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(54) **Title**: NUTRITIONAL COMPOSITIONS COMPRISING A CASEIN HYDROLYSATE, AS WELL AS DIETARY BUTYRATE AND/OR A COMPOUND FOR STIMULATING FORMATION OF ENDOGENOUS BUTYRATE

(57) **Abstract**: Provided are nutritional compositions including a component for stimulating butyrate production in the human gut and/or dietary butyrate. Further disclosed are methods of reducing allergic reaction and promoting tolerance to cow's milk allergy in a pediatric subject by providing said nutritional compositions to a target subject.

DESCRIPTION

NUTRITIONAL COMPOSITIONS COMPRISING A CASEIN HYDROLYSATE, AS WELL AS DIETARY BUTYRATE AND/OR A COMPOUND FOR STIMULATING FORMATION OF ENDOGENOUS BUTYRATE

TECHNICAL FIELD

[0001] The present disclosure relates generally to nutritional compositions comprising dietary butyrate and a component, which can stimulate the production of endogenous butyrate. The nutritional compositions are suitable for administration to pediatric subjects. Additionally, the disclosure relates to nutritional compositions including a prebiotic comprising polydextrose and galacto-oligosaccharides, dietary butyrate, and a protein equivalent source. Further, disclosed are methods for reducing the incidence of allergy and/or improving tolerance to cow's milk allergy in target subjects. The disclosed nutritional compositions may provide additive and or/synergistic beneficial health effects.

BACKGROUND ART

[0002] Administration of nutritional compositions or other compositions including butyrate or butyrate derivatives often suffer from difficulties regarding the bioavailability of butyrate upon administration. For example, certain butyrate derivatives undergo degradation or oxidation, which ultimate affect the bioavailability of the butyrate derivative upon ingestion. As such, compositions including butyrate derivatives may not provide therapeutic efficacy upon ingestion given the degradation of the butyrate derivative.

[0003] Additionally, nutritional compositions including butyrate may suffer from poor palatability. The unpleasant taste and odor of compositions including butyrate can make the oral administration of certain nutritional compositions including butyrate difficult, especially in the pediatric population. For example, certain butyric acid derivatives at room temperature are present as a dense liquid having an unpleasant taste and intense odor.

[0004] Accordingly, it would be beneficial to provide a nutritional composition that includes endogenous butyrate to avoid the palatability issues sometimes found with dietary butyrate. Further, there is a need for palatable, safe, yet effective, nutritional compositions that include a combination of one or more prebiotics, a protein equivalent source, and butyrate to reduce incidence of allergy and increase tolerance to cow's milk allergy in certain subjects.

DISCLOSURE OF THE INVENTION

[0005] Briefly, the present disclosure is directed, in an embodiment, to a nutritional composition that includes dietary butyrate and a component which can stimulate the production of endogenous butyrate in the human gut. In some embodiments, the dietary butyrate may be encapsulated. In some embodiments, the endogenous butyrate may be

provided by stimulating short chain fatty acid ("SCFA") production by the gut microbiota and the dietary butyrate may be provided by an enriched lipid fraction derived from milk.

[0006] It is to be understood that both the foregoing general description and the following detailed description present embodiments of the disclosure and are intended to provide an overview or framework for understanding the nature and character of the disclosure as it is claimed. The description serves to explain the principles and operations of the claimed subject matter. Other and further features and advantages of the present disclosure will be readily apparent to those skilled in the art upon a reading of the following disclosure.

BEST MODE FOR CARRYING OUT THE INVENTION

[0007] Reference now will be made in detail to the embodiments of the present disclosure, one or more examples of which are set forth hereinbelow. Each example is provided by way of explanation of the nutritional composition of the present disclosure and is not a limitation. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made to the teachings of the present disclosure without departing from the scope of the disclosure. For instance, features illustrated or described as part of one embodiment, can be used with another embodiment to yield a still further embodiment.

[0008] Thus, it is intended that the present disclosure covers such modifications and variations as come within the scope of the appended claims and their equivalents. Other objects, features and aspects of the present disclosure are disclosed in or are apparent from the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only and is not intended as limiting the broader aspects of the present disclosure.

[0009] The present disclosure relates generally to nutritional compositions comprising dietary butyrate and a component for stimulating the production of endogenous butyrate. Additionally, the disclosure relates to methods for improving the shelf stability and/or organoleptic properties of nutritional compositions including butyrate.

[0010] "Nutritional composition" means a substance or formulation that satisfies at least a portion of a subject's nutrient requirements. The terms "nutritional(s)", "nutritional formula(s)", "enteral nutritional(s)", and "nutritional supplement(s)" are used as non-limiting examples of nutritional composition(s) throughout the present disclosure. Moreover, "nutritional composition(s)" may refer to liquids, powders, gels, pastes, solids, concentrates, suspensions, or ready-to-use forms of enteral formulas, oral formulas, formulas for infants, formulas for pediatric subjects, formulas for children, growing-up milks and/or formulas for adults.

[0011] "Pediatric subject" means a human less than 13 years of age. In some embodiments, a pediatric subject refers to a human subject that is between birth and 8 years old. In other

embodiments, a pediatric subject refers to a human subject between 1 and 6 years of age. In still further embodiments, a pediatric subject refers to a human subject between 6 and 12 years of age. The term "pediatric subject" may refer to infants (preterm or fullterm) and/or children, as described below.

[0012] "Infant" means a human subject ranging in age from birth to not more than one year and includes infants from 0 to 12 months corrected age. The phrase "corrected age" means an infant's chronological age minus the amount of time that the infant was born premature. Therefore, the corrected age is the age of the infant if it had been carried to full term. The term infant includes low birth weight infants, very low birth weight infants, and preterm infants. "Preterm" means an infant born before the end of the 37th week of gestation. "Full term" means an infant born after the end of the 37th week of gestation.

[0013] "Child" means a subject ranging in age from 12 months to about 13 years. In some embodiments, a child is a subject between the ages of 1 and 12 years old. In other embodiments, the terms "children" or "child" refer to subjects that are between one and about six years old, or between about seven and about 12 years old. In other embodiments, the terms "children" or "child" refer to any range of ages between 12 months and about 13 years.

[0014] "Infant formula" means a composition that satisfies at least a portion of the nutrient requirements of an infant. In the United States, the content of an infant formula is dictated by the federal regulations set forth at 21 C.F.R. Sections 100, 106, and 107.

[0015] The term "medical food" refers enteral compositions that are formulated or intended for the dietary management of a disease or disorder. A medical food may be a food for oral ingestion or tube feeding (nasogastric tube), may be labeled for the dietary management of a specific medical disorder, disease or condition for which there are distinctive nutritional requirements, and may be intended to be used under medical supervision.

[0016] The term "peptide" as used herein describes linear molecular chains of amino acids, including single chain molecules or their fragments. The peptides described herein include no more than 50 total amino acids. Peptides may further form oligomers or multimers consisting of at least two identical or different molecules. Furthermore, peptidomimetics of such peptides where amino acid(s) and/or peptide bond(s) have been replaced by functional analogs are also encompassed by the term "peptide". Such functional analogues may include, but are not limited to, all known amino acids other than the 20 gene-encoded amino acids such as selenocysteine.

[0017] The term "peptide" may also refer to naturally modified peptides where the modification is effected, for example, by glycosylation, acetylation, phosphorylation and similar modification which are well known in the art. In some embodiments, the peptide

component is distinguished from a protein source also disclosed herein. Further, peptides may, for example, be produced recombinantly, semi-synthetically, synthetically, or obtained from natural sources such as after hydrolysation of proteins, including but not limited to casein, all according to methods known in the art.

[0018] The term "molar mass distribution" when used in reference to a hydrolyzed protein or protein hydrolysate pertains to the molar mass of each peptide present in the protein hydrolysate. For example, a protein hydrolysate having a molar mass distribution of greater than 500 Daltons means that each peptide included in the protein hydrolysate has a molar mass of at least 500 Daltons. Accordingly, in some embodiments, the peptides disclosed in Table 1 and Table 2 are derived from a protein hydrolysate having a molar mass distribution of greater than 500 Daltons. To produce a protein hydrolysate having a molar mass distribution of greater than 500 Daltons, a protein hydrolysate may be subjected to certain filtering procedures or any other procedure known in the art for removing peptides, amino acids, and/or other proteinaceous material having a molar mass of less than 500 Daltons. For the purposes of this disclosure, any method known in the art may be used to produce the protein hydrolysate having a molar mass distribution of greater than 500 Dalton.

[0019] The term "protein equivalent" or "protein equivalent source" includes any protein source, such as soy, egg, whey, or casein, as well as non-protein sources, such as peptides or amino acids. Further, the protein equivalent source can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, peptides, amino acids, and the like. Bovine milk protein sources useful in practicing the present disclosure include, but are not limited to, milk protein powders, milk protein concentrates, milk protein isolates, nonfat milk solids, nonfat milk, nonfat dry milk, whey protein, whey protein isolates, whey protein concentrates, sweet whey, acid whey, casein, acid casein, caseinate (*e.g.* sodium caseinate, sodium calcium caseinate, calcium caseinate), soy bean proteins, and any combinations thereof. The protein equivalent source can, in some embodiments comprise hydrolyzed protein, including partially hydrolyzed protein and extensively hydrolyzed protein. The protein equivalent source may, in some embodiments, include intact protein. More particularly, the protein source may include a) about 20% to about 80% of the peptide component described herein, and b) about 20% to about 80 % of an intact protein, a hydrolyzed protein, or a combination thereof.

[0020] The term "protein equivalent source" also encompasses free amino acids. In some embodiments, the amino acids may comprise, but are not limited to, histidine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, alanine, arginine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, proline, serine, carnitine, taurine and mixtures thereof. In some embodiments, the amino acids may be

branched chain amino acids. In certain other embodiments, small amino acid peptides may be included as the protein component of the nutritional composition. Such small amino acid peptides may be naturally occurring or synthesized.

[0021] "Fractionation procedure" includes any process in which a certain quantity of a mixture is divided up into a number of smaller quantities known as fractions. The fractions may be different in composition from both the mixture and other fractions. Examples of fractionation procedures include but are not limited to, melt fractionation, solvent fractionation, supercritical fluid fractionation and/or combinations thereof.

[0022] The term "essential amino acid" as used herein refers to an amino acid that cannot be synthesized *de novo* by the organism being considered or that is produced in an insufficient amount, and therefore must be supplied by diet. For example, in some embodiments, where the target subject is a human, an essential amino acid is one that cannot be synthesized *de novo* by a human.

[0023] The term "non-essential amino acid" as used herein refers to an amino acid that can be synthesized by the organism or derived by the organism from essential amino acids. For example, in some embodiments, where the target subject is a human, a non-essential amino acid is one that can be synthesized in the human body or derived in the human body from essential amino acids.

[0024] "Milk fat globule membrane" includes components found in the milk fat globule membrane including but not limited to milk fat globule membrane proteins such as Mucin 1, Butyrophilin, Adipophilin, CD36, CD14, Lactadherin (PAS6/7), Xanthine oxidase and Fatty Acid binding proteins etc.

[0025] The term "growing-up milk" refers to a broad category of nutritional compositions intended to be used as a part of a diverse diet in order to support the normal growth and development of a child between the ages of about 1 and about 6 years of age.

[0026] "Milk" means a component that has been drawn or extracted from the mammary gland of a mammal. In some embodiments, the nutritional composition comprises components of milk that are derived from domesticated ungulates, ruminants or other mammals or any combination thereof.

[0027] "Nutritionally complete" means a composition that may be used as the sole source of nutrition, which would supply essentially all of the required daily amounts of vitamins, minerals, and/or trace elements in combination with proteins, carbohydrates, and lipids. Indeed, "nutritionally complete" describes a nutritional composition that provides adequate amounts of carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals and energy required to support normal growth and development of a subject.

[0028] A nutritional composition that is "nutritionally complete" for a full term infant will, by definition, provide qualitatively and quantitatively adequate amounts of all carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals, and energy required for growth of the full term infant.

[0029] A nutritional composition that is "nutritionally complete" for a child will, by definition, provide qualitatively and quantitatively adequate amounts of all carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals, and energy required for growth of a child.

[0030] "Exogenous butyrate" or "dietary butyrate" each refer to butyrate or butyrate derivatives which are intentionally included in the nutritional composition of the present disclosure itself, rather than generated in the gut.

[0031] "Endogenous butyrate" or "butyrate from endogenous sources" each refer to butyrate present in the gut as a result of ingestion of the disclosed composition that is not added as such, but is present as a result of other components or ingredients of the composition; the presence of such other components or ingredients of the composition stimulates butyrate production in the gut.

[0032] The term "cow's milk allergy" describes a food allergy, *i.e.* an immune adverse reaction to one or more of the proteins contained in cow's milk in a human subject. The principal symptoms are gastrointestinal, dermatological, and respiratory symptoms. These can translate into skin rashes, hives, vomiting, diarrhea, constipation and distress. The clinical spectrum extends to diverse disorders: anaphylactic reactions, atopic dermatitis, wheeze, infantile colic, gastro esophageal reflux disease (GERD), esophagitis, colitis gastroenteritis, headache/migraine and constipation.

[0033] The nutritional composition of the present disclosure may be substantially free of any optional or selected ingredients described herein, provided that the remaining nutritional composition still contains all of the required ingredients or features described herein. In this context, and unless otherwise specified, the term "substantially free" means that the selected composition may contain less than a functional amount of the optional ingredient, typically less than 0.1% by weight, and also, including zero percent by weight of such optional or selected ingredient.

[0034] All percentages, parts and ratios as used herein are by weight of the total composition, unless otherwise specified.

[0035] All references to singular characteristics or limitations of the present disclosure shall include the corresponding plural characteristic or limitation, and vice versa, unless otherwise specified or clearly implied to the contrary by the context in which the reference is made.

[0036] All combinations of method or process steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0037] The methods and compositions of the present disclosure, including components thereof, can comprise, consist of, or consist essentially of the essential elements and limitations of the embodiments described herein, as well as any additional or optional ingredients, components or limitations described herein or otherwise useful in nutritional compositions.

[0038] As used herein, the term "about" should be construed to refer to both of the numbers specified as the endpoint(s) of any range. Any reference to a range should be considered as providing support for any subset within that range.

[0039] The present disclosure is directed to nutritional compositions including butyrate and LGG. Non-limiting examples of butyrate for use herein include butyric acid, butyrate salts, and glycerol esters of butyric acid. The nutritional compositions may further include a carbohydrate source, a protein source, and a fat or lipid source. In some embodiments, the nutritional compositions may include a component capable of stimulating endogenous butyrate production; in other embodiments, the nutritional compositions may include both dietary and endogenous butyrate.

[0040] The benefit to providing both exogenous and endogenous butyrate is accelerated tolerance acquisition towards cow's milk. Additionally, the benefit to providing both exogenous and endogenous butyrate together with *Lactobacillus rhamnoses* GG ("LGG") is accelerated tolerance acquisition toward cow's milk. Conventional dietary management of cow's milk allergy includes the use of formulations containing protein hydrolysates and amino acids rather than intact proteins, and certain probiotics such as Lactobacillus rhamnoses GG ("LGG"), which contribute to accelerated tolerance acquisition towards cow's milk. The inclusion of a component to stimulate endogenous butyrate production by the gut microbiota may further accelerate tolerance acquisition and/or may be applied as a functional replacement of LGG in a nutritional composition. Further, the inclusion of certain probiotics, such as LGG in combination with butyrate, either endogenous or exogenous butyrate, can contribute to accelerated tolerance acquisition towards cow's milk.

[0041] In an embodiment, the component for stimulating endogenous buyrate is a prebiotic comprising both polydextrose ("PDX") and galacto-oligosaccharides ("GOS"). A prebiotic component including PDX and GOS can enhance endogenous butyrate production by microbiota. Butyrate has epigenetic (histone deacetylase inhibition activity) that results in regulatory responses such as generation of regulatory T-cells. In the context of cow s milk

allergy, these regulatory responses may result in accelerated tolerance acquisition to cow's milk protein.

[0042] In addition to PDX and GOS, the nutritional composition may also contain one or more other prebiotics which can exert additional health benefits, which may include, but are not limited to, selective stimulation of the growth and/or activity of one or a limited number of beneficial gut bacteria, stimulation of the growth and/or activity of ingested probiotic microorganisms, selective reduction in gut pathogens, and favorable influence on gut short chain fatty acid profile. Such prebiotics may be naturally-occurring, synthetic, or developed through the genetic manipulation of organisms and/or plants, whether such new source is now known or developed later. Prebiotics useful in the present disclosure may include oligosaccharides, polysaccharides, and other prebiotics that contain fructose, xylose, soya, galactose, glucose and mannose.

[0043] More specifically, prebiotics useful in the present disclosure include PDX and GOS, and can, in some embodiments, also include, polydextrose powder, lactulose, lactosucrose, raffinose, gluco-oligosaccharide, inulin, fructo-oligosaccharide (FOS), isomalto-oligosaccharide, soybean oligosaccharides, lactosucrose, xylo-oligosaccharide (XOS), chito-oligosaccharide, manno-oligosaccharide, aribino-oligosaccharide, siallyl-oligosaccharide, fuco-oligosaccharide, and gentio-oligosaccharides.

[0044] In an embodiment, the total amount of prebiotics present in the nutritional composition may be from about 1.0 g/L to about 10.0 g/L of the composition. More preferably, the total amount of prebiotics present in the nutritional composition may be from about 2.0 g/L and about 8.0 g/L of the composition. In some embodiments, the total amount of prebiotics present in the nutritional composition may be from about 0.01 g/100 Kcal to about 1.5 g/100 Kcal. In certain embodiments, the total amount of prebiotics present in the nutritional composition may be from about 0.15 g/100 Kcal to about 1.5 g/100 Kcal. In some embodiments, the prebiotic component comprises at least 20% w/w PDX and GOS.

[0045] The amount of PDX in the nutritional composition may, in an embodiment, be within the range of from about 0.015 g/100 Kcal to about 1.5 g/100 Kcal. In another embodiment, the amount of polydextrose is within the range of from about 0.2 g/100 Kcal to about 0.6 g/100 Kcal. In some embodiments, PDX may be included in the nutritional composition in an amount sufficient to provide between about 1.0 g/L and 10.0 g/L. In another embodiment, the nutritional composition contains an amount of PDX that is between about 2.0 g/L and 8.0 g/L. And in still other embodiments, the amount of PDX in the nutritional composition may be from about 0.05 g/100 Kcal to about 1.5 g/100 Kcal.

[0046] The prebiotic component also comprises GOS. The amount of GOS in the nutritional composition may, in an embodiment, be from about 0.015 g/100 Kcal to about 1.0 g/100

Kcal. In another embodiment, the amount of GOS in the nutritional composition may be from about 0.2 g/100 Kcal to about 0.5 g/100 Kcal.

[0047] In a particular embodiment, GOS and PDX are supplemented into the nutritional composition in a total amount of at least about 0.015 g/100 Kcal or about 0.015 g/100 Kcal to about 1.5 g/100 Kcal. In some embodiments, the nutritional composition may comprise GOS and PDX in a total amount of from about 0.1 to about 1.0 g/100 Kcal.

