(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 November 2011 (17.11.2011)

PCT

(10) International Publication Number
WO 2011/143229 A2

(51) International Patent Classification:
A23J 7/00 (2006.01) *A61K 35/12* (2006.01)
A23J 3/20 (2006.01) *A61P 25/28* (2006.01)

(21) International Application Number:
PCT/US2011/035938

(22) International Filing Date:
10 May 2011 (10.05.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/333,173 10 May 2010 (10.05.2010) US

(71) Applicant *(for all designated States except US)*: **J3H, INC.** [US/US]; 30 South Wacker Drive, Chicago, IL 60606 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **PALMER, John Richardson** [US/US]; 30 South Wacker Drive, Chicago, IL 60606 (US). **MILLER, Joseph John** [US/US]; 30 South Wacker Drive, Chiago, IL 60606 (US).

(74) Agent: **CARROLL, Lawrence J.**; Womble Carlyle Sandridge & Rice, PLLC, P.O. Box 7037, Atlanta, GA 30357 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

WO 2011/143229 A2

(54) **Title**: LIPID COMPOSITIONS AND STRUCTURED LIPIDS CONTAINING PHOSPHOLIPIDS, ORAL FORMULATIONS CONTAINING THE SAME AND METHODS OF MAKING THE SAME

(57) **Abstract**: Disclosed are lipid compositions and structured lipids containing phospholipids, oral formulations of the same, methods of making the same, and methods of treating various aliments and diseases with the oral formulations. The lipid compositions and structured lipids comprise omega-3 fatty acids, which are present as fatty acids on the R^1 and R^2 terminal positions of phospholipids. The lipids and methods disclosed herein allow for high purity phospholipid compositions, which aid in the bioavailability of the omega-3 fatty acids. The oral formulations can also contain additional components that further aid in the bioavailability and absorption by the body.

LIPID COMPOSITIONS AND STRUCTURED LIPIDS CONTAINING PHOSPHOLIPIDS, ORAL FORMULATIONS CONTAINING THE SAME AND METHODS OF MAKING THE SAME

[0001] This application claims the benefit of United States Provisional Application Serial No. 61/333,173 filed May 10, 2010, which is incorporated herein by reference in its entirety.

[0002] The invention relates to the dietary supplement industry in general, and to bio-enhanced lipid compositions containing phospholipids for delivery to humans and animals as foods, dietary supplements, medical foods and drugs. The lipid compositions can be marine plant or microorganism based, which contain phospholipids comprising omega-3 fatty acids, or re-randomized, structured phospholipids based on marine animal, marine plant, and plant based phospholipids, where at least one terminal position C20, C18 and lower carbon chain on the phospholipid, has been removed and replaced with another C18 or higher carbon chain. The lipid compositions have high concentrations of omega-3 fatty acids, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), compared to traditional plant and animal based phospholipids. The lipid compositions can be combined with polyethylene glycols (PEG) and other materials, as well as, enteric coatings, to enhance absorption within the digestive system. Also disclosed are processes for providing the bio-enhanced and novel lipid compositions to humans and animals to treat a variety of ailments and diseases.

BACKGROUND OF THE TECHNOLOGY

[0003] Phospholipids are important components to the human diet, since they deliver more bioavailable general omega-3 fatty acids, such as EPA and

DHA, than glycerides and esters. The importance of omega-3 fatty acids to the human diet has been well documented. DHA and EPA have been linked to decreased risk of Alzheimer's disease, decreased risk of certain cancers, and decreased risk of cardiovascular disease. Further, DHA is used as a supplement to infant formula and prenatal vitamins for improved cognitive development and visual acuity. EPA has been linked to decreases in inflammation and as a treatment for schizophrenia.

[0004] Currently, DHA and EPA primarily originate from marine animal origins or microalgae. Marine animals deliver more bioavailability of general omega-3s (including DHA and EPA), however, they are delivered in low levels (8-12% by weight) or low purities (less than 50% phospholipids per gram). Further, EPA and DHA supplied in high concentrations are in the form of glycerides or esters, which are not as readily absorbed by the digestive system or cellular structure.

[0005] Limited studies regarding ingestion of krill oils, containing omega-3 phospholipids, indicate a greater bioavailability of the omega-3 component, possibly due to its being part of a phospholipid. However, krill oils are typically only 9-12% EPA and 8-10% DHA, thus it is theorized that increasing the omega-3s on the hydrophobic tail of the phospholipid would further increase their bioavailability, thus enhancing efficacy.

[0006] PEGs and enteric coatings are used to increase absorption of dietary supplements into the digestive system. U.S. Patent Application Publication No. 2008/0306159 discloses dietary supplements comprising an enteric coated, soluble creatine and polyethylene glycol compositions. U.S. Patent Application Publication No. 2009/0306209 discloses dietary

supplements comprising an enteric coated, soluble amino acids and polyethylene glycol compositions. There is no disclosure of bio-enhanced or structured lipid compositions comprising phospholipids in either of these publications.

SUMMARY OF THE INVENTION

[0007] High concentrations of DHA and EPA dietary supplements are becoming increasingly valuable as the list of health benefits of the two omega-3 fatty acids continues to expand. Currently, the market is focused on either high EPA or DHA from glycerides or esters, or is focused on phospholipids of generally low and equally proportioned DHA and EPA as part of the phospholipid. Unlike glycerides and esters, phospholipids are inherently interpreted in the system as being nutritive, whereas lipid / ester formats may be interpreted by the body as either a fat energy or a nutritional fat source.

[0008] Therefore, it is desirable to create a lipid composition with phospholipids having increased concentrations and purity of DHA and EPA. Further, it is desirable to combine the novel lipid compositions with PEG and PEG compounds, as well as enteric coatings, to enhance absorption within the digestive system. Such a product would be especially beneficial in the dietary supplement industry, since more DHA and EPA would be delivered to the human body in a single dose.

