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(54) **COMPOSITIONS INCLUDING KRILL  
EXTRACTS AND CONJUGATED LINOLEIC  
ACID AND METHODS OF USING SAME**

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(57) **ABSTRACT**

Methods and compositions for the prevention, therapy and/or treatment of several disease states. The methods comprise the administration of a therapeutically effective amount of a composition including krill extract and conjugated linoleic acid. In addition, the present invention provides new and improved therapeutic compositions including krill extracts and conjugated linoleic acid.

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**COMPOSITIONS INCLUDING KRILL EXTRACTS  
AND CONJUGATED LINOLEIC ACID AND  
METHODS OF USING SAME**

**PRIORITY CLAIM**

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/309,456, filed Oct. 8, 2003, the disclosures of which are hereby incorporated by reference.

**BACKGROUND OF THE INVENTION**

[0002] This invention generally relates to compositions and methods for preventing and/or treating diseases.

[0003] PCT Patent Application No. PCT/CA02/00843 published on Dec. 27, 2002 and entitled "Krill and/or Marine Extracts for Prevention and/or Treatment of Cardiovascular Diseases, Arthritis, Skin Cancer, Diabetes, Premenstrual Syndrome and Transdermal Transport" (the disclosure of which is incorporated herein by reference) discloses krill and/or marine extracts.

[0004] Krill is the common name for small, shrimp-like crustaceans, however not shrimp, that swarm in dense shoals, especially in Antarctic waters. It is one of the most important food source for fish, some kind of birds and especially for baleen whales as being an important source of protein. Krill is also a good source of Omega-3 fatty acids, which are well known for their health benefits.

[0005] The PCT application states that it is known in the art to use krill and/or marine enzymes for the treatment of a great variety of diseases in human and animals such as infections, inflammations, cancers, HIV/AIDS, pain, polyps, warts, hemorrhoids, plaque, wrinkles, thin hairs, allergic itch, anti-adhesion, eye disease, acne, cystic fibrosis and immune disorders including autoimmune disease and cancer.

[0006] It is also stated to be known in the art that krill and/or marine oil may be used for the treatment of autoimmune murine lupus and other autoimmune diseases and can also be used for treating cardiovascular diseases.

[0007] However, it is stated that the krill and/or marine oil used for these treatments has only conserved its Omega-3 fatty acids as active ingredients, which is a very small part of all the active ingredients of the krill and/or marine itself. This fact reduces the potential of the krill and/or marine oil as a treatment for these diseases.

[0008] There is an increasing demand for treatments using products derived from a natural source, therefore, it would be highly desirable to be provided with a krill and/or marine extract having an enhanced potential for prevention and/or treatment and/or management of disease. It is known to use conjugated linoleic acid for the treatment of diseases.

[0009] Published PCT Patent Application Nos. PCT/US00/21050, PCT/US00/21047, PCT/US00/21046, and PCT/US00/21044, entitled "Method and Compositions for Preventing and/or Treatment of Diabetes and Glucose Modulation", "Methods and Compositions for Attenuation and/or Prevention of Stress/Catabolic Responses", "Methods and Compositions for the Prevention and Treatment of

tion and Treatment of Syndrome X", respectively, (the disclosures of all of which are incorporated by reference) relate to the use of conjugated linoleic acid. As disclosed therein, conjugated linoleic acid has been used for the treatment of disease states.

**SUMMARY OF THE INVENTION**

[0010] In accordance with the present invention there are provided methods of prevention, therapy and/or treatment of several disease states. The methods comprise the administration of a therapeutically effective amount of a composition including krill extract and conjugated linoleic acid with or without other active or inactive ingredients. In addition, the present invention provides new and improved therapeutic compositions including krill extracts and conjugated linoleic acid.

[0011] To this end, in an embodiment, the present invention provides a method for preventing the onset of a disease state in an individual comprising the step of administering a therapeutically effective amount of a composition including krill extract and conjugated linoleic acid.

[0012] In an embodiment, approximately 1.0 mg to about 15 g per day of krill extract and conjugated linoleic acid are administered.

[0013] In an embodiment, the individual is at risk of a disease or ailment chosen from the group consisting of joint ailment, PMS, Syndrome X, cardiovascular disease, bone disease, immune deficiency, diabetes, stress related disease, and hormonal disease.

