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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 March 2011 (17.03.2011)

PCT

(10) International Publication Number
WO 2011/031602 A1

(51) International Patent Classification:
A23L 1/302 (2006.01) *A61K 35/00* (2006.01)
A61K 31/122 (2006.01) *A61P 29/02* (2006.01)

(21) International Application Number:
PCT/US2010/047468

(22) International Filing Date:
1 September 2010 (01.09.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

61/242,087	14 September 2009 (14.09.2009)	US
61/250,847	12 October 2009 (12.10.2009)	US
61/347,945	25 May 2010 (25.05.2010)	US
61/371,846	9 August 2010 (09.08.2010)	US

(71) Applicant *(for all designated States except US)*: **NESTEC S.A.** [CH/CH]; Avenue Nestle 55, CH-1800 Vevey (CH).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BOLSTER, Douglad Richard** [US/US]; 7020 Beacon Circle, Eden Prairie, Minnesota 55346 (US). **ROUGHEAD, Zamzam Kabiry** [US/US]; 14300 44th Avenue North, Plymouth, Minnesota 55446 (US).

(74) Agent: **LOBEL, Gary M.**; 12 Vreeland Road, 2nd Floor, Florham Park, New Jersey 07932 (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, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

Published:

— *with international search report (Art. 21(3))*

WO 2011/031602 A1

(54) Title: NUTRITIONAL COMPOSITIONS FOR MODULATING INFLAMMATION INCLUDING EXOGENOUS VITAMIN K2

(57) Abstract: Nutritional compositions and methods of making and using the nutritional compositions are provided. In a general embodiment, the present disclosure provides a nutritional composition including exogenous vitamin K2. The nutritional compositions may further include an additional component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof.

TITLE

"NUTRITIONAL COMPOSITIONS FOR MODULATING INFLAMMATION INCLUDING EXOGENOUS VITAMIN K2"

RELATED APPLICATION

[0001] The instant application claims the benefit of U.S. Provisional Application Serial No. 61/242,087 filed on 14 September 2009 (Attorney Docket No. 10358-US-P1), U.S. Provisional Application Serial No. 61/250,847 filed on 12 October 2009 (Attorney Docket No. 10358-US-P2), U.S. Provisional Application Serial No. 61/347,945 filed on May 25, 2010 (Attorney Docket No. 10358-US-P3), and U.S. Provisional Application Serial No. 61/371,846 filed on 9 August 2010 (Attorney Docket No. 10358-US-P4), and is co-dependent with another application, entitled "Nutritional Compositions Including Exogenous Vitamin K2," which is filed concurrently with the instant application.

BACKGROUND

[0002] The present disclosure generally relates to health and nutrition. More specifically, the present disclosure relates to nutritional compositions including exogenous vitamin K_2 and methods of making and using the nutritional compositions.

[0003] There are many types of nutritional compositions currently on the market. Nutritional compositions can be targeted toward certain consumer types, for example, young, elderly, athletic, etc., based on the specific ingredients of the nutritional composition. Nutritional compositions can also be formulated based on the certain physiological conditions that the nutritional compositions are intended to treat or improve.

[0004] One goal of nutritional support is to improve bone health by increasing bone density and strength and reducing the incidence of fracture risk. Due to rapidly changing bone densities in children during normal growth and development, or due to underlying medical conditions, children may require nutritional compositions to improve indices of bone health and promote bone growth and bone quality.

SUMMARY

[0005] Nutritional compositions having exogenous vitamin K2 and methods of making and using the nutritional compositions are provided. In a general embodiment, the present disclosure provides a nutritional composition including exogenous K2. The nutritional composition can be a complete nutritional or as an oral nutritional supplement (incomplete nutritional). The nutritional composition can be in a formulation designed for any mammal such as a human or an animal. The active ingredients in the nutritional composition can also be provided as a modular product. A modular product can be defined as a method of delivering one or more specific nutrients as a supplement and not intended to be used for sole source nutrition.

[0006] In an embodiment, the nutritional composition further includes one or more prebiotics. The prebiotic can be fructooligosaccharides, inulin, lactulose, galactooligosaccharides, acacia gum, soyoligosaccharides, xylooligosaccharides, isomaltooligosaccharides, gentiooligosaccharides, lactosucrose, glucooligosaccharides, pecticoligosaccharides, guar gum, partially hydrolyzed guar gum, sugar alcohols, alpha glucan, beta glucan, or a combination thereof.

[0007] In an embodiment, the nutritional composition further includes one or more probiotics. The probiotic can be Saccharomyces, Debaromyces, Candida, Pichia, Torulopsis, Aspergillus, Rhizopus, Mucor, Penicillium, Bifidobacterium, Bacteroides, Clostridium, Fusobacterium, Melissococcus, Propionibacterium, Streptococcus, Enterococcus, Lactococcus, Staphylococcus, Peptostrepococcus, Bacillus, Pediococcus, Micrococcus, Leuconostoc, Weissella, Aerococcus, Oenococcus, Lactobacillus or a combination thereof.

[0008] In another embodiment, the nutritional composition further includes one or more amino acids. The amino acid can be Alanine, Arginine, Asparagine, Aspartate, Citrulline, Cysteine, Glutamate, Glutamine, Glycine, Histidine, Hydroxyproline, Hydroxyserine, Hydroxytyrosine, Hydroxylysine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine,

Valine, HICA (Alpha-Hydroxyisocaproic Acid), HIVA (Alpha-Hydroxyisovaleric Acid), HIMVA (alpha-hydroxymethylvaleric acid) or a combination thereof.

[0009] In an embodiment, the nutritional composition further includes one or more proteins.

[0010] In an embodiment, the nutritional composition further includes one or more nucleotides.

[0011] In an embodiment, the nutritional composition further includes one or more synbiotics, fish oils, nonmarine omega-3 fatty acid containing dietary fat sources, phytonutrients and/or antioxidants. The antioxidants can be, for example, vitamin A , vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, vitamin D, vitamin E, carotenoids, selenium, flavonoids, Lactowolfberry, Goji (wolfberry), polyphenols, lycopene, lutein, lignan, coenzyme Q10 ("CoQ10"), hesperidine and glutathione.

[0012] In an embodiment, the nutritional composition is in an administerable form such as pharmaceutical formulations, nutritional formulations, tube-feed formulations, dietary supplements, functional foods, beverage products or a combination thereof.

[0013] In another embodiment, the present disclosure provides a method of making a nutritional composition. The method comprises adding exogenous vitamin K_2 and a component selected from the group consisting of phosphorus, magnesium, calcium, vitamin D, osteopontin, or combinations thereof to a nutritional composition.