[0048] In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 5 g/100 Kcal to about 500 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 15 g/100 Kcal to about 450 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 20 g/100 Kcal to about 400 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 25 g/100 Kcal to about 350 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 30 g/100 Kcal to about 280 g/100 kcal.

[0049] In some embodiments, the nutritional composition includes from about 0.01 g to about 10 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.1 g to about 8 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.4 g to about 7 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.7 g to about 6.5 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 1.2 g to about 5.1 g of dietary butyrate per 100 g of total fat in the nutritional composition.

[0050] In some embodiments the dietary butyrate is provided by one or more of the following: butyric acid; butyrate salts, including sodium butyrate, potassium butyrate, calcium butyrate, and/or magnesium butyrate; glycerol esters of butyric acid; and/or corresponding mixtures and corresponding salts of pharmaceutically acceptable bases or acids, pure diastereoisomeric forms and enantiomeric forms or mixtures thereof.

[0051] The dietary butyrate can be supplied by any suitable source known in the art. Non-limiting sources of dietary butyrate includes animal source fats and derived products, such as but not limited to milk, milk fat, butter, buttermilk, butter serum, cream; microbial fermentation derived products, such as but not limited to yogurt and fermented buttermilk; and plant source derived seed oil products, such as pineapple and/or pineapple oil, apricot

and/or apricot oil, barley, oats, brown rice, bran, green beans, legumes, leafy greens, apples, kiwi, oranges. In some embodiments, the dietary butyrate is synthetically produced. In embodiments where the dietary butyrate is synthetically produced, the chemical structure of the dietary butyrate may be modified as necessary. Further, the dietary butyrate produced synthetically can be purified by any means known in the art to produce a purified dietary butyrate additive that can be incorporated into the nutritional compositions disclosed herein. The dietary butyrate may be provided by dairy lipids and/or triglyceride bound forms of butyrate.

[0052] In some embodiments, the dietary butyrate may be provided in an encapsulated form. In certain embodiments, the encapsulation of the dietary butyrate may provide for longer shelf-stability and may provide for improved organoleptic properties of the nutritional composition. For example, in some embodiments, the dietary butyrate may be encapsulated or coated by the use of, or combination of, fat derived materials, such as mono- and di-glycerides; sugar and acid esters of glycerides; phospholipids; plant, animal and microbial derived proteins and hydrocolloids, such as starches, maltodextrins, gelatin, pectins, glucans, caseins, soy proteins, and/or whey proteins.

[0053] The dietary butyric acid may also be provided in a coated form. For example, coating certain glycerol esters of butyric acids and/or amide derivatives of butyric acids with fat derived materials, such as mono- and di-glycerides; sugar and acid esters of glycerides; phospholipids; plant, animal and microbial derived proteins and hydrocolloids, such as starches, maltodextrins, gelatin, pectins, glucans, caseins, soy proteins, and/or whey proteins may improve the shelf-stability of the dietary butyrate and may further improve the overall organoleptic properties of the nutritional composition.

[0054] In certain embodiments, the dietary butyrate comprises glycerol esters of butyric acid. Glycerol esters of butyric acid may offer minimal complexity when formulated and processed in the nutritional composition. Additionally, glycerol esters of butyric acid may improve the shelf life of the nutritional composition including dietary butyrate an may further have a low impact on the sensory attributes of the finished product.

[0055] In some embodiments, the dietary butyrate may comprise butyrate salts, for example, sodium butyrate, potassium butyrate, calcium butyrate, magnesium butyrate, and combinations thereof. In some embodiments, the use of selected dietary butyrate salts may improve intestinal health when provided to target subjects. In certain embodiments, dietary butyrate comprises a suitable butyrate salt that has been coated with one or more fats or lipids. In certain embodiments wherein the dietary butyrate comprises a fat coated butyrate salt, the nutritional composition may be a dry-powdered composition into which the dietary butyrate is incorporated.

[0056] In some embodiments, the dietary butyrate may comprise any of the butyrate compounds disclosed herein that are formulated to be in complex form with chitosan or one or cyclodextrins. For example, cyclodextrins are cyclic oligosaccharides composed of six (α-cyclodextrin), seven (β-cyclodextrin), or eight (gamma-cyclodextrin) units of α-1,4-glucopyranose. Cyclodextrins are further characterized by a hydrophilic exterior surface and a hydrophobic core. Without being bound by any particular theory, the aliphatic butyrate chain would form a complex with the cyclodextrin core, thus increasing its molecular weight and, thus, reducing the volatility of the butyrate compound. Accordingly, the bioavailability of dietary butyrate may be improved when the dietary butyrate includes butyrate compounds in complex form with one or more cyclodextrins. Further, cyclodextrins are bulky hydrophobic molecules that are resistant to stomach acid as well as gastrointestinal enzymes, thus administration of the butyrate-cyclodextrin complex as described herein would promote absorption of the dietary butyrate in the small intestines.

[0057] In some embodiments the dietary butyrate is provided from an enriched lipid fraction derived from milk. For example, bovine milk fat has a butyric acid content that may be 20 times higher than the butyric acid content in human milk fat. Furthermore, among the short chain fatty acids ("SCFAs") present in human milk, *i.e.* fatty acids having a carbon chain length from 4 to 12, butyric acid (C4) is one of the most predominant in bovine milk. As such, bovine milk fat and/or enriched fractions of bovine milk fat may be included in a nutritional composition to provide dietary butyrate.

[0058] In embodiments where the dietary butyrate is provided by an enriched lipid fraction derived from milk the enriched lipid fraction derived from milk may be produced by any number of fractionation techniques. These techniques include but are not limited to melting point fractionation, organic solvent fractionation, super critical fluid fractionation, and any variants and combinations thereof.

[0059] Furthermore, mixtures that may be subjected to the fractionation procedures to produce the enriched lipid fraction include, but are not limited to, bovine whole milk, bovine cream, caprine milk, ovine milk, yak milk, and/or mixtures thereof. In a preferred embodiment the milk mixture used to create the enriched lipid fraction is bovine milk.

[0060] In addition to providing dietary butyrate, the enriched lipid fraction may comprise an one of the following ingredients: saturated fatty acids; trans-fatty acids; branched-chain fatty acids ("BCFAs"), including odd-branched chain fatty acids ("OBCFAs"); conjugated linoleic acid ("CLA"); monounsaturated fatty acids; polyunsaturated fatty acids; cholesterol; phospholipids; and milk fat globule membrane, including milk fat globule membrane protein.

[0061] In some embodiments the enriched lipid fraction includes, per 100 Kcal, one or more of the following:

from about 0.1 g to 8.0 g of saturated fatty acids;

from about 0.2 g to 7.0 g trans-fatty acids;

from about 0.003 g to about 6.1 g branched-chain fatty acids;

from about 0.026 g to about 2.5 g conjugated linoleic acid;

from about 0.8 g to about 2.5 g monounsaturated fatty acids;

from about 2.3 g to about 4.4 g polyunsaturated fatty acids;

from about 100 mg to about 400 mg of cholesterol;

from about 50 mg to about 400 mg of phospholipids; and/or

from about 10 mg to about 500 mg of milk fat globule membrane.

[0062] The following example illustrates a milk fat fraction having an enriched concentration of butyric acid (C4) that may be produced by a fractionation procedure.

Example 1

[0063] Illustrated below is a lipid profile of fractionated milk fat produced by super critical carbon extraction fractionation procedure and by melt-fractionation.

Milk Fat composition (g fatty acid /100 g TOTAL fatty acids)

	AMF	SCCO2	MeltFrac 10C
C 4:0	3.9	6.0	4.7
C 6:0	2.5	3.3	2.9
C 8:0	1.4	1.9	1.8
C 10:0	3.1	3.9	3.8
C 12:0	4.2	4.1	4.8
C 14:0	11.4	12.2	10.9
C 14:1	1.1	1.0	1.3
C 15:0	1.1	1.0	0.9
C 16:0	29.4	29.6	22.3
C 16:1	1.9	1.4	2.2
C 17:0	0.6	0.5	0.4
C 18:0	11.4	8.2	6.1
C 18:1, cis, ω9	21.9	16.5	25.3
C 18:1, trans, ω9	0.3	1.6	1.9
C 18:2, ω6	1.9	2.2	1.9
C 18:3, ω3, α	0.6	0.4	0.6
C 20:0	0.0	0.1	0.1

C 20:1, ω9	0.1	0.1	0.2
Saturated	68.7	70.7	58.6
Unsaturated	27.8	23.1	33.3

AMF = anhydrous milk fat; SCCO2 = super-critical carbon dioxide fraction (super olein). MeltFrac = melt crystallization fraction separated at 10°C.

[0064] In certain embodiments, the PDX- and GOS-containing prebiotic and dietary butyrate is incorporated into a nutritional composition that is an infant formula. Currently, many infant formulas are not formulated with dietary butyrate. One reason that infant formulas include little to no dietary butyrate is due to the unpleasant organoleptic properties exhibited by the nutritional composition when butyrate compounds are incorporated into the nutritional composition. For example, many butyrate compounds exhibit an odor that makes consuming the nutritional composition in which they are incorporated an unpleasant experience. Furthermore, the pediatric and infant population will not readily consume nutritional products having an unpleasant odor, taste, and/or mouthfeel. Accordingly, there exists a need for a nutritional composition formulated for administration to a pediatric subject or an infant that provides butyrate in the gut yet does not have diminished organoleptic properties. The incorporation of a prebiotic to stimulate butyrate production by gut microbiota and certain dietary butyrate compounds disclosed herein, *i.e.* glycerol esters of butyric acid and amide derivatives of amino acids, into pediatric and infant nutritional compositions will provide butyrate while still providing a pleasant sensory experience.

[0065] In some embodiments, the nutritional composition includes a protein equivalent source, wherein the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63. In some embodiments, the peptide component may comprise additional peptides disclosed in Table 1. For example, the composition may include at least 10 additional peptides disclosed in Table 1. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component, and 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, and combinations thereof. In some embodiments, the term additional means selecting different peptides than those enumerated.

[0066] In another embodiment 1% to 99% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID

NO 63, and at least 5 additional peptides selected from Table 1; and wherein 1% to 99% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof. In some embodiments 2% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 2% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof. In some embodiments 20% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof.

[0067] Table 1 below identifies the amino acid sequences of the peptides that may be included in the peptide component of the present nutritional compositions.

TABLE 1

Seq. ID Number	Amino Acid Sequence											(aa)
1	Ala	Ile	Asn	Pro	Ser	Lys	Glu	Asn				8
2	Ala	Pro	Phe	Pro	Glu							5
3	Asp	Ile	Gly	Ser	Glu	Ser						6
4	Asp	Lys	Thr	Glu	Ile	Pro	Thr					7
5	Asp	Met	Glu	Ser	Thr							5
6	Asp	Met	Pro	Ile								4
7	Asp	Val	Pro	Ser								4
n/a	Glu	Asp	Ile									3
n/a	Glu	Leu	Phe									3
n/a	Glu	Met	Pro									3
8	Glu	Thr	Ala	Pro	Val	Pro	Leu					7
9	Phe	Pro	Gly	Pro	Ile	Pro						6
10	Phe	Pro	Gly	Pro	Ile	Pro	Asn					7
11	Gly	Pro	Phe	Pro								4
12	Gly	Pro	Ile	Val								4

13	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln			9
14	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser				8
15	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala			9
16	Ile	Asn	Pro	Ser	Lys	Glu						6
17	Ile	Pro	Asn	Pro	Ile							5
18	Ile	Pro	Asn	Pro	Ile	Gly						6
19	Ile	Pro	Pro	Leu	Thr	Gln	Thr	Pro	Val			9
20	Ile	Thr	Ala	Pro								4
21	Ile	Val	Pro	Asn								4
22	Lys	His	Gln	Gly	Leu	Pro	Gln					7
23	Leu	Asp	Val	Thr	Pro							5
24	Leu	Glu	Asp	Ser	Pro	Glu						6
25	Leu	Pro	Leu	Pro	Leu							5
26	Met	Glu	Ser	Thr	Glu	Val						6
27	Met	His	Gln	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr	11
28	Asn	Ala	Val	Pro	Ile							5
29	Asn	Glu	Val	Glu	Ala							5
n/a	Asn	Leu	Leu									3
30	Asn	Gln	Glu	Gln	Pro	Ile						6
31	Asn	Val	Pro	Gly	Glu							5
32	Pro	Phe	Pro	gly	Pro	Ile						6
33	Pro	Gly	Pro	Ile	Pro	Asn						6
34	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr				8
35	Pro	Ile	Thr	Pro	Thr							5
36	Pro	Asn	Pro	Ile								4
37	Pro	Asn	Ser	Leu	Pro	Gln						6
38	Pro	Gln	Leu	Glu	Ile	Val	Pro	Asn				8
39	Pro	Gln	Asn	Ile	Pro	Pro	Leu					7
40	Pro	Val	Leu	Gly	Pro	Val						6
41	Pro	Val	Pro	Gln								4
42	Pro	Val	Val	Val	Pro							5
43	Pro	Val	Val	Val	Pro	Pro						6
44	Ser	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala	Glu	11
45	Ser	Ile	Ser	Ser	Ser	Glu	Glu					7

46	Ser	Ile	Ser	Ser	Ser	Glu	Glu	Ile	Val	Pro	Asn	11
47	Ser	Lys	Asp	Ile	Gly	Ser	Glu					7
48	Ser	Pro	Pro	Glu	Ile	Asn						6
49	Ser	Pro	Pro	Glu	Ile	Asn	Thr					7
50	Thr	Asp	Ala	Pro	Ser	Phe	Ser					7
51	Thr	Glu	Asp	Glu	Leu							5
52	Val	Ala	Thr	Glu	Glu	Val						6
53	Val	Leu	Pro	Val	Pro							5
54	Val	Pro	Gly	Glu								4
55	Val	Pro	Gly	Glu	Ile	Val						6
56	Val	Pro	Ile	Thr	Pro	Thr						6
57	Val	Pro	Ser	Glu								4
58	Val	Val	Pro	Pro	Phe	Leu	Gln	Pro	Glu			9
59	Val	Val	Val	Pro	Pro							5
60	Tyr	Pro	Phe	Pro	Gly	Pro						6
61	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro				8
62	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro	Asn			9
63	Tyr	Pro	Ser	Gly	Ala							5
64	Tyr	Pro	Val	Glu	Pro							5

[0068] Table 2 below further identifies a subset of amino acid sequences from Table 1 that may be included in the peptide component disclosed herein.

TABLE 2

Seq ID Number		**Amino Acid Sequence**											**(aa)**
4		Asp	Lys	Thr	Glu	Ile	Pro	Thr					7
13		Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln			9
17		Ile	Pro	Asn	Pro	Ile	Gly						6
21		Ile	Val	Pro	Asn								4
24		Leu	Glu	Asp	Ser	Pro	Glu						6
30		Asn	Gln	Glu	Gln	Pro	Ile						6
31		Asn	Val	Pro	Gly	Glu							5
32		Pro	Phe	Pro	Gly	Pro	Ile						6
51		Thr	Glu	Asp	Glu	Leu							5
57		Val	Pro	Ser	Glu								4

60		Tyr	Pro	Phe	Pro	Gly	Pro						6
63		Tyr	Pro	Ser	Gly	Ala							5

[0069] In some embodiments, the peptide component may be present in the nutritional composition in an amount from about 0.2 g/100 Kcal to about 5.6 g/100 Kcal. In other embodiments the peptide component may be present in the nutritional composition in an amount from about 1 g/100 Kcal to about 4 g/100 Kcal. In still other embodiments, the peptide component may be present in the nutritional composition in an amount from about 2 g/100 Kcal to about 3 g/100 Kcal.

[0070] The peptide component disclosed herein may be formulated with other ingredients in the nutritional composition to provide appropriate nutrient levels for the target subject. In some embodiments, the peptide component is included in a nutritionally complete formula that is suitable to support normal growth.

[0071] The peptide component may be provided as an element of a protein equivalent source. In some embodiments, the peptides identified in Tables 1 and 2, may be provided by a protein equivalent source obtained from cow's milk proteins, including but not limited to bovine casein and bovine whey. In some embodiments, the protein equivalent source comprises hydrolyzed bovine casein or hydrolyzed bovine whey. Accordingly, in some embodiments, the peptides identified in Table 1 and Table 2 may be provided by a casein hydrolysate. Such peptides may be obtained by hydrolysis or may be synthesized in vitro by methods know to the skilled person.

[0072] A non-limiting example of a method of hydrolysis is disclosed herein. In some embodiments, this method may be used to obtain the protein hydrolysate and peptides of the present disclosure. The proteins are hydrolyzed using a proteolytic enzyme, Protease N. Protease N "Amano" is commercially available from Amano Enzyme U.S.A. Co., Ltd., Elgin, Ill. Protease N is a proteolytic enzyme preparation that is derived from the bacterial species Bacillus subtilis. The protease powder is specified as "not less than 150,000 units/g", meaning that one unit of Protease N is the amount of enzyme which produces an amino acid equivalent to 100 micrograms of tyrosine for 60 minutes at a pH of 7.0. To produce the infant formula of the present disclosure, Protease N can be used at levels of about 0.5% to about 1.0% by weight of the total protein being hydrolyzed.

[0073] The protein hydrolysis by Protease N is typically conducted at a temperature of about 50° C. to about 60° C. The hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis between about 4% and 10%. In a particular embodiment, hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis between about 6% and 9%. In another

embodiment, hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis of about 7.5%. This level of hydrolysis may take between about one half hour to about 3 hours.

[0074] A constant pH should be maintained during hydrolysis. In the method of the present disclosure, the pH is adjusted to and maintained between about 6.5 and 8. In a particular embodiment, the pH is maintained at about 7.0.

[0075] In order to maintain the optimal pH of the solution of whey protein, casein, water and Protease N, a caustic solution of sodium hydroxide and/or potassium hydroxide can be used to adjust the pH during hydrolysis. If sodium hydroxide is used to adjust the pH, the amount of sodium hydroxide added to the solution should be controlled to the level that it comprises less than about 0.3% of the total solid in the finished protein hydrolysate. A 10% potassium hydroxide solution can also be used to adjust the pH of the solution to the desired value, either before the enzyme is added or during the hydrolysis process in order to maintain the optimal pH.

[0076] The amount of caustic solution added to the solution during the protein hydrolysis can be controlled by a pH-stat or by adding the caustic solution continuously and proportionally. The hydrolysate can be manufactured by standard batch processes or by continuous processes.

[0077] To better ensure the consistent quality of the protein partial hydrolysate, the hydrolysate is subjected to enzyme deactivation to end the hydrolysis process. The enzyme deactivation step may consist include at heat treatment at a temperature of about 82° C. for about 10 minutes. Alternatively, the enzyme can be deactivated by heating the solution to a temperature of about 92° C. for about 5 seconds. After enzyme deactivation is complete, the hydrolysate can be stored in a liquid state at a temperature lower than 10° C.