[0014] In an embodiment, the conjugated linoleic acid is chosen from the group consisting of a pure isomer of octadecadienoic acid and a mixture of octadecadienoic acid isomers including: cis-8, cis-10; cis-8, trans-10; trans-8, cis-10; trans-8, trans-10; cis-9, cis-11; cis-9, trans-11; trans-9, cis-11; trans-9, trans-11; cis-10, cis-12; cis-9, trans-12; trans-9, cis-12; trans-10, trans-12; cis-11, cis-13; cis-11, trans-13; trans-11, cis-13; trans-11, trans-13 octadecadienoic acid; 18:3 cis-6, cis-9, trans-11; 18:3 cis-6, trans-10, cis-12; 18:3 cis-8, trans-12, cis-14; 20:3 cis-8, cis-11, trans-13; 20:4 cis-5, cis-8, cis-11, trans-13; 20:4 cis-5, cis-8, trans-12, cis-14; metabolites thereof; and precursors and derivatives thereof.

[0015] In an embodiment, the composition includes a flavor.

[0016] In an embodiment, the composition includes an artificial sweetener.

[0017] In another embodiment of the present invention, a composition for treating a disease state or reducing the risk of a disease state in a patient is provided comprising an effective amount of krill oil in association with conjugated linoleic acid and a pharmaceutically acceptable carrier, wherein said krill oil is obtained from a process comprising the steps of: placing krill and/or marine material in a ketone solvent, preferably acetone to achieve extraction of the soluble lipid fraction from the marine and/or aquatic animal material; separating the liquid and solid contents; recovering a first lipid rich fraction from the liquid contents by evaporation of the solvent present in the liquid contents; placing

isopropanol or t-butanol and esters of acetic acid, preferably ethyl acetate to achieve extraction of the remaining soluble lipid fraction from said marine and/or aquatic animal material; separating the liquid and solid contents; recovering a second lipid rich fraction by evaporation of the solvent from the liquid contents; and recovering the solid contents.

**[0018]** In yet another embodiment of the present invention, a therapeutic composition is provided comprising an effective amount of krill oil and conjugated linoleic acid in association with a pharmaceutically acceptable carrier, wherein said krill oil comprises Eicosapentanoic acid, Docosahexanoic acid, Phosphatidylcholine, Phosphatidylinositol, Phosphatidylserine, Phosphatidylethanolamine, Sphingomyelin,  $\alpha$ -tocopherol, Astaxanthin, and flavonoid.

**[0019]** Still further, the present invention provides a method of treating a disease state comprising the steps of administering a therapeutically effective amount of a composition including conjugated linoleic acid and a krill extract.

**[0020]** In an embodiment, the individual suffers from a disease or ailment chosen from the group consisting of joint ailment, PMS, Syndrome X, cardiovascular disease, bone disease, immune deficiency, diabetes, stress related disease, and hormonal disease.

**[0021]** In a further embodiment of the present invention, a method of producing a therapeutic composition is provided comprising preparing a krill extract obtained from a process comprising the steps of: placing krill and/or marine material in a ketone solvent, preferably acetone to achieve extraction of the soluble lipid fraction from the marine and/or aquatic animal material; separating the liquid and solid contents; recovering a first lipid rich fraction from the liquid contents by evaporation of the solvent present in the liquid contents; placing the solid contents in an organic solvent selected from the group of solvents consisting of alcohol, preferably ethanol, isopropanol or t-butanol and esters of acetic acid, preferably ethyl acetate to achieve extraction of the remaining soluble lipid fraction from the marine and/or aquatic material; separating the liquid and solid contents; recovering a second lipid rich fraction by evaporation of the solvent from the liquid contents; recovering the solid contents; and adding the solid contents to a conjugated linoleic acid containing composition.

**[0022]** Additional features and advantages of the present invention are described in, and will be apparent from, the following Detailed Description of the Invention.

#### DETAILED DESCRIPTION OF THE INVENTION

**[0023]** In accordance with the present invention, there is provided therapeutic compositions comprising krill extract and conjugated linoleic acid for the prevention and/or treatment and/or therapy of diseases. A variety of treatments and compositions are possible pursuant to the present invention. The compositions can also be used prophylactically to prevent the onset of diseases as well as to maintain a healthy individual.