[0014] In an alternative embodiment, the present disclosure provides a method of making a nutritional composition. The method comprises adding exogenous vitamin K_2 and a component selected from the group consisting of phosphorous, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin or combinations thereof to a nutritional composition.

[0015] In yet another embodiment, the present disclosure provides a method of improving bone health (i.e. growth, mineralization, microarchitecture, bone organic matrix constituents, density, elasticity and strength) in pediatric patients. The method comprises administering to a child in need of same a nutritional composition including an effective amount of exogenous vitamin K_2. The nutritional composition may further

include a component selected from the group consisting of phosphorous, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin or combinations thereof.

[0016] In still another embodiment, the present disclosure provides a method of promoting bone growth and bone quality in a pediatric patient having an underlying medical condition. The method comprises administering to a pediatric patient having an underlying medical condition a nutritional composition including an effective amount of exogenous vitamin K_2.

[0017] In another embodiment, the present disclosure provides a method of reducing the risk of bone fracture in a pediatric patient. The method comprises administering to a pediatric patient at risk of bone fracture a nutritional composition including an effective amount of exogenous vitamin K_2.

[0018] In another embodiment, the present disclosure provides a method for improving skeletal muscle health (i.e. metabolic function, lean body mass and mobility). The method comprises administering to a patient who can benefit from improved skeletal muscle health a nutritional composition including an effective amount of exogenous vitamin K_2.

[0019] An advantage of the present disclosure is to provide an improved nutritional composition having exogenous vitamin K_2.

[0020] Another advantage of the present disclosure is to provide a method of making an improved nutritional composition.

[0021] Yet another advantage of the present disclosure is to provide a nutritional composition that promotes bone health.

[0022] Another advantage of the present disclosure is to provide a nutritional composition that promote bone growth and bone quality in patients having underlying medical conditions.

[0023] Still another advantage of the present disclosure is to provide a nutritional composition that minimizes bone fracture risk.

[0024] Additional features and advantages are described herein, and will be apparent from the following Detailed Description.

DETAILED DESCRIPTION

[0025] Maintenance of bone health is essential for mobility and the bone matrix is an important reservoir for critical minerals. On average, 90 percent of peak bone mass is acquired by the age of 18 for women and 20 for men. As such, it is important to promote proper bone health and bone growth and bone quality during the period of normal growth and development in children prior to these ages. Given the accelerated rate of bone accretion during the adolescent period, providing essential nutrients ensures the optimal functioning of the bone formation process. Further, failure to promote bone mineral density during this critical period can lead to decreased bone strength and bone tissue microarchitecture, which can elicit the onset of fragility fractures in the pediatric population.

[0026] During childhood bones grow because resorption (the process of breaking down bone) occurs inside the bone while formation of new bone occurs on its outer (periosteal) surface. At puberty the bones get thicker because formation can occur on both the outer and inner (endosteal) surfaces. The remodeling process occurs throughout life and becomes the dominant process by the time that bone reaches its peak mass (typically by the early 20s). In remodeling, a small amount of bone on the surface of trabeculae or in the interior of the cortex is removed and then replaced at the same site. The remodeling process does not change the shape of the bone, but it is nevertheless vital for bone health. Modeling and remodeling continue throughout life so that most of the adult skeleton is replaced about every 10 years. While remodeling predominates by early adulthood, modeling can still occur particularly in response to weakening of the bone.

[0027] While Calcium and vitamin D are important nutrients for the development of the inorganic matrix of the bone, several nutrients are needed for normal development of the organic matrix of bone. Specifically, adequate vitamin K, and trace minerals such as zinc, copper, iron nutriture are required for the normal metabolism of noncollagenous proteins such as osteocalcin, osteopontin. Provision of these nutrients during rapid growth, can lead to prevention of osteomalacia and osteoporosis later in life. This improves quality of life and also will save healthcare costs related to hip fractures.

[0028] Vitamin K denotes a group of lipophilic, hydrophobic and essential vitamins having a common chemical ring structure (napthoquinone). The two most important forms of vitamin K are vitamin K_1, a single compound known as phylloquinone or phytomenadione, and vitamin K_2, a series of vitamers known as menaquinones or menatetrenones. There are also several synthetic forms of vitamin K including, for example, vitamins K_3, K_4 and K_5.

[0029] Vitamin K_1 is the major form of vitamin K in a normal diet and is synthesized by plants including, for example, certain plant oils such as canola and soybean and in green leafy vegetables such as spinach, swiss chard, broccoli, cabbage, cauliflower, kale, and brussels sprouts.

[0030] Vitamin K_2 is a group of compounds called menaquinones ("MK") having side chains composed of a variable number of unsaturated isoprenoid residues generally designated as MK-n, where n specifies the number of isoprenoids. The most common MKs are MK-4 and MK-7. MK-4 is typically synthesized by animal organs and muscle, while MK-7 is typically synthesized by bacteria during fermentation. Accordingly, MK-7 is particularly abundant in fermented products including cheese, curd cheese and natto (fermented soybeans) and has a particularly long half-life when compared to vitamin K_1.

[0031] The estimated average requirement for vitamin K in children ages 1 to 18 years in the United States is based upon median intakes of vitamin K for adults. These levels are designed to meet the vitamin K levels required for normal blood coagulation and not other vitamin K-dependent proteins such as osteocalcin. The ratio of under-carboxylated (i.e., inactive) to carboxylated osteocalcin can be a surrogate marker for vitamin K status. Recent evidence suggests that children between the ages of 6 and 18 years of age have elevated levels of undercarboxylated osteocalcin relative to adults. Rather than attempting to increase the intake levels via higher vitamin K_1 intake, vitamin K_2 allows for administration of a more potent form of vitamin K without negatively impacting parameters of anticoagulation.

[0032] As compared to vitamin K_1, vitamin K_2 provides better absorption and more stable serum levels through a longer half-life. The improved bioavailability of vitamin K_2 to extrahepatic tissue may also allow for a greater impact on bone health (i.e.

mineralization, microarchitecture and strength) during normal growth and development. Therefore, vitamin K_2 provides for a more potent form of the vitamin in which its enhanced bioavailability can impact bone health during normal growth and development.

[0033] Additionally, there exists several medical conditions in which bone growth and bone quality in pediatric patients may be compromised. Such conditions may include, for example, developmental delay, failure-to-thrive, neuromuscular dysfunction, severe food allergy and inflammatory bowel disease (e.g., Crohns disease or ulcerative colitis). For example, the incidence of low bone mass in children having inflammatory bowel disease ("IBD") ranges from about 30-50%. Vitamin K is a cited nutrition deficiency in this population and its limited bioavailability may reduce osteocalcin carboxylation as well as reduce bone strength, bone mineralization and bone microarchitecture. Accordingly, children suffering from any of the above-mentioned medical conditions may benefit from a more effective dose of vitamin K.

