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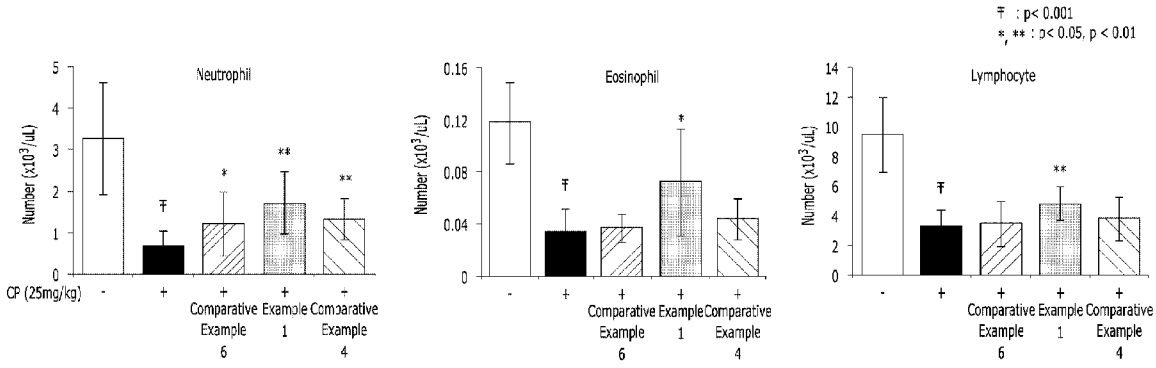
(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING OMEGA FATTY ACIDS, AND INFUSION PREPARATION COMPRISING THE SAME



(57) Abstract: The present invention relates to a pharmaceutical composition and an infusion preparation comprising omega-3 and omega-6 fatty acids, and the composition of the present invention comprises omega-3 and omega-6 fatty acids in a certain weight ratio to enhance an anti-inflammatory and immune-boosting effect, and thus exhibits an excellent effect on inflammatory diseases and immuno-compromised diseases, caused by nutritional deficiency. An infusion preparation of the present invention not only exhibits an excellent clinical validity, but also shows an effect of remarkably improving stability of the preparation.

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Description

Title of Invention: PHARMACEUTICAL COMPOSITION COMPRISING OMEGA FATTY ACIDS, AND INFUSION PREPARATION COMPRISING THE SAME

Technical Field

[1] The present invention relates to a pharmaceutical composition comprising omega fatty acids for preventing or treating inflammatory diseases or immuno-compromised diseases and, more particularly, to a pharmaceutical composition and an infusion preparation comprising the same, in which the pharmaceutical composition not only supplies lipid nutrients, but also has an excellent anti-inflammatory and immune-boosting effect, and thus has an excellent effect of preventing or treating inflammatory diseases or a decline in immune functions, caused by nutritional deficiency

Background Art

[2] An infusion supplements severely dehydrated persons with physiologically essential electrolytes or moisture, and an infusion preparation is an artificial solution which is intravenously administered to parenterally supply moisture and nutrients. In particular, patients who have a problem with digestive organs or lose their consciousness easily fall into a nutritional deficiency state, and thus the infusion serves as an important means to supply such patients with essential nutrients.

[3] The nutritional deficiency state refers to a state in which at least one essential nutrient or calories are deficient. If such nutritional deficiency state continues, there occur inflammatory diseases or diseases caused by a decline in immune functions. To suppress the occurrence of such diseases, drugs such as anti-inflammatory agents and immune-enhancing agents are also contained together in the infusion preparation for supplying nutrients.

[4] As the nutrients contained in the infusion preparation, there are carbohydrates, proteins, fats and the like, out of which a small amount of fats supply a large amount of energy (1 g=9 kcal). The infusion preparation, which is used in total parenteral nutrition (TPN) to supply nutrients entirely through the veins, contains an intravenous lipid emulsion in order to prevent complications caused by an excessive administration of carbohydrates and to supply essential fatty acids which are impossible to be synthesized in the human body.

[5] The first lipid emulsion is soybean oil, which has been commercially developed and used in a number of products so far. However, in case of using some soybean oil as the lipid emulsion, it has been reported that there occur side effects associated with immune dysfunctions and hepatic dysfunctions. Linoleic acid contained in soybean oil

is a precursor of arachidonic acid. If there is an increase in the concentration of linoleic acid in blood, eicosanoid is produced therefrom to affect immune functions, inflammatory responses, vessel functions, platelet aggregation, etc. in the human body, and thus causes an increased risk of developing complications.

[6] To overcome such risk, the recent lipid emulsion tends to be developed in a mixed form of oils derived from various materials such as olive oil, fish oil, etc. The lipid emulsion in the recent spotlight is fish oil collected from aquatic animals. As fish oil, there exist shark liver oil, pollack liver oil, whale oil, cuttlefish oil, anchovy oil, etc., which contain a large amount of omega-3 fatty acids in a form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

[7] When selecting the intravenous lipid emulsion for patients in an intensive care unit (ICU), an absolute amount of omega fatty acids and certain polyunsaturated fatty acids (PUFA) is important. According to the guidelines of the European Society for Parenteral and Enteral Nutrition (ESPEN), it is recommended that the amount of omega-3 fatty acids supplied to the ICU patients should be 0.1-0.2 g/kg/d.

[8] Against this backdrop, the present inventors have tried to develop a pharmaceutical composition and an infusion preparation comprising omega fatty acids, which may alleviate various kinds of inflammatory diseases and immune diseases resulting from nutritional deficiency and sufficiently supply essential lipid nutrients at the same time.

[9] [Prior Art Reference]

[10] [Patent Document]

[11] (Patent Document 1) Patent Document 1: Korean Patent Publication No. 2011-0107615

[12]

Disclosure of Invention

Technical Problem

[13] An objective of the present invention is to provide a pharmaceutical composition comprising omega fatty acids for preventing or treating inflammatory diseases or immuno-compromised diseases.

[14] Another objective of the present invention is to provide an infusion preparation comprising omega fatty acids, which may not only supply lipid nutrients to subjects deficient in nutrition, but also alleviate inflammatory diseases or immuno-compromised diseases, caused by nutritional deficiency.

[15]

Solution to Problem

[16] This is described in detail as follows. Meanwhile, each description and embodiment disclosed in the present invention may be also applied to other descriptions and em-

bodiments thereof, respectively. In other words, all the combinations of various elements disclosed in the present invention fall within the scope of the present invention. Also, it cannot be seen that the scope of the present invention is limited to the specific description described below.

[17] In one aspect of the present invention, there is provided a pharmaceutical composition comprising omega-3 and omega-6 fatty acids for preventing or treating inflammatory diseases and immuno-compromised diseases.

[18] The composition of the present invention may exhibit a remarkable effect on inflammatory diseases or immuno-compromised diseases by comprising omega-3 and omega-6 fatty acids in an optimal ratio out of omega fatty acids. Particularly, the composition may contain omega-3 and omega-6 in the weight ratio of 1 : 0.75 to 1 : 1.25, preferably in the weight ratio of 1 : 1.

[19] A content of omega-3 and omega-6 fatty acids contained in the composition of the present invention may be 47 to 53 mg/mL, in which particularly omega-3 may be contained in the amount of 23 to 27 mg/mL and omega-6 fatty acids may be contained in the amount of 20 to 30 mg/mL. Such content may be appropriately adjusted in the range that maintains the weight ratio of omega-3 and omega-6 fatty acids.

[20] Omega-3 is a range of fatty acids having a double bond at a 3 rd carbon counted from a methyl group terminal of fatty acids, in which there are linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. Omega-3 fatty acids are most commonly found in canola oil, flaxseed oil, perilla seed oil or external blue colored fish, and omega-3 lowers a level of neutral fats in blood by suppressing neutral fats and VLDL synthesis in the liver. Also, omega-3 is known to suppress the synthesis of neutral fats by changing a degree of expression of nuclear receptors which synthesize neutral fats.

[21] In the present invention, omega-3 may be natural or synthetic omega-3 fatty acids, pharmaceutically acceptable salts thereof and mixtures thereof and, for example, may be alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), but is not limited thereto.