**[0024]** It is believed that there are synergistic effects achieved by combining conjugated linoleic acid and krill oil

but produce enhanced or synergistic benefits through shared eicosanoid mechanisms. These mechanisms include changing membrane composition through phospholipid incorporation, longer chain fatty acid incorporation and conjugated linoleic acid incorporation. In addition to these synergistic shared mechanisms the ability of conjugated linoleic acid to activate peroxisome peroxidation activation receptors (PPAR), which are thought to be involved with glucose and lipid metabolism as well as adipocyte apoptosis produces a synergistic effect. These combined oils are believed to be beneficial in indications, applications and compositions listed below.

**[0025]** Various combinations of the oils can be used. The oils can be topically applied or, parenterally and/or orally delivered. By way of example, a daily dosage can provide as little as 1 mg of the oils or as much as 15 g of the oils; in an embodiment, between 100 mg to 12 g of oil is provided daily. Efficacious doses will depend on the condition being addressed. By way of example, combinations of either oil can be used in a 1:1 ratio or a ratio of 0.05:1 to 1:0.05. These oils can be combined with other organic or inorganic compounds known to further enhance the conditions being addressed.

**[0026]** With respect to the krill extract, a multi-therapeutic oil extract free of enzyme is derived from krill and/or marine, found in any marine environment around the world, for example, the Antarctic ocean (*euphasia superba*), the Pacific ocean (*euphasia pacifica*), the Atlantic ocean, the Indian ocean, in particular coastal regions of Mauritius Island and/or Reunion Island of Madagascar, Canadian West Coast, Japanese Coast, St-Lawrence Gulf and Fundy Bay, and this oil extract is a free fatty acid lipid fraction.

**[0027]** The extraction process can be described as the following:

**[0028]** (a) placing marine and/or aquatic krill and/or marine in a ketone solvent, preferably acetone, to achieve the extraction of grease from the krill and/or marine;

**[0029]** (b) separating the liquid and the solid phases;

**[0030]** (c) recovering a lipid rich fraction from the liquid phase obtained at step (b) by evaporation of the solvent present in the liquid phase;

**[0031]** (d) placing the solid phase in an organic solvent, which can be alcohol, preferably ethanol, isopropanol or t-butanol, or esters of acetic acid, preferably ethyl acetate. This in order to extract the remaining soluble lipid fraction from the solid phase;

**[0032]** (e) separating the liquid and the solid phases; and

**[0033]** (f) recovering a lipid rich fraction from the liquid phase obtained at step (e) by evaporation of the solvent present in the liquid phase.

**[0034]** As set forth in PCT Application No. PCT/CA02/00843, the active components of the enzyme-free krill and/or marine oil extract are:

**[0035]** Lipids

**[0036]** i) Omega-3:

**[0037]** i. Eicosapentanoic acid: 8 g/100 g

- [0039] iii. Linoleic acid: 0.10 g/100 g
- [0040] iv. Alpha-linolenic acid: >0.3 g/100 g
- [0041] The PCT application states that in the preferred embodiment, the Omega-3 fatty acids are found in more than 30 g/100 g
- [0042] ii) Omega-6:
- [0043] i. Linoleic acid: >0.9 g/100 g
- [0044] ii. Arachidonic acid: <0.45 g/100 g, preferably <0.6 g/100 g
- [0045] iii) Omega-9:
- [0046] i. Oleic acid: >5 g/100 g
- [0047] iv) palmitic acid: >10 g/100 g
- [0048] v) palmitoleic acid: 0.08 g/100 g
- [0049] vi) stearic acid: >0.5 g/100 g
- [0050] Phospholipids
- [0051] Phosphatidylcholine: >4.5 g/100 g
- [0052] Phosphatidylinositol: >107 mg/100 g
- [0053] Phosphatidylserine: >75 mg/100 g
- [0054] Phosphatidylethanolamine: >0.5 g/100 g
- [0055] Sphingomyelin: >107 mg/100 g
- [0056] Neutral lipids
- [0057] Cholesterol: <3 g/100 g
- [0058] Triglycerides: <55 g/100 g
- [0059] Monoglycerides: >0.5 g/100 g
- [0060] As set forth in the PCT application, the neutral lipids of the krill and/or marine extract also comprises:
- [0061] Diglycerides: >0.5 g/100 g
- [0062] Antioxydants
- [0063] A-tocopherol (vitamin E): >1.0 IU/100 g
- [0064] All-trans retinol (vitamin A): >1500 IU/100 g
- [0065] B-carotene: >3000 µg/100 ml
- [0066] Pigments
- [0067] Astaxanthin: >20 mg/100 g
- [0068] Canthaxanthin: >2 mg/100 g
- [0069] Metals
- [0070] Zinc: >0.1 mg/100 g
- [0071] Selenium: >0.1 mg/100 g
- [0072] The PCT application states in another embodiment, the krill and/or marine extract also comprises:
- [0073] Flavonoids: >0.5 mg/100 g
- [0074] Sodium: <500 mg/100 g
- [0075] Calcium: >0.1 mg/100 g
- [0076] Potassium: >50 mg/100 g
- [0077] Aluminum: <8.5 mg/100 g
- [0078] Protein: >4 g/100 g