[0034] Rather than attempting to increase the intake levels via higher vitamin K1 intake, Vitamin K2 allows for a more potent form of vitamin K without negatively impacting parameters of anticoagulation. Specifically, vitamin K2 provides better absorption and more stable serum levels through a longer half-life when compared to phylloquinones (vitamin K1). Improved bioavailability of vitamin K2 to extraheptic tissue may allow for a greater impact for improving musculoskeletal health in patients with inflammatory bowel disease (IBD) (Crohn's Disease and Colitis), especially pediatric patients. The incidence of low bone mass ranges from 30-50% in children with IBD. Vitamin K is a cited nutrition deficiency in this population and its limited availability may reduce osteocalcin carboxylation as well as reduce bone strength, bone mineralization and bone micro-architecture. In addition, a low vitamin K status may be a causative factor in Crohn's Disease-associated osteopenia. The osteopenia and elevated rate of bone resorption noted in some Crohn's Disease patients is a multifactorial process and vitamin K deficiency is certainly only one factor in this process. Low vitamin K levels can lead to an increase in the rate of bone resorption, without a compensatory increase in the rate of bone formation. An increased rate of bone turnover is associated with an increased risk of bone loss in Crohn's Disease patients. In terms of nutrition-related etiological factors for

[0035] Further, vitamin K_2 may also be effective for bone health in pediatric patients undergoing concurrent drug treatments including, for example, corticosteroids, bisphosphonates or anti-coagulative drugs. Similarly, pediatric patients undergoing biologic therapies or having conditions of gastrointestinal ("GI") impairment including, for example, short bowel syndrome, ulcerative colitis, celiac disease, cystic fibrosis, renal dysfunction and androgen deficiency, gluten intolerance, Crohns disease or severe allergy, may also benefit from administration of nutritional compositions having exogenous vitamin K_2.

[0036] Applicant has surprisingly found that administering exogenous vitamin K_2 as part of a nutritional formulation will improve osteocalcin carboxylation and improve indicies of bone health during normal growth and development in children. Additionally, vitamin K_2 supplementation can also promote bone growth and bone quality in pediatric patients with underlying medical conditions in which bone growth and bone quality may be compromised. As a result, Applicant has found that administration of exogenous vitamin K_2 increases bone density and improves bone tissue microarchitecture in pediatric patients, thereby reducing the incidence for fracture risk. The effects of vitamin K_2 may be seen directly on bone quality such that this form of vitamin K modulates formation of proteins in the organic matrix of the bone involved in microarchitectural morphology, mineralization, density, elasticity and mechanical stiffness, as measured by peripheral quantitative computer tomography ("pQCT") or Dual Energy X-ray absorptiometry ("DEXA"). Vitamin K_2 may also be effective for bone health in patients undergoing concurrent drug treatment.

[0037] Generally speaking, bone density is expressed as the relationship between bone mass (expressed as the degree of photon attenuation through the bone, or bone mineral content (BMC)) and the image of the bone on a film (i.e., the area) (expressed as BMC/cm^2). Additionally, pQCT is a procedure that evaluates peripheral bone in 3

dimensions (volumetric) and is commonly applied to the forearm or tibia. A radiation source (typically x-rays) and a sensor revolve around the bone under examination, which is them reconstructed on the computer screen in a three-dimensional (3-D) image. pQCT is an optimal technique for evaluating bone geometry even though sensitivity varies with the site under evaluation. Unlike most other techniques, pQCT measures true bone density (volumetric mineral bone density) because it normalizes the bone mineral content derived not from the projected area but rather from the volume of the examined bone. pQCT can also be used to calculate the SSI, an index of bone resistance to torsion. The index takes into account bone geometry and the bone's mineral characteristics. See, Geometry and bone density, Radetti, G., et al., Panminerva Med 2006; 48:181-6.

[0038] DEXA is based on x-ray spectrometry and it's fundamental principle is based on the degree of attenuation of x-rays emitted from 2 different sources of energy. DEXA is normally used to evaluate lumbar or proximal femoral bone mineralization. DEXA has an accuracy of 4-10% and a coefficient of variation of 1-1.5%. See, Id.

[0039] Accordingly, the present disclosure relates to nutritional compositions including exogenous K_2 and methods of making and using the nutritional compositions. The present disclosure also relates to the use of pQCT and DEXA to measure bone density and bone tissue microarchitecture. Embodiments of the nutritional compositions of the present disclosure can promote the increase of bone density, mineralization and mechanical stiffness as well as improved bone tissue microarchitecture while minimizing potentially negative effects on blood coagulation and risk of bone fracture. Thus, the use of exogenous vitamin K_2 may allow for increase bone health and its associated benefits in pediatric patients. Using pQCT and DEXA, as described above, it is possible to accurately measure bone density and bone microarchitecture to demonstrate the effects of the presently claimed nutritional compositions.

[0040] In a general embodiment, the present disclosure provides a nutritional composition including exogenous vitamin K_2. The nutritional composition may further include a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof.

[0041] As used herein, the term "nutritional composition" includes, but is not limited to, complete nutritional compositions, partial or incomplete nutritional compositions, and disease or condition specific nutritional compositions. A complete nutritional composition (i.e., those which contain all the essential macro and micro nutrients) can be used as a sole source of nutrition for the patient. Patients can receive 100% of their nutritional requirements from such complete nutritional composition. A partial or incomplete nutritional composition does not contain all the essential macro and micro nutrients and cannot be used as a sole source of nutrition for the patient. Partial or incomplete nutritional compositions can be used as a nutritional supplement. A disease or condition specific nutritional composition is a composition that delivers nutrients or pharmaceuticals and can be a complete or partial nutritional composition.

[0042] The exogenous vitamin K_2 can be combined with other ingredients for promotion of bone growth and bone quality. For example, exogenous vitamin K_2 could work more effectively to support bone health in pediatric patients when used in combination with a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. Exogenous vitamin K_2 may also work more effectively to support bone health when used in combination with amino acids (e.g., leucine), protein with low sulfur-containing amino acid content, lipids (n3:n6), bioactive peptides, protease inhibitors, creatine, etc.

[0043] In an embodiment, the nutritional composition further includes one or more prebiotics. As used herein, a prebiotic is a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confers benefits upon host well-being and health. Non-limiting examples of prebiotics include fructooligosaccharides, inulin, lactulose, galactooligosaccharides, acacia gum, soyoligosaccharides, xylooligosaccharides, isomaltooligosaccharides, gentiooligosaccharides, lactosucrose, glucooligosaccharides, pecticoligosaccharides, guar gum, partially hydrolyzed guar gum, sugar alcohols, alpha glucan, beta glucan, or a combination thereof.