[22] A daily amount of omega-3 fatty acids supplied by the composition of the present invention may be 0.1 to 0.2 g/kg/day, particularly 0.125 g/kg or more.

[23] In the present invention, omega-6 is a range of fatty acids having a double bond at a 6 th carbon counted from a methyl group terminal of fatty acids, in which a large amount thereof is contained in eggs, dairy products, walnuts, nuts, seeds, soybean oil, safflower oil and corn oil. Omega-6 is an important component in producing skin and hair in vivo and maintaining cholesterol metabolism and reproductive functions.

[24] The omega-6 of the present invention may be natural or synthetic omega-6 fatty acids, pharmaceutically acceptable salts thereof and mixtures thereof and, for example, may be linoleic acid, γ linolenic acid, calendic acid, eicosadienoic acid, dihomo-

gamma-linolenic acid, arachidonic acid, docosadienoic acid, docosatetraenoic acid, docosapentaenoic acid, tetracosatetraenoic acid or tetracosapentaenoic acid, but is not limited thereto.

[25] Particularly, the present invention provides a pharmaceutical composition comprising omega-3 and omega-6 fatty acids for preventing or treating inflammatory diseases.

[26] The inflammatory diseases may be caused by nutritional deficiency, and may be characterized by pain, reddening phenomenon, swelling, fever and an ultimate loss of functions in infected regions. Inflammatory diseases may be at least one selected from the group consisting of gastritis, enteritis, nephritis, hepatitis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, irritable bowel syndrome, inflammatory pain, migraine, headache, backache, fibromyalgia, fascia disease, viral infection, bacterial infection, mycotic infection, burn, injury caused by surgical operation or dental surgery, hyper-PGE syndrome, atherosclerosis, gout, Hodgkin's disease, pancreatitis, conjunctivitis, iritis, scleritis, uveitis, and acute and chronic inflammatory diseases.

[27] According to one experimental example of the present invention, it was identified that a composition with an adjusted ratio of omega-3 and omega-6 fatty acids may be valuably utilized in preventing or treating inflammatory diseases by remarkably suppressing IL-1β, i.e, an index of inflammatory diseases.

[28] Particularly, the present invention provides a pharmaceutical composition comprising omega-3 and omega-6 fatty acids for preventing or treating immuno-compromised diseases.

[29] In the present invention, immuno-compromised diseases may arise from a decline in immune functions caused by nutritional deficiency, and may be, for example, at least one selected from the group consisting of asthma, seasonal or perennial rhinitis, allergic rhinitis, conjunctivitis, atopic dermatitis, hives, hemolysis of erythrocytes, acute glomerulonephritis, flu, chronic fatigue and cancer.

[30] Also, the present invention provides a composition comprising omega-3 and omega-6 fatty acids for boosting immunity.

[31] According to one experimental example of the present invention, it was identified that the composition with an adjusted ratio of omega-3 and omega-6 fatty acids may be valuably utilized for immuno-compromised diseases by significantly reducing a weight loss of the spleen, i.e., a key immune system and recovering blood cell indexes of immune functions.

[32] The pharmaceutical composition of the present invention may contain omega-3 and omega-6 fatty acids by 22 to 30% with regard to the total weight of the composition.

[33] The pharmaceutical composition of the present invention may further contain at least one type of pharmaceutically acceptable carriers for administration thereof, in addition

to the omega-3 and omega-6. As the pharmaceutically acceptable carriers, the followings may be used: saline solution, sterilized water, Ringer's solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, and a combination of at least one component thereof, and other conventional additives such as antioxidants, buffer solutions, bacteriostatic agents, etc., may be added thereto, if needed.

[34] The pharmaceutical composition of the present invention may be parenterally administered (for example, applied intravenously, hypodermically, intraperitoneally or locally) according to an intended method, particularly intravenously administered, and more particularly administered into central veins or peripheral veins. A dosage may be variously adjusted in a range thereof depending on a patient's weight, age, gender, health condition, diet, an administration time, an administration method, an excretion rate, a severity of a disease and the like.

[35] In case of formulating the pharmaceutical composition of the present invention into an injectable solution, the pharmaceutical composition of the present invention may be prepared into solution or suspension in such a way that the inventive composition is mixed in water along with stabilizers or buffers, but a formulation method is not limited thereto. As one example of an injectable dosage form using the pharmaceutical composition of the present invention, the inventive composition may be formulated into a preparation for a unit dosage form of bottle.

[36] In the pharmaceutical composition of the present invention, a dosage thereof may be calculated based on a target subject's weight by age. As one preferable example, an administered dose of the pharmaceutical composition for adults may amount to 5 to 10 mL/kg/day of infusion, which corresponds to 1 to 2 g/kg/day of daily fat intake.

[37] Also, a pharmaceutically effective amount and an effective dosage of the pharmaceutical composition of the present invention may vary depending on a method for formulating the pharmaceutical composition, an administration mode, an administration time and/or administration route, etc., and may be diversified according to various factors including a type and degree of reaction to be achieved by means of administration of the pharmaceutical composition, a type of an individual for administration, such individual's age, weight, general health condition, disease symptom or severity, gender, diet and excretion, components of other drug compositions to be used for the corresponding individual at the same time or different times, etc., as well as other similar factors well known in a pharmaceutical field, and those skilled in the art may determine and prescribe the dosage within a range of intended treatment. As one example, administration of the pharmaceutical composition of the present invention may be performed once a day, but is not limited thereto. The pharmaceutical composition of the present invention may be administered as an individual therapeutic agent or in combination with other therapeutic agents, and may be administered se-

quentially or simultaneously with a conventional therapeutic agent. Considering all the factors above, the pharmaceutical composition of the present invention may be administered in such an amount that a maximum effect may be achieved by a minimum amount without a side effect, and such amount may be easily determined by those skilled in the art to which the present invention pertains.

[38] The pharmaceutical composition of the present invention may contain at least one oil selected from the group consisting of fish oil, soybean oil, olive oil, cottonseed oil, safflower oil, sesame oil, coconut oil and corn oil. Particularly, the omega-3 and omega-6 fatty acids contained in the composition of the present invention may be derived from at least one oil selected from the group consisting of fish oil, soybean oil, olive oil, cottonseed oil, safflower oil, sesame oil, coconut oil and corn oil.

[39] The fish oil may be obtained by mixing marine oils, for example, fish oils abundant in fats such as Engraulidae, Carangidae, Clupeidae, Osmeridae, Salmonidae and Scombridae as a main source of supplying omega-3 fatty acids.

[40] The oil may further contain a synthetic oil such as medium chain triglyceride.

[41] Particularly, the pharmaceutical composition may contain 3.0 g to 5.0 g of soybean oil, 3.5 g to 4.5 g of medium chain triglyceride, 5.0 g to 6.0 g of olive oil, and 6.0 g to 7.0 g of fish oil based on the total 100 ml of the composition, and more particularly may contain 4 g of soybean oil, 4 g of medium chain triglyceride, 5.5 g of olive oil, and 6.5 g of fish oil based on the total 100 ml of the composition, which may be appropriately adjusted in the range that maintains the weight ratio of omega-3 and omega-6 fatty acids.

[42] The pharmaceutical composition of the present invention may further contain at least one additive selected from the group consisting of emulsifiers, osmo-regulators, pH regulators and antioxidants.

[43] The emulsifiers are a material which forms stable oil particles and maintains stability of the particles formed, and may be at least one selected from the group consisting of egg yolk lecithin, hydrogenated egg yolk lecithin, soybean lecithin, hydrogenated soybean lecithin, sodium oleate and the like. Preferably, the emulsifiers may be egg yolk lecithin and sodium oleate, which may be 0.6-1.8% (w/v) egg yolk lecithin and 0.01-0.05% (w/v) sodium oleate based on 100 ml of the composition for intravenous administration, but are not limited thereto.

[44] The osmo-regulators may be at least one selected from the group consisting of sodium chloride, glucose, D-mannitol, sorbitol, trehalose and glycerol, and preferably may be 1.7-2.5% (w/v) of glycerol based on 100 ml of the composition for intravenous administration, but are not limited thereto.