[0078] In some embodiments, the protein equivalent source comprises a hydrolyzed protein, which includes partially hydrolyzed protein and extensively hydrolyzed protein, such as casein. In some embodiments, the protein equivalent source comprises a hydrolyzed protein including peptides having a molar mass distribution of greater than 500 Daltons. In some embodiments, the hydrolyzed protein comprises peptides having a molar mass distribution in the range of from about 500 Daltons to about 1,500 Daltons. Still, in some embodiments the hydrolyzed protein may comprise peptides having a molar mass distribution range of from about 500 Daltons to about 2,000 Daltons.

[0079] In some embodiments, the protein equivalent source may comprise the peptide component, intact protein, hydrolyzed protein, including partially hydrolyzed protein and/or extensively hydrolyzed protein, and combinations thereof. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component disclosed herein. In some embodiments, 30% to 60% of the protein equivalent source comprises the peptide

component disclosed herein. In still other embodiments, 40% to 50% of the protein equivalent source comprises the peptide component.

[0080] In some embodiments, 20% to 80% of the protein equivalent source comprises intact protein, partially hydrolyzed protein, extensively hydrolyzed protein, or combinations thereof. In some embodiments, 40% to 70% of the protein equivalent source comprises intact proteins, partially hydrolyzed proteins, extensively hydrolyzed protein, or a combination thereof. In still further embodiments, 50% to 60% of the protein equivalent source may comprise intact proteins, partially hydrolyzed protein, extensively hydrolyzed protein, or a combination thereof.

[0081] In some embodiments the protein equivalent source comprises partially hydrolyzed protein having a degree of hydrolysis of less than 40%. In still other embodiments, the protein equivalent source may comprise partially hydrolyzed protein having a degree of hydrolysis of less than 25%, or less than 15%.

[0082] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein equivalent source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein equivalent source per 100 Kcal.

[0083] Without being bound by any particular theory, the administration of a nutritional composition as disclosed herein may reduce allergic response and may improve tolerance to cow's milk allergy in certain subjects. In some embodiments, the combination of prebiotic, dietary butyrate, and the protein equivalent source provide synergistic health benefits.

[0084] The nutritional composition may be protein-free in some embodiments and comprise free amino acids as an element of the protein equivalent source. In some embodiments, the amino acids may be branched chain amino acids. In certain other embodiments, small amino acid peptides may be included as the protein component of the nutritional composition. Such small amino acid peptides may be naturally occurring or synthesized. In some embodiments, the amount of free amino acids in the nutritional composition may vary from about 1 g/100 Kcal to about 5 g/100 Kcal.

[0085] In certain embodiments, the protein equivalent source comprises amino acids and is substantially free of whole, intact protein. Further in certain embodiments, the protein equivalent source comprises amino acids and is substantially free of peptides. In certain embodiments, the protein equivalent source includes from about 10% to about 90% w/w of essential amino acids based on the total amino acids included in the protein equivalent source. In certain embodiments, the protein equivalent source includes from about 25% to about 75% w/w of essential amino acids based on the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes

from about 40% to about 60% of essential amino acids based on the total amino acids included in the protein equivalent source.

[0086] In some embodiments, the protein equivalent source includes non-essential amino acids. In certain embodiments, the protein equivalent source includes from about 10% to about 90% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source. In certain embodiments, the protein equivalent source includes from about 25% to about 75% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 40% to about 60% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source.

[0087] In some embodiments, the protein equivalent source includes leucine. In some embodiments, the protein equivalent source includes from about 2% to about 15% w/w leucine per the total amount of amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 10% w/w leucine per the total amount of amino acids included in the protein equivalent source.

[0088] In some embodiments, the protein equivalent source includes lysine. In some embodiments, the protein equivalent source includes from about 2% to about 10% w/w lysine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 8% w/w lysine per the total amino acids in the protein equivalent source.

[0089] In some embodiments, the protein equivalent source includes valine. In some embodiments, the protein equivalent source includes from about 2% to about 15% w/w valine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 10% w/w valine per the total amino acids in the protein equivalent source.

[0090] In some embodiments, the protein equivalent source includes isoleucine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w isoleucine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w isoleucine per the total amino acids in the protein equivalent source.

[0091] In some embodiments, the protein equivalent source includes threonine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w threonine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w threonine per the total amino acids in the protein equivalent source.

[0092] In some embodiments, the protein equivalent source includes tyrosine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w tyrosine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w tyrosine per the total amino acids in the protein equivalent source.

[0093] In some embodiments, the protein equivalent source includes phenylalanine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w phenylalanine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w phenylalanine per the total amino acids in the protein equivalent source.

[0094] In some embodiments, the protein equivalent source includes histidine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w histidine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w histidine per the total amino acids in the protein equivalent source.

[0095] In some embodiments, the protein equivalent source includes cystine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w cystine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w cystine per the total amino acids in the protein equivalent source.

[0096] In some embodiments, the protein equivalent source includes tryptophan. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w tryptophan per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w tryptophan per the total amino acids in the protein equivalent source.

[0097] In some embodiments, the protein equivalent source includes methionine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w methionine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w methionine per the total amino acids in the protein equivalent source.

[0098] In some embodiments, the protein equivalent source includes aspartic acid. In some embodiments, the protein equivalent source includes from about 7% to about 20% w/w aspartic acid per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 10% to about 17% w/w aspartic acid per the total amino acids in the protein equivalent source.

[0099] In some embodiments, the protein equivalent source includes proline. In some embodiments, the protein equivalent source includes from about 5% to about 12% w/w proline per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 7% to about 10% w/w proline per the total amino acids in the protein equivalent source.

[0100] In some embodiments, the protein equivalent source includes alanine. In some embodiments, the protein equivalent source includes from about 3% to about 10% w/w alanine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 5% to about 8% w/w alanine per the total amino acids in the protein equivalent source.

[0101] In some embodiments, the protein equivalent source includes glutamate. In some embodiments, the protein equivalent source includes from about 1.5% to about 8% w/w glutamate per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 6% w/w glutamate per the total amino acids in the protein equivalent source.

[0102] In some embodiments, the protein equivalent source includes serine. In some embodiments, the protein equivalent source includes from about 1.5% to about 8% w/w serine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 5% w/w serine per the total amino acids in the protein equivalent source.

[0103] In some embodiments, the protein equivalent source includes arginine. In some embodiments, the protein equivalent source includes from about 2% to about 8% w/w arginine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3.5% to about 6% w/w arginine per the total amino acids in the protein equivalent source.

[0104] In some embodiments, the protein equivalent source includes glycine. In some embodiments, the protein equivalent source includes from about 0.5% to about 6% w/w glycine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w glycine per the total amino acids in the protein equivalent source.

[0105] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein equivalent source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein equivalent source per 100 Kcal.

[0106] In some embodiments, the nutritional composition comprises between about 0.5 g/100 Kcal and about 2.5 g/100 Kcal of essential amino acids. In certain embodiments, the

nutritional composition comprises between about 1.3 g/100 Kcal to about 1.6 Kcal of essential amino acids.

[0107] In some embodiments, the nutritional composition comprises between about 0.5 g/100 Kcal and about 2.5 g/100 Kcal of essential amino acids. In certain embodiments, the nutritional composition comprises between about 1.3 g/100 Kcal to about 1.6 Kcal of non-essential amino acids.

[0108] In some embodiments, the nutritional composition comprises from about 0.2 g/100 Kcal to about 0.5 g/100 Kcal of leucine. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of lysine. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of valine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.23 g/100 Kcal of isoleucine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.20 g/100 Kcal of threonine. In some embodiments, the nutritional composition comprises from about 0.10 g/100 Kcal to about 0.15 g/100 Kcal of tyrosine. In some embodiments, the nutritional composition comprises from about 0.05 g/100 Kcal to about 0.15 g/100 Kcal of phenylalanine. In some embodiments, the nutritional composition comprises from about 0.01 g/100 Kcal to about 0.09 g/100 Kcal of histidine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of cystine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of tryptophan. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of methionine.

[0109] In some embodiments, the nutritional composition comprises from about 0.2 g/100 Kcal to about 0.7 g/100 Kcal of aspartic acid. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of proline. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.3 g/100 Kcal of alanine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.25 g/100 Kcal of glutamate. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.2 g/100 Kcal of serine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.15 g/100 Kcal of arginine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of glycine.

[0110] The nutritional composition(s) of the present disclosure including the protein equivalent source, may be administered in one or more doses daily. Any orally acceptable dosage form is contemplated by the present disclosure. Examples of such dosage forms include, but are not limited to pills, tablets, capsules, soft-gels, liquids, liquid concentrates,

powders, elixirs, solutions, suspensions, emulsions, lozenges, beads, cachets, and combinations thereof.

[0111] In some embodiments, the protein equivalent source may provide from about 5% to about 20% of the total calories for the nutritional composition. In some embodiments, the protein equivalent source may provide from about 8% to about 12 % of the total calories for the nutritional composition.

[0112] In some embodiments, without being bound by any particular theory, the nutritional compositions including dietary butyrate, prebiotic, and the protein equivalent source disclosed herein, may reduce the incidence of allergic reactions in human subjects when administered. For example, in certain embodiments the nutritional compositions may include dietary butyrate, prebiotic, and a protein equivalent source, where the protein equivalent source is substantially free of whole and/or intact protein. As such, the protein equivalent source provides amino acids in addition to dietary butyrate, which, in combination, may further prevent allergic reaction and decrease inflammation when administered.

[0113] The nutritional composition(s) of the present disclosure may also comprise a carbohydrate source. Carbohydrate sources can be any used in the art, e.g., lactose, glucose, fructose, corn syrup solids, maltodextrins, sucrose, starch, rice syrup solids, and the like. The amount of carbohydrate in the nutritional composition typically can vary from between about 5 g and about 25 g/100 Kcal. In some embodiments, the amount of carbohydrate is between about 6 g and about 22 g/ 100 Kcal. In other embodiments, the amount of carbohydrate is between about 12 g and about 14 g/100 Kcal. In some embodiments, corn syrup solids are preferred. Moreover, hydrolyzed, partially hydrolyzed, and/or extensively hydrolyzed carbohydrates may be desirable for inclusion in the nutritional composition due to their easy digestibility. Specifically, hydrolyzed carbohydrates are less likely to contain allergenic epitopes.

[0114] Non-limiting examples of carbohydrate materials suitable for use herein include hydrolyzed or intact, naturally or chemically modified, starches sourced from corn, tapioca, rice or potato, in waxy or non-waxy forms. Non-limiting examples of suitable carbohydrates include various hydrolyzed starches characterized as hydrolyzed cornstarch, maltodextrin, maltose, corn syrup, dextrose, corn syrup solids, glucose, and various other glucose polymers and combinations thereof. Non-limiting examples of other suitable carbohydrates include those often referred to as sucrose, lactose, fructose, high fructose corn syrup, indigestible oligosaccharides such as fructooligosaccharides and combinations thereof.

[0115] The nutritional composition(s) of the disclosure may also comprise a protein source. The protein source can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, amino acids, and the like. Bovine milk protein sources useful in

practicing the present disclosure include, but are not limited to, milk protein powders, milk protein concentrates, milk protein isolates, nonfat milk solids, nonfat milk, nonfat dry milk, whey protein, whey protein isolates, whey protein concentrates, sweet whey, acid whey, casein, acid casein, caseinate (*e.g.* sodium caseinate, sodium calcium caseinate, calcium caseinate) and any combinations thereof.

[0116] In one embodiment, the proteins of the nutritional composition are provided as intact proteins. In other embodiments, the proteins are provided as a combination of both intact proteins and partially hydrolyzed proteins, with a degree of hydrolysis of between about 4% and 10%. In certain other embodiments, the proteins are more completely hydrolyzed. In still other embodiments, the protein source comprises amino acids. In yet another embodiment, the protein source may be supplemented with glutamine-containing peptides.

[0117] In a particular embodiment of the nutritional composition, the whey:casein ratio of the protein source is similar to that found in human breast milk. In an embodiment, the protein source comprises from about 40% to about 80% whey protein and from about 20% to about 60% casein.

[0118] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein per 100 Kcal.

[0119] In some embodiments, the nutritional composition described herein comprises a fat source. The enriched lipid fraction described herein may be the sole fat source or may be used in combination with any other suitable fat or lipid source for the nutritional composition as known in the art. In certain embodiments, appropriate fat sources include, but are not limited to, animal sources, e.g., milk fat, butter, butter fat, egg yolk lipid; marine sources, such as fish oils, marine oils, single cell oils; vegetable and plant oils, such as corn oil, canola oil, sunflower oil, soybean oil, palm olein oil, coconut oil, high oleic sunflower oil, evening primrose oil, rapeseed oil, olive oil, flaxseed (linseed) oil, cottonseed oil, high oleic safflower oil, palm stearin, palm kernel oil, wheat germ oil; medium chain triglyceride oils and emulsions and esters of fatty acids; and any combinations thereof.

[0120] In some embodiment the nutritional composition comprises between about 1 g/100 Kcal to about 10 g/100 Kcal of a fat or lipid source. In some embodiments, the nutritional composition comprises between about 2 g/100 Kcal to about 7 g/100 Kcal of a fat source. In other embodiments the fat source may be present in an amount from about 2.5 g/100 Kcal to about 6 g/100 Kcal. In still other embodiments, the fat source may be present in the nutritional composition in an amount from about 3 g/100 Kcal to about 4 g/100 Kcal.

[0121] In some embodiments, the fat or lipid source comprises from about 10% to about 35% palm oil per the total amount of fat or lipid. In some embodiments, the fat or lipid

source comprises from about 15% to about 30% palm oil per the total amount of fat or lipid. Yet in other embodiments, the fat or lipid source may comprise from about 18% to about 25 % palm oil per the total amount of fat or lipid.

[0122] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% soybean oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% soybean oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% soybean oil based on the total amount of fat or lipid.

[0123] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% coconut oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% coconut oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% coconut oil based on the total amount of fat or lipid.

[0124] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% sunflower oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% sunflower oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% sunflower oil based on the total amount of fat or lipid.

[0125] In some embodiments, the oils, *i.e.* sunflower oil, soybean oil, sunflower oil, palm oil, etc. are meant to cover fortified versions of such oils known in the art. For example, in certain embodiments, the use of sunflower oil may include high oleic sunflower oil. In other examples, the use of such oils may be fortified with certain fatty acids, as known in the art, and may be used in the fat or lipid source disclosed herein.

[0126] In some embodiments, the fat or lipid source includes an oil blend including sunflower oil, medium chain triglyceride oil, and soybean oil. In some embodiments, the fat or lipid source includes a ratio of sunflower oil to medium chain triglyceride oil of about 1:1 to about 2:1. In certain other embodiments, the fat or lipid source includes a ratio of sunflower oil to soybean oil of from about 1:1 to about 2:1. In still other embodiments, the fat or lipid source may include a ratio of medium chain triglyceride oil to soybean oil of from about 1:1 to about 2:1.

[0127] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w sunflower oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w sunflower oil based on the total

fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w sunflower oil based on the total fat or lipid content.

[0128] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w medium chain triglyceride oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w medium chain triglyceride oil based on the total fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w medium chain triglyceride oil based on the total fat or lipid content.

[0129] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w soybean oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w soybean oil based on the total fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w soybean oil based on the total fat or lipid content.

[0130] In some embodiments, the nutritional composition comprises from about 1 g/100 Kcal to about 3 g/100 Kcal of sunflower oil. In some embodiments, the nutritional composition comprises from about 1.3 g/100 Kcal to about 2.5 g/100 Kcal of sunflower oil. In still other embodiments, the nutritional composition comprises from about 1.7 g/100 Kcal to about 2.1 g/100 Kcal of sunflower oil. The sunflower oil as described herein may, in some embodiments, include high oleic sunflower oil.

[0131] In certain embodiments, the nutritional composition if formulated to include from about 1 g/100 Kcal to about 2.5 g/100 Kcal of medium chain triglyceride oil. In other embodiments, the nutritional composition includes from about 1.3 g/100 Kcal to about 2.1 g/100 Kcal of medium chain triglyceride oil. Still in further embodiments, the nutritional composition includes from about 1.6 g/100 Kcal to about 1.9 g/100 Kcal of medium chain triglyceride oil.

[0132] In some embodiments, the nutritional composition may be formulated to include from about 1 g/100 Kcal to about 2.3 g/100 Kcal of soybean oil. In certain embodiments, the nutritional composition may be formulated to include from about 1.2 g/100 Kcal to about 2 g/100 Kcal of soybean oil. Still in certain embodiments, the nutritional composition may be formulated to include from about 1.5 g/100 Kcal to about 1.8 g/100 Kcal of soybean oil.

[0133] In some embodiments, the term "sunflower oil", "medium chain triglyceride oil", and "soybean oil" are meant to cover fortified versions of such oils known in the art. For example, in certain embodiments, the use of sunflower oil may include high oleic sunflower oil. In other examples, the use of such oils may be fortified with certain fatty acids, as known in the art, and may be used in the fat or lipid source disclosed herein.

[0134] In some embodiments, the fat or lipid source provides from about 35% to about 55% of the total calories of the nutritional composition. In other embodiments, the fat or lipid source provides from about 40% to about 47% of the total calories of the nutritional composition.

[0135] In certain embodiments the nutritional composition may be formulated, in some embodiments, such that from about 10% to about 23 % of the total calories of the nutritional composition are provided by sunflower oil. In other embodiments, from about 13% to about 20% of the total calories in the nutritional composition may be provided by sunflower oil. Still, in other embodiments, from about 15 % to about 18% of the total calories of the nutritional composition may be provided by sunflower oil.

[0136] In some embodiments, the nutritional composition may be formulated such that from about 10% to about 20% of the total calories are provided by MCT oil. In certain embodiments, from about 12% to about 18% of the total calories in the nutritional composition may be provided by MCT oil. Still , in certain embodiments, from about 14% to about 17% of the calories of the nutritional composition may be provided by MCT oil.

[0137] In some embodiments, the nutritional composition may be formulated such that from about 10% to 20% of the total calories of the nutritional composition are provided by soybean oil. In certain embodiments, from about 12% to about 18% of the total calories of the nutritional composition may be provided by soybean oil. In certain embodiments, from about 13% to about 16% of the total calories may be provided by soybean oil.

[0138] In some embodiments the nutritional composition may also include a source of LCPUFAs. In one embodiment the amount of LCPUFA in the nutritional composition is advantageously at least about 5 mg/100 Kcal, and may vary from about 5 mg/100 Kcal to about 100 mg/100 Kcal, more preferably from about 10 mg/100 Kcal to about 50 mg/100 Kcal. Non-limiting examples of LCPUFAs include, but are not limited to, DHA, ARA, linoleic (18:2 n-6), γ-linolenic (18:3 n-6), dihomo- γ-linolenic (20:3 n-6) acids in the n-6 pathway, α-linolenic (18:3 n-3), stearidonic (18:4 n-3), eicosatetraenoic (20:4 n-3), eicosapentaenoic (20:5 n-3), and docosapentaenoic (22:6 n-3).

[0139] In some embodiments, the LCPUFA included in the nutritional composition may comprise DHA. In one embodiment the amount of DHA in the nutritional composition is advantageously at least about 17 mg/100 Kcal, and may vary from about 5 mg/100 Kcal to about 75 mg/100 Kcal, more preferably from about 10 mg/100 Kcal to about 50 mg/100 Kcal.

