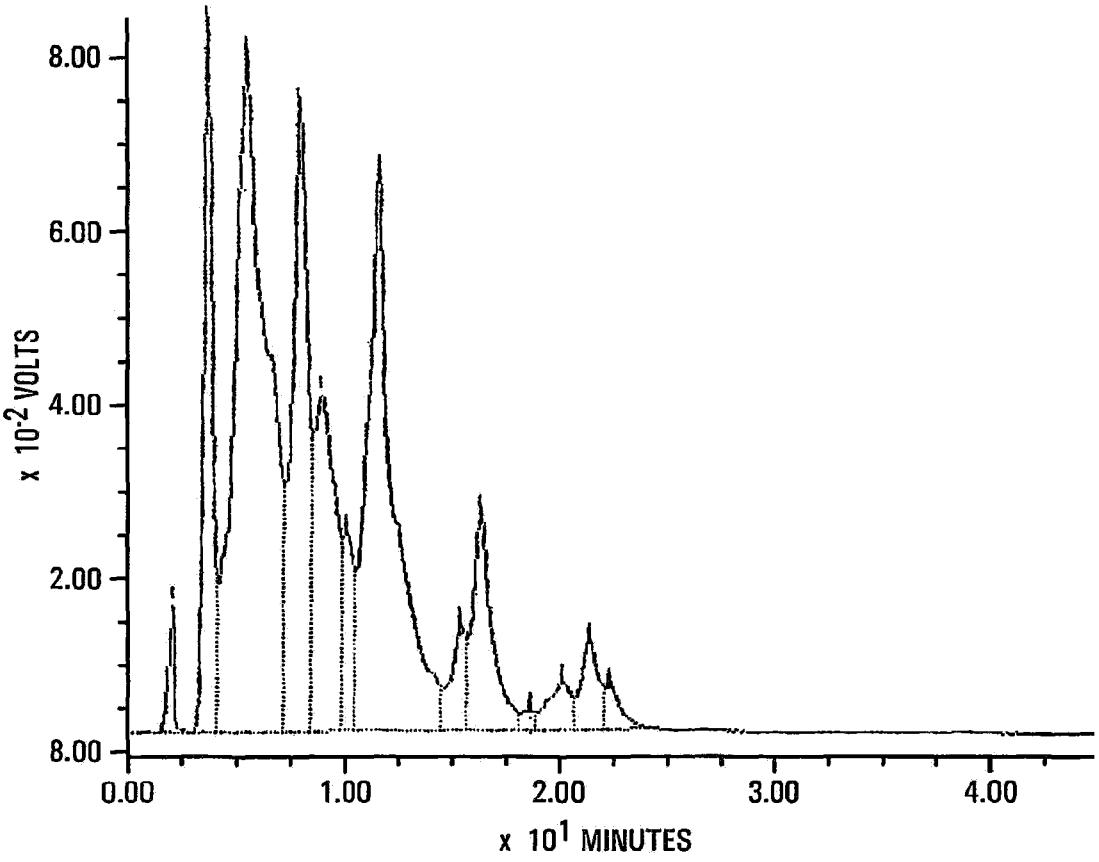

Fig. 1

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.