[0080] The PCT application sets forth that after characterization of the krill and/or marine oil extract, it was determined that the extract contains less than 25 ppm of solvent residue from the extraction process.

[0081] The oil has the following stability indexes:

[0082] Peroxide value: <0.1 (mEq/kg)

[0083] Oil Stability index: <0.1 after 50 hours at 97.8° C.

[0084] Saponification index: 7-180

[0085] Iodine value: 60-130%

[0086] Pursuant to the present invention, the method and composition comprises administering krill extract and conjugated linoleic acid. If desired, the composition can include non-active ingredients and/or agents such as flavors, artificial sweeteners, excipients, etc. The product of the present invention is intended to provide a physiologically based means to aid in maintaining normal physiological homeostasis.

[0087] Conjugated linoleic acid refers to a group of dienoic derivatives of linoleic acid that occur naturally in milk and meat of ruminating animals. It can be synthesized in the laboratory and in commercial scale and is currently available commercially as a dietary supplement.

[0088] Conjugated linoleic acid is believed to be absorbed efficiently into the body in a manner similar to that of other fatty acids, e.g., linoleic acid. The safety of conjugated linoleic acid has been demonstrated in detailed toxicological assessments and through extensive use in humans, both as a naturally occurring substance and as a dietary supplement. It is believed that conjugated linoleic acid is safe for human consumption.

[0089] Pursuant to the present invention, the conjugated linoleic acid can be conjugated linoleic acid such as that set forth in U.S. Pat. No. 5,986,116 the disclosure of which is incorporated herein by reference.

[0090] In an embodiment, the conjugated linoleic acid is either a pure isomer of octadecadienoic acid, or a mixture of octadecadienoic acid isomers selected from the group consisting of: cis-8, cis-10; cis-8, trans-10; trans-8, cis-10; trans-8, trans-10; cis-9, cis-11; cis-9, trans-11; trans-9, cis-11; trans-9, trans-11; cis-10, cis-12; cis-9, trans-12; trans-9, cis-12; trans-10, trans-12; cis-11, cis-13; cis-11, trans-13; trans-11, cis-13; trans-11, trans-13 octadecadienoic acid; metabolites thereof, including but not limited to 18:3 cis-6, cis-9, trans-11; 18:3 cis-6, trans-10, cis-12; 18:3 cis-8, trans-12, cis-14; 20:3 cis-8, cis-11, trans-13; 20:4 cis-5, cis-8, cis-11, trans-13; 20:4 cis-5, cis-8, trans-12, cis-14; as well as precursors or derivatives thereof.

[0091] Pursuant to the present invention, the composition can be taken as a dietary supplement or a pharmacological product.