[0140] In another embodiment, especially if the nutritional composition is an infant formula, the nutritional composition is supplemented with both DHA and ARA. In this embodiment,

the weight ratio of ARA:DHA may be between about 1:3 and about 9:1. In a particular embodiment, the ratio of ARA:DHA is from about 1:2 to about 4:1.

[0141] The DHA and ARA can be in natural form, provided that the remainder of the LCPUFA source does not result in any substantial deleterious effect on the infant. Alternatively, the DHA and ARA can be used in refined form.

[0142] The disclosed nutritional composition described herein can, in some embodiments, also comprise a source of ß-glucan. Glucans are polysaccharides, specifically polymers of glucose, which are naturally occurring and may be found in cell walls of bacteria, yeast, fungi, and plants. Beta glucans (β-glucans) are themselves a diverse subset of glucose polymers, which are made up of chains of glucose monomers linked together via beta-type glycosidic bonds to form complex carbohydrates.

[0143] β-1,3-glucans are carbohydrate polymers purified from, for example, yeast, mushroom, bacteria, algae, or cereals. (Stone BA, Clarke AE. Chemistry and Biology of (1-3)-Beta-Glucans. London:Portland Press Ltd; 1993.) The chemical structure of β-1,3-glucan depends on the source of the β-1,3-glucan. Moreover, various physiochemical parameters, such as solubility, primary structure, molecular weight, and branching, play a role in biological activities of β-1,3-glucans. (Yadomae T., *Structure and biological activities of fungal beta-1,3-glucans.* Yakugaku Zasshi. 2000;120:413-431.)

[0144] β-1,3-glucans are naturally occurring polysaccharides, with or without β-1,6-glucose side chains that are found in the cell walls of a variety of plants, yeasts, fungi and bacteria. β-1,3;1,6-glucans are those containing glucose units with (1,3) links having side chains attached at the (1,6) position(s). β-1,3;1,6 glucans are a heterogeneous group of glucose polymers that share structural commonalities, including a backbone of straight chain glucose units linked by a β-1,3 bond with β-1,6-linked glucose branches extending from this backbone. While this is the basic structure for the presently described class of β-glucans, some variations may exist. For example, certain yeast β-glucans have additional regions of β(1,3) branching extending from the β(1,6) branches, which add further complexity to their respective structures.

[0145] β-glucans derived from baker's yeast, *Saccharomyces cerevisiae*, are made up of chains of D-glucose molecules connected at the 1 and 3 positions, having side chains of glucose attached at the 1 and 6 positions. Yeast-derived β-glucan is an insoluble, fiber-like, complex sugar having the general structure of a linear chain of glucose units with a β-1,3 backbone interspersed with β-1,6 side chains that are generally 6-8 glucose units in length. More specifically, β-glucan derived from baker's yeast is poly-(1,6)-β-D-glucopyranosyl-(1,3)-β-D-glucopyranose.

[0146] Furthermore, β-glucans are well tolerated and do not produce or cause excess gas, abdominal distension, bloating or diarrhea in pediatric subjects. Addition of β-glucan to a nutritional composition for a pediatric subject, such as an infant formula, a growing-up milk or another children's nutritional product, will improve the subject's immune response by increasing resistance against invading pathogens and therefore maintaining or improving overall health.

[0147] In some embodiments, the β-glucan is β-1,3;1,6-glucan. In some embodiments, the β-1,3;1,6-glucan is derived from baker's yeast. The nutritional composition may comprise whole glucan particle β-glucan, particulate β-glucan, PGG-glucan (poly-1,6-β-D-glucopyranosyl-1,3-β-D-glucopyranose) or any mixture thereof.

[0148] In some embodiments, the amount of β-glucan in the nutritional composition is between about 3 mg and about 17 mg per 100 Kcal. In another embodiment the amount of β-glucan is between about 6 mg and about 17 mg per 100 Kcal.

[0149] The disclosed nutritional composition described herein can, in some embodiments, also comprise a source of probiotic. The term "probiotic" means a microorganism that exerts beneficial effects on the health of the host. Any probiotic known in the art may be acceptable in this embodiment. In a particular embodiment, the probiotic may be selected from any *Lactobacillus* species, *Lactobacillus rhamnosus* GG (ATCC number 53103), *Bifidobacterium* species, *Bifidobacterium longum* BB536 (BL999, ATCC: BAA-999), *Bifidobacterium longum* AH1206 (NCIMB: 41382), *Bifidobacterium breve* AH1205 (NCIMB: 41387), *Bifidobacterium infantis* 35624 (NCIMB: 41003), and *Bifidobacterium animalis subsp. lactis* BB-12 (DSM No. 10140) or any combination thereof.

[0150] If included, the nutritional composition may comprise between about 1 x 10^4 to about 1.5 x 10^{10} cfu of probiotics per 100 Kcal, more preferably from about 1 x 10^6 to about 1 x 10^9 cfu of probiotics per 100 Kcal.

[0151] In an embodiment, the probiotic(s) may be viable or non-viable. As used herein, the term "viable", refers to live microorganisms. The term "non-viable" or "non-viable probiotic" means non-living probiotic microorganisms, their cellular components and/or metabolites thereof. Such non-viable probiotics may have been heat-killed or otherwise inactivated, but they retain the ability to favorably influence the health of the host. The probiotics useful in the present disclosure may be naturally-occurring, synthetic or developed through the genetic manipulation of organisms, whether such new source is now known or later developed.

[0152] The disclosed nutritional composition described herein, can, in some embodiments also comprise an effective amount of iron. The iron may comprise encapsulated iron forms,

such as encapsulated ferrous fumarate or encapsulated ferrous sulfate or less reactive iron forms, such as ferric pyrophosphate or ferric orthophosphate.

[0153] One or more vitamins and/or minerals may also be added in to the nutritional composition in amounts sufficient to supply the daily nutritional requirements of a subject. It is to be understood by one of ordinary skill in the art that vitamin and mineral requirements will vary, for example, based on the age of the child. For instance, an infant may have different vitamin and mineral requirements than a child between the ages of one and thirteen years. Thus, the embodiments are not intended to limit the nutritional composition to a particular age group but, rather, to provide a range of acceptable vitamin and mineral components.

[0154] In embodiments providing a nutritional composition for a child, the composition may optionally include, but is not limited to, one or more of the following vitamins or derivations thereof: vitamin B_1 (thiamin, thiamin pyrophosphate, TPP, thiamin triphosphate, TTP, thiamin hydrochloride, thiamin mononitrate), vitamin B_2 (riboflavin, flavin mononucleotide, FMN, flavin adenine dinucleotide, FAD, lactoflavin, ovoflavin), vitamin B_3 (niacin, nicotinic acid, nicotinamide, niacinamide, nicotinamide adenine dinucleotide, NAD, nicotinic acid mononucleotide, NicMN, pyridine-3-carboxylic acid), vitamin B_3-precursor tryptophan, vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine, pyridoxine hydrochloride), pantothenic acid (pantothenate, panthenol), folate (folic acid, folacin, pteroylglutamic acid), vitamin B_{12} (cobalamin, methylcobalamin, deoxyadenosylcobalamin, cyanocobalamin, hydroxycobalamin, adenosylcobalamin), biotin, vitamin C (ascorbic acid), vitamin A (retinol, retinyl acetate, retinyl palmitate, retinyl esters with other long-chain fatty acids, retinal, retinoic acid, retinol esters), vitamin D (calciferol, cholecalciferol, vitamin D_3, 1,25,-dihydroxyvitamin D), vitamin E (α-tocopherol, α-tocopherol acetate, α-tocopherol succinate, α-tocopherol nicotinate, α-tocopherol), vitamin K (vitamin K_1, phylloquinone, naphthoquinone, vitamin K_2, menaquinone-7, vitamin K_3, menaquinone-4, menadione, menaquinone-8, menaquinone-8H, menaquinone-9, menaquinone-9H, menaquinone-10, menaquinone-11, menaquinone-12, menaquinone-13), choline, inositol, β-carotene and any combinations thereof.

[0155] In embodiments providing a children's nutritional product, such as a growing-up milk, the composition may optionally include, but is not limited to, one or more of the following minerals or derivations thereof: boron, calcium, calcium acetate, calcium gluconate, calcium chloride, calcium lactate, calcium phosphate, calcium sulfate, chloride, chromium, chromium chloride, chromium picolonate, copper, copper sulfate, copper gluconate, cupric sulfate, fluoride, iron, carbonyl iron, ferric iron, ferrous fumarate, ferric orthophosphate, iron trituration, polysaccharide iron, iodide, iodine, magnesium, magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium stearate, magnesium sulfate,

manganese, molybdenum, phosphorus, potassium, potassium phosphate, potassium iodide, potassium chloride, potassium acetate, selenium, sulfur, sodium, docusate sodium, sodium chloride, sodium selenate, sodium molybdate, zinc, zinc oxide, zinc sulfate and mixtures thereof. Non-limiting exemplary derivatives of mineral compounds include salts, alkaline salts, esters and chelates of any mineral compound.

[0156] The minerals can be added to growing-up milks or to other children's nutritional compositions in the form of salts such as calcium phosphate, calcium glycerol phosphate, sodium citrate, potassium chloride, potassium phosphate, magnesium phosphate, ferrous sulfate, zinc sulfate, cupric sulfate, manganese sulfate, and sodium selenite. Additional vitamins and minerals can be added as known within the art.

[0157] The nutritional compositions of the present disclosure may optionally include one or more of the following flavoring agents, including, but not limited to, flavored extracts, volatile oils, cocoa or chocolate flavorings, peanut butter flavoring, cookie crumbs, vanilla or any commercially available flavoring. Examples of useful flavorings include, but are not limited to, pure anise extract, imitation banana extract, imitation cherry extract, chocolate extract, pure lemon extract, pure orange extract, pure peppermint extract, honey, imitation pineapple extract, imitation rum extract, imitation strawberry extract, or vanilla extract; or volatile oils, such as balm oil, bay oil, bergamot oil, cedarwood oil, cherry oil, cinnamon oil, clove oil, or peppermint oil; peanut butter, chocolate flavoring, vanilla cookie crumb, butterscotch, toffee, and mixtures thereof. The amounts of flavoring agent can vary greatly depending upon the flavoring agent used. The type and amount of flavoring agent can be selected as is known in the art.

[0158] The nutritional compositions of the present disclosure may optionally include one or more emulsifiers that may be added for stability of the final product. Examples of suitable emulsifiers include, but are not limited to, lecithin (*e.g.*, from egg or soy), alpha lactalbumin and/or mono- and di-glycerides, and mixtures thereof. Other emulsifiers are readily apparent to the skilled artisan and selection of suitable emulsifier(s) will depend, in part, upon the formulation and final product.

[0159] The nutritional compositions of the present disclosure may optionally include one or more preservatives that may also be added to extend product shelf life. Suitable preservatives include, but are not limited to, potassium sorbate, sodium sorbate, potassium benzoate, sodium benzoate, calcium disodium EDTA, and mixtures thereof.

[0160] The nutritional compositions of the present disclosure may optionally include one or more stabilizers. Suitable stabilizers for use in practicing the nutritional composition of the present disclosure include, but are not limited to, gum arabic, gum ghatti, gum karaya, gum tragacanth, agar, furcellaran, guar gum, gellan gum, locust bean gum, pectin, low methoxyl

pectin, gelatin, microcrystalline cellulose, CMC (sodium carboxymethylcellulose), methylcellulose hydroxypropyl methyl cellulose, hydroxypropyl cellulose, DATEM (diacetyl tartaric acid esters of mono- and diglycerides), dextran, carrageenans, and mixtures thereof.

[0161] The nutritional compositions of the disclosure may provide minimal, partial or total nutritional support. The compositions may be nutritional supplements or meal replacements. The compositions may, but need not, be nutritionally complete. In an embodiment, the nutritional composition of the disclosure is nutritionally complete and contains suitable types and amounts of lipid, carbohydrate, protein, vitamins and minerals. The amount of lipid or fat typically can vary from about 1 to about 25 g/100 Kcal. The amount of protein typically can vary from about 1 to about 7 g/100 Kcal. The amount of carbohydrate typically can vary from about 6 to about 22 g/100 Kcal.

[0162] In an embodiment, the children's nutritional composition may contain between about 10 and about 50% of the maximum dietary recommendation for any given country, or between about 10 and about 50% of the average dietary recommendation for a group of countries, per serving of vitamins A, C, and E, zinc, iron, iodine, selenium, and choline. In another embodiment, the children's nutritional composition may supply about 10 – 30% of the maximum dietary recommendation for any given country, or about 10 – 30% of the average dietary recommendation for a group of countries, per serving of B-vitamins. In yet another embodiment, the levels of vitamin D, calcium, magnesium, phosphorus, and potassium in the children's nutritional product may correspond with the average levels found in milk. In other embodiments, other nutrients in the children's nutritional composition may be present at about 20% of the maximum dietary recommendation for any given country, or about 20% of the average dietary recommendation for a group of countries, per serving.

[0163] In some embodiments the nutritional composition is an infant formula. Infant formulas are fortified nutritional compositions for an infant. The content of an infant formula is dictated by federal regulations, which define macronutrient, vitamin, mineral, and other ingredient levels in an effort to simulate the nutritional and other properties of human breast milk. Infant formulas are designed to support overall health and development in a pediatric human subject, such as an infant or a child.

[0164] In some embodiments, the nutritional composition of the present disclosure is a growing-up milk. Growing-up milks are fortified milk-based beverages intended for children over 1 year of age (typically from 1-3 years of age, from 4-6 years of age or from 1-6 years of age). They are not medical foods and are not intended as a meal replacement or a supplement to address a particular nutritional deficiency. Instead, growing-up milks are designed with the intent to serve as a complement to a diverse diet to provide additional insurance that a child achieves continual, daily intake of all essential vitamins and minerals,

macronutrients plus additional functional dietary components, such as non-essential nutrients that have purported health-promoting properties.

[0165] The exact composition of a growing-up milk or other nutritional composition according to the present disclosure can vary from market-to-market, depending on local regulations and dietary intake information of the population of interest. In some embodiments, nutritional compositions according to the disclosure consist of a milk protein source, such as whole or skim milk, plus added sugar and sweeteners to achieve desired sensory properties, and added vitamins and minerals. The fat composition includes an enriched lipid fraction derived from milk. Total protein can be targeted to match that of human milk, cow milk or a lower value. Total carbohydrate is usually targeted to provide as little added sugar, such as sucrose or fructose, as possible to achieve an acceptable taste. Typically, Vitamin A, calcium and Vitamin D are added at levels to match the nutrient contribution of regional cow milk. Otherwise, in some embodiments, vitamins and minerals can be added at levels that provide approximately 20% of the dietary reference intake (DRI) or 20% of the Daily Value (DV) per serving. Moreover, nutrient values can vary between markets depending on the identified nutritional needs of the intended population, raw material contributions and regional regulations.

[0166] The disclosed nutritional composition(s) may be provided in any form known in the art, such as a powder, a gel, a suspension, a paste, a solid, a liquid, a liquid concentrate, a reconstituteable powdered milk substitute or a ready-to-use product. The nutritional composition may, in certain embodiments, comprise a nutritional supplement, children's nutritional product, infant formula, human milk fortifier, growing-up milk or any other nutritional composition designed for an infant or a pediatric subject. Nutritional compositions of the present disclosure include, for example, orally-ingestible, health-promoting substances including, for example, foods, beverages, tablets, capsules and powders. Moreover, the nutritional composition of the present disclosure may be standardized to a specific caloric content, it may be provided as a ready-to-use product, or it may be provided in a concentrated form. In some embodiments, the nutritional composition is in powder form with a particle size in the range of 5 μm to 1500 μm, more preferably in the range of 10 μm to 300μm.

[0167] The nutritional compositions of the present disclosure may be provided in a suitable container system. For example, non-limiting examples of suitable container systems include plastic containers, metal containers, foil pouches, plastic pouches, multi-layered pouches, and combinations thereof. In certain embodiments, the nutritional composition may be a powdered composition that is contained within a plastic container. In certain other

embodiments, the nutritional composition may be contained within a plastic pouch located inside a plastic container.

[0168] The nutritional compositions described herein, in some embodiments, advantageously reduce the incidence of allergic reaction and improve tolerance to cow's milk allergy in a subject. Further, in some embodiments, the nutritional compositions advantageously reduce the inflammatory response caused by allergy in a subject. Accordingly, the disclosure relates to methods of improving tolerance to cow's milk allergy in a subject. Further, the disclosure relates to methods of reducing the incidence of allergic reaction and reducing the inflammatory response caused by allergy in a subject via administration of the nutritional compositions including PDX/GOS and dietary butyrate as disclosed herein.

[0169] In some embodiments, the method comprises the step of subjecting the target subject to cow's milk and then providing the nutritional composition disclosed herein including PDX/GOS and dietary butyrate to the target subject. In certain embodiments, after the target subject has been subjected to cow's milk, the target subject may be provided with a nutritional composition that includes PDX/GOS and dietary butyrate and a protein equivalent source as disclosed herein. In certain embodiments, the target subject, after being exposed to cow's milk or other allergen, may be administered a nutritional composition comprising PDX/GOS and dietary butyrate, and a protein equivalent source. In certain embodiments, the protein equivalent source may be substantially free of whole and/or intact protein. In certain other embodiments, the protein equivalent source may comprise hydrolyzed protein, amino acids, the peptide component disclosed herein, and combinations thereof. In some embodiments, the nutritional composition includes a protein equivalent source includes amino acids and no hydrolyzed or whole/intact protein.

[0170] In some embodiments, the target subject is not subjected to cow's milk or an allergen prior to administration of the nutritional composition. Thus, in some embodiments, the method is directed to reducing allergic response in a target subject via providing the nutritional compositions disclosed herein including dietary butyrate to the target subject, and subsequently exposing the target subject to cow's milk or other allergen.

[0171] The nutritional compositions described herein, in some embodiments, advantageously reduce the inflammatory response in a subject. Accordingly, the disclosure relates to methods of reducing a proinflammatory response in a subject by administering to a subject a nutritional composition containing the protein equivalent source described herein in combination with PDX/GOS and dietary butyrate. For example, the present methods may reduce the production of proinflammatory cytokines in a subject.

[0172] In some embodiments, the method for reducing an inflammatory response in a subject comprises administering to a subject a nutritional composition comprising a

carbohydrate source, a protein equivalent source, fat source, PDX/GOS and dietary butryate, wherein the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63. In some embodiments, the peptide component may comprise additional peptides disclosed in Table 1. For example, the composition may include at least 10 additional peptides disclosed in Table 1. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component, and 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, and combinations thereof.

[0173] In another embodiment, the method comprises administering to a subject a nutritional composition, wherein 20% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof.

[0174] In yet other embodiments, the method for reducing the inflammatory response includes providing a nutritional composition comprising a peptide component from Table 1, wherein the peptide component is derived from a casein hydrolysate having a molar mass distribution of greater than 500 Daltons. In some embodiments, the molar mass distribution of the casein hydrolysate is in a range of 500 to 2000 Daltons. In other embodiments, the method for reducing the inflammatory response includes providing a nutritional composition comprising the peptide component described herein, wherein the peptide component is derived from a casein hydrolysate that does not include peptides having a molar mass distribution of less than 200 Daltons.