[0009] The invention disclosed herein provides a bio-enhanced lipid composition with phospholipids having high (greater than about 15% by weight) concentrations of omega-3 fatty acids, including DHA and EPA. The phospholipids can be yeast based, marine animal based, such as krill, plant

based, and marine plant based, such as microalgae, that substantially comprise fatty acid carbon chains of C20 and higher. The phospholipids can also be catalytically re-randomized via esterfication/transesterfication/acylation to replace lower fatty acid chain terminal carbons on the R^1 and R^2 positions, including C16, C18, and C20 carbon chains. Enzymes, chemical catalysts, ultrasound, electromagnetic energy, or a combination thereof can be used as the catalyst. The re-randomization comprises reacting plant lecithin with marine fatty acids, to rearrange one or more of the terminal positions associated with the phospholipid, removing at least one lower fatty acid carbon chains, e.g. C16 and C18, and attaching at least one fatty acid carbon chain of another C18 or higher, e.g. C18, C20, or C22.

[00010] The lipid compositions can be combined with emulsifiers, vitamins, micronutrients, PEG and PEG compounds, as well as, enteric coatings to increase absorption within the digestive system. By compounding these lipid compositions with PEG and enteric coatings, the omega-3 uptake is increased and protected from initial gastric degradation. Further, the phospholipids allow for a more focused impact on the efficacy against condition specific diseases or malady. Also, the structured, re-randomized lipid compositions are more environmentally friendly and lower cost than pure marine based phospholipids. The result is an enhanced omega-3 dietary supplement with increased bioavailability and nutritive effect.

[00011] In one aspect, a lipid composition is disclosed, which comprises a first microbial phospholipid comprising DHA in a concentration greater than about 25% by weight phospholipid and a second microbial phospholipid

comprising EPA in a concentration greater than about 25% by weight phospholipid, wherein said first microbial phospholipid is isolated and purified from a first marine biomass and said second microbial phospholipid is isolated and purified from a second marine biomass.

[00012] In another aspect, a lipid composition is disclosed, which comprises a microbial phospholipid comprising EPA in a concentration greater than about 25% by weight phospholipid, wherein said microbial phospholipid is isolated and purified from a marine biomass.

[00013] In a further aspect, a lipid composition is disclosed, which comprises a microbial phospholipid comprising DHA in a concentration greater than about 25% by weight phospholipid, wherein said microbial phospholipid is isolated and purified from a marine biomass.

[00014] In yet another aspect, a structured lipid composition comprising phospholipids is disclosed, where the structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source, at least one fatty acid carbon chain derived from a second lipid source, and at least one fatty acid carbon chain derived from a third lipid source, and further wherein said structured lipid contains EPA in a concentration greater than about 25% by weight of said second lipid source and DHA in a concentration greater than about 25% by weight of said third lipid source.

[00015] In yet a further aspect, a structured lipid composition comprising phospholipids is disclosed, where the structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source and at least one fatty acid carbon chain derived from a second lipid source, and further wherein

said structured lipid contains EPA in a concentration greater than about 25% by weight of said second lipid source.

[00016] In even another aspect, a structured lipid composition comprising phospholipids is disclosed, where the structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source and at least one fatty acid carbon chain derived from a second lipid source, and further wherein said structured lipid contains DHA in a concentration greater than about 25% by weight of said second lipid source.

[00017] In even a further aspect, a method of making a structured lipid composition is disclosed, comprising providing a first lipid source to reactor; contacting said first lipid source with a second lipid source and a third lipid source to form a mixture; providing a lipase-based enzyme to said reactor; and reacting said first lipid source, said second lipid source, and said third lipid source to re-randomize the fatty acid carbon chains of said first, second, and third lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced by at least one C20 carbon chain from said second lipid source, and wherein at least one C18 or lower carbon chain of said first lipid source is replaced by at least one C22 carbon chain from said third lipid source. Further, a C16 or C18 carbon chain can be replaced by another C18 carbon chain including DPA, ALA, GLA, CLA, and SDA.

[00018] In yet even another aspect, a method of making a structured lipid composition is disclosed, comprising providing a first lipid source to a reactor; contacting said first lipid source with a second lipid source to form a mixture; providing a lipase-based enzyme to said reactor; and reacting said first lipid source and said second lipid source to re-randomize the fatty acid carbon

chains of said first and second lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced by at least one C20 carbon chain from said second lipid source. Further, a C16 or C18 carbon chain can be replaced by another C18 carbon chain including DPA, ALA, GLA, CLA, and SDA.

[00019] In yet even a further aspect, a method of making a structured lipid composition is disclosed, comprising providing a first lipid source to a reactor; contacting said first lipid source with a second lipid source to form a mixture; providing a lipase-based enzyme to said reactor; and reacting said first lipid source and said second lipid source to re-randomize the fatty acid carbon chains of said first and second lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced by at least one C22 carbon chain from said second lipid source. Further, a C16 or C18 carbon chain can be replaced by another C18 carbon chain including DPA, ALA, GLA, CLA, and SDA.

[00020] In another aspect, a method of treating various ailments in humans and animals with oral formulations of the various aspects of the lipid composition is disclosed. Such ailments and diseases including: Alzheimer's disease, inflammation (e.g. arthritis and Crohn's disease), cardiovascular disease (e.g. high cholesterol, heart disease, and hypertension), schizophrenia, stress, depression, ADD, AHD, ADHD, decreased libido, and menopause. Also, oral formulations of the various aspects of the lipid composition can be used to increase memory retention and cognitive response.

DEFINITIONS

[00021] While mostly familiar to those versed in the art, the following definitions are provided in the interest of clarity.

[00022] C16: Refers to a carbon chain with 16 carbons.

[00023] C18: Refers to a carbon chain with 18 carbons.

[00024] C20: Refers to a carbon chain with 20 carbons.

[00025] C22: Refers to a carbon chain with 22 carbons

[00026] Omega-3 Fatty Acids: A family of unsaturated fatty acids that have in common a final carbon–carbon double bond in the *n*−3 position; that is, the third bond from the methyl end of the fatty acid, including:

[00027] DHA: Docosahexaenoic acid.

[00028] EPA: Eicosapentaenoic acid.