[45] The pH regulators may be at least one selected from the group consisting of sodium hydroxide, hydrochloric acid, phosphoric acid, phosphate and citric acid, but are not

limited thereto. The antioxidants may be at least one selected from the group consisting of ascorbic acid, dibutyl hydroxy anisole, dibutyl hydroxy toluene, sorbitol and tocopherol, but are not limited thereto.

[46] The antioxidants may be at least one selected from the group consisting of ascorbic acid and salts thereof, dibutyl hydroxy anisole, dibutyl hydroxy toluene, sorbitol and tocopherol, but are not limited thereto.

[47] In another aspect of the present invention to achieve the objectives above, there is provided an infusion preparation comprising omega-3 and omega-6 fatty acids.

[48] The infusion preparation of the present invention may contain the composition having omega-3 and omega-6 fatty acids.

[49] The infusion preparation of the present invention may contain omega-3 and omega-6 fatty acids in a certain ratio, and thus may not only exhibit its clinical validity such as anti-inflammation, alleviation of decline in immunity and the like, but also show an effect of remarkably improving stability of the preparation such as alleviation of lipid peroxidation caused by polyunsaturated fatty acids, etc. Particularly, the infusion preparation may contain omega-3 and omega-6 in the weight ratio of 1 : 0.75 to 1 : 1.25, particularly in the weight ratio of 1 : 1.

[50] In the infusion preparation, omega-3 and omega-6 fatty acids may be contained in a single chamber, and the chamber may further contain amino acids, electrolytes and sugars.

[51] Also, the infusion preparation may be received in a plurality of chambers, which are distanced from each other by divisions in such a connectable way that the preparation may be mixed when being used. Omega-3 and omega-6 fatty acids or a composition comprising the same may be received in one chamber thereof. Particularly, the infusion preparation of the present invention may be received in a chamber divided into a first chamber, a second chamber and a third chamber. The first chamber may receive a first chamber fluid for supplying amino acids and electrolytes; the second chamber may receive a second chamber fluid for supplying sugars; and the third chamber may receive a third chamber fluid for supplying fats.

[52] The electrolytes may refer to an electrolyte in a sense that the electrolyte is used in an infusion field, particularly an electrolyte contained in body fluid (for example, blood and intracellular fluid), and more particularly calcium, phosphorus, sodium, magnesium, potassium, zinc, chlorine, etc., but are not limited thereto.

[53] The calcium may be calcium gluconate, calcium chloride, calcium glycerophosphate or calcium pantothenate; the salts may be inorganic salts including calcium phosphate and magnesium phosphate or organic salts including sodium glycerophosphate and potassium glycerophosphate; the sodium may be sodium chloride, sodium lactate, sodium acetate, sodium sulfate, sodium glycerophosphate, sodium citrate or hydrate

forms thereof; the magnesium may be magnesium sulfate, magnesium chloride or magnesium acetate; the potassium may be potassium chloride, potassium acetate, potassium glycerophosphate, potassium sulfate, potassium lactate or hydrate forms thereof; the zinc may be zinc sulfate, zinc chloride or hydrate forms thereof; the chlorine may be sodium chloride, potassium chloride, magnesium chloride or calcium chloride, but are not limited thereto.

[54] Particularly, the electrolytes may be at least one selected from the group consisting of calcium chloride dihydrate, sodium glycerophosphate, sodium acetate hydrate, magnesium sulfate heptahydrate, potassium chloride and zinc sulfate heptahydrate. The electrolytes may be 72-76 mg of calcium chloride dihydrate, 400-440 mg of sodium glycerophosphate anhydrous, 555-570 mg of sodium acetate hydrate, 245-250 mg of magnesium sulfate heptahydrate, 445-451 mg of potassium chloride and 2.0-2.6 mg of zinc sulfate heptahydrate, and preferably 74 mg of calcium chloride dihydrate, 418 mg of sodium glycerophosphate anhydrous, 562 mg of sodium acetate hydrate, 247 mg of magnesium sulfate heptahydrate, 448 mg of potassium chloride, and 2.3 mg of zinc sulfate heptahydrate based on 100 mL of the first chamber fluid, but are not limited thereto.

[55] The amino acids include free amino acid and amino acid salt forms. The free amino acid forms may be at least one selected from the group consisting of L-alanine, L-arginine, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-serine, taurine, L-threonine, L-tryptophan, L-tyrosine, L-valine and L-glutamic acid. The amino acid salt forms may be at least one selected from the group consisting of inorganic acid salts such as L-arginine hydrochloride, L-histidine hydrochloride, L-lysine hydrochloride, etc.; L-lysine acetate; and L-lysine malate.

[56] In a viewpoint of supplying nutrition, the infusion preparation may contain at least two amino acids, and may validly contain essential amino acids, i.e., L-arginine, L-histidine, L-isoleucine, L-leucine, L-lysine, L-methionine, L-phenylalanine, taurine, L-threonine, L-tryptophan and L-valine.

[57] Particularly, such preparation may contain 2.05-2.10 g of L-alanine, 1.10-1.20 g of L-arginine, 0.98-1.08 g of glycine, 0.45-0.50 g of L-histidine, 0.50-0.70 g of L-isoleucine, 0.68-0.78 g of L-leucine, 0.715-0.735 g of L-lysine hydrochloride, 0.30-0.50 g of L-methionine, 0.50-0.62 g of L-phenylalanine, 0.63-0.73 g of L-proline, 0.40-0.60 g of L-serine, 0.05-0.15 g of taurine, 0.37-0.47 g of L-threonine, 0.13-0.23 g of L-tryptophan, 0.03-0.05 g of L-tyrosine and 0.53-0.63 g of L-valine based on 100 mL of the first chamber fluid, and preferably 2.07 g of L-alanine, 1.15 g of L-arginine, 1.03 g of glycine, 0.48 g of L-histidine, 0.60 g of L-isoleucine, 0.73 g of L-leucine, 0.725 g of L-lysine hydrochloride, 0.40 g of L-methionine, 0.56 g of L-phenylalanine,

0.68 g of L-proline, 0.50 g of L-serine, 0.10 g of taurine, 0.42 g of L-threonine, 0.18 g of L-tryptophan, 0.04 g of L-tyrosine and 0.58 g of L-valine based on 100 mL of the first chamber fluid.

[58] The first chamber fluid may further contain pH regulators. The pH regulators are contained therein and thus may maintain an optimal pH stable enough not to destroy the amino acids contained therein, when the first chamber fluid is mixed with the second chamber fluid and the third chamber fluid. The pH regulators may be selected from within a conventional category. Preferably, acetic anhydride may be used.

[59] The infusion preparation may contain sugars, which may be reducing sugars such as glucose, fructose, maltose, etc., and non-reducing sugars such as xylitol, sorbitol, etc., and preferably may be glucose which is most easily absorbed into the body.

[60] The second chamber fluid may further contain pH regulators, and the pH regulators may be hydrochloric acid, phosphoric acid, acetic acid, citric acid or sulfuric acid.

[61] The infusion preparation of the present invention may be administered into central veins or peripheral veins. If the infusion preparation is administered into the central veins, the second chamber fluid may contain 46.1-46.3 g of glucose monohydrate, preferably 46.2 g thereof based on 100 ml of the second chamber fluid. If the infusion preparation is administered into the peripheral veins, the second chamber fluid may contain 14.2-14.4 g of glucose monohydrate, preferably 14.3 g thereof based on 100 ml of the second chamber fluid.

[62] The third chamber fluid contains oil, emulsifiers, osmo-regulators, pH regulators and antioxidants, and is the inventive composition for intravenous administration.

[63] In the infusion preparation of the present invention, the third chamber fluid, i.e., the composition for intravenous administration may be used alone, or may be used in such a way that the first chamber fluid and the second chamber fluid are mixed together depending on the state of subjects in need for infusion administration.