[0092] By way of example and not limitation, contemplative examples of indications/applications that can be treated benefit from the present invention are as follows:

#### INDICATIONS/APPLICATIONS

[0093] 1. Joint

- [0095] 3. Syndrome X
- [0096] 4. Body Composition
- [0097] 5. Cardiovascular
- [0098] 6. Bone Content (Health)
- [0099] 7. Immune enhancement
- [0100] 8. Diabetes
- [0101] 9. Anticarcinogen
- [0102] 10. Hormonal Fluctuations
- [0103] 11. Quality of Life-feel good
- [0104] 12. Stress Catabolic Response
- [0105] 13. Skin, hair and nails
- [0106] 14. Anti-inflammatory
- [0107] 15. Antioxidant
- [0108] 1. Joint

[0109] Anti-inflammatory reactions: Both conjugated linoleic acid and krill oil reduce the adverse effects that occur when the eicosanoid pathway through COX-1 and COX-2 enzymatic reactions leading to prostaglandin synthesis, such as PGE-2, PGE-1, leukotrienes and thromboxanes, are extended beyond normal, physiological needs from those signals initially produced by stress or injury. The continuation of eicosanoid production leads to chronic inflammation as indicated in osteoarthritis, joint pain, cartilage breakdown, increased adipose deposition, bone breakdown. In addition, involvement of those eicosanoids (proinflammatory) known to increase platelet aggregation and eventual plaque formation when endothelial injury has occurred—all involved with cardiovascular disease.

[0110] 2. PMS

[0111] The most probable cause of the physical symptoms of PMS seems to be the combined interaction of hormones and essential nutrients leading to an increased inflammatory response.

[0112] The emotional symptoms of PMS seem to be propagated by an exaggerated response of neurotransmitters to psychosocial stresses. Reducing arachidonic incorporation or its release from phospholipids (SN-2 position) decreases formation of prostaglandin E2 which when elevated continues inflammatory response. By increasing the ratio of Omega-3 fatty acids to Omega-6 (as in the case of krill oil): and by reducing the synthesis of arachidonic acid (by decreasing linoleic acid, its precursor) (both conjugated linoleic acid and krill oil accomplish this by two different mechanisms) will lead to reduced inflammatory responses.

[0113] 3. Syndrome X

[0114] Metabolic syndrome encompasses specific abnormalities such as elevated plasma TG's, low levels of HDL, increased blood pressure, fasting glucose and increased abdominal adipose tissue. Having three or more of these conditions constitutes Syndrome X. Conjugated linoleic acid decreases elevated glucose levels, decrease elevated TG levels and decrease high blood pressure. Krill oil lowers

these two oils should have a positive impact on those specific parameters involved with this syndrome.

[0115] 4. Body Composition

[0116] Conjugated linoleic acid reduces fat accumulation in humans by decreasing lipoprotein lipase (LPL) synthesis, hormone lipase synthesis, decrease adipose cell number by apoptosis at early cell development, and increase fat as a fuel source (beta-oxidation). In addition, conjugated linoleic acid increases muscle mass (LBM) even under catabolic conditions such as calorie reduction via weight loss. Krill increases energy level, feelings of wellness and energy levels, skin, hair and nails improvement, which combined with fat loss will give physical and emotional benefits in those using these oils.

[0117] 5. Cardiovascular Health

[0118] Cardiovascular health can be improved via the present invention due to the ability of the compositions to achieve the following:

[0119] LDL cholesterol lowering (conjugated linoleic acid, krill oil)

[0120] HDL elevation or maintenance (krill oil)

[0121] TG lowering (conjugated linoleic acid and krill oil)

[0122] Reducing elevated glucose (conjugated linoleic acid and krill oil)

[0123] Reducing abdominal adipose (conjugated linoleic acid)

[0124] Increasing elasticity of endothelial lining and reducing platelet aggregation precursors (anti-inflammatory response) (conjugated linoleic acid and krill oil)

[0125] 6. Bone Health

[0126] Reducing the chronic stress catabolic response and inflammatory response by intake of both conjugated linoleic acid and krill oil should dramatically favor an environment of bone synthesis and reduce bone degradation. The Omega-3 present in krill oil improves the ability of conjugated linoleic acid to increase bone mineral content possibly by conjugated linoleic acid's ability to decrease inflammatory prostaglandins. Krill oil also contains other compounds such as antioxidants and flavonoids that would likely improve the micro-environment surrounding bone cells and joints.

[0127] 7. Immune Enhancement

[0128] Conjugated linoleic acid increases antibody response to viral invasion. Combined with the antioxidants, Omega-3, vitamin and mineral profile and phospholipids present in krill oil, enhancing macrophage ability to respond to immune challenge.

[0129] 8. Diabetes

[0130] Conjugated linoleic acid decreases elevated glucose and increase insulin sensitivity. Krill oil decreases elevated glucose; combining these oils will strengthen their



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