[00029] SDA: Stearidonic acid

[00030] ALA: α-Linolenic acid

[00031] Omega-6 Fatty Acids: A family of unsaturated fatty acids that have in common a final carbon–carbon double bond in the *6* position; that is, sixth bond counting from the end opposite the carboxyl group of the fatty acid, including:

[00032] GLA: Gamma-linolenic acid

[00033] CLA: Calendic acid

[00034] DPA: Docosapentaenoic acid

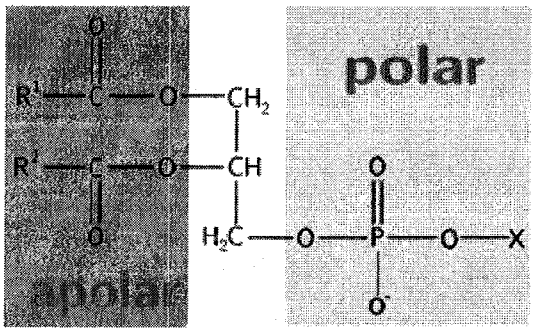
DETAILED DESCRIPTION OF THE INVENTION

[00035] In one aspect, a lipid composition is disclosed, which comprises a first microbial phospholipid comprising DHA in a concentration greater than

about 25% by weight phospholipid and a second microbial phospholipid comprising EPA in a concentration greater than about 25% by weight phospholipid, wherein said first microbial phospholipid is isolated and purified from a first marine biomass and said second microbial phospholipid is isolated and purified from a second marine biomass. Alternatively, the lipid composition can comprise EPA at a concentration greater than about 25% by weight phospholipid and DHA at a concentration less than about 10% by weight phospholipid. Further, the lipid composition can comprise DHA at a concentration greater than about 25% by weight phospholipid and EPA at a concentration less than about 10% phospholipid. This variation in DHA and EPA concentration depends on the type of marine biomass used.

[00036] The concentration of each of DHA and EPA in the lipid composition can vary from less than about 10% to about 95% by weight phospholipid, including about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90% and 95% by weight phospholipid, depending on the type of marine biomass used. Other fatty acids, such as DPA, ALA, GLA, CLA, and SDA may also be present in the phospholipids. The concentration of these other phospholipids is typically less than the concentration of DHA and EPA. The total fatty acid content in the phospholipids is from about 15% to about 95%, including about 20%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, and 95%. For example, the disclosed lipid composition can contain about 45% DHA and about 45% EPA (for a total of about 90%) in the phospholipids.

[00037] The fatty acids are attached to the phospholipids in the R^1 and R^2 terminal positions (see Figure below).



[00038] Either saturated or unsaturated fatty acids or esters thereof can be attached to one or both of the terminal positions so as to complete or partially complete the phospholipid, including having both terminals occupied with the targeted fatty acid, including omega-3, so as to maximize their delivery of nutritive effect. When present in the free fatty acid form, rather than the glyceride or ester form, the fatty acids are more bioavailable by the body.

[00039] The total concentration of the phospholipids in the lipid composition can vary from about 30% to about 95% by weight of the lipid composition, including about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, and 95% by weight of the lipid composition. For example, the disclosed lipid composition can contain about 90% phospholipids by weight, where the concentration of DHA and EPA is each 45% by weight phospholipid. This results in a lipid composition with about a 40% by weight DHA and about a 40% by weight EPA concentration in the lipid composition, for a total fatty acid content in the lipid composition of around 80%.

[00040] The phospholipids containing DHA and EPA can be derived from any plant based marine biomass, including plankton, fungi, macroalage, and microalgae. For phospholipids containing DHA, the microalgae can include species from the genera *Thraustochytrium*, *Schizochytrium*, and *Crypthecodinium*, including *Crypthecodinium cohnii* (*C. cohnii*). Also,

members of the class Dinophyceae, Bacillariophyceae, Chlorophyceae, Prymnesiophyceae, and Euglenophyceae can produce suitable phospholipids with high concentrations of DHA. For phospholipids containing EPA, the microalgae can include species from the genera *Thraustochytrium Schizochytrium*, *Phaeodactylum*, *Nannochloropsis*, *Porphydrium*, and *Monodus*, including *Phaeodactylum tricomulum*, *Porphyridium cruentum*, and *Monodus subterranous* (described in Chemicals from Microalgae, Edited by Zvi Cohen, Taylor & Francis Ltd., 1999, hereby incorporated by reference in its entirety).

[00041] Additional microalgae that produce DHA and EPA can include *Odentella aurita* (described in Braud JP, "Simultaneous culture in pilot tanks of the microalgage *Chondrus crispus* and the microalgage *Odentella aurita* producing EPA", 1998), *Pavolova lutheri* (described in Guiheneuf et al., "Effect of UV stress on the fatty acid and lipid class composition in two marine microalgae: *Pavlova lutheri* and *Odentella aurita*", Springer Science and Business, 2010), *Isochysis galbana* (described in Chemicals from Microalgage, edited by Zvi Cohen, Talory and Francis Ltd., 1999), *Nannochloropsis* (described in Chemicals from Microalgage), and *Porphyridium cruentum* (described in Chemicals from Microalgae).

[00042] Further, the microalgae can be *Chaetoceros calcitrans*, *Chaeotoceros gracilis*, *Nitzichia cloesterium*, *Skeletonema costatum*, *Thalassiosira pseudonana*, *Dunaliella tertiolecta*, *Nannochloris atomus*, *Chroomonas salina*, *Nannochloropsis oculata*, *Tetraselmis chui*, *Tetraselmis suecica*, *Pavlova salina*; all described at

www.fao.org/docrep/003/w3732e/w3732e07.htm. The above references are hereby incorporated by reference in their entirety.

[00043] Cultivation techniques of the above microalgae are well known. For example, *Thraustochytrium* and *Schizochytrium* have been well documented in U.S. Patent No. 5,340,594, hereby incorporated by reference in its entirety. Cultivation of *C. cohnii* has been well documented in U.S. Patent Nos. 5,397,591 and 5,492,538 and Japanese Patent Publication (to Kokai) No. 1-199588 (1989), all hereby incorporated by reference in their entirety.