[0044] In an embodiment, the nutritional composition further includes one or more probiotics. As used herein, probiotic micro-organisms (hereinafter "probiotics") are preferably microorganisms (alive, including semi-viable or weakened, and/or non-replicating), metabolites, microbial cell preparations or components of microbial cells that could confer health benefits on the host when administered in adequate amounts., more specifically that beneficially affect a host by improving its intestinal microbial balance, leading to effects on the health or well-being of the host. In general, it is believed that these micro-organisms inhibit or influence the growth and/or metabolism of pathogenic bacteria in the intestinal tract. The probiotics may also activate the immune function of the host. For this reason, there have been many different approaches to include probiotics into food products. Non-limiting examples of probiotics include Saccharomyces, Debaromyces, Candida, Pichia, Torulopsis, Aspergillus, Rhizopus, Mucor, Penicillium, Bifidobacterium, Bacteroides, Clostridium, Fusobacterium, Melissococcus, Propionibacterium, Streptococcus, Enterococcus, Lactococcus, Staphylococcus, Peptostrepococcus, Bacillus, Pediococcus, Micrococcus, Leuconostoc, Weissella, Aerococcus, Oenococcus, Lactobacillus or a combination thereof.

[0045] In another embodiment, the nutritional composition further includes one or more amino acids. Non-limiting examples of amino acids include Alanine, Arginine, Asparagine, Aspartate, Citrulline, Cysteine, Glutamate, Glutamine, Glycine, Histidine, Hydroxyproline, Hydroxyserine, Hydroxytyrosine, Hydroxylysine, Isoleucine, Leucine, Lysine, Methionine, Phenylalanine, Proline, Serine, Taurine, Threonine, Tryptophan, Tyrosine, Valine, HICA (Alpha-Hydroxyisocaproic Acid), HIVA (Alpha-Hydroxyisovaleric Acid), HIMVA (alpha-hydroxymethylvaleric acid) or a combination thereof. In a preferred embodiment, non-limiting examples of amino acids include proline, hydroxyproline, hydroxytyrosine, hydroxylysine and hydroxyserine and combinations thereof.

[0046] In an embodiment, the nutritional composition further includes one or more proteins.

[0047] In an embodiment, the nutritional composition further includes one or more nucleotides.

[0048] In an embodiment, the nutritional composition further includes one or more synbiotics, fish oils, nonmarine omega-3 fatty acid containing dietary fat sources, Bowman Birk Inhibitor, phytonutrients and/or antioxidants. As used herein, a synbiotic is a supplement that contains both a prebiotic and a probiotic that work together to improve the microflora of the intestine. Non-limiting examples of fish oils include docosahexaenoic acid ("DHA") and eicosapentaenoic acid ("EPA"). Non-limiting examples of phytonutrients include quercetin, curcumin and limonin. Antioxidants are molecules capable of slowing or preventing the oxidation of other molecules. Non-limiting examples of antioxidants include vitamin A, carotenoids, vitamin C, vitamin E, selenium, flavonoids, Lactowolfberry, Goji (wolfberry), polyphenols, lycopene, lutein, lignan, coenzyme Q10 ("CoQ10"), hesperidine and glutathione.

[0049] In another embodiment, the present disclosure provides a method of making a nutritional composition. The method comprises adding an effective amount of exogenous K_2 and a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin or combinations thereof to a nutritional composition, for example, to improve bone health of pediatric patients. The nutritional composition can be in an administerable form such as pharmaceutical formulations, nutritional formulations, tube-feed formulations, dietary supplements, functional foods, beverage products or a combination thereof.

[0050] In another embodiment, the present disclosure provides a method of tailoring a treatment or dosage to a patient based on a genetic predisposition as a parameter to assess when determining the potential for Vitamin K2 to impact bone health. Supplementation with Vitamin K2 may be more effective in individuals carrying unique genotypes.

[0051] As used herein, a "tube feed" formulation is preferably a complete or incomplete nutritional product that is administered to an animal's gastrointestinal system, other than through oral administration, including but not limited to a nasogastric tube, orogastric tube, gastric tube, jejunostomy tube (J-tube), percutaneous endoscopic gastrostomy (PEG), port, such as a chest wall port that provides access to the stomach, jejunum and other suitable access ports.

[0052] As used herein, "effective amount" is preferably an amount that prevents a deficiency, treats a disease or medical condition in an individual or, more generally, reduces symptoms, manages progression of the diseases or provides a nutritional, physiological, or medical benefit to the individual. A treatment can be patient- or doctor-related. In addition, while the terms "individual" and "patient" are often used herein to refer to a human, the invention is not so limited. Accordingly, the terms "individual" and "patient" refer to any animal, mammal or human having or at risk for a medical condition that can benefit from the treatment.

[0053] As used herein, animals include, but is not limited to mammals, which include, but is not limited to rodents, aquatic mammals, domestic animals such as dogs and cats, farm animals such as sheep, pigs, cows and horses, and humans. Wherein the terms animal or mammal or their plurals are used, it is contemplated that it also applies to any animals that are capable of the effect exhibited or intended to be exhibited by the context of the passage.

[0054] As used herein, "complete nutrition" are preferably nutritional products that contain sufficient types and levels of macronutrients (protein, fats and carbohydrates) and micronutrients to be sufficient to be a sole source of nutrition for the animal to which it is being administered to.

[0055] As used herein, "incomplete nutrition" are preferably nutritional products that do not contain sufficient levels of macronutrients (protein, fats and carbohydrates) or micronutrients to be sufficient to be a sole source of nutrition for the animal to which it is being administered to.

[0056] As used herein, "Long term administrations" are preferably continuous administrations for more than 6 weeks.

[0057] As used herein, mammal preferably includes but is not limited to rodents, aquatic mammals, domestic animals such as dogs and cats, farm animals such as sheep, pigs, cows and horses, and humans. Wherein the term mammal is used, it is contemplated that it also applies to other animals that are capable of the effect exhibited or intended to be exhibited by the mammal.

[0058] The term "microorganism" is meant to include the bacterium, yeast and/or fungi, a cell growth medium with the microorganism or a cell growth medium in which microorganism was cultivated.

[0059] As used herein, a "Prebiotic" is preferably a food substances that selectively promote the growth of beneficial bacteria or inhibit the growth of pathogenic bacteria in the intestines. They are not inactivated in the stomach and/or upper intestine or absorbed in the GI tract of the person ingesting them, but they are fermented by the gastrointestinal microflora and/or by probiotics. Prebiotics are for example defined by Glenn R. Gibson and Marcel B. Roberfroid, Dietary Modulation of the Human Colonic Microbiota: Introducing the Concept of Prebiotics, J. Nutr. 1995 125: 1401-1412.