[64] If the inventive composition for intravenous administration is mixed with the first chamber fluid and the second chamber fluid, a mixing ratio and a total dose thereof may be appropriately adjusted according to each patient's nutritional state and calorie requirement. If the infusion preparation of the present invention is administered into the central veins, a volume ratio of the first chamber fluid, the second chamber fluid and the third chamber fluid may be 2.66 : 1.59 : 1.00. If the inventive infusion preparation is administered into the peripheral veins, the volume ratio of the first chamber fluid, the second chamber fluid and the third chamber fluid may be 2.24 : 3.86 : 1.00. However, the volume ratio of the first chamber fluid, the second chamber fluid and the third chamber fluid is not limited thereto, and may well be variously divided according to criteria for nutritional calories.

[65] The infusion preparation of the present invention may supply calories, amino acids,

essential fatty acids and omega-3 fatty acids to patients who need nutrition supply through the jugular veins because an oral or gastrointestinal nutrition supply is impossible, insufficient or limited. Also, the infusion preparation of the present invention may be used to manage the nutrition of trauma patients who undergo major surgical operations such as cancer, AIDS, ischemic bowel disease, malabsorption, bronchial block/removal, intestinal obstruction, serious hepatic dysfunction, serious acute pancreatitis, etc.

[66] The present invention provides a method for preventing or treating inflammatory diseases or immuno-compromised diseases, comprising a step of administering the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 into subjects in need for treatment.

[67] As used herein, the term "subject in need for treatment" means mammals including humans, and the term "administration" means providing a predetermined material to subjects by means of any appropriate method. The term "therapeutically effective amount" means an amount of an active component or a pharmaceutical composition which induces animals or humans to show the biological or medical responses considered by investigators, veterinarians, doctors or clinicians, and such amount includes an amount thereof for inducing a symptom relief of diseases or disorders to be treated. It is apparent to those skilled in the art that the therapeutically effective dosage and the number of administration for effective components of the present invention may vary depending on a desired effect.

[68] The pharmaceutical composition of the present invention may be administered once a day or at least twice a day at a certain interval of time.

[69] The present invention provides a use of the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 for preventing or treating inflammatory diseases or immuno-compromised diseases.

[70] The present invention provides a use of the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 for preparing a pharmaceutical preparation for preventing or treating inflammatory diseases or immuno-compromised diseases.

[71] Matters mentioned in the pharmaceutical composition, treatment method and use of the present invention are applied the same, if not contradictory to each other.

Advantageous Effects of Invention

[72] A pharmaceutical composition of the present invention may contain omega-3 and omega-6 fatty acids in a certain weight ratio, and thus may enhance an anti-inflammatory and immune-boosting effect, and thus may prevent or treat inflammatory diseases and immuno-compromised diseases, caused by nutritional deficiency. Also, an

infusion preparation of the present invention may not only exhibit an excellent clinical validity, but also show an effect of remarkably improving stability of the preparation.

[73]

Brief Description of Drawings

[74] Fig. 1 is a graph of showing an anti-inflammatory effect according to a ratio of omega fatty acids.

[75] Fig. 2 is a graph of showing an inhibitory effect on decline in immunity according to a ratio of omega fatty acids.

[76] Fig. 3 is a graph of showing a blood cell index according to a ratio of omega fatty acids.

[77] Fig. 4 is a graph of showing a serum biochemical index according to a ratio of omega fatty acids.

[78]

Mode for the Invention

[79] Hereinafter, the configuration and effects of the present invention will be described in more detail through Examples. The following Examples are provided only for the purpose of illustrating the present invention, and thus the scope of the present invention is not limited thereto.

[80]

[81] **Preparation Example 1: Preparation of pharmaceutical composition**

[82] According to the present invention, the compositions of Example and Comparative Examples were prepared by means of the following method.

[83] Two tanks for preparation were made ready in such a way that one was used as a tank for preparing a water phase, and the other was used as a tank for preparing an oil phase.

[84] Water for injection and osmo-regulators, i.e., glycerol were inserted into the tank for compounding the water phase and then mixed together, after which purified soybean oil, purified olive oil, medium chain triglyceride, purified fish oil, purified egg yolk lecithin, sodium oleate and tocopherol were inserted into the tank for compounding the oil phase and then homogeneously mixed with a homo mixer (e.g., IKA homogenizer).

[85] A detailed composition of Example and Comparative Examples prepared according to the preparation method above was shown in the following table 1.

[86]

[Table 1]

Component (g/100ml)	Example 1	Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4	Comparative Example 5	Comparative Example 6
Purified soybean oil	4.0	9.7	6.8	5.6	2.0	6.0	6.0
Medium chain triglyceride	4.0	4.0	4.0	4.0	4.0	6.0	5.0
Purified olive oil	5.5	4.1	4.8	5.1	5.7	5.0	5.0
Purified fish oil	6.5	2.2	4.4	5.3	8.3	3.0	4.0
Purified egg yolk lecithin	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Sodium oleate	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Glycerol	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tocopherol	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194	0.0194
Sodium hydroxide	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount
Water for injection	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount	Suitable amount

[87] Each of resulting mixtures was stirred in one tank to compound a pre-emulsion, and then emulsified with a high pressure homogenizer (APV-2000, Demark) under the condition of pressure at 600-1,400 bar, after which pH was adjusted with 1N sodium hydroxide.

[88] Each of omega-3, omega-6 and omega-9 fatty acids contained in the medium chain triglyceride, purified soybean oil, purified olive oil and purified fish oil was practically measured according to the standards of the European Pharmacopoeia. An amount of medium chain triglyceride, purified soybean oil, purified olive oil and purified fish oil was adjusted according to a content of the omega-3, omega-6 and omega-9 fatty acids.

[89] The ratio and content of omega fatty acids in Example 1 and Comparative Examples 1 to 6 prepared above were as shown in the following table 2.

[90] [Table 2]

	Example 1	Comparative Example 1	Comparative Example 2	Comparative Example 3	Comparative Example 4	Comparative Example 5	Comparative Example 6
Ratio of omega-6/-3	**1.0 / 1.0**	**4.0 / 1.0**	**2.0 / 1.0**	**1.5 / 1.0**	**0.5/ 1.0**	**2.5 / 1.0**	**2.0 / 1.0**
Omega-3 fatty acids (mg/mL)	25.0	13.4	19.4	21.8	30.1	14.0	17.5
Omega-6 fatty acids (mg/mL)	25.1	53.3	39.0	33.0	15.1	34.8	34.9
Omega-9 fatty acids (mg/mL)	58.8	58.6	58.6	58.7	56.9	56.9	57.8

[91] **Preparation Example 2: Preparation of infusion preparation**

[92] To prepare an infusion preparation according to the present invention, a first chamber

fluid and a second chamber fluid were respectively prepared and then mixed in such a way that the composition of Example 1 obtained in Preparation Example 1 above was used as a third chamber fluid.

[93] In the first chamber fluid, the followings were inserted into water for injection: L-alanine, L-arginine, glycine, L-histidine, L-isoleucine, L-leucine, L-lysine hydrochloride, L-methionine, L-phenylalanine, L-proline, L-serine, taurine, L-threonine, L-tryptophan, L-tyrosine, L-valine, calcium chloride dihydrate, sodium glycerophosphate anhydrous, sodium acetate hydrate, magnesium sulfate heptahydrate, potassium chloride and zinc sulfate heptahydrate, and then completely dissolved, after which pH was adjusted with acetic acid.

[94] In the second chamber fluid, glucose monohydrate was inserted and completely dissolved, after which pH was adjusted with hydrochloric acid.

[95] The first chamber fluid, the second chamber fluid and the third chamber fluid obtained above were filled into a plastic bag for infusion, which was divided into three chambers. After that, an empty space above the filler fluid thereof was sealed through nitrogen-substitution, then charged into an outer packaging with multilayer film along with a deoxidant, and then sealed. After that, the resulting product was steam-sterilized under high pressure according to a conventional known method.

[96] A composition of Examples 2 and 3 prepared according to the preparation method above was as shown in the following table 3.