[00044] The phospholipids must be isolated and purified from the above marine biomasses. Impurities, such as bacteria, particulates, and extraction chemicals, are almost always present when the phospholipids are extracted. Extraction of the phospholipids can be done using known methods, including polar and non-polar solvent extraction, spray drying, super critical extraction, centrifuge, enzymatic extraction, mechanical press, extrusion, sonication, decanter extraction, and combinations thereof.

[00045] One method of extracting phospholipids is to spray dry the marine biomass, which will lyse the cells, and then use a non-polar solvent, such as hexane, to remove the fatty acid phospholipid portion. Such process, and other suitable processes, is described in detail in U.S. Patent No. 6,372,460, herein incorporated by reference in its entirety. Another method is to pretreat the biomass to deactivate any potential phospholipase, which would otherwise degrade the phospholipids. The lipids and phospholipids are extracted from the biomass using known techniques, including polar and non-polar solvent extraction, spray drying, super critical extraction, centrifuge, enzymatic extraction, mechanical press, extrusion, and decanter extraction. The

phospholipids are then isolated and purified from the total lipid fraction with water wash, acetone, or other solvents that cause separation of the neutral from polar and glycolipids. The phospholipids are then dried using known methods including wiped-film evaporation.

[00046] Any bacteria present in the mircobiomass or phospholipid can be inactivated using an anti-bacterial agent. Particulates can be filtered out using various filtration methods, such as centrifuge, filter press, cyclone filtration, gravity decanter, or filter media. Extraction of the solvents can be removed using flash distillation, evaporation, and gravity decanting.

[00047] *C. cohnii* contains high concentrations of phospholipids (e.g. 20% - 30%), which in turn contain high concentrations of DHA (e.g. 25% - 45%) as bonded to the R terminals on the phospholipid (the polar lipid fraction). The phospholipids can be further purified and isolated to reach concentrations of around 90% in the lipid composition. Species from the genera *Phaeodactylum*, *Nannochloropsis*, *Porphydrium*, and *Monodus,* also contain high concentrations of phospholipids, which in turn contain high concentrations of EPA bonded to the R terminals. As with *C. cohnii*, the phospholipids from these microorganisms can be further purified and isolated to reach concentrations of around 90% in the lipid composition.

[00048] Further isolation and purification of the phospholipids from the above microorganisms allows the disclosed lipid composition to contain a tailored amount of fatty acid concentrations. For example, the lipid composition can contain about 40% DHA and about 40% EPA (present as 90% by weight phospholipids), as disclosed above, or 70% EPA and 10% DHA, or 10% EPA and 70% DHA. Further, DPA, SDA, GLA, ALA, and CLA

fatty acid phospholipids can be incorporated into the lipid composition by isolating and purifying the phospholipids containing these carbon chains on the R terminal positions. Thus, a truly tailored lipid composition can be obtained.

[00049] In another aspect, a structured lipid composition comprising phospholipids is disclosed, wherein the structured lipid comprises at least one carbon chain derived from a first lipid source, at least one carbon chain derived from a second lipid source, and at least one carbon chain derived from a third lipid source. The structured lipids contain EPA and DHA each at a concentration greater than about 25% by weight of the second and third lipid sources, respectively. Alternatively, the lipid composition can contain at least one carbon chain derived from a first lipid source and at least one carbon chain derived from a second lipid source, where DHA or EPA is present in the structured lipids at a concentration greater than about 25% by weight of the second lipid source.

[00050] The concentration of each of DHA and EPA in the lipid composition can vary from less than about 10% to about 90% by weight phospholipids, including about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, and 90%. Other fatty acids, such as DPA, ALA, GLA, CLA, and SDA may also be present in the phospholipids. The concentration of these other fatty acids is typically less than the concentration of DHA and EPA. The total fatty acid content in the phospholipids is greater than about 15% to about 90%, including about 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, and 90%.

[00051] The first lipid source is typically plant based and contains phosphatidylcholine, including soy lecithin, borage oil, primrose oil, sunflower oil, echium, and combinations thereof. T he second and third lipid sources can comprise lipids derived from microbial phospholipids, fish oil, krill oil, and combinations thereof. Further, the second and third lipid sources can comprise saturated or unsaturated fatty acids in the form of free fatty acids, fatty acid chlorides, fatty acid alkyl esters, fatty acid vinyl esters, fatty acid anhydrides, mono, di, or tri-glycerides, or any other activated from of a fatty acid serving as a fatty acyl donor. When a microbial phospholipid is selected, the phospholipid can be isolated and purified from a marine biomass derived from plankton, fungi, macroalgae, and microalgae. Suitable microalgae can include, species from the genera *Thraustochytrium*, *Schizochytrium*, and *Crypthecodinium*, including *Crypthecodinium cohnii* (*C. cohnii*), Dinophyceae, Bacillariophyceae, Chlorophyceae, Prymnesiophyceae, Euglenophyceae, *Phaeodactylum*, *Nannochloropsis*, *Porphydrium*, and *Monodus*, including *Phaeodactylum tricomulum*, *Porphyridium cruentum*, and *Monodus subterranous*. The additional microalgae described above can also be used as the source of the microbial phospholipid.

[00052] Microalgae cultivation, phospholipid extraction techniques, and isolation and purification techniques are discussed above.

[00053] The total concentration of the phospholipids in the lipid composition can vary from about 30% to about 95% by weight of the lipid composition, including about 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, and 95% by weight of the lipid composition.

[00054] The first carbon chain derived from the first lipid source is typically a C16, C18, or C20 carbon chain. The carbon chains derived from the second and third lipid sources can be C20 and C22 carbon chains, respectively. For example, a C20 carbon chain derived lipid source can be EPA, in any of the fatty acid forms described above, and a C22 carbon chain derived lipid source can be DHA, in any of the fatty acid forms described above. When only two lipid sources are present, the first lipid source carbon chain is a C16, C18 and/or C20, and the second lipid source carbon chain is a C20 or C22. The second and third lipid source carbon chains can also be other C18 carbon chains derived from DPA, ALA, GLA, CLA, and SDA fatty acids. In the structured lipid, the second and third carbon chains are present at a higher concentration than the first carbon chain.