[0060] As used herein, "Short term administrations" are preferably continuous administrations for less than 6 weeks.

[0061] As used herein, the terms "treatment", "treat" and "to alleviate" is preferably to both prophylactic or preventive treatment (that prevent and/or slow the development of a targeted pathologic condition or disorder) and curative, therapeutic or disease-modifying treatment, including therapeutic measures that cure, slow down, lessen symptoms of, and/or halt progression of a diagnosed pathologic condition or disorder; and treatment of patients at risk of contracting a disease or suspected to have contracted a disease, as well as patients who are ill or have been diagnosed as suffering from a disease or medical condition. The terms "treatment" and "treat" also refer to the maintenance and/or promotion of health in an individual not suffering from a disease but who may be susceptible to the development of an unhealthy condition, such as nitrogen imbalance or muscle loss. The terms "treatment", "treat" and "to alleviate" are also intended to include the potentiation or otherwise enhancement of one or more primary prophylactic or therapeutic measure.

[0062] As used herein, a synbiotic is a supplement that contains both a prebiotic and a probiotic that work together to improve the microflora of the intestine.

[0063] As used herein, "normal bone growth" preferably includes: during childhood and adolescence bones are sculpted by modeling, which allows for the formation of new bone at one site and the removal of old bone from another site within the

[0064] As used herein, a "nucleotide" is preferably understood to be a subunit of deoxyribonucleic acid ("DNA") or ribonucleic acid ("RNA"). It is an organic compound made up of a nitrogenous base, a phosphate molecule, and a sugar molecule (deoxyribose in DNA and ribose in RNA). Individual nucleotide monomers (single units) are linked together to form polymers, or long chains. Exogenous nucleotides are specifically provided by dietary supplementation. The exogenous nucleotide can be in a monomeric form such as, for example, 5' Adenosine Monophosphate ("5'-AMP"), 5'-Guanosine Monophosphate ("5'-GMP"), 5'-Cytosine Monophosphate ("5'-CMP"), 5'-Uracil Monophosphate ("5'-UMP"), 5'-Inosine Monophosphate ("5'-IMP"), 5'-Thymine Monophosphate ("5'-TMP") or a combination thereof. The exogenous nucleotide can also be in a polymeric form such as, for example, an intact RNA. There can be multiple sources of the polymeric form such as, for example, yeast RNA.

[0065] Nutritional products are preferably understood to further include any number of additional ingredients, including, for example one or more, vitamin, mineral, sugar, a pharmaceutically acceptable carrier, excipient, flavor agent, or colorants.

[0066] The term "protein", "peptide", "oligopeptides" or "polypeptide" as used herein is preferably understood to refer to any composition that includes, a single amino

acids (monomers), two or more amino acids joined together by a peptide bond (dipeptide, tripeptide, or polypeptide), collagen, precursor, homolog, analog, mimetic, salt, prodrug, metabolite, or fragment thereof or combination. For the sake of clarity, the use of any of the above terms is interchangeable unless otherwise specified. It will be appreciated that polypeptides (or peptides or proteins or oligopeptides) often contain amino acids other than the 20 amino acids commonly referred to as the 20 naturally occurring amino acids, and that many amino acids, including the terminal amino acids, may be modified in a given polypeptide, either by natural processes such as glycosylation and other post-translational modifications, or by chemical modification techniques which are well known in the art. Among the known modifications which may be present in polypeptides of the present invention include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of a flavanoid or a heme moiety, covalent attachment of a polynucleotide or polynucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycation, glycosylation, glycosylphosphatidyl inositol (GPI) membrane anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to polypeptides such as arginylation, and ubiquitination. The term "protein" also includes "artificial proteins" which refers to linear or non-linear polypeptides, consisting of alternating repeats of a peptide

[0067] As used herein, "phytochemicals" or "phytonutrients" are non-nutritive compounds that are found in many foods. Phytochemicals are functional foods that have health benefits beyond basic nutrition, and are health promoting compounds that come from plant sources. As used herein, "Phytochemicals" and "Phytonutrients" refers to any chemical produced by a plant that imparts one or more health benefit on the user. Phytochemicals can be administered by any means, including topically, enterally, and/or parenterally. As used herein, non-limiting examples of phytochemicals and phytonutrients include those that are:

1. Phenolic compounds which include Monophenols (such as: Apiole, Carnosol, Carvacrol, Dillapiole, Rosemarinol); Flavonoids (polyphenols) including Flavonols (such as: Quercetin, Gingerol, Kaempferol, Myricetin, Rutin, Isorhamnetin), Flavanones (such as: Hesperidin, Naringenin, Silybin, Eriodictyol), Flavones (such as: Apigenin, Tangeritin, Luteolin), Flavan-3-ols (such as: Catechins, (+)-Catechin, (+)-Gallocatechin, (-)-Epicatechin, (-)-Epigallocatechin, (-)-Epigallocatechin gallate (EGCG), (-)-Epicatechin 3-gallate, Theaflavin, Theaflavin-3-gallate, Theaflavin-3'-gallate, Theaflavin-3,3'-digallate, Thearubigins), Anthocyanins (flavonals) and Anthocyanidins (such as: Pelargonidin, Peonidin, Cyanidin, Delphinidin, Malvidin, Petunidin), Isoflavones (phytoestrogens) (such as: Daidzein (formononetin), Genistein (biochanin A), Glycitein), Dihydroflavonols, Chalcones, Coumestans (phytoestrogens), and Coumestrol; Phenolic acids (such as: Ellagic acid, Gallic acid, Tannic acid, Vanillin, Curcumin); Hydroxycinnamic acids (such as: Caffeic acid, Chlorogenic acid, Cinnamic acid, Ferulic acid, Coumarin); Lignans (phytoestrogens), Silymarin, Secoisolariciresinol, Pinoresinol and lariciresinol); Tyrosol esters (such as: Tyrosol, Hydroxytyrosol, Oleocanthal, Oleuropein); Stilbenoids (such as: Resveratrol, Pterostilbene, Piceatannol) and Punicalagins;

2. Terpenes (isoprenoids) which include Carotenoids (tetraterpenoids) including Carotenes (such as: α-Carotene, β-Carotene, γ-Carotene, δ-Carotene, Lycopene, Neurosporene, Phytofluene, Phytoene), and Xanthophylls (such as: Canthaxanthin, Cryptoxanthin, Zeaxanthin, Astaxanthin, Lutein, Rubixanthin); Monoterpenes (such as: Limonene, Perillyl alcohol); Saponins; Lipids including : Phytosterols (such as: Campesterol, beta Sitosterol, gamma sitosterol, Stigmasterol), Tocopherols (vitamin E), and omega-3, 6, and 9 fatty acids (such as: gamma-linolenic acid); Triterpenoid (such as: Oleanolic acid, Ursolic acid, Betulinic acid, Moronic acid);