[0175] In some embodiments the target subject may be a pediatric subject. Further, in one embodiment, the nutritional composition provided to the pediatric subject may be an infant formula. The peptide component identified herein, PDX/GOS and dietary butyrate as disclosed herein may be added to the infant formula and, further, each may be selected from a specific source and concentrations thereof may be adjusted to maximize health benefits. In another embodiment of this method, the nutritional composition comprising the peptide component disclosed herein, PDX/GOS and dietary butyrate is a growing up milk.

[0176] In embodiments when the nutritional composition is an infant formula, the composition may advantageously reduce a pro-inflammatory response in the infant, and thereby reduce the incidence of inflammatory disease. Moreover, the reduction in

inflammatory disease may last throughout childhood and into adulthood. Similarly, when the nutritional composition is a growing-up milk, a child who ingests the growing-up milk may experience a reduction in the incidence of inflammatory disease in adulthood, as well as during childhood.

[0177] In certain embodiments, the disclosure is directed to a method for improving the absorption of butyrate in a target subject by providing or administering the nutritional compositions disclosed herein including PDX/GOS and dietary butyrate to the target subject. In some embodiments, the target subject is a pediatric subject or an infant. In some embodiments, the nutritional composition is an infant formula or a growing-up milk.

[0178] All combinations of method or process steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0179] The methods and compositions of the present disclosure, including components thereof, can comprise, consist of, or consist essentially of the essential elements and limitations of the embodiments described herein, as well as any additional or optional ingredients, components or limitations described herein or otherwise useful in nutritional compositions.

[0180] Formulation examples are provided to illustrate some embodiments of the nutritional composition of the present disclosure but should not be interpreted as any limitation thereon. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from the consideration of the specification or practice of the nutritional composition or methods disclosed herein. It is intended that the specification, together with the example, be considered to be exemplary only, with the scope and spirit of the disclosure being indicated by the claims which follow the example.

FORMULATION EXAMPLES

[0181] Table 3 provides an example embodiment of a peptide component including 8 peptides from Table1.

Table 3. Example peptide component

Example of Selected Peptides for Peptide Component
SEQ ID NO 5
SEQ ID NO 24
SEQ ID NO 33
SEQ ID NO 56
SEQ ID NO 64

SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60

[0182] Table 4 provides an example embodiment of a peptide component including certain peptides from Table 1.

Table 4. Example peptide component

Example of Selected Peptides for Peptide Component
SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60
SEQ ID NO 5
SEQ ID NO 11
SEQ ID NO 22
SEQ ID NO 25
SEQ ID NO 33
SEQ ID NO 45
SEQ ID NO 46
SEQ ID NO 47
SEQ ID NO 48
SEQ ID NO 52
SEQ ID NO 34
SEQ ID NO 36
SEQ ID NO 61
SEQ ID NO 62
SEQ ID NO 64

[0183] Table 2 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 2 are based on a weight-to-weight percentage based on the total amino acids in the protein equivalent source.

Table 2. Example protein equivalent source

Amino Acid	w/w % amount based on total amino acids
L-leucine	9.94
L-lysine	7.93
L-valine	9.21
L-isoleucine	5.48
L-threonine	4.95
L-tyrosine	4.38
L-phenylalanine	4.05
L-histidine	2.12
L-cystine	2.12
L-tryptophan	1.93
L-methionine	1.87

[0184] Table 3 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 3 are based on a weight-to-weight percentage based on the total amino acids in the protein equivalent source.

Table 3. Example protein equivalent source

Amino Acid	w/w % amount based on total amino acids
L-aspartic acid	16.16
L-proline	8.05
L-alanine	7.87
Monosodium glutamate	5.54
L-serine	4.95
L-arginine	4.27
glycine	2.12

[0185] Table 4 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 4 are based on grams per 100 Kcal of the nutritional composition.

Table 4. Example protein equivalent source

Amino Acid (g)	per 100 Kcal

L-leucine	0.25
L-lysine	0.20
L-valine	0.23
L-isoleucine	0.14
L-threonine	0.12
L-tyrosine	0.11
L-phenylalanine	0.10
L-histidine	0.053
L-cystine	0.053
L-tryptophan	0.049
L-methionine	0.047

[0186] Table 5 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 5 are based on grams per 100 Kcal of the nutritional composition.

Table 5. Example protein equivalent source

Amino Acid (g)	per 100 Kcal
L-leucine	0.31
L-lysine	0.24
L-valine	0.28
L-isoleucine	0.17
L-threonine	0.15
L-tyrosine	0.13
L-phenylalanine	0.12
L-histidine	0.07
L-cystine	0.07
L-tryptophan	0.06
L-methionine	0.06

[0187] Table 6 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 6 are based on grams per 100 Kcal of the nutritional composition.

Table 6. Example protein equivalent source

Amino Acid (g)	per 100 Kcal
L-aspartic acid	0.41

L-proline	0.20
L-alanine	0.20
Monosodium glutamate	0.14
L-serine	0.13
L-arginine	0.11
Glycine	0.05

[0188] Table 7 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 7 are based on grams per 100 Kcal of the nutritional composition.

Table 7. Example protein equivalent source

Amino Acid (g)	**per 100 Kcal**
L-aspartic acid	0.50
L-proline	0.28
L-alanine	0.24
Monosodium glutamate	0.17
L-serine	0.15
L-arginine	0.13
Glycine	0.07

[0189] Table 8, illustrated below, provides an example embodiment of the nutritional profile of a nutritional composition including PDX/GOS and dietary butyrate and describes the amount of each ingredient to be included per 100 Kcal serving of nutritional composition.

Table 8. Nutrition profile of an example nutritional composition including dietary butyrate

	per 100 Kcal	
Nutrient		
	Minimum	**Maximum**
Protein Equivalent Source (g)	1.0	7.0
Dietary butyrate (mg)	22	280
Lactobacillus rhamnosus GG (cfu)	$1x10^4$	$1.5x10^{12}$
Carbohydrates (g)	6	22
Fat (g)	1.3	7.2
Prebiotic (g)	0.3	1.2

DHA (g)	4	22
Beta glucan (mg)	2.9	17
Probiotics (cfu)	0.5	5.0
Vitamin A (IU)	9.60×10^5	3.80×10^8
Vitamin D (IU)	134	921
Vitamin E (IU)	22	126
Vitamin K (mcg)	0.8	5.4
Thiamin (mcg)	2.9	18
Riboflavin (mcg)	63	328
Vitamin B6 (mcg)	68	420
Vitamin B12 (mcg)	52	397
Niacin (mcg)	0.2	0.9
Folic acid (mcg)	690	5881
Panthothenic acid (mcg)	8	66
Biotin (mcg)	232	1211
Vitamin C (mg)	1.4	5.5
Choline (mg)	4.9	24
Calcium (mg)	4.9	43
Phosphorus (mg)	68	297
Magnesium (mg)	54	210
Sodium (mg)	4.9	34
Potassium (mg)	24	88
Chloride (mg)	82	346
Iodine (mcg)	53	237
Iron (mg)	8.9	79
Zinc (mg)	0.7	2.8
Manganese (mcg)	0.7	2.4
Copper (mcg)	7.2	41

[0190] All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and

no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

[0191] Although embodiments of the disclosure have been described using specific terms, devices, and methods, such description is for illustrative purposes only. The words used are words of description rather than of limitation. It is to be understood that changes and variations may be made by those of ordinary skill in the art without departing from the spirit or the scope of the present disclosure, which is set forth in the following claims. In addition, it should be understood that aspects of the various embodiments may be interchanged in whole or in part. Therefore, the spirit and scope of the appended claims should not be limited to the description of the versions contained therein.

CLAIMS

What is claimed is:

1. A nutritional composition comprising:

a carbohydrate source;

a protein equivalent source, wherein 1% to 99% of the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63; and 1% to 99% of the protein equivalent source comprises a partially hydrolyzed protein, an extensively hydrolyzed protein, or combinations thereof;

a fat or lipid source; and

at least one of the following:

(i) dietary butyrate;

(ii) a component for stimulating endogenous butyrate; or

(iii) combinations thereof.

2. The nutritional composition of claim 1, wherein the peptide component is present in an amount from about 0.2 g/100 Kcal to about 5.6 g/100 Kcal.

3. The nutritional composition of claim 1, wherein the peptide component further comprises at least 10 additional peptides selected from Table 1.

4. The nutritional composition of claim 1, wherein the protein equivalent source comprises partially hydrolyzed protein having a degree of hydrolysis of less than 40%.

5. The nutritional composition of claim 1, wherein the nutritional composition comprise dietary butyrate present in an amount of from about 22 mg/100 kcal to about 280 mg/100 kcal.

6. The nutritional composition of claim 1, comprising dietary butyrate, wherein the dietary butyrate comprises sodium butyrate.

7. The nutritional composition of claim 1, comprising dietary butyrate, wherein the dietary butyrate is provided by an enriched lipid fraction derived from milk.

8. The nutritional composition of claim 7, wherein the enriched lipid fraction derived from milk further comprises milk fat globule membrane.

9. The nutritional composition of claim 1, further comprising one or more long chain polyunsaturated fatty acids.

10. The nutritional composition of claim 9, wherein the one or more long chain polyunsaturated fatty acids comprises docosahexaenoic acid, arachidonic acid, and combinations thereof.

11. The nutritional composition of claim 1, further comprising one or more probiotics.

12. The nutritional composition of claim 1, further comprising β-glucan.

13. The nutritional composition of claim 1, wherein the nutritional composition is an infant formula.

14. A nutritional composition, comprising per 100 Kcal:

(i) between about 6 g and about 22 g of a carbohydrate source;

(ii) between about 1 g and about 7 g of a protein source, wherein 1% to 99% of the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63; and 1% to 99% of the protein equivalent source comprises a partially hydrolyzed protein, and extensively hydrolyzed protein, or combinations thereof;

(iii) between about 1 g and about 10.3 g of a fat source;

(iv) between about 0.15 g and about 1.5 g of a prebiotic component comprising polydextrose and galacto-oligosaccharide; and

(v) between about 22 mg and 280mg of dietary butyrate.

15. The nutritional composition of claim 14, wherein the peptide component further comprises at least 10 additional peptides selected from Table 1.

16. The nutritional composition of claim 14, further comprising one or more long chain polyunsaturated fatty acids.

17. The nutritional composition of claim 14, further comprising one or more probiotics.

18. A nutritional composition comprising:

(i) a carbohydrate source;

(ii) a fat or lipid source;

(iii) a protein equivalent source, wherein the protein equivalent source comprises amino acids, wherein from about 10% to about 90% of the protein equivalent source comprises essential amino acids and wherein about 10% to about 90% of the protein equivalent source comprises non-essential amino acids; and at least one of the following:

(iv) dietary butyrate;

(v) a component for stimulating endogenous butyrate; or

(vi) combinations thereof.

19. The composition of claim 18, wherein the nutritional composition comprises one or more probiotics.

20. The composition of claim 18, wherein the nutritional composition is an infant formula.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/057646

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/057646

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L33/10 A23L33/12 A23L33/135 A23L33/18 A23L33/19
A23L33/21 A61P37/00
ADD.
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 A61P

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 practicable, search terms used)
EPO-Internal, WPI Data, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2014/271553 A1 (HONDMANN DIRK [US] ET AL) 18 September 2014 (2014-09-18) the whole document --- US 2014/271554 A1 (HONDMANN DIRK [US] ET AL) 18 September 2014 (2014-09-18) the whole document --- -/--	1-4,9-13 5-8, 14-20 1-13, 18-20

[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 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
15 December 2016	03/01/2017

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	ROBERTO BERNI CANANI ET AL: "Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants", THE I S M E JOURNAL: MULTIDISCIPLINARY JOURNAL OF MICROBIAL ECOLOGY, vol. 10, no. 3, 22 September 2015 (2015-09-22), pages 742-750, XP055328755, United Kingdom ISSN: 1751-7362, DOI: 10.1038/ismej.2015.151 the whole document	1-20
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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A61P 37/00(2006.01)

权利要求书2页 说明书29页
序列表12页

(54)发明名称

包含酪蛋白水解物以及膳食丁酸和/或用于刺激内源性丁酸形成的化合物的营养组合物

(57)摘要

提供了营养组合物,其包含用于刺激人类肠中丁酸产生的组分和/或膳食丁酸。进一步公开了通过向目标个体提供所述营养组合物来在儿科个体中减少过敏反应并促进对牛乳过敏的耐受性的方法。

CN 108347984 A

1.营养组合物,其包含:

碳水化合物来源;

蛋白质等价物来源,其中1%-99%的蛋白质等价物来源包含肽组分,所述肽组分包含SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63;和1%-99%的蛋白质等价物来源包含部分水解蛋白、深度水解蛋白,或其组合;

脂肪或脂质来源;和

下列的至少一种:

(i) 膳食丁酸;

(ii) 用于刺激内源性丁酸的组分;或者

(iii) 其组合。

2.如权利要求1所述的营养组合物,其中所述肽组分以约0.2 g/100 Kcal至约5.6 g/100 Kcal的量存在。

3.如权利要求1所述的营养组合物,其中所述肽组分进一步包含选自表1的至少10个另外的肽。

4.如权利要求1所述的营养组合物,其中所述蛋白质等价物来源包含水解度小于40%的部分水解蛋白。

5.如权利要求1所述的营养组合物,其中所述营养组合物包含以约22 mg/100 kcal至约280 mg/100 kcal的量存在的膳食丁酸。

6.如权利要求1所述的营养组合物,其包含膳食丁酸,其中所述膳食丁酸包含丁酸钠。

7.如权利要求1所述的营养组合物,其包含膳食丁酸,其中所述膳食丁酸由源自乳的富集脂质级分提供。

8.如权利要求7所述的营养组合物,其中所述源自乳的富集脂质级分进一步包含乳脂球膜。

9.如权利要求1所述的营养组合物,其进一步包含一种或多种长链多不饱和脂肪酸。

10.如权利要求9所述的营养组合物,其中所述一种或多种长链多不饱和脂肪酸包含二十二碳六烯酸、花生四烯酸及其组合。

11.如权利要求1所述的营养组合物,其进一步包含一种或多种益生菌。

12.如权利要求1所述的营养组合物,其进一步包含β-葡聚糖。

13.如权利要求1所述的营养组合物,其中所述营养组合物为婴儿配方。

14.营养组合物,其每100 Kcal包含:

(i) 约6 g至约22 g碳水化合物来源;

(ii) 约1 g至约7 g蛋白质来源,其中1%-99%的蛋白质等价物来源包含肽组分,所述肽组分包含SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63;和1%-99%的蛋白质等价物来源包含部分水解蛋白、深度水解蛋白,或其组合;

(iii) 约1 g至约10.3 g脂肪来源;

(iv) 约0.15 g至约1.5 g益生元组分,其包含聚葡萄糖和低聚半乳糖;和

(v) 约22 mg至280mg膳食丁酸。

15.如权利要求14所述的营养组合物,其中所述肽组分进一步包含选自表1的至少10个另外的肽。

16.如权利要求14所述的营养组合物,其进一步包含一种或多种长链多不饱和脂肪酸。

17.如权利要求14所述的营养组合物,其进一步包含一种或多种益生菌。

18.营养组合物,其包含:

(i) 碳水化合物来源;

(ii) 脂肪或脂质来源;

(iii) 蛋白质等价物来源,其中所述蛋白质等价物来源包含氨基酸,其中约10%至约90%的蛋白质等价物来源包含必需氨基酸并且其中约10%至约90%的蛋白质等价物来源包含非必需氨基酸;和下列的至少一种:

(iv) 膳食丁酸;

(v) 用于刺激内源性丁酸的组分;或者

(vi) 其组合。

19.如权利要求18所述的组合物,其中所述营养组合物包含一种或多种益生菌。

20.如权利要求18所述的组合物,其中所述营养组合物为婴儿配方。

包含酪蛋白水解物以及膳食丁酸和/或用于刺激内源性丁酸形成的化合物的营养组合物

技术领域

[0001] 本公开大体上涉及包含膳食丁酸和可刺激内源性丁酸产生的组分的营养组合物。营养组合物适合施用于儿科个体。此外，本公开涉及营养组合物，其包含含有聚葡萄糖和低聚半乳糖的益生元、膳食丁酸和蛋白质等价物来源(protein equivalent source)。此外，公开了用于在目标个体中降低过敏发生率和/或改善对牛乳过敏的耐受性的方法。所公开的营养组合物可以提供累加和/或协同的有益健康效果。

背景技术

[0002] 施用包含丁酸或丁酸衍生物的营养组合物或其他组合物经常在施用后丁酸的生物利用度方面遇到困难。例如，某些丁酸衍生物经历降解或氧化，这最终影响摄取后丁酸衍生物的生物利用度。因此，考虑到丁酸衍生物的降解，包含丁酸衍生物的组合物在摄取后可能不提供治疗功效。

[0003] 另外，包含丁酸的营养组合物可能遭受糟糕的适口性。包含丁酸的组合物的令人不快的味道和气味可能使包含丁酸的某些营养组合物的口服施用变得困难，特别是在儿科人群中。例如，某些丁酸衍生物在室温下作为具有令人不快的味道和强烈气味的稠密液体存在。

[0004] 因此，提供包含内源性丁酸的营养组合物以避免有时发现的膳食丁酸适口性问题将是有益的。此外，需要包含一种或多种益生元、蛋白质等价物来源和丁酸的组合的可口、安全而有效的营养组合物，以在某些个体中减少过敏发生率并增加对牛乳过敏的耐受性。

[0005] 发明公开

简而言之，在实施方案中，本公开涉及包含膳食丁酸和可刺激人肠中内源性丁酸产生的组分的营养组合物。在一些实施方案中，膳食丁酸可以被包封。在一些实施方案中，可以通过刺激肠道微生物群产生短链脂肪酸(“SCFA”)来提供内源性丁酸，并且可以通过源自乳的富集脂质级分提供膳食丁酸。

[0006] 应该理解的是，前面的一般性描述和下面的详细描述都呈现了本公开的实施方案，并且旨在提供用于理解所要求保护的本公开的性质和特征的概述或框架。该描述用于解释所要求保护的主题的原理和操作。在阅读以下公开后，本公开的其他和进一步的特征和优点对于本领域技术人员而言将是显而易见的。

[0007] 实施本发明的最佳方式

现在将详细提及本公开的实施方案，其一个或多个实例在下文中阐述。通过解释本公开的营养组合物来提供每个实例，而不是限制。实际上，对于本领域技术人员而言显而易见地是，在不脱离本公开的范围的情况下，可以对本公开的教导进行各种修改和变化。例如，作为一个实施方案的一部分示出或描述的特征可以与另一个实施方案一起使用以产生又一个实施方案。

[0008] 因此，本公开旨在覆盖落入所附权利要求及其等价物的范围内的这些修改和变

化。本公开的其他目的、特征和方面公开于以下详细描述中或从以下详细描述中显而易见。本领域的普通技术人员应该理解，本讨论仅是对示例性实施方案的描述，而不意图限制本公开的更广泛的方面。