[00055] The carbon chains are present on the phospholipids on the R^1 and R^2 terminal positions. The carbon chains can be present as fatty acids in ester or glyceride form. The fatty acids can be both saturated and unsaturated, including omega-3 unsaturated fatty acids such as DHA and EPA. The resulting phospholipid is a 1,2 diacylatedphospholipid, where the 1-acyl and 2-acyl groups are present as the fatty acids. The C20 and C22 fatty acids are present on the phospholipid in a purely random fashion, i.e. some phospholipids may have all C20 or C22s, a mixture of both, or a mixture of C20s, C22s, C16s, and C18s. Thus, there is no predetermination of the fatty acid carbon chains on the R^1 and R^2 terminal positions.

[00056] Further isolation and purification of the phospholipids from the above microorganisms allows the disclosed lipid composition to contain a tailored amount of fatty acid concentrations. For example, the lipid

composition can contain about 40% DHA and about 40% EPA (present as 90% by weight phospholipids), or 70% EPA and 10% DHA, or 10% EPA and 70% DHA. Further, DPA, SDA, GLA, ALA, and CLA fatty acid phospholipids can be incorporated into the lipid composition by isolating and purifying the phospholipids containing these carbon chains on the R terminal positions. Thus, a truly tailored, but random, lipid composition can be obtained.

[00057] In a further aspect, a method of making the structured lipid composition is disclosed, comprising providing a first lipid source to a reactor; contacting said first lipid source with a second lipid source and a third lipid source to form a mixture; providing a lipase-based enzyme to said reactor; and reacting said first, second, and third lipid sources. The first lipid source contains at least one C20, C18 or lower carbon chain, the second lipid source contains at least one C20 carbon chain, and the third lipid source contains at least one C22 carbon chain. Alternatively, the method can include providing a first lipid source to a reactor and contacting said first lipid source a second lipid source, where the first lipid source contains a C20, C18 or lower carbon chain and the second lipid source contains a C20 or C22 carbon chain.

[00058] The reaction of the lipid sources and lipase-based enzyme re-randomizes the fatty acid carbon chains of the lipid sources via esterfication/transesterfication/acylation, whereby at least one C20, C18 or lower carbon chain of the first lipid source is replaced with at least one C20 and/or C22 carbon chain from the second and third lipid sources, respectively, depending on the concentration of EPA and DHA that is desired in the lipid composition. For example, when an EPA lipid composition is desired, the second lipid source contains C20 carbon chains, which replace the C18 or

lower carbon chains from the first lipid source. Further, when an EPA and DHA lipid composition is desired, the second lipid source contains C20 carbon chains and the third lipid source contains C22 carbon chains, which both replace the C20, C18 or lower carbon chains from the first lipid source. Also, additional lipid sources can be added to the reactor, including DPA, ALA, GLA, CLA, and SDA, which will replace the C20, C18 or lower carbon chains from the first lipid source.

[00059] The second and third lipid sources can be phospholipids derived from the microalgae described above, as well as, marine based phospholipids from fish or krill, or plant based phospholipids. Additionally, the second and third lipid sources can comprise saturated or unsaturated fatty acids in the form of free fatty acids, fatty acid chlorides, fatty acid alkyl esters, fatty acid vinyl esters, fatty acid anhydrides, mono, di, and tri-glycerides, or any other activated from of a fatty acid serving as a fatty acyl donor.

[00060] The lipase-based enzyme can be a phospholipase enzyme that demonstrates acylation activity at the R^1 and/or R^2 terminal position. Such phospholipases include Phospholipase A (Lecitase) provided by Sankyo and Novozymes (435 and 525). The phospholipase can be immobilized onto an insoluble matrix and/or by coating the same with a surfactant material.

[00061] For example, soy lecithin phospholipids containing phosphatidylcholine are combined in a reactor with high purity phospholipid fractions disclosed above in a weight ratio of from about 25:75 to 75:25 soy lecithin phospholipid to marine phospholipid, including 50:50 weight ratio, 35:65 weight ratio, 65:35 weight ratio, 40:60 weight ratio, and 60:40 weight

ratio. Lipase-based enzymes are added to the reactor in a concentration range from about 2% - 5% by weight of total phospholipids.

[00062] The disclosed process allows for the composition of a structured, but randomized, lipid with tailored concentrations of EPA and/or DHA, and one or more of DPA, ALA, GLA, CLA, and SDA, if desired. The advantages of a structured lipid are low cost, since the first lipid source is plant based, tailored fatty acid concentrations, and high purity. The tailored fatty acid allows specific formulations to be readily manufactured (i.e., a high EPA with phosphatidylcholine (PC) or a high DHA with phosphatidylserine (PS)), which assists in providing effective treatment options of various diseases and ailments.

[00063] The reaction can also be repeated several times to increase the concentration of fatty acids in the structured lipid. As the randomization reaches equilibrium between distribution of carbon chains amongst glycerides and phospholipids, isolation of the phospholipids from the glycerides is possible. The isolated phospholipids can be placed into new glycerides (or esters) fraction whose availability of the target carbon chain(s) is higher than that of the previous glyceride media, thus, continually reaching higher proportions of the target carbon chain(s) in the final structured lipid product.

[00064] A chemical catalyst can also be added to the reactor to increase the re-randomization rate. The catalyst can be any alkali catalyst such as sodium ethoxide and sodium methoxide, though (similarly) other metals can replace the sodium in the catalyst, including potassium, calcium, magnesium, strontium, etc. Organic amines may also be used to incite the reaction, or

sodium or potassium acetate. Further, sonification may be used, either by itself or in combination with the enzymes or catalysts.

[00065] The reactor can be any vessel for holding the lipid sources, including a stainless steel tank, glass lined tank, steel-alloy blend tank. The reaction temperature is between about 40°C and about 100°C, including from about 50°C to about 90°C, about 60°C to about 80°C, and 70°C. The reaction times can range from about 4 hours to about 24 hours, including 6 hours to 20 hours, and 10 hours to 15 hours. Also, the reaction can take place at ambient temperatures, about 20°C, for about 3 months. This allows the restructuring to occur during storage of the structured lipid composition and forgoes the need to supply additional heat.