3. Betalains which include Betacyanins (such as: betanin, isobetanin, probetanin, neobetanin); and Betaxanthins (non glycosidic versions) (such as: Indicaxanthin, and Vulgaxanthin);

4 Organosulfides which include Dithiolthiones (isothiocyanates) (such as: Sulphoraphane); and Thiosulphonates (allium compounds) (such as: Allyl methyl trisulfide, and Diallyl sulfide), Indoles, glucosinolates which include Indole-3-

carbinol; sulforaphane; 3,3'-Diindolylmethane; Sinigrin; Allicin; Alliin; Allyl isothiocyanate; Piperine; Syn-propanethial-S-oxide;

5. Protein inhibitors which include protease inhibitors;

6. Other organic acids which include Oxalic acid, Phytic acid (inositol hexaphosphate); Tartaric acid; and Anacardic acid; and

7. combinations thereof.

[0068] As used herein the term "antioxidant" is preferably understood to include any one or more of various substances (as beta-carotene (a vitamin A precursor), vitamin C, vitamin E, and selenium) that inhibit oxidation or reactions promoted by Reactive Oxygen Species (ROS) and other radical and non-radical species.

[0069] As used herein the term "vitamin" is preferably understood to include any of various fat-soluble or water-soluble organic substances (non-limiting examples include vitamin A, vitamin B_1, vitamin B_6, vitamin B_{12}, vitamin C, vitamin D, vitamin E) essential in minute amounts for normal growth and activity of the body and obtained naturally from plant and animal foods or synthetically made, and include their pro-vitamins, derivatives, and analogs.

[0070] As used in this specification and the appended claims, the singular forms “a”, “an” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a polypeptide” includes a mixture of two or more polypeptides, and the like.

[0071] As used herein, "about," is preferably understood to refer to numbers in a range of numerals. Moreover, all numerical ranges herein should be understood to include all integer, whole or fractions, within the range.

[0072] In an alternative embodiment, the present disclosure provides a method of making a nutritional composition. The method comprises adding exogenous vitamin K_2 and a component selected from the group consisting of phosphorous, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, vitamin analogs, osteopontin or combinations thereof to a nutritional composition. In yet another embodiment, the present disclosure provides a method of improving bone health (i.e. growth, mineralization, microarchitecture, bone organic matrix constituents, density, elasticity and strength) in

pediatric patients. The method comprises administering to a child in need of same a nutritional composition including an effective amount of exogenous vitamin K_2. The nutritional composition may further include a component selected from the group consisting of phosphorous, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin or combinations thereof. In still another embodiment, the present disclosure provides a method of promoting bone growth and bone quality in a pediatric patient having an underlying medical condition. The method comprises administering to a pediatric patient having an underlying medical condition a nutritional composition including an effective amount of exogenous vitamin K_2. In another embodiment, the present disclosure provides a method of reducing the risk of bone fracture in a pediatric patient. The method comprises administering to a pediatric patient at risk of bone fracture a nutritional composition including an effective amount of exogenous vitamin K_2.

[0073] The nutritional composition can include the exogenous vitamin K_2 in an amount to be administered ranging from about 1 μg/day to about 100 μg/day. The exogenous vitamin K_2 can also be administered in an amount ranging from about 10 μg/day to about 95 μg/day, or from about 20 μg/day to about 90 μg/day, or from about 30 μg/day to about 85 μg/day, or from about 50 μg/day to about 80 μg/day, or 1 μg/day, 5 μg/day, or 10 μg/day, or 15 μg/day, or 20 μg/day, or 25 μg/day, or 30 μg/day, or 35 μg/day, or 40 μg/day, or 45 μg/day, or 50 μg/day, or 55 μg/day, or 60 μg/day, or 65 μg/day, or 70 μg/day, or 75 μg/day, or 80 μg/day, or 85 μg/day, or 90 μg/day, 95 μg/day, or 100 μg/day.

[0074] By using the nutritional compositions in embodiments of the present disclosure, improved osteocalcin carboxylation and improved indicies of bone health during normal growth and development in children will aid in reducing the risk of bone fracture. Similarly, administration of the present nutritional compositions may also result in increased bioavailability of vitamin K, which can result in increased osteocalcin carboxylation, bone strength, bone mineralization and bone microarchitecture.

[0075] In another embodiment, this invention provides for a method for improving skeletal muscle health (i.e. metabolic function, lean body mass and mobility). Skeletal muscle isoenzymes of creatine kinase are sensitive to Vitamin K deficiency. Creatine

kinase is a reaction essential to anaerobic energy production. An improvement in Vitamin K status may minimize muscular fatigue and optimize energy production to support anabolic processes such as protein synthesis for muscle mass accretion. Preservation of lean body mass can faciliate the maintenance of funtional mobility. The method comprises administering to a patient who can benefit from improved skeletal muscle health a nutritional composition including an effective amount of exogenous vitamin K_2.

[0076] In another embodiment, this invention provides for a method for reducing inflammation by administering Vitamin K2.

K2 AND INFLAMMATION

[0077] The acute control of global rates of protein synthesis is predominantly executed at the level of translational initiation with the modulation of various eukaryotic initiation factors (eIFs). The protein kinase referred to as the mammalian target of rapamycin (mTOR), which serves as a convergence point for signaling by growth factors and amino acids to the mRNA binding step of translation initiation is involved in modulation of the phosphorylation of the binding protein for the eukaryotic initiation factor 4E, *i.e.* 4E-BP1. It also acts to control the phosphorylation status of the 70-kDa ribosomal protein S6 kinase (S6K1). Modulation of these translation initiation events allows for more immediate control of protein synthesis and is responsive to changes associated with acute metabolic or nutritional alterations.

[0078] The canonical NF-κB pathway involves nuclear transport of a p65-p50 heterodimer. Activation of NF-κB occurs when IκBs are phosphorylated by the IκB kinase complex, leading to ubiquitination and degradation of IκB and nuclear translocation of the NF-κB dimer. Cytokines such as TNF-α are potent activators of the canonical NF-κB heterodimer, and this activation is associated with muscle protein loss.