[0009] 本公开大体上涉及包含膳食丁酸和用于刺激内源性丁酸产生的组分的营养组合物。此外，本公开涉及用于改善包含丁酸的营养组合物的货架稳定性和/或感官特性的方法。

[0010] “营养组合物”是指满足个体营养需求的至少一部分的物质或制剂。术语“营养物”、“营养配方”、“肠内营养物”和“营养补充物”在整个本公开中用作营养组合物的非限制性实例。此外，“营养组合物”可以指肠内配方、口服配方、婴儿配方、儿科个体配方、儿童配方、成长乳和/或成人配方的液体、粉末、凝胶、糊剂、固体、浓缩物、悬浮液或即用形式。

[0011] “儿科个体”是指小于13岁的人。在一些实施方案中，儿科个体是指出生至8岁的人类个体。在其他实施方案中，儿科个体是指1至6岁的人类个体。在更进一步的实施方案中，儿科个体是指6至12岁的人类个体。如下所述，术语“儿科个体”可以指婴儿(早产儿或足月儿)和/或儿童。

[0012] “婴儿”是指年龄范围从出生到不超过一岁的人类个体，并包括0至12个月矫正年龄的婴儿。“矫正年龄”一词是指婴儿的实龄减去婴儿提早出生的时间量。因此，矫正年龄是婴儿的年龄，如果他已经到了足月。术语婴儿包括低出生体重婴儿，极低出生体重婴儿和早产儿。“早产儿”是指在妊娠第37周结束前出生的婴儿。“足月儿”是指在妊娠第37周结束后出生的婴儿。

[0013] “儿童”是指年龄范围从12个月龄到约13岁的个体。在一些实施方案中，儿童是1至12岁的个体。在其他实施方案中，术语“儿童(children或child)”是指1岁至约6岁或者约7岁至约12岁的个体。在其他实施方案中，术语“儿童”是指12个月龄至约13岁的任何年龄范围。

[0014] “婴儿配方”是指满足婴儿营养需求的至少一部分的组合物。在美国，婴儿配方的内容物由美国联邦法规第21篇第100、106和107节所列的联邦法规规定。

[0015] 术语“医疗食品”是指经配制或预期用于疾病或病症的饮食管理的肠内组合物。医疗食品可以是用于口服摄取或管饲(鼻胃管)的食品，可以标记用于有独特营养要求的特定医学病症、疾病或疾病状态的饮食管理，并且可以预期在医疗监督下使用。

[0016] 如本文所用的术语“肽”描述了氨基酸的线性分子链，包括单链分子或其片段。本文所述的肽包含总计不超过50个氨基酸。肽可以进一步形成由至少两个相同或不同的分子组成的寡聚物或多聚体。此外，术语“肽”也包括其中氨基酸和/或肽键已被官能类似物替换的此类肽的拟肽。这种官能类似物可以包括但不限于除了20种基因编码的氨基酸之外的所有已知氨基酸，例如硒代半胱氨酸。

[0017] 术语“肽”还可以指天然修饰的肽，其中修饰例如通过本领域公知的糖基化、乙酰化、磷酸化和类似的修饰来实现。在一些实施方案中，肽组分与也在本文中公开的蛋白质来源不同。此外，肽可以例如重组生产、半合成生产、合成生产或从天然来源获得，例如在水解蛋白质包括但不限于酪蛋白后，以上均根据本领域已知的方法。

[0018] 当涉及水解蛋白或蛋白质水解物使用时，术语“摩尔质量分布”涉及蛋白质水解物中存在的各肽的摩尔质量。例如，具有500道尔顿以上的摩尔质量分布的蛋白质水解物是指

包含在蛋白质水解物中的各肽具有至少500道尔顿的摩尔质量。因此，在一些实施方案中，表1和表2中公开的肽源自具有500道尔顿以上的摩尔质量分布的蛋白质水解物。为了生产具有500道尔顿以上的摩尔质量分布的蛋白质水解物，可以对蛋白质水解物进行某些过滤程序或本领域已知的任何其他程序，以去除摩尔质量小于500道尔顿的肽、氨基酸和/或其他蛋白质材料。为了本公开的目的，可以使用本领域已知的任何方法来生产具有500道尔顿以上的摩尔质量分布的蛋白质水解物。

[0019] 术语“蛋白质等价物”或“蛋白质等价物来源”包括任何蛋白质来源，例如大豆、蛋、乳清或酪蛋白，以及非蛋白质来源，例如肽或氨基酸。此外，蛋白质等价物来源可以是本领域中使用的任何蛋白质等价物来源，例如脱脂乳、乳清蛋白、酪蛋白、大豆蛋白、水解蛋白、肽、氨基酸等。可用于实施本公开的牛乳蛋白来源包括但不限于乳蛋白粉、乳蛋白浓缩物、乳蛋白分离物、脱脂乳固体、脱脂乳、脱脂乳粉、乳清蛋白、乳清蛋白分离物、乳清蛋白浓缩物、甜乳清、酸乳清、酪蛋白、酸性酪蛋白、酪蛋白酸盐(例如酪蛋白酸钠、酪蛋白酸钙钠、酪蛋白酸钙)、大豆蛋白及其任何组合。在一些实施方案中，蛋白质等价物来源可以包含水解蛋白，包括部分水解蛋白和深度水解蛋白。在一些实施方案中，蛋白质等价物来源可以包括完整蛋白质。更特别地，蛋白质来源可以包含a)约20％至约80％的本文所述的肽组分，和b)约20％至约80％的完整蛋白质、水解蛋白或其组合。

[0020] 术语“蛋白质等价物来源”还涵盖游离氨基酸。在一些实施方案中，氨基酸可以包括但不限于组氨酸、异亮氨酸、亮氨酸、赖氨酸、甲硫氨酸、半胱氨酸、苯丙氨酸、酪氨酸、苏氨酸、色氨酸、缬氨酸、丙氨酸、精氨酸、天冬酰胺、天冬氨酸、谷氨酸、谷氨酰胺、甘氨酸、脯氨酸、丝氨酸、肉毒碱、牛磺酸及其混合物。在一些实施方案中，氨基酸可以是支链氨基酸。在某些其他实施方案中，可以包含小氨基酸肽作为营养组合物的蛋白质组分。这种小氨基酸肽可以是天然存在的或合成的。

[0021] “分级程序”包括其中将一定量的混合物分成许多称为级分的较小量的任何过程。级分的组成可能与混合物和其它级分都不同。分级程序的实例包括但不限于熔融分级、溶剂分级、超临界流体分级和/或其组合。

[0022] 如本文所用的术语“必需氨基酸”是指不能由所考虑的生物体从头合成或以不足量生产的氨基酸，因此必须通过饮食来供应。例如，在目标个体是人的一些实施方案中，必需氨基酸是不能由人类从头合成的必需氨基酸。

[0023] 如本文所用的术语“非必需氨基酸”是指可由生物体合成或由生物体从必需氨基酸衍生的氨基酸。例如，在目标个体是人的一些实施方案中，非必需氨基酸是可在人体中合成或在人体中由必需氨基酸衍生的非必需氨基酸。

[0024] “乳脂球膜”包括在乳脂球膜中发现的组分，包括但不限于乳脂球膜蛋白，如粘蛋白1、嗜乳脂蛋白、脂肪分化相关蛋白(Adipophilin)、CD36、CD14、乳凝集素(PAS6/7)、黄嘌呤氧化酶和脂肪酸结合蛋白等。

[0025] 术语“成长乳”是指旨在用作多样化饮食的一部分以支持年龄为约1岁至约6岁的儿童的正常生长和发育的广泛类别的营养组合物。

[0026] “乳”是指已经从哺乳动物的乳腺中抽取或提取的组分。在一些实施方案中，营养组合物包含衍生自驯化的有蹄类动物、反刍动物或其他哺乳动物或其任何组合的乳组分。

[0027] “营养完全”是指可以用作唯一营养来源的组合物，其提供基本上所有所需的每日

量的维生素、矿物质和/或痕量元素与蛋白质、碳水化合物和脂质的组合。事实上，“营养完全”描述了提供支持个体正常生长和发育所需的足量的碳水化合物、脂质、必需脂肪酸、蛋白质、必需氨基酸、条件必需氨基酸、维生素、矿物质和能量的营养组合物。

[0028] 根据定义，对于足月婴儿“营养完全”的营养组合物将在定性和定量上提供足月婴儿生长所需的足量的所有碳水化合物、脂质、必需脂肪酸、蛋白质、必需氨基酸、条件必需氨基酸、维生素、矿物质和能量。

[0029] 根据定义，对于儿童“营养完全”的营养组合物将在定性和定量上提供儿童生长所需的足量的所有碳水化合物、脂质、必需脂肪酸、蛋白质、必需氨基酸、条件必需氨基酸、维生素、矿物质和能量。

[0030] “外源性丁酸”或“膳食丁酸”各自是指旨在包括在本公开的营养组合物本身中而不是在肠中产生的丁酸或丁酸衍生物。

[0031] “内源性丁酸”或“来自内源性来源的丁酸”各自是指由于摄取所公开的组合物而存在于肠中的丁酸，所述丁酸不以其本身加入，而是由于组合物的其它组分或成分而存在；组合物的这种其它组分或成分的存在刺激肠中丁酸的产生。

[0032] 术语“牛乳过敏”描述食物过敏，即人类个体中对牛乳中包含的一种或多种蛋白质的免疫不良反应。主要症状是胃肠道、皮肤病学和呼吸系统症状。这些可以转化为皮疹、荨麻疹、呕吐、腹泻、便秘和痛苦。临床范围扩展到多种病症：过敏反应、特应性皮炎、喘息、婴儿肠绞痛、胃食管反流病(GERD)、食管炎、结肠炎、肠胃炎、头痛/偏头痛和便秘。

[0033] 本公开的营养组合物可以基本上不含本文所述的任何任选的或选择的成分，条件是剩余的营养组合物仍含有本文所述的所有所需的成分或特征。在本文中，并且除非另外指明，否则术语“基本上不含”是指所选择的组合物可以含有小于功能量的任选成分，通常小于0.1重量％，并且还包含0重量％的这种任选的或选择的成分。

[0034] 除非另外指明，否则本文所用的所有百分数、份数和比例均按总组合物的重量计。

[0035] 除非另外指明或通过其中提及的上下文明确暗示相反，否则对本公开的单数特征或限制的所有提及应包括相应的复数特征或限制，反之亦然。

[0036] 除非另外指明或通过其中提及组合的上下文明确暗示相反，否则如本文所用的方法或工艺步骤的所有组合可以以任何顺序执行。

[0037] 本公开的方法和组合物，包括其组分，可以包含下列、由下列组成或基本由下列组成：本文描述的实施方案的基本元素和限制以及本文描述的或在营养组合物中另外有用的任何另外的或任选的成分、组分或限制。

[0038] 如本文所用的术语“约”应被解释为指代被指定为任何范围的端点的两个数字。任何对范围的提及应被视为为该范围内的任何子集提供支持。

[0039] 本公开涉及包含丁酸和LGG的营养组合物。用于在本文使用的丁酸的非限制性实例包括丁酸、丁酸盐和丁酸的甘油酯。营养组合物可进一步包含碳水化合物来源、蛋白质来源和脂肪或脂质来源。在一些实施方案中，营养组合物可以包含能够刺激内源性丁酸产生的组分；在其他实施方案中，营养组合物可以包含膳食和内源性丁酸二者。

[0040] 提供外源性和内源性丁酸二者的益处是加速的对牛乳的耐受性的获得。此外，提供外源性和内源性丁酸二者以及鼠李糖乳杆菌(*Lactobacillus rhamnoses*) GG (“LGG”)的益处是加速的对牛乳的耐受性的获得。对牛乳过敏的常规饮食管理包括使用含有蛋白质

水解物和氨基酸而不是完整蛋白质，以及某些益生菌如鼠李糖乳杆菌GG (“LGG”)的制剂，其有助于加速的对牛乳的耐受性的获得。包含刺激肠道微生物群产生内源性丁酸的组分可以进一步加速耐受性获得和/或可以作为LGG在营养组合物中的功能性替代物应用。此外，包含某些益生菌如LGG与丁酸(内源性或外源性丁酸)的组合可以促进加速的对牛乳的耐受性的获得。

[0041] 在一个实施方案中，用于刺激内源性丁酸的组分是包含聚葡萄糖(“PDX”)和低聚半乳糖(“GOS”)的益生元。包含PDX和GOS的益生元组分可增强微生物群产生内源性丁酸。丁酸具有后生的(组蛋白去乙酰化酶抑制活性)，导致调节反应如调节性T细胞的产生。在牛乳过敏的情况下，这些调节反应可能导致加速的对牛乳蛋白质的耐受性的获得。

[0042] 除了PDX和GOS之外，营养组合物还可以包含一种或多种其他益生元，其可以发挥额外的健康益处，其可以包括但不限于选择性刺激一种或有限数量的有益肠道细菌的生长和/或活性，刺激摄取的益生菌微生物的生长和/或活性，选择性减少肠病原体以及对肠短链脂肪酸特性的有利影响。这样的益生元可以是天然存在的，合成的或通过生物体和/或植物的基因操作开发的，无论这种新来源是现在已知的还是后来开发的。可用于本公开的益生元可以包括低聚糖、多糖和其他益生元，其含有果糖、木糖、大豆、半乳糖、葡萄糖和甘露糖。

[0043] 更具体地，可用于本公开的益生元包括PDX和GOS，并且在一些实施方案中还可以包括聚葡萄糖粉、乳果糖、低聚乳果糖、棉子糖、低聚葡萄糖、菊糖、低聚果糖(FOS)、低聚异麦芽糖、大豆低聚糖、低聚乳果糖、低聚木糖(XOS)、低聚壳聚糖、低聚甘露糖、低聚阿拉伯糖(aribino-oligosaccharide)、唾液酸寡糖(siallyl-oligosaccharide)、低聚岩藻糖(fuco-oligosaccharide)和低聚龙胆糖(gentio-oligosaccharide)。

[0044] 在一个实施方案中，营养组合物中存在的益生元的总量可以为约1.0 g/L至约10.0 g/L组合物。更优选地，营养组合物中存在的益生元的总量可以为约2.0 g/L至约8.0 g/L组合物。在一些实施方案中，营养组合物中存在的益生元的总量可以为约0.01 g/100 Kcal至约1.5 g/100 Kcal。在某些实施方案中，营养组合物中存在的益生元的总量可以为约0.15 g/100 Kcal至约1.5 g/100 Kcal。在一些实施方案中，益生元组分包含至少20% w/w的PDX和GOS。

[0045] 在一个实施方案中，营养组合物中的PDX的量可以在约0.015 g/100 Kcal至约1.5 g/100 Kcal的范围内。在另一个实施方案中，聚葡萄糖的量在约0.2 g/100 Kcal至约0.6 g/100 Kcal的范围内。在一些实施方案中，PDX可以足以提供约1.0 g/L至10.0 g/L的量包含在营养组合物中。在另一个实施方案中，营养组合物含有约2.0 g/L至8.0 g/L的量的PDX。并且在其他实施方案中，营养组合物中PDX的量可以为约0.05 g/100 Kcal至约1.5 g/100 Kcal。

[0046] 益生元组分还包含GOS。在一个实施方案中，营养组合物中GOS的量可以为约0.015 g/100 Kcal至约1.0 g/100 Kcal。在另一个实施方案中，营养组合物中GOS的量可以为约0.2 g/100 Kcal至约0.5 g/100 Kcal。

[0047] 在一个具体的实施方案中，GOS和PDX以至少约0.015 g/100 Kcal或约0.015 g/100 Kcal至约1.5 g/100 Kcal的总量补充到营养组合物中。在一些实施方案中，营养组合物可以包含总量为约0.1至约1.0 g/100 Kcal的GOS和PDX。

[0048] 在一些实施方案中，营养组合物包含膳食丁酸来源，其以约5 g/100 Kcal至约500 g/100 kcal的量存在。在一些实施方案中，营养组合物包含膳食丁酸来源，其以约15 g/100 Kcal至约450 g/100 kcal的量存在。在一些实施方案中，营养组合物包含膳食丁酸来源，其以约20 g/100 Kcal至约400 g/100 kcal的量存在。在一些实施方案中，营养组合物包含膳食丁酸来源，其以约25 g/100 Kcal至约350 g/100 kcal的量存在。在一些实施方案中，营养组合物包含膳食丁酸来源，其以约30 g/100 Kcal至约280 g/100 kcal的量存在。

[0049] 在一些实施方案中，营养组合物包含约0.01 g至约10 g膳食丁酸每100 g营养组合物中的总脂肪。在一些实施方案中，营养组合物包含约0.1 g至约8 g膳食丁酸每100 g营养组合物中的总脂肪。在一些实施方案中，营养组合物包含约0.4 g至约7 g膳食丁酸每100 g营养组合物中的总脂肪。在一些实施方案中，营养组合物包含约0.7 g至约6.5 g膳食丁酸每100 g营养组合物中的总脂肪。在一些实施方案中，营养组合物包含约1.2 g至约5.1 g膳食丁酸每100 g营养组合物中的总脂肪。

[0050] 在一些实施方案中，膳食丁酸由以下的一种或多种提供：丁酸；丁酸盐，包括丁酸钠、丁酸钾、丁酸钙和/或丁酸镁；丁酸甘油酯；和/或其药学上可接受的碱或酸的相应混合物和相应的盐，纯非对映异构体形式和对映异构体形式，或混合物。

[0051] 膳食丁酸可以通过本领域已知的任何合适的来源供应。膳食丁酸的非限制性来源包括动物源脂肪和衍生产品，例如但不限于乳、乳脂、黄油、酪乳、奶油乳清(butter serum)、奶油；微生物发酵衍生产品，例如但不限于酸奶和发酵酪乳；和植物源衍生的种子油产品，例如菠萝和/或菠萝油、杏和/或杏油、大麦、燕麦、糙米、麸、青豆、豆科植物、绿叶蔬菜、苹果、猕猴桃、橙。在一些实施方案中，膳食丁酸是合成制备的。在合成制备膳食丁酸的实施方案中，膳食丁酸的化学结构可以根据需要进行修饰。此外，合成制备的膳食丁酸可以通过本领域已知的任何方式来纯化，以产生可掺入本文公开的营养组合物中的纯化膳食丁酸添加剂。膳食丁酸可以由乳制品脂质和/或甘油三酯结合形式的丁酸提供。

[0052] 在一些实施方案中，膳食丁酸可以以包封形式提供。在某些实施方案中，膳食丁酸的包封可以提供更长的货架稳定性并且可以提供改善的营养组合物的感官特性。例如，在一些实施方案中，可以通过使用或组合脂肪衍生物质如甘油单酯和甘油二酯；甘油糖脂和甘油酸酯；磷脂；植物、动物和微生物衍生的蛋白质和水解胶体，例如淀粉、麦芽糖糊精、明胶、果胶、葡聚糖、酪蛋白、大豆蛋白和/或乳清蛋白来包封或包衣膳食丁酸。