[00066] The disclosed lipid compositions and structured lipids can also comprise antioxidants, including tocopherol, BHT, BHA, TBQH, ethoxyquin, beta-carotene, vitamin E, and vitamin C to prevent degradation of the omega-3s. The lipid compositions and structured lipids can further comprise binding agents, mono and triglycerides, including those derived from oils containing high-purity omega-3s or from concentrations of omega-3s, esters and ester compounds, and other thinning agents, including Sorbitol. This assists in making the lipids a flowable powder or liquid for further processing. Further, the lipid compositions and structured lipids can be encapsulated using known encapsulation techniques or pressed into pills.

[00067] The lipid compositions and structured lipids may also be reacted with lipase-based compounds, including those previously processed by chemical catalysts, to hydrolyze the ester-bonds in the phospholipids. The result is a lipid or oil with a lower fish or chemical odor and an increased fruity

odor. In one aspect, a krill based phospholipid is reacted with a lipase to deodorize it. The reaction takes place from about 40°C – 65°C under vacuum and agitation for a period from about 4 to about 48 hours. The lipase is then deactivated or filtered out of the final phospholipid product.

[00068] In yet another aspect, an oral formulation comprising the disclosed lipid compositions and structured lipids is disclosed. The oral formulation includes PEG or PEG compounds, such as Vitamin E TPGS. Optionally, the oral formulation can include an enteric coating to aid in the absorption of the lipid compositions and structured lipids by the intestine.

[00069] In solid oral formulations, the PEG components contain an average molecular weight from 150 to 9000, including 3015 to 4800, 1305 to 1595, 3600 to 4400, 4400 to 4800, 7000 to 9000, 6000 to 7500, and 3150 to 3685. The PEG is present in a ratio by weight percent phospholipid to PEG from 99:1 to 50:50, including 95:5 and 85:15. The PEG is a hard, opaque, granular solid under the following trade names: Carbowax® PEG 3350, Carbowax® PEG 1450, Carbowax® PEG 4000, Carbowax® PEG 4600, Carbowax® PEG 8000, and Carbowax® 6000. The PEG may also be any other commercial formulation suitable for food grade use.

[00070] In liquid oral formulations, the PEG components contain an average molecular weight from 190 to 630, including 190 to 210, 285 to 315, 380 to 420, and from 570 to 630. The PEG can be the following commercial products: Carbowax® PEG 200, Carbowax® PEG 300, Carbowax® PEG 400, and Carbowax® PEG 600.

[00071] The oral formulation can also contain additional compounds selected from the group consisting of Resveratrol, quinones,

diferuloylmethanes, sterols, β-glucans, glucosamine, carotenoids, turpines, xanthpohylls, omega-3 fatty acids, probiotics, prebiotics, and combinations thereof. This can be mixed with the PEG, PEG compounds, phospholipids, or lipid compositions or structured lipids.

[00072] The concentration of the lipid compositions and structured lipids in the oral formulations depends on the particular use. Phospholipids may typically be present in the final formulation in the range of 30-95% of the formulary, most typically 40-60% for general use and 75-95% for high-potency products. The fatty acid compositions for these typically are driven by market demands, which do not remain constant. Current desires have driven achievement levels of 30-85% of the phospholipid content being either EPA, DHA, or a combination thereof, though typically 40-60%. SDA, DPA, or other fatty acids or their combinations in proportions similar to those listed above may also be achieved. The specific phospholipids may be significantly weighted to be one or more select phospholipids, such as PC, PS, PE, PI, sphingomyelin, etc. Thus, the disclosed methods can be used to create new combinations of fatty acids (single or blended) paired with select phospholipids or phospholipid combinations.

[00073] In yet a further aspect, methods of treating various aliments and diseases with the disclosed oral formulations is disclosed by providing an effective amount of the oral formulation. Such aliments and diseases include: Alzheimer's disease, inflammation (e.g. arthritis and Crohn's disease), cardiovascular disease (e.g. high cholesterol, heart disease, and hypertension), schizophrenia, stress, depression, ADD, AHD, ADHD, decreased libido, and menopause. Also, oral formulations of the various

aspects of the lipid composition can be used to increase memory retention and cognitive response. The oral formulations can be provided to both humans and animals, depending on the specific aliment or disease.

[00074] The effective amount of the oral formulation will depend on several factors, including, weight of the individual, age of the individual, severity of the symptoms, and past medical history. For example, an effective amount of an oral formulation containing >25 % DHA for treating general cognitive disorders, including memory enhancement, would be 1,000 mg/day (i.e. >250 mg of DHA).

Table 1: Effective amount range for several aliments and diseases

Aliment or Disease	% DHA in oral formulation	% EPA in oral formulation	Weight of individual (kg)	Daily dosage (range) in mg/day
Alzheimer's	>40	>10	70	2,000
Inflammation	<5	>25	70	1,500
Cardiovascular disease	>5	>30	70	1,500
Schizophrenia	>5	>30	70	3,000
Stress	>25	>10	70	1,500
Depression	>30	>10	70	1,500
ADD	>25	>20	70	1,500
AHD	>25	>20	70	1,500
ADHD	>25	>20	70	1,500
Decreased libido	>20	>20	70	1,500
Menopause	>20	>20	70	1,500

Table 2: Effective amount range for increasing memory retention and cognitive response

Benefit	% DHA in oral formulation	% EPA in oral formulation	Weight of individual	Daily dosage (range) in mg/day
Increased memory retention	>25	>20	70	1,000
Cognitive Response	>25	>20	70	1,000

[00075] The invention has been described above with reference to the various aspects of the disclosed lipid compositions, structured lipids, oral formulations comprising the lipid compositions and structured lipids, and methods of treating various aliments. Obvious modifications and alterations will occur to others upon reading and understanding the proceeding detailed description. It is intended that the invention be construed as including all such modifications and alterations insofar as they come within the scope of the claims.