METHODS

[0079] Male Sprague-Dawley rats (175 g) are kept on a 12-h light:dark cycle with food (Harlan-Teklad Rodent Chow, Madison, WI) and water provided freely. Animals are administered daily doses of vitamin K2 (MK-7) or saline (control) via oral gavage over 7

days. Stock solutions of vitamin K2 are prepared containing 3.5 g/L HCO-60 and 1 g/L of M&-7 in buffer A (0.15 M NaCl, 0.05 M Tris-HCl, pH 7.5). The K2 is dissolved by sonication during five pulses of 5 set with an amplitude of 6 pm. Solutions thus obtained are clear, homogeneous, and stable. Shortly before vitamin K administration the stock solutions are diluted five times with buffer A, leading to a final HCO-60 concentration of 0.7 g/L. Further dilutions (as required) are made with 0.7 g/L HCO-60 in buffer A. Each dilution step is followed by sonication as described above. In all cases vitamin K2 is administered to the rats in 0.5 mL samples, with either 25 or 50 microgram oral doses.

[0080] On the final day (Day 7), rodents are administered vitamin K2 and 2 hours later were given an IP dose of LPS (Escherichia coli serotype O111:B4, L2630, Sigma) intraperitoneally (0.5 mg/kg of body weight). Four hours later animals are sacrificed.

[0081] *Measurement of Protein Synthesis*—The fractional rate of synthesis (*Ks*) is estimated from the rate of incorporation of radioactive phenylalanine into total mixed muscle protein using the specific radioactivity of serum phenylalanine as representative of the precursor pool. The actual time for incorporation of the radiolabeled phenylalanine into protein is taken as the time elapsed from injection until freezing of muscle in liquid nitrogen.

[0082] *Analysis of mTOR Signaling to eIFs*—Gastrocnemius muscles are weighed and homogenized in 7 volumes of buffer containing 20 mM HEPES (pH 7.4), 100 mM potassium chloride, 0.2 mM EDTA, 2 mM EGTA, 50 mM sodium fluoride, 50 mM glycerophosphate, 0.1 mM phenylmethylsulfonyl fluoride, 1 mM benzamidine, 1 mM dithiothreitol (DTT), and 0.5 mM sodium vanadate. The remaining homogenate is centrifuged at 10,000 x *g* for 10 min at 4 °C. The resulting supernatant is combined with an equal volume of SDS sample buffer and then subjected to protein immunoblot analysis. Samples are analyzed for the phosphorylation status of 4E-BP1 (Thr37) and ribosomal protein S6 (Ser 235/236), the anti-phosphospecific antibodies were obtained from Cell Signaling Technology, Beverly, MA. Additionally, samples are analyzed for phosphorylated IKKα/β (Ser176/180; Cell Signaling Technology) and phosphorylated p65 (Ser536; Cell Signaling Technology).

RESULTS

[0083] Treatment of rodents with K2 results in a significant decrease in the rise of plasma TNF-α compared to LPS treated animals. Additionally, vitamin K2 results in a significant blunting of the drop in phosphorlyation for IKKα/β and NFκB p65 induction compared to LPS treatment. Finally, K2 abrogates the decrease in 4E-BP1(Thr-37) and ribosomal protein S6 phosphorylation compared to LPS treatment along with a greater preservation of the fractional rate of mixed muscle protein synthesis under conditions of inflammatory sepsis.

[0084] In another embodiment, this invention provides for a method for reducing inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0085] In another embodiment, this invention provides for a method for reducing the effects of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0086] In another embodiment, this invention provides for a method for preventing the effects of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from

the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0087] In another embodiment, this invention provides for a method for decreasing the rise of plasma TNF-α under conditions of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0088] In another embodiment, this invention provides for a method for blunting the drop in phosphorlyation for IKKα/β and NFκB p65 induction under conditions of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0089] In another embodiment, this invention provides for a method for abrogating the decrease in 4E-BP1(Thr-37) and ribosomal protein S6 phosphorylation under conditions of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium,

vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0090] In another embodiment, this invention provides for a method for preserving the fractional rate of mixed muscle protein synthesis under conditions of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising exogenous vitamin K2. In another embodiment, this nutritional composition further comprises a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof. In another embodiment, this nutritional composition further comprises at least one antioxidant. In another embodiment, this nutritional composition further comprises at least one phytonutrient. In another embodiment, the patient is a child.

[0091] It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

CLAIMS

The invention is claimed as follows:

1. A method of modulating the effects of inflammation, the method comprising: administering to a patient in need of same a nutritional composition comprising effective amount of exogenous vitamin K2.

2. The method of claim 1 wherein the exogenous vitamin K2 is selected from the group consisting of MK-4, MK-7 and combinations thereof.

3. The method of claim 1, wherein the exogenous vitamin K2 is MK-7.

4. The method of claim 1, wherein the effective amount of exogenous vitamin K2 is from about 1 μg to about 100 μg.

5. The method of claim 1, wherein the effective amount of exogenous vitamin K2 is from about 20 μg to about 90 μg.

6. The method of claim 1, wherein the effective amount of exogenous vitamin K2 is from about 50 μg to about 80 μg.

7. The method of claim 1, wherein the nutritional composition is in an administrable form selected from the group consisting of pharmaceutical formulations, nutritional formulations, tube-feed formulations, dietary supplements, functional foods and beverage products.

8. The method of claim 1, the nutritional composition further comprising at least one of prebiotic, probiotics, symbiotic, amino acid, protein, nucleotides, a fish oil, non-marine omega-3 fatty acid containing dietary fat source, phytonutrients, antioxidant, and combinations thereof.

9. The nutritional composition of claim 7, wherein the amino acid is selected from the group consisting of proline, hydroxyproline, hydroxytyrosine, hydroxylysine and hydroxyserine and combinations thereof.

10. The method of claim 1, wherein said modulation of the effects of inflammation is a reducing of the effects of inflammation.

11. The method of claim 1, wherein said modulation of the effects of inflammation is a preventing of the effects of inflammation.

12. The method of claim 1, wherein said modulation of the effects of inflammation is decreasing the rise of plasma TNF-α under conditions of inflammation.

13. The method of claim 1, wherein said modulation of the effects of inflammation is blunting the drop in phosphorlyation for IKKα/β and NFκB p65 induction under conditions of inflammation.

14. The method of claim 1, wherein said modulation of the effects of inflammation is abrogating the decrease in 4E-BP1(Thr-37) and ribosomal protein S6 phosphorylation under conditions of inflammation.

15. The method of claim 1, wherein said modulation of the effects of inflammation is preserving the fractional rate of mixed muscle protein synthesis under conditions of inflammation.

16. The method of claim 1, further comprising the steps of:
a) determining the patient's genetic predisposition to determine the likely efficacy of treatment with exogenous Vitamin K2; and
b) if determined to be efficacious, administering to a child in need of same a nutritional composition comprising an effective amount of exogenous vitamin K2

and a component selected from the group consisting of phosphorus, magnesium, zinc, iron, copper, manganese, calcium, vitamin D, osteopontin and combinations thereof.