[0053] 膳食丁酸也可以以包衣形式提供。例如，用脂肪衍生的物质，例如甘油单酯和甘油二酯；甘油糖脂和甘油酸酯；磷脂；植物、动物和微生物衍生的蛋白质和水解胶体，例如淀粉、麦芽糖糊精、明胶、果胶、葡聚糖、酪蛋白、大豆蛋白和/或乳清蛋白包衣某些丁酸的甘油酯和/或丁酸的酰胺衍生物可以改善膳食丁酸的货架稳定性并且可以进一步改善营养组合物的整体感官特性。

[0054] 在某些实施方案中，膳食丁酸包含丁酸的甘油酯。当在营养组合物中配制和加工时，丁酸的甘油酯可提供最小的复杂性。此外，丁酸的甘油酯可以改善包含膳食丁酸的营养组合物的保质期，并且可进一步对成品的感觉特性具有低影响。

[0055] 在一些实施方案中，膳食丁酸可以包含丁酸盐，例如丁酸钠、丁酸钾、丁酸钙、丁酸镁及其组合。在一些实施方案中，当提供给目标个体时，使用选择的膳食丁酸盐可改善肠道健康。在某些实施方案中，膳食丁酸包含已用一种或多种脂肪或脂质包衣的合适的丁酸盐。

在其中膳食丁酸包含脂肪包衣的丁酸盐的某些实施方案中，营养组合物可以是掺入膳食丁酸的干粉组合物。

[0056] 在一些实施方案中，膳食丁酸可以包含本文公开的任何丁酸化合物，其被配制为与壳聚糖或一种或多种环糊精的络合形式。例如，环糊精是由六个(α-环糊精)，七个(β-环糊精)或八个(γ-环糊精)α-1,4-吡喃葡萄糖单元组成的环状低聚糖。环糊精的特征还在于亲水外表面和疏水核心。不受任何特定理论的束缚，脂肪族丁酸链将与环糊精核心形成络合物，从而增加其分子量，从而降低丁酸化合物的挥发性。因此，当膳食丁酸包含为与一种或多种环糊精的络合形式的丁酸化合物时，膳食丁酸的生物利用度可以得到改善。此外，环糊精是体积大的疏水分子，其对胃酸以及胃肠酶具有抗性，因此如本文所述的丁酸-环糊精络合物的施用会促进膳食丁酸在小肠中的吸收。

[0057] 在一些实施方案中，膳食丁酸由源自乳的富集脂质级分提供。例如，牛乳脂肪的丁酸含量可能是人乳脂肪中的丁酸含量的20倍。此外，在人乳中存在的短链脂肪酸(“SCFAs”)，即碳链长度为4-12的脂肪酸中，丁酸(C4)是牛乳中最主要的之一。因此，牛乳脂肪和/或牛乳脂肪的富集级分可以包含在营养组合物中以提供膳食丁酸。

[0058] 在其中膳食丁酸由源自乳的富集脂质级分提供的实施方案中，可以通过任何数量的分级技术来产生源自乳的富集脂质级分。这些技术包括但不限于熔点分级、有机溶剂分级、超临界流体分级以及其任何变体和组合。

[0059] 此外，可能进行分级程序以产生富集脂质级分的混合物包括但不限于牛全脂乳、牛乳脂、山羊乳、绵羊乳、牦牛乳和/或其混合物。在一个优选的实施方案中，用于产生富集脂质级分的乳混合物是牛乳。

[0060] 除了提供膳食丁酸之外，富集脂质级分可以包含以下成分之一：饱和脂肪酸；反式脂肪酸；支链脂肪酸(“BCFAs”)，包括奇数支链脂肪酸(“OBCFAs”)；共轭亚油酸(“CLA”)；单不饱和脂肪酸；多不饱和脂肪酸；胆固醇；磷脂；和乳脂球膜，包括乳脂球膜蛋白。

[0061] 在一些实施方案中，富集脂质级分每100 Kcal包括以下的一种或多种：

约0.1 g至8.0 g饱和脂肪酸；

约0.2 g至7.0 g反式脂肪酸；

约0.003 g至约6.1 g支链脂肪酸；

约0.026 g至约2.5 g共轭亚油酸；

约0.8 g至约2.5 g单不饱和脂肪酸；

约2.3 g至约4.4 g多不饱和脂肪酸；

约100 mg至约400 mg胆固醇；

约50 mg至约400 mg磷脂；和/或

约10 mg至约500 mg乳脂球膜。

[0062] 以下实施例例示可以通过分级程序产生的具有富集浓度的丁酸(C4)的乳脂级分。

[0063] 实施例1

下面例示通过超临界碳萃取分级程序和通过熔融分级产生的分级乳脂的脂质简况。

乳脂组成(g脂肪酸/100 g总脂肪酸)

	AMF	SCCO2	MeltFrac 10C
C 4:0	3.9	6.0	4.7
C 6:0	2.5	3.3	2.9
C 8:0	1.4	1.9	1.8
C 10:0	3.1	3.9	3.8
C 12:0	4.2	4.1	4.8
C 14:0	11.4	12.2	10.9
C 14:1	1.1	1.0	1.3
C 15:0	1.1	1.0	0.9
C 16:0	29.4	29.6	22.3
C 16:1	1.9	1.4	2.2
C 17:0	0.6	0.5	0.4
C 18:0	11.4	8.2	6.1
C 18:1,顺式, ω9	21.9	16.5	25.3
C 18:1,反式, ω9	0.3	1.6	1.9
C 18:2, ω6	1.9	2.2	1.9
C 18:3, ω3, α	0.6	0.4	0.6
C 20:0	0.0	0.1	0.1
C 20:1, ω9	0.1	0.1	0.2
饱和	68.7	70.7	58.6
不饱和	27.8	23.1	33.3

AMF = 无水乳脂; SCCO2 = 超临界二氧化碳级分 (超级油精(super olein)). MeltFrac = 在10℃分离的熔融结晶级分。

[0064] 在某些实施方案中,将含有PDX和GOS的益生元和膳食丁酸掺入到为婴儿配方的营养组合物中。目前,许多婴儿配方不是用膳食丁酸配制的。婴儿配方包含很少至不包含膳食丁酸的一个原因是由于当将丁酸化合物掺入营养组合物中时营养组合物表现出的令人不快的感官特性。例如,许多丁酸化合物表现出使得食用其中掺入它们的营养组合物成为令人不快的经历的气味。此外,儿科和婴儿群体将不容易食用具有令人不快的气味、味道和/或口感的营养产品。因此,需要配制用于施用于儿科个体或婴儿的营养组合物,其在肠中提供丁酸但不具有减少的感官特性。将刺激肠道微生物群产生丁酸的益生元和本文公开的某些膳食丁酸化合物(即丁酸的甘油酯和氨基酸的酰胺衍生物)掺入到儿科和婴儿营养组合物中将提供丁酸,同时仍提供令人愉快的感觉经历。

[0065] 在一些实施方案中,营养组合物包含蛋白质等价物来源,其中蛋白质等价物来源

包含肽组分，其含有SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63。在一些实施方案中，肽组分可以包含表1公开的另外的肽。例如，组合物可以包含表1中公开的至少10个另外的肽。在一些实施方案中，20％至80％的蛋白质等价物来源包含肽组分，并且20％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白及其组合。在一些实施方案中，术语另外的意思是选择不同于所列举的那些的肽。

[0066] 在另一个实施方案中，1％至99％的蛋白质等价物来源包含肽组分，其包含至少3个选自SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63的肽，以及至少5个选自表1的另外的肽；并且其中1％至99％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白或其组合。在一些实施方案中，2％至80％的蛋白质等价物来源包含肽组分，其包含至少3个选自SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63的肽，以及至少5个选自表1的另外的肽；并且其中2％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白或其组合。在一些实施方案中，20％至80％的蛋白质等价物来源包含肽组分，其包含至少3个选自SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63的肽，以及至少5个选自表1的另外的肽；并且其中20％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白或其组合。

[0067] 下表1鉴定了可以包含在本发明营养组合物的肽组分中的肽的氨基酸序列。

表1

Seq. ID号	氨基酸序列											(aa)
1	Ala	Ile	Asn	Pro	Ser	Lys	Glu	Asn				8
2	Ala	Pro	Phe	Pro	Glu							5
3	Asp	Ile	Gly	Ser	Glu	Ser						6
4	Asp	Lys	Thr	Glu	Ile	Pro	Thr					7
5	Asp	Met	Glu	Ser	Thr							5
6	Asp	Met	Pro	Ile								4
7	Asp	Val	Pro	Ser								4
n/a	Glu	Asp	Ile									3
n/a	Glu	Leu	Phe									3
n/a	Glu	Met	Pro									3
8	Glu	Thr	Ala	Pro	Val	Pro	Leu					7
9	Phe	Pro	Gly	Pro	Ile	Pro						6
10	Phe	Pro	Gly	Pro	Ile	Pro	Asn					7
11	Gly	Pro	Phe	Pro								4
12	Gly	Pro	Ile	Val								4

13	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln			9
14	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser				8
15	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala			9
16	Ile	Asn	Pro	Ser	Lys	Glu						6
17	Ile	Pro	Asn	Pro	Ile							5
18	Ile	Pro	Asn	Pro	Ile	Gly						6
19	Ile	Pro	Pro	Leu	Thr	Gln	Thr	Pro	Val			9
20	Ile	Thr	Ala	Pro								4
21	Ile	Val	Pro	Asn								4
22	Lys	His	Gln	Gly	Leu	Pro	Gln					7
23	Leu	Asp	Val	Thr	Pro							5
24	Leu	Glu	Asp	Ser	Pro	Glu						6
25	Leu	Pro	Leu	Pro	Leu							5
26	Met	Glu	Ser	Thr	Glu	Val						6
27	Met	His	Gln	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr	11
28	Asn	Ala	Val	Pro	Ile							5
29	Asn	Glu	Val	Glu	Ala							5
n/a	Asn	Leu	Leu									3
30	Asn	Gln	Glu	Gln	Pro	Ile						6
31	Asn	Val	Pro	Gly	Glu							5
32	Pro	Phe	Pro	gly	Pro	Ile						6
33	Pro	Gly	Pro	Ile	Pro	Asn						6
34	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr				8
35	Pro	Ile	Thr	Pro	Thr							5
36	Pro	Asn	Pro	Ile								4
37	Pro	Asn	Ser	Leu	Pro	Gln						6
38	Pro	Gln	Leu	Glu	Ile	Val	Pro	Asn				8
39	Pro	Gln	Asn	Ile	Pro	Pro	Leu					7
40	Pro	Val	Leu	Gly	Pro	Val						6
41	Pro	Val	Pro	Gln								4
42	Pro	Val	Val	Val	Pro							5
43	Pro	Val	Val	Val	Pro	Pro						6
44	Ser	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala	Glu	11
45	Ser	Ile	Ser	Ser	Ser	Glu	Glu					7

46	Ser	Ile	Ser	Ser	Ser	Glu	Glu	Ile	Val	Pro	Asn	11
47	Ser	Lys	Asp	Ile	Gly	Ser	Glu					7
48	Ser	Pro	Pro	Glu	Ile	Asn						6
49	Ser	Pro	Pro	Glu	Ile	Asn	Thr					7
50	Thr	Asp	Ala	Pro	Ser	Phe	Ser					7
51	Thr	Glu	Asp	Glu	Leu							5
52	Val	Ala	Thr	Glu	Glu	Val						6
53	Val	Leu	Pro	Val	Pro							5
54	Val	Pro	Gly	Glu								4
55	Val	Pro	Gly	Glu	Ile	Val						6
56	Val	Pro	Ile	Thr	Pro	Thr						6
57	Val	Pro	Ser	Glu								4
58	Val	Val	Pro	Pro	Phe	Leu	Gln	Pro	Glu			9
59	Val	Val	Val	Pro	Pro							5
60	Tyr	Pro	Phe	Pro	Gly	Pro						6
61	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro				8
62	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro	Asn			9
63	Tyr	Pro	Ser	Gly	Ala							5
64	Tyr	Pro	Val	Glu	Pro							5

[0068] 下表2进一步鉴定了可以包含在本文公开的肽组分中的来自表1的氨基酸序列的子集。

表2

Seq ID号		氨基酸序列										(aa)
4		Asp	Lys	Thr	Glu	Ile	Pro	Thr				7
13		Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln		9
17		Ile	Pro	Asn	Pro	Ile	Gly					6
21		Ile	Val	Pro	Asn							4
24		Leu	Glu	Asp	Ser	Pro	Glu					6
30		Asn	Gln	Glu	Gln	Pro	Ile					6
31		Asn	Val	Pro	Gly	Glu						5
32		Pro	Phe	Pro	Gly	Pro	Ile					6
51		Thr	Glu	Asp	Glu	Leu						5
57		Val	Pro	Ser	Glu							4
60		Tyr	Pro	Phe	Pro	Gly	Pro					6
63		Tyr	Pro	Ser	Gly	Ala						5

[0069] 在一些实施方案中,肽组分可以以约0.2 g/100 Kcal至约5.6 g/100 Kcal的量存在于营养组合物中。在其他实施方案中,肽组分可以以约1 g/100 Kcal至约4 g/100 Kcal

的量存在于营养组合物中。在又其他实施方案中，肽组分可以以约2 g/100 Kcal至约3 g/100 Kcal的量存在于营养组合物中。

[0070] 本文公开的肽组分可与营养组合物中的其他成分一起配制以为目标个体提供适当的营养水平。在一些实施方案中，肽组分被包含在适合支持正常生长的营养完全配方中。

[0071] 肽组分可以作为蛋白质等价物来源的元素提供。在一些实施方案中，表1和2中鉴定的肽可以由从牛乳蛋白获得的蛋白质等价物来源提供，其包括但不限于牛酪蛋白和牛乳清。在一些实施方案中，蛋白质等价物来源包含水解的牛酪蛋白或水解的牛乳清。因此，在一些实施方案中，表1和表2中鉴定的肽可以由酪蛋白水解物提供。这样的肽可以通过水解获得或者可以通过技术人员已知的方法在体外合成。

[0072] 本文公开了水解方法的非限制性实例。在一些实施方案中，该方法可用于获得本公开的蛋白质水解物和肽。使用蛋白水解酶蛋白酶N水解蛋白质。蛋白酶N“Amano”可从Amano Enzyme U.S.A. Co., Ltd., Elgin, Ill商购获得。蛋白酶N是蛋白水解酶制剂，其衍生自细菌物种枯草芽孢杆菌(Bacillus subtilis)。蛋白酶粉末被规定为“不小于150,000单位/g”，这意味着一个单位的蛋白酶N是在7.0的pH下60分钟产生与100微克酪氨酸相当的氨基酸的酶的量。为了生产本公开的婴儿配方，蛋白酶N可以以约0.5％至约1.0％的水平使用，以被水解的总蛋白质的重量计。

[0073] 通过蛋白酶N水解蛋白质典型地在约50℃至约60℃的温度下进行。水解发生一段时间以获得约4％至10％的水解度。在特定的实施方案中，水解发生一段时间以获得约6％至9％的水解度。在另一个实施方案中，水解发生一段时间以获得约7.5％的水解度。这种水解水平可能花费约半小时至约3小时。

[0074] 在水解过程中应保持恒定的pH。在本公开的方法中，将pH调节至并保持在约6.5至8。在特定实施方案中，pH保持在约7.0。

[0075] 为了保持乳清蛋白、酪蛋白、水和蛋白酶N的溶液的最佳pH，可以使用氢氧化钠和/或氢氧化钾的苛性碱溶液来调节水解期间的pH。如果使用氢氧化钠来调节pH，则加入到溶液中的氢氧化钠的量应该被控制到它占成品蛋白质水解物中总固体的小于约0.3％的水平。为了保持最佳pH，也可以在加入酶之前或在水解过程中使用10％氢氧化钾溶液将溶液的pH调节至所需值。

[0076] 在蛋白质水解过程中加入到溶液中的苛性碱溶液的量可以通过pH-stat或通过连续地和按比例地加入苛性碱溶液来控制。水解物可以通过标准分批法或连续法制造。

[0077] 为了更好地确保蛋白质部分水解物的一致品质，将水解物进行酶失活以终止水解过程。酶失活步骤可以包括在约82℃的温度下热处理约10分钟。或者，可通过将溶液加热至约92℃的温度约5秒来使酶失活。酶失活完成后，水解物可以在低于10℃的温度下以液态存储。

[0078] 在一些实施方案中，蛋白质等价物来源包含水解蛋白，其包括部分水解蛋白和深度水解蛋白，例如酪蛋白。在一些实施方案中，蛋白质等价物来源包含水解蛋白，其包含摩尔质量分布为500道尔顿以上的肽。在一些实施方案中，水解蛋白包含摩尔质量分布范围为约500道尔顿至约1,500道尔顿的肽。仍然，在一些实施方案中，水解蛋白可以包含摩尔质量分布范围为约500道尔顿至约2,000道尔顿的肽。

[0079] 在一些实施方案中，蛋白质等价物来源可包含肽组分、完整蛋白质、包括部分水解

蛋白和/或深度水解蛋白的水解蛋白，及其组合。在一些实施方案中，20％至80％的蛋白质等价物来源包含本文公开的肽组分。在一些实施方案中，30％至60％的蛋白质等价物来源包含本文公开的肽组分。在又其他实施方案中，40％至50％的蛋白质等价物来源包含肽组分。

[0080] 在一些实施方案中，20％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白、深度水解蛋白或其组合。在一些实施方案中，40％至70％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白、深度水解蛋白或其组合。在更进一步的实施方案中，50％至60％的蛋白质等价物来源可包含完整蛋白质、部分水解蛋白、深度水解蛋白或其组合。

[0081] 在一些实施方案中，蛋白质等价物来源包含水解度小于40％的部分水解蛋白。在又其他实施方案中，蛋白质等价物来源可以包含水解度小于25％或小于15％的部分水解蛋白。

[0082] 在一些实施方案中，营养组合物包含约1g至约7g蛋白质等价物来源/100 Kcal。在其他实施方案中，营养组合物包含约3.5g至约4.5g蛋白质等价物来源/100 Kcal。

[0083] 不受任何具体理论的束缚，如本文所公开的营养组合物的施用可以减少过敏反应并且可以改善某些个体对牛乳过敏的耐受性。在一些实施方案中，益生元、膳食丁酸和蛋白质等价物来源的组合提供协同的健康益处。

[0084] 营养组合物在一些实施方案中可以不含蛋白质且包含游离氨基酸作为蛋白质等价物来源的元素。在一些实施方案中，氨基酸可以是支链氨基酸。在某些其他实施方案中，可以包含小氨基酸肽作为营养组合物的蛋白质组分。这种小氨基酸肽可以是天然存在的或合成的。在一些实施方案中，营养组合物中游离氨基酸的量可以从约1 g/100 Kcal至约5 g/100 Kcal变化。

[0085] 在某些实施方案中，蛋白质等价物来源包含氨基酸且基本上不含全蛋白、完整蛋白质。进一步在某些实施方案中，蛋白质等价物来源包含氨基酸且基本上不含肽。在某些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约10％至约90％ w/w的必需氨基酸。在某些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约25％至约75％ w/w的必需氨基酸。在一些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约40％至约60％的必需氨基酸。