[97]

[Table 3]

Classification	Component name	Example 2	Example 3
		Content (g/100 mL)	
First chamber fluid (amino acids and electrolytes)	L-alanine	2.07	2.07
	L-arginine	1.15	1.15
	Glycine	1.03	1.03
	L-histidine	0.48	0.48
	L-isoleucine	0.60	0.60
	L-leucine	0.73	0.73
	L-lysine hydrochloride	0.725	0.725
	L-methionine	0.40	0.40
	L-phenylalanine	0.56	0.56
	L-proline	0.68	0.68
	L-serine	0.50	0.50
	Taurine	0.10	0.10
	L-threonine	0.42	0.42
	L-tryptophan	0.18	0.18
	L-tyrosine	0.04	0.04
	L-valine	0.58	0.58
	Calcium chloride dihydrate	0.074	0.074
	Sodium glycerophosphate	0.418	0.418
	Magnesium sulfate heptahydrate	0.247	0.247
	Potassium chloride	0.448	0.448
	Sodium acetate hydrate	0.562	0.562
	Zinc sulfate heptahydrate	0.0023	0.0023
	Acetic acid (100)	Suitable amount	Suitable amount
	Water for injection	Suitable amount	Suitable amount
Second chamber fluid	Glucose monohydrate	46.20	14.30
	Hydrochloric acid	Suitable amount	Suitable amount
	Water for injection	Suitable amount	Suitable amount

[98] **Experimental Example 1: Evaluation of anti-inflammatory effect according to composition ratio of omega fatty acids**

[99] An inhibitory capacity of inflammatory cytokines was evaluated to assess an anti-inflammatory effect of the compositions of Example and Comparative Examples according to the present invention.

[100] Particularly, mononuclear cells were isolated from human peripheral blood mononuclear cells (PBMC), after which 2 x 10^5 mononuclear cells were inserted into each well, and then incubated. In 16 hours later, each well was treated with 20 μl of the compositions of Example and Comparative Examples, and then treated with lipopolysaccharide (LPS) in 30 minutes later such that a final concentration thereof may reach 1 μg/ml. In 24 hours later, a level of IL-1β expression was measured with an enzyme immunoassay method (ELISA), such that the results thereof were shown in Fig. 1.

[101] As seen in Fig. 1, it was identified that the level of IL-1β expression is suppressed as a ratio of omega-3 fatty acids is increased.

[102]

[103] **Experimental Example 2: Evaluation of immune-boosting efficacy according to composition ratio of omega fatty acids**

[104] **Experimental Example 2-1: Measurement of spleen weights**

[105] A change in spleen weights and a change in immune cells, involved in immunity of animal models, were evaluated to assess an immune-boosting effect of the compositions of Example and Comparative Examples according to the present invention.

[106] Particularly, rats (seven-week-old male SD rat, Hallym Experimental Animals, Inc.) were used as an animal model, and then infused with cyclophosphamide (CP) at 25 mg/kg to induce an acute decline in immunity, after which each of the rats was intravenously dosed with 0.4 g of each composition of Example 1 and Comparative Examples 4 and 6 in 30 minutes, 8 hours and 24 hours after CP administration. After that, a key immune system, i.e., spleens were collected from the animal models to identify a change in their weights, such that the results thereof were shown in Fig. 2.

[107] As seen in Fig. 2, it was identified that a control group treated with cyclophosphamide shows a decrease in spleen weights, while a group treated with the composition of Example 1 of the present invention shows an increase in spleen weights to significantly suppress a decline in immunity, thus being excellent compared to Comparative Examples 4 and 6.

[108] **Experimental Example 2-2: Measurement of blood cell index**

[109] A blood cell index was measured in animal models of Example 2-1 in order to evaluate an immune-boosting effect of the compositions of Example and Comparative Examples according to the present invention.

[110] Particularly, rats were dosed with cyclophosphamide (CP) at 25 mg/kg to induce an acute decline in immunity, and then dosed with the compositions of Example 1 and Comparative Examples 4 and 6. In 48 hours after administration, blood was collected from a heart of each rat, and then treated with heparin to measure the number of immune function-associated cells, i.e., neutrophils, eosinophils and lymphocytes with an automatic hematology analyzer, such that the results thereof were shown in Fig. 3.

[111] As seen in Fig. 3, it was identified that a group treated with the composition of Example 1 of the present invention remarkably enhances neutrophils, eosinophils and lymphocytes, which have been decreased due to the decline in immunity, thus being excellent compared to Comparative Examples 4 and 6 with a different ratio of omega fatty acids.

[112]

[113] **Experimental Example 3: Identification of change in serum biochemical index according to composition ratio of omega fatty acids**

[114] According to a ratio of omega fatty acids, an effect on serum biochemical index, i.e., lactic acid dehydrogenase (LDH) and creatinine (CREA) was evaluated.

[115] Particularly, in 48 hours after CP administration, blood was collected from a heart of each rat to isolate serum therefrom, after which each serum index was measured with a serum biochemical analyzer, such that the results thereof were shown in Fig. 4.

[116] As seen in Fig. 4, it was identified that a group treated with the composition of Example 1 of the present invention remarkably suppresses LDH and CREA.

[117]

[118] **Experimental Example 4: Toxicity test on single intravenous administration**

[119] To evaluate the safety of the composition for intravenous administration according to the present invention, the animal models were intravenously injected therewith to assess its safety.

[120] The composition of Example 1 for intravenous administration was intravenously administered once into beagle dogs (male, 28-months old, about 11 kg). As for a clinical administered dose (based on adult 60 kg), the composition was administered at a triple dose for up to eight hours. After administration, there was no dead animal and no change was observed in weights, presence of clinical symptoms and blood composition.

[121]

[122] **Experimental Example 5: Stability test 1 on lipid infusion preparation**

[123] A one-month stability evaluation on Example 1 and Comparative Examples 2 to 6 above was performed under accelerated conditions (40°C/RH 75%). A particle size of lipid emulsion was measured with a NICOMP equipment. With regard to criteria for lipid nutrient infusion by items, the criteria for lipid injectable emulsion monograph were applied, but those for free fatty acids and lysophosphatidylcholine (LPC), associated with degradation products caused by fatty acid oxidation, were set in detail. Lipid particles of the emulsion were homogeneously formed and maintained regardless of a ratio of omega fatty acids. Also, as seen in the following table 4, the required criteria for stability were satisfied, for example, by showing no great difference in a fatty acid oxidation index according to the ratio of omega fatty acids.

[124]

[Table 4]

Items	Criteria	Example 1		Comparative Example 2		Comparative Example 3	
		Initial	1 month	Initial	1 month	Initial	1 month
pH	6.0~9.0	8.3	8.2	8.2	8.2	8.1	8.2
Free fatty acids	≤8.0mg/mL	2.4	2.9	2.3	2.8	2.4	2.9
Average particles	≤500nm	192	214	180	199	198	205
Maximum particles	≤1um	0.30	0.35	0.38	0.27	0.34	0.30
Dispersity	≤0.25	0.04	0.05	0.12	0.02	0.06	0.03
Lysophosphatidylcholine	≤2mg/mL	Less than 0.5	Less than 0.5	Less than 0.5	Less than 0.5	-	Less than 0.5
Items	**Criteria**	**Comparative Example 4**		**Comparative Example 5**		**Comparative Example 6**	
		Initial	**1 month**	**Initial**	**1 month**	**Initial**	**1 month**
pH	6.0~9.0	8.3	8.2	8.3	8.2	8.1	8.1
Free fatty acids	≤8.0mg/mL	2.6	3.1	2.3	2.8	2.2	2.8
Average particles	≤500nm	200	197	200	210	190	195
Maximum particles	≤1um	0.39	0.30	0.35	0.32	0.33	0.41
Dispersity	≤0.25	0.09	0.04	0.06	0.04	0.06	0.12
Lysophosphatidylcholine	≤2mg/mL	Less than 0.5	Less than 0.5	Less than 0.5	Less than 0.5	Less than 0.5	Less than 0.5

[125] **Experimental Example 6: Stability test 2 on lipid nutrient infusion**

[126] A six-month stability evaluation on Example 1 and Comparative Examples 4 to 6 above was performed under long-term (25℃/RH 60%), accelerated (40℃/RH 75%) storage conditions, such that the results thereof were shown in the following table 5.