17. The method of claim 16 wherein said genetic predisposition is determining the genotype.

18. The method of claim 16 wherein said genetic predisposition is used to determine the dosage of said exogenous Vitamin K2.

19. The method of claim 1, wherein the patient is a child.

20. The method of claim 1, wherein the patient has at least one of developmental delay, failure-to-thrive, inflammatory bowel disease, Crohn's disease, Crohn's Disease-associated osteopenia, Colitis, ulcerative colitis, celiac disease, gluten intolerance, neuromuscular dysfunction, cystic fibrosis, renal dysfunction, androgen deficiency, severe food allergy, short bowel syndrome, or combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/047468

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/302 A61K31/122 A61K35/00 A61P29/02

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)
A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/006607 A2 (NATTOPHARMA ASA [NO]; VERMEER CEES [NL]; SCHURGERS LEON J [NL]; KLAVEN) 17 January 2008 (2008-01-17)	1-8, 10-15,20
Y	See claim 1, 2, 3, 9, 22; page 14 line 2-9; section from page 5 line 19 to page 6, line 4: vitamin k2: nutraceutical compositions comprising vitamin K2, and preferably MK-7 for the treatment of inflammation (e.g. arthritis) See claims, in particular 1, 9, 12, 13, 21, 22: combination of vitamin K2 with prebiotics (fish oil and krill oil) See amounts of K2 in claim 23	1-20
	----- -/--	

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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
1 December 2010	22/12/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Fax: (+31–70) 340–3016	Veronese, Andrea

4

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 200580 Thomson Scientific, London, GB; AN 2005-786583 XP002611870 -& WO 2005/107731 A1 (EISAI CO LTD) 17 November 2005 (2005-11-17) See abstract: vitamin K2 compositions for the treatment of inflammation (e.g. as anti-rheumatic) and see inhibition of NF-kappa B activation	1,7, 10-15
X	DATABASE EPODOC [Online] EUROPEAN PATENT OFFICE, THE HAGUE, NL; 1992, XP002611871 Database accession no. JP4099758 See abstract: composition to be incorporated in a food, comprising menadione and use of such composition for the treatment of inflammation & JP 04 099758 A (NIPPON CATALYTIC CHEM IND) 31 March 1992 (1992-03-31)	1,10-15
Y	WO 97/39746 A1 (ADVANCED POLYMER SYSTEMS INC [US]) 30 October 1997 (1997-10-30) See page 1 line 10, page 5 line 28, page claims 1, 13, 15, 16: vitamin K2 for the treament of inflammatory conditions, such as rosacea and contact dermatitis. See page 4, line 6: reference to ingestion of vitamin K	1-20
Y	EP 1 153 548 A1 (UNILEVER NV [NL]; UNILEVER PLC [GB] VITAK B V [NL] NATTOPHARMA ASA [NO]) 14 November 2001 (2001-11-14) Food products comprising vitamin K2, preferrably being MK-4	1-20
Y	WO 2005/030190 A1 (NATURAL ASA [NO]; DALLAND JOSTEIN [NO]; SAEBO ASGEIR [NO]) 7 April 2005 (2005-04-07) See page 1, lines 8-10. examples, figures and description: nutricional additives comprising menaquinone MK7	1-20
X,P	US 2009/234022 A1 (SALENTINE CHRISTOPHER G [US] ET AL) 17 September 2009 (2009-09-17) See the compositions of the examples and the claims comprising menadione (vitamin K2), and their use for the treatment of inflammation (paragraphs 34 and 64)	1,4,5,7, 10,11

-/--

4

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	YUSUKE OHSAKI, ET AL.: "Vitamin K Suppresses Lipopolysaccharide-Induced Inflammation in the Rat" BIOSCIENCE, BIOTECHNOLOGY, AND BIOCHEMISTRY, vol. 70, no. 4, April 2006 (2006-04), pages 926-932, XP002611872 ISSN: 0916-8451 See abstract rsults and discussion: vitamin K reduces inflammation and influences gene expression in the liver	1-20
A	OZAKI IWATA ET AL: "Menatetrenone, a vitamin K2 analogue, inhibits hepatocellular carcinoma cell growth by suppressing cyclin D1 expression through inhibition of nuclear factor kappaB activation." CLINICAL CANCER RESEARCH : AN OFFICIAL JOURNAL OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, vol. 13, no. 7, 1 April 2007 (2007-04-01), pages 2236-2245, XP002611873 ISSN: 1078-0432 See abstract: a vitamin K2 analogue suppresses TNF -alfa induced NF-kB activation, and expression of the IKK/IkB/NF-kB pathway	12-14
T	YUKUSE OHSAKI, ET AL.: "Vitamin K suppresses the lipopolysaccharide-induced expression of inflammatory cytokines in cultured macrophage-like cells via the inhibition of the activation of nuclear factor kB through the repression of IKKAalpha/beta phosphorylation" THE JOURNAL OF NUTRITIONAL BIOCHEMISTRY, vol. 21, no. 11, November 2010 (2010-11), pages 1120-1126, XP002611874 ISSN: 1873-4847 the whole document	
A	WO 2009/095240 A1 (FRIESLAND BRANDS BV [NL]; SCHAAFSMA ANNE [NL]; GLAS CORNELIS [NL]; VAN) 6 August 2009 (2009-08-06) See passage from page 7, line 10 to page 8, line 30; examples 1, 2, 4, 5, 7, 8-11, 11, 16; claims: nutraceutical compositions comprising vitamin K2 and calcium, magnesium, phosphorous (phosphate). See page 1, 2, example 18, claims 22-32: use of the compositions for the treatment of bone conditions	16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/047468

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008006607 A2	17-01-2008	AU 2007271900 A1	17-01-2008
		CA 2657748 A1	17-01-2008
		EP 2046312 A2	15-04-2009
		JP 2009544590 T	17-12-2009
		US 2010048704 A1	25-02-2010
WO 2005107731 A1	17-11-2005	NONE	
JP 4099758 A	31-03-1992	JP 2086542 C	02-09-1996
		JP 7119191 B	20-12-1995
WO 9739746 A1	30-10-1997	AU 2804297 A	12-11-1997
EP 1153548 A1	14-11-2001	NONE	
WO 2005030190 A1	07-04-2005	EP 1675580 A1	05-07-2006
US 2009234022 A1	17-09-2009	AU 2009223158 A1	17-09-2009
		CA 2718262 A1	17-09-2009
		WO 2009114745 A1	17-09-2009
WO 2009095240 A1	06-08-2009	EP 2247199 A1	10-11-2010
		NL 1034964 C2	30-07-2009