CLAIMS

What is claimed is:

1. A lipid composition comprising a first microbial phospholipid comprising DHA in a concentration greater than about 25% by weight phospholipid and a second microbial phospholipid comprising EPA in a concentration greater than about 25% by weight phospholipid, wherein said first microbial phospholipid is isolated and purified from a first marine biomass and said second microbial phospholipid is isolated and purified from a second marine biomass.

2. A lipid composition comprising a microbial phospholipid comprising EPA in a concentration greater than about 25% by weight phospholipid, wherein said microbial phospholipid is isolated and purified from a marine biomass.

3. A lipid composition comprising a microbial phospholipid comprising DHA in a concentration greater than about 25% by weight phospholipid, wherein said microbial phospholipid is isolated and purified from a marine biomass.

4. The lipid composition of one of claims 1-3, wherein said phospholipids are present at a total concentration greater than about 45% by weight of said lipid composition.

5. The lipid composition of one of claims 1-3, wherein said phospholipids are present at a total concentration greater than about 80% by weight of said lipid composition.

6. The lipid composition of claim 1, wherein said DHA is present at a concentration from about 25% to about 45% by weight of said first microbial phospholipid and said EPA is present at a concentration from about 25% to about 45% by weight of said second microbial phospholipid.

7. The lipid composition of claim 2, wherein said EPA is present at a concentration from about 25% to about 45% by weight of said microbial phospholipid.

8. The lipid composition of claim 3, wherein said DHA is present at a concentration from about 25% to about 45% by weight of said microbial phospholipid.

9. The lipid composition of claim 2, further comprising DHA present at a concentration less than about 10% by weight of said microbial phospholipid, and wherein said EPA is present at a concentration of from about 25% to about 45% by weight of said microbial phospholipid.

10. The lipid composition of claim 3, further comprising EPA present at a concentration less than about 10% by weight of said microbial phospholipid, and wherein said DHA is present at a concentration of from about 25% to about 45% by weight of said microbial phospholipid.

11. The lipid composition of one of claims 1, 6, 9, or 10, wherein said first marine biomass is derived from a microalgae comprising *Crypthecodinium cohnii*.

12. The lipid composition of one of claims 1, 6, 9, or 10, wherein said second marine biomass is derived from a microalgae selected from the group consisting of *Phaeodactylum tricornulum, Nannochloropsis, Porphyridium cruentum, Monodus subterranous*, and combinations thereof.

13. The lipid composition of claim 2 or 7, wherein said marine biomass is derived from a microalgae selected from the group consisting of *Phaeodactylum tricornulum, Nannochloropsis, Porphyridium cruentum, Monodus subterranous*, and combinations thereof.

14. The lipid composition of claim 3 or 8, wherein said marine biomass is derived from a microalgae comprising *Crypthecodinium cohnii.*

15. The lipid composition of claim 11, wherein said first and second microbial phospholipids are present at a concentration from about 4% to about 16% of the total dry weight of the microalgae.

16. The lipid composition of claim 12, wherein said first and second microbial phospholipids are present at a concentration from about 4% to about 16% of the total dry weight of the microalgae.

17. The lipid composition of claim 13, wherein said microbial phospholipid is present at a concentration from about 4% to about 16% of the total dry weight of the microalgae.

18. The lipid composition of claim 14, wherein said microbial phospholipid is present at a concentration from about 4% to about 16% of the total dry weight of the microalgae.

19. An oral formulation comprising the lipid composition of one of claims 1-3, and 6-10; and polyethylene glycol or a polyethylene glycol compound.

20. The oral formulation of claim 19, further comprising an enteric coating.

21. The oral formulation of claim 20, wherein said polyethylene glycol compound is Vitamin E TGPS.

22. The oral formulation of claim 20, further comprising a component selected from the group consisting of Resveratrol, quinones, diferuloylmethanes, sterols, β-glucans, glucosamine, carotenoids, turpines, xanthpohylls, omega-3 fatty acids, probiotics, prebiotics, and combinations

thereof.

23. The oral formulation of claim 22, wherein said quinones includes CoQ10.

24. The oral formulation of claim 22, wherein said turpines, carotenoids, or, xanthpohylls are selected from the group consisting of astaxanthin, α-carotene, β-carotene, lycopene, fucoaxanthin, zeaxanthin, and lutein.

25. A structured lipid composition comprising phospholipids, wherein said structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source, at least one fatty acid carbon chain derived from a second lipid source, and at least one fatty acid carbon chain derived from a third lipid source, and further wherein said structured lipid contains EPA in a concentration greater than about 25% by weight of said second lipid source and DHA in a concentration greater than about 25% by weight of said third lipid source.

26. A structured lipid composition comprising phospholipids, wherein said structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source and at least one fatty acid carbon chain derived from a second lipid source, and further wherein said structured lipid contains EPA in a concentration greater than about 25% by weight of said second lipid source.

27. A structured lipid composition comprising phospholipids, wherein said structured lipid comprises at least one fatty acid carbon chain derived from a first lipid source and at least one fatty acid carbon chain derived from a second lipid source, and further wherein said structured lipid contains DHA in a concentration greater than about 25% by weight of said second lipid source.

28. The lipid composition of one of claims 25-27, wherein said first lipid source is plant based.

29. The lipid composition of one of claims 25-27, wherein said first lipid source comprises soy lecithin.

30. The lipid composition of claim 25 or 26, wherein said second lipid source comprises a component selected from the group consisting of a first microbial phospholipid, fish oil, krill oil, and combinations thereof.

31. The lipid composition of claim 25, wherein said third lipid source comprises a component selected from the group consisting of a second microbial phospholipid, fish oil, krill oil, and combinations thereof.

32. The lipid composition of claim 27, wherein said second lipid source comprises a component selected from the group consisting of a second microbial phospholipid, fish oil, krill oil, and combinations thereof.

33. The lipid composition of claim 30, wherein said first microbial phospholipid is isolated and purified from a marine biomass derived from a microalgae selected from the group consisting of *Phaeodactylum tricornulum, Nannochloropsis, Porphyridium cruentum, Monodus subterranous*, and combinations thereof.