[127]

[Table 5]

Items	Criteria	Example 1			Comparative Example 4		
		Initial	Long-term 6M	Accelerated 6M	Initial	Long-term 6M	Accelerated 6M
pH	6.0~9.0	8.3	8.2	7.2	8.3	8.1	7.1
Free fatty acids	≤8.0mg/mL	2.4	3.3	6.0	2.6	3.3	6.6
Average particles	≤500nm	192	223	219	200	220	232
Maximum particles	≤1um	0.30	0.29	0.47	0.39	0.35	0.39
Dispersity	≤0.25	0.04	0.01	0.13	0.09	0.04	0.06
Lysophosphatidylcholine	≤2mg/mL	Less than 0.5	0.54	1.18	Less than 0.5	0.49	1.35
Items	Criteria	Comparative Example 5			Comparative Example 6		
		Initial	Long-term 6M	Accelerated 6M	Initial	Long-term 6M	Accelerated 6M
pH	6.0~9.0	8.3	8.0	7.1	8.1	8.1	7.0
Free fatty acids	≤8.0mg/mL	2.3	3.3	5.8	2.2	3.3	5.8
Average particles	≤500nm	201	236	224	190	213	221
Maximum particles	≤1um	0.35	0.39	0.43	0.33	0.55	0.35
Dispersity	≤0.25	0.06	0.05	0.09	0.06	0.20	0.04
Lysophosphatidylcholine	≤2mg/mL	Less than 0.5	0.64	1.18	Less than 0.5	0.56	1.14

[128] As seen in the table 5 above, it was identified that Example 1 is stable in terms of quality compared to Comparative Examples 5 and 6 in spite of comprising a large amount of polyunsaturated fatty acids. However, judging from the results of Comparative Example 4 comprising the relatively most amount of omega-3 fatty acids, it may be assumed that there is a limit in the concentration of omega-3 fatty acids, in case of considering a valid period of actual products (24 months from a manufacturing date) (Table 5).

[129]

[130] **Experimental Example 7: Quality evaluation on infusion preparation**

[131] A quality evaluation was performed on each chamber fluid of the infusions prepared in Examples 2 and 3 above as well as a fluid mixed with first to third chamber fluids, such that the results thereof were shown in the following table 6.

[132]

[Table 6]

Classification	Items	Criteria	Example 2	Example 3
First chamber fluid	Property	Transparent and colorless to light yellow solution	Suitable	Suitable
	pH	5.4 - 5.8	5.6	5.6
Second chamber fluid	Property	Colorless and transparent solution	Suitable	Suitable
	pH	3.5 - 5.5	4.1	4.5
	Purity	Absorbance of 0.25 or less	0.04	0.01
Third chamber fluid	Property	Ivory white homogeneous emulsion	Suitable	Suitable
	pH	6.0 - 9.0	8.5	8.2
	Total amount of fats	199 – 219 mg/mL	208	207
	Free fatty acids	≤8.0 mEq/L	2.5	2.5
	Dispersity	Average particles: ≤500 nm	247	232
		Maximum particles: ≤1 um	0.46	0.39
		Dispersity: ≤0.25	0.07	0.04
	Particle size	1.5 um or more: ≤2%	0.57	0.39
		5 um or more: ≤0.05%	0.00	0.00
	Lysophosphatidylcholine	≤2 mg/mL	0.6	0.6
Mixture	Property	White emulsion	Suitable	Suitable
	pH	5.5 ~ 5.7	5.6	5.6
	Particle size	Maximum particle 7 um or more: 0%	0	0
	Asepsis	No bacteria growth	Suitable	Suitable
	Endotoxin	≤0.5 EU/mL	0.25 or less	0.25 or less

[133] As seen in the table 6 above, it was identified that the infusion preparation of the present invention is suitable in all the items evaluated for quality. In particular, it was identified that there is no problem with stability because 0.00% is a ratio of particles 5 um or more (PFAT 5, percentage of fat globules with a diameter of > 5 um), closely associated with the safety of products (histological transformation in some animal test models (guinea pig model), occurrence of disease symptoms in the liver and lung (rat model), or the like).

Claims

[Claim 1] A pharmaceutical composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 for preventing or treating inflammatory diseases or immuno-compromised diseases.

[Claim 2] The pharmaceutical composition according to claim 1, wherein the weight ratio of omega-3 and omega-6 fatty acids is 1 : 1.

[Claim 3] The pharmaceutical composition according to claim 1, wherein the omega-3 fatty acids are at least one selected from the group consisting of alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

[Claim 4] The pharmaceutical composition according to claim 1, wherein a daily amount of the omega-3 fatty acids supplied is 0.1 to 0.2 g/kg/day.

[Claim 5] The pharmaceutical composition according to claim 1, wherein the omega-6 fatty acids are at least one selected from the group consisting of linoleic acid, γ linolenic acid, calendic acid, eicosadienoic acid, dihomo-gamma-linolenic acid, arachidonic acid, docosadienoic acid, docosatetraenoic acid, docosapentaenoic acid, tetracosatetraenoic acid and tetracosapentaenoic acid.

[Claim 6] The pharmaceutical composition according to claim 1, wherein the inflammatory diseases are selected from the group consisting of gastritis, enteritis, nephritis, hepatitis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, irritable bowel syndrome, inflammatory pain, migraine, headache, backache, fibromyalgia, fascia disease, viral infection, bacterial infection, mycotic infection, burn, injury caused by surgical operation or dental surgery, hyper-PGE syndrome, atherosclerosis, gout, Hodgkin's disease, pancreatitis, conjunctivitis, iritis, scleritis, uveitis, and acute and chronic inflammatory diseases.

[Claim 7] The pharmaceutical composition according to claim 1, wherein the composition suppresses an expression of IL-1β

[Claim 8] The pharmaceutical composition according to claim 1, wherein the immuno-compromised diseases are selected from the group consisting of asthma, seasonal or perennial rhinitis, allergic rhinitis, conjunctivitis, atopic dermatitis, hives, hemolysis of erythrocytes, acute glomerulonephritis, flu, chronic fatigue and cancer.

[Claim 9] The pharmaceutical composition according to claim 1, wherein the composition is parenterally administered.

[Claim 10] The pharmaceutical composition according to claim 1, wherein the

composition comprises at least one oil selected from the group consisting of fish oil, soybean oil, olive oil, cottonseed oil, safflower oil, sesame oil, coconut oil and corn oil.

[Claim 11] The pharmaceutical composition according to claim 1, wherein the composition comprises at least one additive selected from the group consisting of emulsifiers, osmo-regulators, pH regulators and antioxidants.

[Claim 12] An infusion preparation comprising omega-3 and omega-6 fatty acids.

[Claim 13] The infusion preparation according to claim 12, wherein a weight ratio of omega-3 and omega-6 fatty acids comprised in the infusion preparation is 1 : 0.75 to 1 : 1.25.

[Claim 14] The infusion preparation according to claim 12, wherein the weight ratio of omega-3 and omega-6 fatty acids comprised in the infusion preparation is 1 : 1.

[Claim 15] The infusion preparation according to claim 12, wherein the infusion preparation is received in a single chamber.

[Claim 16] The infusion preparation according to claim 12, wherein the infusion preparation is received in a plurality of chambers, which are distanced from each other by divisions in such a connectable way that the preparation is mixed when being used.

[Claim 17] The infusion preparation according to claim 16, wherein the chamber is divided into a first chamber, a second chamber and a third chamber, and wherein the first chamber receives a first chamber fluid for supplying amino acids and electrolytes; the second chamber receives a second chamber fluid for supplying sugars; and the third chamber receives a third chamber fluid for supplying fats.

