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### ## ##	<u> </u>	ENCLOSED APPLICATION PARTS (check all that apply)											
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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, O.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C.



NATURAL MARINE SOURCE PHOSPHOLIPIDS COMPRISING FLAVONOIDS, POLYUNSATURATED FATTY ACIDS AND THEIR APPLICATIONS

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### Field of the Invention

The present invention is directed to nutraceutical, pharmaceutical or cosmetic compositions, particularly to phospholipid compositions derived from natural marine or aquatic sources.

#### Background of the Invention

Phospholipids are complex lipids containing phosphorus. The phosphatides, known as phospholipids, are usually divided into groups on the basis of compounds from which they are derived. In addition to two chains of fatty acids they contain phosphoric acid, glycerol and nitrogenous bases such as choline. The phospholipids considered most important are phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol. Their nature as amphophilic molecules provides them with unique physicochemical properties. Their function as the principle components of cell membranes makes phospholipids essential for all vital cell processes. They are widespread as secretory and structural components of the body and can mimic or enhance natural physiological processes.

Phospholipid production may be either synthetic or through extraction from natural tissues. The chief source of commercial natural phospholipids is soybean, egg yolk and cows (brain and liver). Since an individual phospholipid may contain a variety of fatty acid residues, it may be described as pure only with this limitation in mind. Naturally occurring essential polyunsaturated fatty acids, can contribute to the activation of cellular metabolism. The main fatty acid found in phospholipid products is linoleic acid, present in soybean at more than 65%. The longest chain polyunsaturated fatty acids found in commercial available phospholipids either as



preparations or individually are 20:4 among the eicosanoids, known as arachidonic acid and 22:6 known as decisahexanoic acid.

Arachidonic acid is a fatty acid that is found as part of the phospholipid membrane, generally as part of phosphatidylcholine and phosphatidylnositol. Adverse cellular stimuli will activate enzymes (phospholipase) that cleave arachidonic acid from the phospholipid backbone in the cell membrane. Arachidonic acid, which serves as the precursor for prostaglandins and prostacyclin (PGs, PGl<sub>2</sub>) and thromboxane (TXs) can then be metabolized by one of two major pathways: the cyclooxygenase (COX) pathway or the lipoxygenase pathway. The COX pathway products, PGG<sub>2</sub> and PGH<sub>2</sub> can then be acted upon by thromboxane synthase (in platelets) or prostacyclin synthase (in endothelium) to form TXs or PGl<sub>2</sub>, respectively. Arachidonic acid can also be acted upon by 5-lipoxygenase, primarily in leukocytes, to form laukotrienes (LTs). One or more of these metabolites can mediate all the signs and symptoms associated with arachidonic acid, i.e. inflammatory disease and pain.

Platelets, leukocytes, smooth muscle, and endothelium can produce vasoactive aubstances, products of arachidonic acid metabolism such as prostaglandins (PG9), prostacyclin (PGI<sub>2</sub>), leukotrienes (LTs), and thromboxanes (TXs). These substances can either act as vasodilators or as vasoconstrictors. PGI<sub>2</sub> is essential in vascular function since it inhibits platelet adhesion to the vascular endothelium and has significant vasodilatation qualities. Damaged endothelial cells cannot produce PGI<sub>2</sub>, making the vessel more susceptible to thrombosis and vasospasm. Thromboxanes and leukotrienes serve a vascular function during inflammation, generally producing vasoconstriction. Prostaglandins have a vascular role during inflammation, and also play a more subtle role in normal flow regulation, most notably as modulators of other control mechanisms. Prostaglandins have both vasoconstrictor and vasodilator activities. Leukotrienes and prostaglandins can also increase the endothelial membrane permeability thus promoting edema during inflammation. Arachidonic acid is naturally present in most phospholipid mixtures or emulsions available today.

Nervonic acid (C24:1) is also called selacholeic acid or tertracosenic acid. Nervonic acid is the symbol of white matter in glucoside, which is quantitatively contained in nerve tissue and white matter. The absence of nervonic acid may result in cerebral lesion, fatigue, hypodynamia, amentia, and senile dementia.



Nervonic acid, tertracosenic acid in another name, is monounsaturated, non-oxidable/decomposed and absorptive. It is called a rare tonic as it is rare existent in nature, may be micro-obtained by compounded in cerebral chondriosome. Therefore, the substance is far below the demand of human body. In foreign countries, nervonic acid mainly comes from shark brain and oil.

Flavonoids are polyphenolic compounds ubiquitous in nature. They are categorized into isoflavones, anthrocyanidins, flavans, flavonois, flavones, citrus flavonoids, hesperidin, chalcones, catechins, rutin, and flavanones. Essential flavonoids, such as quercetin in onions and genistein in soy are actually considered subcategories rather than independent categories. Over 4,000 flavonoids have been identified in fruits, vegetables and beverages (tea, coffee, beer, wine and fruit drinks). Even though they have a similar molecular structure between them, their functions are different from each other. Flavonoids have been shown to have antibacterial, anti-Inflammatory, antiallergic, antimutagenic, antiviral, antineoplastic, anti-thrombotic, and vascellatory activity. Quercetin has been proven to block the "sorbitol pathway" which is directly associated with diabetes as well as to prevent LDL-cholesterol exidative damage, which is essential for the maintenance of a healthy cardiovascular system.

Flavonoids are found in a wide range of fruits and vegetables. For example, Quercetin (a flavonoi in vegetables, fruit and onions), Xanthohumoi (a prenylated chalcone in beer), Isoxanthohumoi (a prenylated flavanone in beer), Genistein (an isoflavone in soy), Chalconaringenin (a non-prenylated chalcone in citrus fruits) and Naringenin (a non-prenylated flavanone in citrus fruits).

In plants flavonoids have very well defined functions. First, the accumulation of pigment in flower petals, seeds and leafs. Flowers, as pollinators, must attract pollen carriers. Second, they protect plants from UV damage, by absorbing UV at the epidermal layer. Third, they protect the plants against insects and pathogens.

The flavonoid biosynthetic pathway is one of the best understood plant secondary metabolism pathways (1992, Garats). The key enzymes are phenylalanine-ammonia lyase and chalcone synthase. Phenylalanine-ammonia lyase converts phenylalanine into cinnamic acid as it controls the total flow of carbons into phenolics which is shown to be the limiting step in this pathway (1974, Cressy). Another key enzyme of the flavonoid pathway is the chalcone synthase. It condenses three molecules of



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