34. The lipid composition of claim 31, wherein said second microbial phospholipid is isolated and purified from a marine biomass derived from a microalgae comprising *Crypthecodinium cohnii.*

35. The lipid composition of claim 32, wherein said second microbial phospholipid is isolated and purified from a marine biomass derived from a microalgae comprising *Crypthecodinium cohnii.*

36. The lipid composition of one of claims 31-35, wherein said first lipid source comprises soy lecithin.

37. The lipid composition of one of claims 25-27, wherein said phospholipids are present at a concentration greater than about 45% by weight of said lipid composition.

38. The lipid composition of one of claims 25-27, wherein said phospholipids are present at a concentration greater than about 80% by weight of said lipid composition.

39. The lipid composition of one of claims 25-27, wherein said EPA is present at a concentration of from about 25% to about 45% by weight of said phospholipids.

40. The lipid composition of one of claims 25-27, wherein said DHA is present at a concentration of from about 25% to about 45% by weight of said phospholipids.

41. The lipid composition of one of claims 25-27, wherein said DHA is present at a concentration of from about 25% to about 45% by weight of said phospholipids and said EPA is present at a concentration of less than about 10% by weight of said phospholipids.

42. The lipid composition of one of claims 25-27, wherein said EPA is present at a concentration of from about 25% to about 45% by weight of phospholipids and said DHA is present at a concentration of less than about 10% by weight of phospholipids.

43. The lipid composition of claims 25 or 26, wherein said at least one carbon chain derived from a second lipid source is a C20 carbon chain.

44. The lipid composition of claim 25, wherein said at least one carbon chain derived from a third lipid source is a C22 carbon chain.

45. The lipid composition of claim 27, wherein said at least one carbon chain derived from a second lipid source is a C22 carbon chain.

46. An oral formulation comprising the lipid composition of one of claims 25-27 and 31-35; and polyethylene glycol or polyethylene glycol compound.

47. The oral formulation of claim 46, further comprising an enteric coating.

48. The oral formulation of claim 47, wherein said polyethylene glycol compound is Vitamin E TGPS.

49. The oral formulation of claim 47, further comprising a component selected from the group consisting of Resveratrol, quinones, diferuloylmethanes, sterols, β-glucans, glucosamine, carotenoids, turpines, xanthpohylls, omega-3 fatty acids, probiotics, prebiotics, and combinations thereof.

50. The oral formulation of claim 49, wherein said quinones includes CoQ10.

51. The oral formulation of claim 49, wherein said turpines, carotenoids, or, xanthpohylls are selected from the group consisting of astaxanthin, α-carotene, β-carotene, lycopene, fucoaxanthin, zeaxanthin, and lutein.

52. A method of making a structured lipid composition comprising:
providing a first lipid source to reactor;
contacting said first lipid source with a second lipid source and a third lipid source to form a mixture;
providing a lipase-based enzyme to said reactor; and
reacting said first lipid source, said second lipid source, and said third lipid source to re-randomize the fatty acid carbon chains of said first, second, and third lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced by at least one C20 carbon chain from said second lipid source, and wherein at least one C18 or lower carbon chain of said first

lipid source is replaced with at least one C22 carbon chain from said third lipid source.

53. A method of making a structured lipid composition comprising:
providing a first lipid source to a reactor;
contacting said first lipid source with a second lipid source to form a mixture;
providing a lipase-based enzyme to said reactor; and
reacting said first lipid source and said second lipid source to re-randomize the fatty acid carbon chains of said first and second lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced with at least one C20 carbon chain from said second lipid source.

54. A method of making a structured lipid composition comprising:
providing a first lipid source to a reactor;
contacting said first lipid source with a second lipid source to form a mixture;
providing a lipase-based enzyme to said reactor; and
reacting said first lipid source and said second lipid source to re-randomize the fatty acid carbon chains of said first and second lipid sources, wherein at least one C18 or lower carbon chain of said first lipid source is replaced with at least one C22 carbon chain from said second lipid source.

55. The method of one of claims 52-54, wherein said first lipid source is plant based.

56. The method of one of claims 52-54, wherein said first lipid source comprises soy lecithin.

57. The method of claim 52 or 53, wherein said second lipid source comprises a component selected from the group consisting of a first microbial phospholipid, fish oil, krill oil, and combinations thereof.

58. The method of claim 52, wherein said third lipid source comprises a component selected from the group consisting of a second microbial phospholipid, fish oil, krill oil, and combinations thereof.

59. The method of claim 54, wherein said second lipid source comprises a component selected from the group consisting of a second microbial phospholipid, fish oil, krill oil, and combinations thereof.

60. The method of claim 57, wherein said first microbial phospholipid is isolated and purified from a marine biomass derived from a microalgae selected from the group consisting of *Phaeodactylum tricornulum, Nannochloropsis, Porphyridium cruentum, Monodus subterranous*, and combinations thereof.

61. The method of claim 58 or 59, wherein said second microbial phospholipid is isolated and purified from a marine biomass derived from a microalgae comprising *Crypthecodinium cohnii.*

62. The method of claim 52 or 53, wherein said second lipid source is the lipid composition from claim 2 or 7.

63. The method of claim 52, wherein said third lipid source is the lipid composition from claim 3 or 8.

64. The method of claim 54, wherein said second lipid source is the lipid composition from claim 3 or 8.

65. The method of one of claims 52-54, further comprising providing a chemical catalyst to said reactor.

66. The method of claim 65, wherein said chemical catalyst is selected from the group consisting of alkali catalysts, sodium ethoxide and sodium methoxide.

67. The method of one of claims 52-54, further comprising sonicating said mixture.

68. The method of one of claims 52-54, wherein said reacting is done at a temperature of from about 40°C to about 100°C, and at a time of at least about 4 hours.

69. A method of treating Alzheimer's disease in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

70. A method of treating inflammation in a human or animal comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

71. A method of treating cardiovascular disease in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

72. A method of treating schizophrenia in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

73. A method of treating stress or depression in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

74. A method of treating AHD, ADD, or ADHD in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

75. A method of increasing cognitive response in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

76. A method of increasing memory retention in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

77. A method of increasing libido in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.

78. A method of treating the symptoms of menopause in a human comprising providing an effective amount of the oral formulation from one of claims 19-24 and 46-51.