[Claim 18] The infusion preparation according to claim 17, wherein the first chamber receives the first chamber fluid comprising 2.07 g of L-alanine, 1.15 g of L-arginine, 1.03 g of glycine, 0.48 g of L-histidine, 0.60 g of L-isoleucine, 0.73 g of L-leucine, 0.725 g of L-lysine hydrochloride, 0.40 g of L-methionine, 0.56 g of L-phenylalanine, 0.68 g of L-proline, 0.50 g of L-serine, 0.10 g of taurine, 0.42 g of L-threonine, 0.18 g of L-tryptophan, 0.04 g of L-tyrosine, 0.58 g of L-valine, 74 mg of calcium chloride dihydrate, 418 mg of sodium glycerophosphate anhydrous, 562 mg of sodium acetate hydrate, 247 mg of magnesium sulfate heptahydrate, 448 mg of potassium chloride and 2.3 mg of zinc sulfate heptahydrate based on 100 mL of the first chamber fluid;

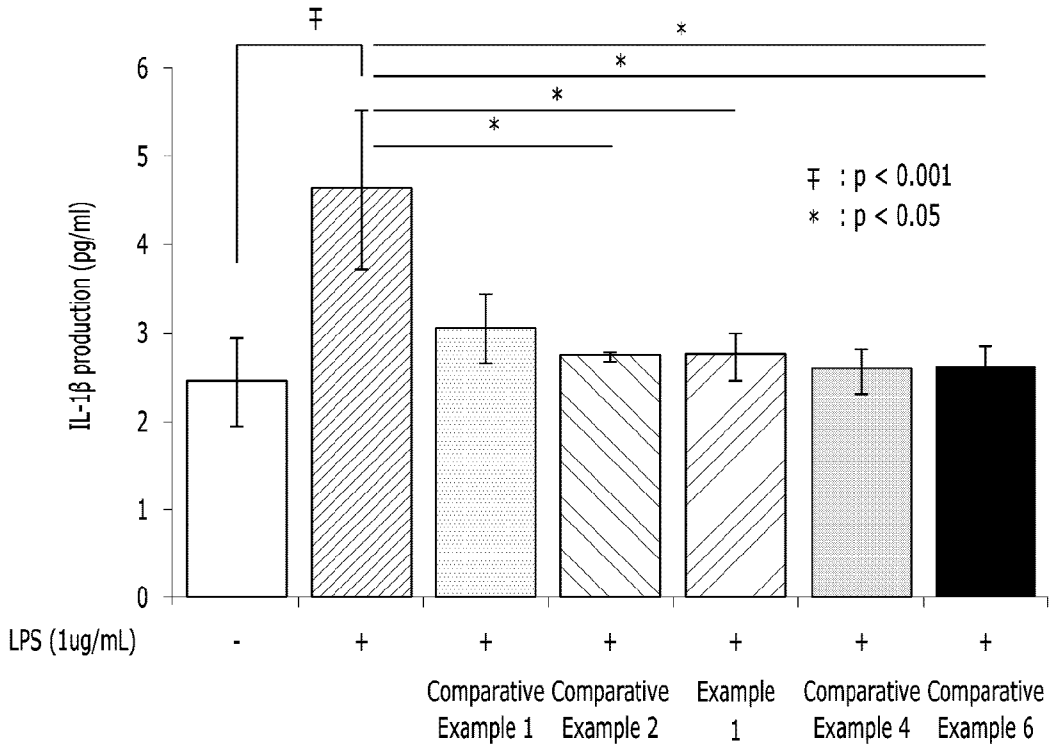
wherein the second chamber receives the second chamber fluid comprising 14.3 g or 46.2 g of glucose monohydrate based on 100 mL of the second chamber fluid; and
wherein the third chamber receives the third chamber fluid comprising 4.0 g of purified soybean oil, 4.0 g of medium chain triglyceride, 5.5 g of purified olive oil, and 6.5 g of purified fish oil based on 100 ml of the third chamber fluid.

[Claim 19] A method for preventing or treating inflammatory diseases or immuno-compromised diseases, comprising a step of administering the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 into subjects in need for treatment.

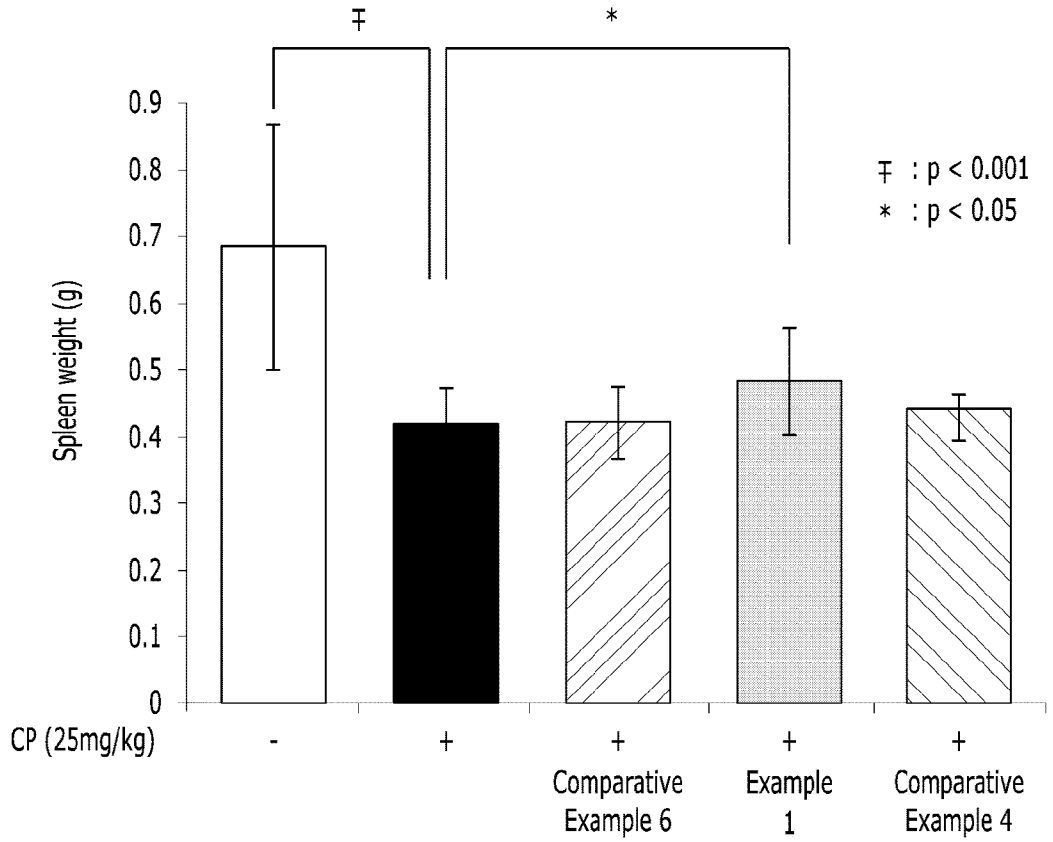
[Claim 20] A use of the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 for preventing or treating inflammatory diseases or immuno-compromised diseases.

[Claim 21] A use of the composition comprising omega-3 and omega-6 fatty acids in the weight ratio of 1 : 0.75 to 1 : 1.25 for preparing a pharmaceutical preparation for preventing or treating inflammatory diseases or immuno-compromised diseases.

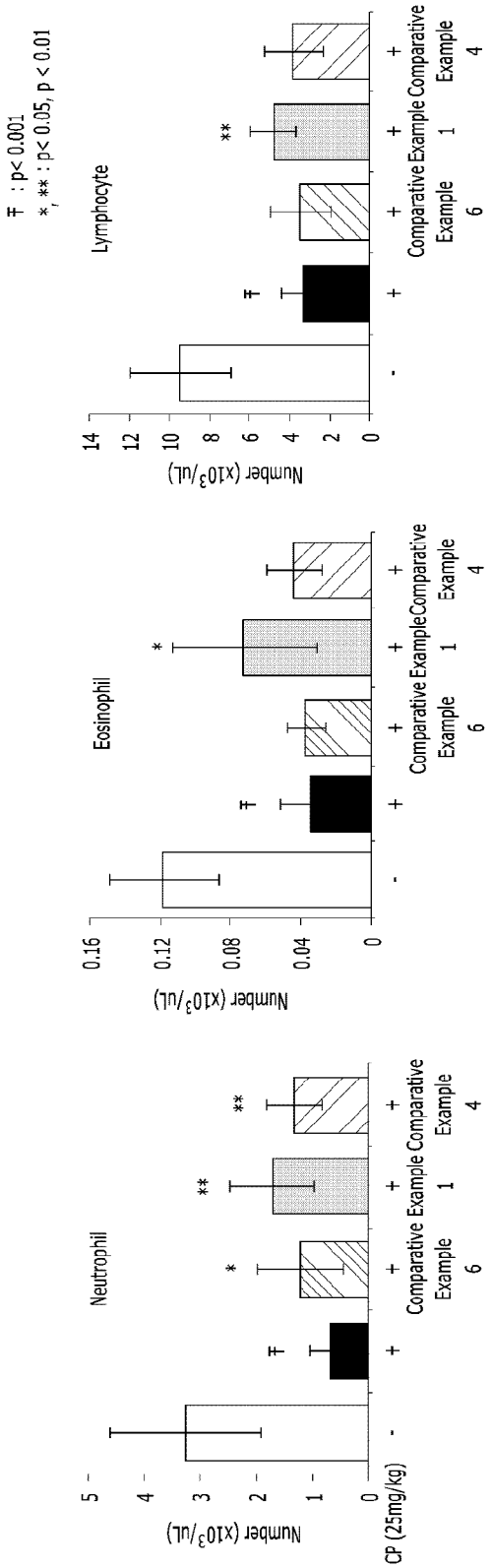
[Fig. 1]


IL-1β production (pg/ml)
0
1
2
3
4
5
6
∓ : p < 0.001
* : p < 0.05
LPS (1ug/mL) - + + + + + +
Comparative Example 1
Comparative Example 2
Example 1
Comparative Example 4
Comparative Example 6

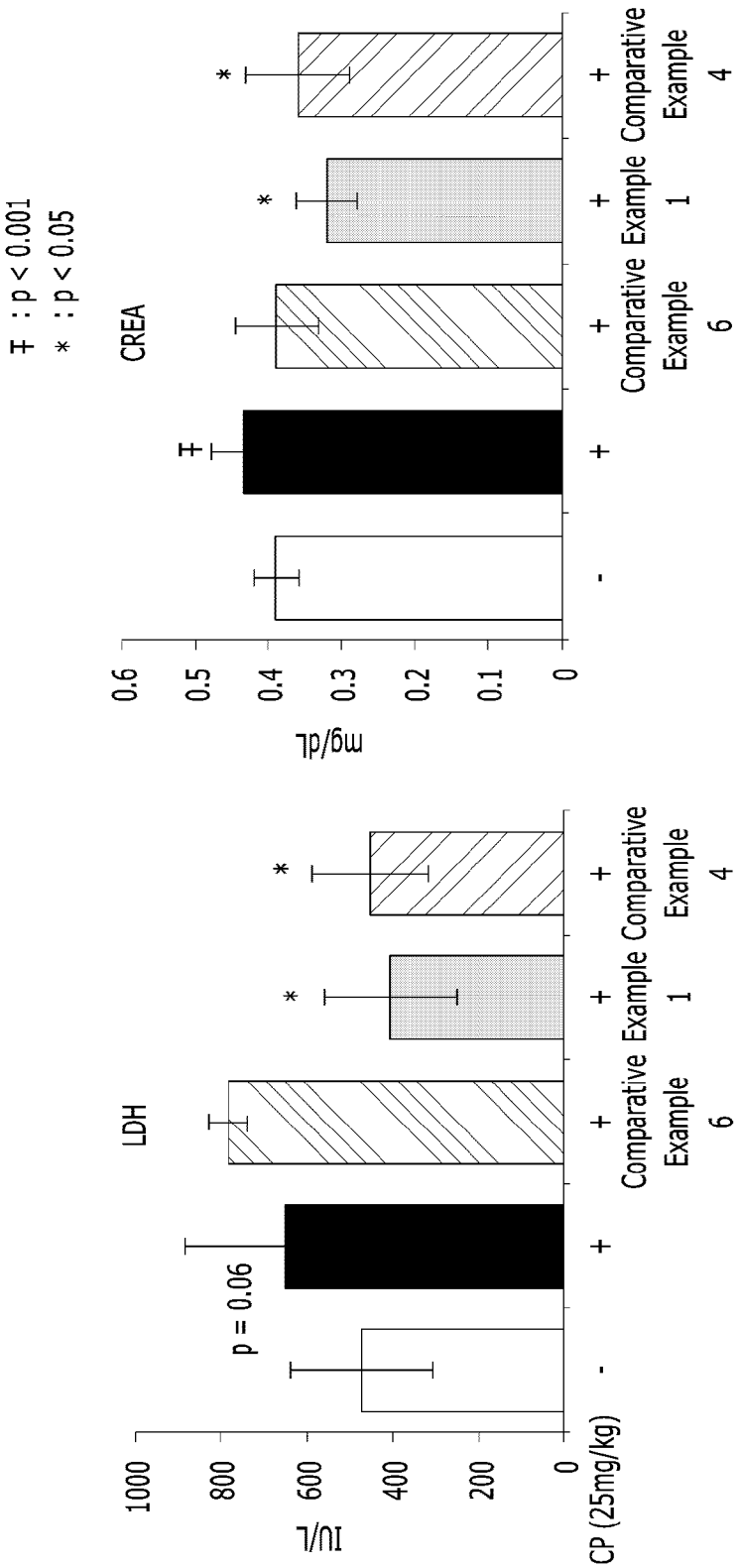
[Fig. 2]


Spleen weight (g)
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
∓ : p < 0.001
* : p < 0.05
CP (25mg/kg) - + + + +
Comparative Example 6
Example 1
Comparative Example 4

[Fig. 3]


Neutrophil
Eosinophil
Lymphocyte
Number (x10³/uL)
CP (25mg/kg)
Comparative Example 6
Comparative Example 1
Comparative Example 4
∓ : p< 0.001
*, ** : p< 0.05, p < 0.01

[Fig. 4]


LDH
p = 0.06
IU/L
1000
800
600
400
200
0
CP (25mg/kg)
-
+
+
+
+
Comparative Example 6
Comparative Example 1
Comparative Example 4
CREA
∓ : p < 0.001
* : p < 0.05
mg/dL
0.6
0.5
0.4
0.3
0.2
0.1
0

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2020/001419

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/202(2006.01)i, A61K 31/201(2006.01)i, A61K 9/08(2006.01)i, A61K 9/00(2006.01)i, A61P 29/00(2006.01)i, A61P 37/02(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K 31/202; A61J 1/20; A61K 9/00; A61K 31/201; A61K 9/08; A61P 29/00; A61P 37/02

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: omega-3, omega-6, inflammation, immune, infusion preparation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DINICOLANTONIO, JAMES J et al., 'Importance of maintaining a low omega-6/omega-3 ratio for reducing inflammation', Open Heart, 2018, vol. 5, e000946, pp. 1-4 See pages 1-2.	1-11,20-21
Y		13-14
A		12,15-18
X	KR 10-1672347 B1 (JW LIFE SCIENCE CORPORATION) 04 November 2016 See abstract; paragraph [0076].	12,15-18
Y		13-14
X	WANG, SHU et al., 'Reduction in dietary omega-6 polyunsaturated fatty acids: eicosapentaenoic acid plus docosahexaenoic acid ratio minimizes atherosclerotic lesion formation and inflammatory response in the LDL receptor null mouse', Atherosclerosis, 2009, vol. 204, pp. 147-155 See pages 148, 152, 154.	1-11,20-21
A	ZHAO, YAJIE et al., 'Effect of ω-3 polyunsaturated fatty acid-supplemented parenteral nutrition on inflammatory and immune function in postoperative patients with gastrointestinal malignancy: a meta-analysis of randomized control trials in China', Medicine, 2018, vol. 97, issue 16, e0472, pp. 1-12 See the whole document.	1-18,20-21

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2020 (25.05.2020)	**25 May 2020 (25.05.2020)**

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOHNSON, MELISSA et al., 'Omega-3, omega-6 and omega-9 fatty acids: implications for cardiovascular and other diseases', Journal of Glycomics & Lipidomics, 2014, vol. 4, issue 4, 1000123, pp. 1-8 See the whole document.	1-18,20-21

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2020/001419

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19
because they relate to subject matter not required to be searched by this Authority, namely:
Claim 19 pertains to a method for treatment of the human body by therapy (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2020/001419

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 10-1672347 B1	04/11/2016	None	