[0086] 在一些实施方案中，蛋白质等价物来源包含非必需氨基酸。在某些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约10％至约90％ w/w的非必需氨基酸。在某些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约25％至约75％ w/w的非必需氨基酸。在一些实施方案中，基于蛋白质等价物来源中包含的总氨基酸，蛋白质等价物来源包含约40％至约60％ w/w的非必需氨基酸。

[0087] 在一些实施方案中，蛋白质等价物来源包含亮氨酸。在一些实施方案中，蛋白质等价物来源包含约2％至约15％ w/w亮氨酸，根据蛋白质等价物来源中包含的氨基酸总量。在一些实施方案中，蛋白质等价物来源包含约4％至约10％ w/w亮氨酸，根据蛋白质等价物来源中包含的氨基酸总量。

[0088] 在一些实施方案中，蛋白质等价物来源包含赖氨酸。在一些实施方案中，蛋白质等价物来源包含约2％至约10％ w/w赖氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约4％至约8％ w/w赖氨酸，根据蛋白质等价物来源

中的总氨基酸。

[0089] 在一些实施方案中，蛋白质等价物来源包含缬氨酸。在一些实施方案中，蛋白质等价物来源包含约2％至约15％ w/w缬氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约4％至约10％ w/w缬氨酸，根据蛋白质等价物来源中的总氨基酸。

[0090] 在一些实施方案中，蛋白质等价物来源包含异亮氨酸。在一些实施方案中，蛋白质等价物来源包含约1％至约8％ w/w异亮氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约7％ w/w异亮氨酸，根据蛋白质等价物来源中的总氨基酸。

[0091] 在一些实施方案中，蛋白质等价物来源包含苏氨酸。在一些实施方案中，蛋白质等价物来源包含约1％至约8％ w/w苏氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约7％ w/w苏氨酸，根据蛋白质等价物来源中的总氨基酸。

[0092] 在一些实施方案中，蛋白质等价物来源包含酪氨酸。在一些实施方案中，蛋白质等价物来源包含约1％至约8％ w/w酪氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约7％ w/w酪氨酸，根据蛋白质等价物来源中的总氨基酸。

[0093] 在一些实施方案中，蛋白质等价物来源包含苯丙氨酸。在一些实施方案中，蛋白质等价物来源包含约1％至约8％ w/w苯丙氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约7％ w/w苯丙氨酸，根据蛋白质等价物来源中的总氨基酸。

[0094] 在一些实施方案中，蛋白质等价物来源包含组氨酸。在一些实施方案中，蛋白质等价物来源包含约0.5％至约4％ w/w组氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约3.5％ w/w组氨酸，根据蛋白质等价物来源中的总氨基酸。

[0095] 在一些实施方案中，蛋白质等价物来源包含胱氨酸。在一些实施方案中，蛋白质等价物来源包含约0.5％至约4％ w/w胱氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约3.5％ w/w胱氨酸，根据蛋白质等价物来源中的总氨基酸。

[0096] 在一些实施方案中，蛋白质等价物来源包含色氨酸。在一些实施方案中，蛋白质等价物来源包含约0.5％至约4％ w/w色氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约3.5％ w/w色氨酸，根据蛋白质等价物来源中的总氨基酸。

[0097] 在一些实施方案中，蛋白质等价物来源包含甲硫氨酸。在一些实施方案中，蛋白质等价物来源包含约0.5％至约4％ w/w甲硫氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约3.5％ w/w甲硫氨酸，根据蛋白质等价物来源中的总氨基酸。

[0098] 在一些实施方案中，蛋白质等价物来源包含天冬氨酸。在一些实施方案中，蛋白质等价物来源包含约7％至约20％ w/w天冬氨酸，根据蛋白质等价物来源中包含的总氨基酸。

在一些实施方案中，蛋白质等价物来源包含约10％至约17％ w/w天冬氨酸，根据蛋白质等价物来源中的总氨基酸。

[0099] 在一些实施方案中，蛋白质等价物来源包含脯氨酸。在一些实施方案中，蛋白质等价物来源包含约5％至约12％ w/w脯氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约7％至约10％ w/w脯氨酸，根据蛋白质等价物来源中的总氨基酸。

[0100] 在一些实施方案中，蛋白质等价物来源包含丙氨酸。在一些实施方案中，蛋白质等价物来源包含约3％至约10％ w/w丙氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约5％至约8％ w/w丙氨酸，根据蛋白质等价物来源中的总氨基酸。

[0101] 在一些实施方案中，蛋白质等价物来源包含谷氨酸盐。在一些实施方案中，蛋白质等价物来源包含约1.5％至约8％ w/w谷氨酸盐，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约6％ w/w谷氨酸盐，根据蛋白质等价物来源中的总氨基酸。

[0102] 在一些实施方案中，蛋白质等价物来源包含丝氨酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约8％ w/w丝氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3％至约5％ w/w丝氨酸，根据蛋白质等价物来源中的总氨基酸。

[0103] 在一些实施方案中，蛋白质等价物来源包含精氨酸。在一些实施方案中，蛋白质等价物来源包含约2％至约8％ w/w精氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约3.5％至约6％ w/w精氨酸，根据蛋白质等价物来源中的总氨基酸。

[0104] 在一些实施方案中，蛋白质等价物来源包含甘氨酸。在一些实施方案中，蛋白质等价物来源包含约0.5％至约6％ w/w甘氨酸，根据蛋白质等价物来源中包含的总氨基酸。在一些实施方案中，蛋白质等价物来源包含约1.5％至约3.5％ w/w甘氨酸，根据蛋白质等价物来源中的总氨基酸。

[0105] 在一些实施方案中，营养组合物包含约1 g至约7 g蛋白质等价物来源/100 Kcal。在其他实施方案中，营养组合物包含约3.5 g至约4.5 g蛋白质等价物来源/100 Kcal。

[0106] 在一些实施方案中，营养组合物包含约0.5 g/100 Kcal至约2.5 g/100 Kcal的必需氨基酸。在某些实施方案中，营养组合物包含约1.3 g/100 Kcal至约1.6 Kcal的必需氨基酸。

[0107] 在一些实施方案中，营养组合物包含约0.5 g/100 Kcal至约2.5 g/100 Kcal的必需氨基酸。在某些实施方案中，营养组合物包含约1.3 g/100 Kcal至约1.6 Kcal的非必需氨基酸。

[0108] 在一些实施方案中，营养组合物包含约0.2 g/100 Kcal至约0.5 g/100 Kcal的亮氨酸。在一些实施方案中，营养组合物包含约0.1 g/100 Kcal至约0.4 g/100 Kcal的赖氨酸。在一些实施方案中，营养组合物包含约0.1 g/100 Kcal至约0.4 g/100 Kcal的缬氨酸。在一些实施方案中，营养组合物包含约0.08 g/100 Kcal至约0.23 g/100 Kcal的异亮氨酸。在一些实施方案中，营养组合物包含约0.08 g/100 Kcal至约0.20 g/100 Kcal的苏氨

酸。在一些实施方案中，营养组合物包含约0.10 g/100 Kcal至约0.15 g/100 Kcal的酪氨酸。在一些实施方案中，营养组合物包含约0.05 g/100 Kcal至约0.15 g/100 Kcal的苯丙氨酸。在一些实施方案中，营养组合物包含约0.01 g/100 Kcal至约0.09 g/100 Kcal的组氨酸。在一些实施方案中，营养组合物包含约0.02 g/100 Kcal至约0.08 g/100 Kcal的胱氨酸。在一些实施方案中，营养组合物包含约0.02 g/100 Kcal至约0.08 g/100 Kcal的色氨酸。在一些实施方案中，营养组合物包含约0.02 g/100 Kcal至约0.08 g/100 Kcal的甲硫氨酸。

[0109] 在一些实施方案中，营养组合物包含约0.2 g/100 Kcal至约0.7 g/100 Kcal的天冬氨酸。在一些实施方案中，营养组合物包含约0.1 g/100 Kcal至约0.4 g/100 Kcal的脯氨酸。在一些实施方案中，营养组合物包含约0.1 g/100 Kcal至约0.3 g/100 Kcal的丙氨酸。在一些实施方案中，营养组合物包含约0.08 g/100 Kcal至约0.25 g/100 Kcal的谷氨酸盐。在一些实施方案中，营养组合物包含约0.08 g/100 Kcal至约0.2 g/100 Kcal的丝氨酸。在一些实施方案中，营养组合物包含约0.08 g/100 Kcal至约0.15 g/100 Kcal的精氨酸。在一些实施方案中，营养组合物包含约0.02 g/100 Kcal至约0.08 g/100 Kcal的甘氨酸。

[0110] 本公开的包含蛋白质等价物来源的营养组合物可以一个或多个剂量每日施用。本公开涵盖任何口服可接受的剂型。此类剂型的实例包括但不限于丸剂、片剂、胶囊剂、软胶囊剂、液体、液体浓缩物、粉剂、酏剂、溶液剂、混悬剂、乳剂、锭剂、珠、扁囊剂及其组合。

[0111] 在一些实施方案中，蛋白质等价物来源可以为营养组合物提供总卡路里的约5％至约20％。在一些实施方案中，蛋白质等价物来源可以为营养组合物提供总卡路里的约8％至约12％。

[0112] 在一些实施方案中，在不受任何具体理论束缚的情况下，本文公开的包含膳食丁酸、益生元和蛋白质等价物来源的营养组合物可降低施用时人类个体中过敏反应的发生率。例如，在某些实施方案中，营养组合物可包含膳食丁酸、益生元和蛋白质等价物来源，其中蛋白质等价物来源基本上不含全蛋白和/或完整蛋白质。因此，除了膳食丁酸之外，蛋白质等价物来源还提供氨基酸，其在组合时可以进一步防止施用时的过敏反应并减少施用时的炎症。

[0113] 本公开的营养组合物还可以包含碳水化合物来源。碳水化合物来源可以是本领域中使用的任何碳水化合物来源，例如乳糖、葡萄糖、果糖、玉米糖浆固体、麦芽糖糊精、蔗糖、淀粉、大米糖浆固体等。营养组合物中碳水化合物的量通常可以在约5g至约25 g/100 Kcal之间变化。在一些实施方案中，碳水化合物的量为约6 g至约22 g/ 100 Kcal。在其他实施方案中，碳水化合物的量为约12 g至约14 g/100 Kcal。在一些实施方案中，玉米糖浆固体是优选的。而且，水解、部分水解和/或深度水解的碳水化合物由于其易于消化而可能期望被包含在营养组合物中。具体而言，水解碳水化合物不太可能含有过敏原表位。

[0114] 适用于本文使用的碳水化合物材料的非限制性实例包括水解或完整的、天然或化学改性的源自玉米、木薯、大米或土豆的蜡质或非蜡质形式的淀粉。合适的碳水化合物的非限制性实例包括以水解玉米淀粉、麦芽糖糊精、麦芽糖、玉米糖浆、右旋糖、玉米糖浆固体、葡萄糖和各种其他葡萄糖聚合物及其组合为特征的各种水解淀粉。其他合适的碳水化合物的非限制性实例包括通常称为蔗糖、乳糖、果糖、高果糖玉米糖浆、非消化性低聚糖如低聚

果糖及其组合的那些。

[0115] 本公开的营养组合物还可以包含蛋白质来源。蛋白质来源可以是本领域中使用的任何蛋白质来源，例如脱脂乳、乳清蛋白、酪蛋白、大豆蛋白、水解蛋白、氨基酸等。可用于实施本公开的牛乳蛋白来源包括但不限于乳蛋白粉、乳蛋白浓缩物、乳蛋白分离物、脱脂乳固体、脱脂乳、脱脂乳粉、乳清蛋白、乳清蛋白分离物、乳清蛋白浓缩物、甜乳清、酸乳清、酪蛋白、酸性酪蛋白、酪蛋白酸盐(例如酪蛋白酸钠、酪蛋白酸钙钠、酪蛋白酸钙)及其任意组合。

[0116] 在一个实施方案中，营养组合物的蛋白质作为完整蛋白质提供。在其他实施方案中，蛋白质作为完整蛋白质和部分水解蛋白二者的组合提供，水解度为约4％至10％。在某些其他实施方案中，蛋白质更完全水解。在又其他实施方案中，蛋白质来源包含氨基酸。在又一个实施方案中，蛋白质来源可以补充有含谷氨酰胺的肽。

[0117] 在营养组合物的具体实施方案中，蛋白质来源的乳清:酪蛋白比例类似于在人母乳中发现的比例。在一个实施方案中，蛋白质来源包含约40％至约80％乳清蛋白和约20％至约60％酪蛋白。

[0118] 在一些实施方案中，营养组合物包含约1 g至约7 g的蛋白质来源/100 Kcal。在其他实施方案中，营养组合物包含约3.5 g至约4.5 g的蛋白质/100 Kcal。

[0119] 在一些实施方案中，本文所述的营养组合物包含脂肪来源。本文所述的富集脂质级分可以是唯一的脂肪来源或者可以与本领域已知的用于营养组合物的任何其他合适的脂肪或脂质来源组合使用。在某些实施方案中，合适的脂肪来源包括但不限于动物来源，例如乳脂(milk fat)、黄油、乳脂(butter fat)、蛋黄脂质;海洋来源，例如鱼油、海洋油、单细胞油;蔬菜和植物油，例如玉米油、菜籽油、葵花油、大豆油、棕榈油精油、椰子油、高油酸葵花油、月见草油、菜籽油、橄榄油、亚麻仁(亚麻籽)油、棉籽油、高油酸红花油、棕榈硬脂精、棕榈仁油、小麦胚芽油;中链甘油三酯油和脂肪酸的乳液和酯;及其任何组合。

[0120] 在一些实施方案中，营养组合物包含约1 g/100 Kcal至约10 g/100 Kcal的脂肪或脂质来源。在一些实施方案中，营养组合物包含约2 g/100 Kcal至约7 g/100 Kcal的脂肪来源。在其他实施方案中，脂肪来源可以以约2.5 g/100 Kcal至约6 g/100 Kcal的量存在。在又其他实施方案中，脂肪来源可以以约3 g/100 Kcal至约4 g/100 Kcal的量存在于营养组合物中。

[0121] 在一些实施方案中，脂肪或脂质来源包含约10％至约35％的棕榈油，根据脂肪或脂质总量。在一些实施方案中，脂肪或脂质来源包含约15％至约30％的棕榈油，根据脂肪或脂质总量。在又其他实施方案中，脂肪或脂质来源可以包含约18％至约25％的棕榈油，根据脂肪或脂质总量。

[0122] 在某些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约2％至约16％的大豆油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约4％至约12％的大豆油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约6％至约10％的大豆油。

[0123] 在某些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约2％至约16％的椰子油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约4％至约12％的椰子油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约6％至约10％的椰子油。

[0124] 在某些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约2％至约16％的葵花油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约4％至约12％的葵花油。在一些实施方案中，基于脂肪或脂质的总量，可将脂肪或脂质来源配制成包含约6％至约10％的葵花油。

[0125] 在一些实施方案中，油，即葵花油、大豆油、葵花油、棕榈油等意欲涵盖本领域已知的这种油的强化形式。例如，在某些实施方案中，葵花油的使用可以包括高油酸葵花油。在其他实例中，如本领域已知的，这种油的使用可以用某些脂肪酸强化，并且可以用于本文公开的脂肪或脂质来源中。

[0126] 在一些实施方案中，脂肪或脂质来源包含油混合物，其包含葵花油、中链甘油三酯油和大豆油。在一些实施方案中，脂肪或脂质来源包含约1:1至约2:1的比例的葵花油与中链甘油三酯油。在某些其他实施方案中，脂肪或脂质来源包含约1:1至约2:1的比例的葵花油与大豆油。在又其他实施方案中，脂肪或脂质来源可以包含约1:1至约2:1的比例的中链甘油三酯油与大豆油。

[0127] 在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源可包含约15%至约50% w/w的葵花油。在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约25%至约40% w/w的葵花油。在一些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约30%至约35% w/w的葵花油。

[0128] 在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源可包含约15%至约50% w/w的中链甘油三酯油。在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约25%至约40% w/w的中链甘油三酯油。在一些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约30%至约35% w/w的中链甘油三酯油。

[0129] 在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源可包含约15%至约50% w/w的大豆油。在某些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约25%至约40% w/w的大豆油。在一些实施方案中，基于总脂肪或脂质含量，脂肪或脂质来源包含约30%至约35% w/w的大豆油。

[0130] 在一些实施方案中，营养组合物包含约1 g/100 Kcal至约3 g/100 Kcal的葵花油。在一些实施方案中，营养组合物包含约1.3 g/100 Kcal至约2.5 g/100 Kcal的葵花油。在其他实施方案中，营养组合物包含约1.7 g/100 Kcal至约2.1 g/100 Kcal的葵花油。在一些实施方案中，本文所述的葵花油可以包含高油酸葵花油。

[0131] 在某些实施方案中，营养组合物配制成包含约1 g/100 Kcal至约2.5 g/100 Kcal的中链甘油三酯油。在其他实施方案中，营养组合物包含约1.3 g/100 Kcal至约2.1 g/100 Kcal的中链甘油三酯油。仍然在进一步的实施方案中，营养组合物包含约1.6 g/100 Kcal至约1.9 g/100 Kcal的中链甘油三酯油。

[0132] 在一些实施方案中，可以将营养组合物配制成包含约1 g/100 Kcal至约2.3 g/100 Kcal的大豆油。在某些实施方案中，可以将营养组合物配制成包含约1.2 g/100 Kcal至约2 g/100 Kcal的大豆油。仍然在某些实施方案中，可以将营养组合物配制成包含约1.5 g/100 Kcal至约1.8 g/100 Kcal的大豆油。

[0133] 在一些实施方案中，术语“葵花油”、“中链甘油三酯油”和“大豆油”意在涵盖本领域已知的这种油的强化形式。例如，在某些实施方案中，葵花油的使用可以包括高油酸葵花

油。在其他实例中，如本领域已知的，这种油的使用可以用某些脂肪酸强化，并且可以用于本文公开的脂肪或脂质来源中。

[0134] 在一些实施方案中，脂肪或脂质来源提供营养组合物总卡路里的约35％至约55％。在其他实施方案中，脂肪或脂质来源提供营养组合物总卡路里的约40％至约47％。

[0135] 在某些实施方案中，可以配制营养组合物，在一些实施方案中，使得营养组合物总卡路里的约10％至约23％由葵花油提供。在其他实施方案中，营养组合物中总卡路里的约13％至约20％可由葵花油提供。仍然，在其他实施方案中，营养组合物总卡路里的约15％至约18％可由葵花油提供。

[0136] 在一些实施方案中，可配制营养组合物使得总卡路里的约10％至约20％由MCT油提供。在某些实施方案中，营养组合物中总卡路里的约12％至约18％可由MCT油提供。仍然，在某些实施方案中，营养组合物卡路里的约14％至约17％可由MCT油提供。

[0137] 在一些实施方案中，可配制营养组合物使得营养组合物总卡路里的约10％至20％由大豆油提供。在某些实施方案中，营养组合物的总卡路里的约12％至约18％可由大豆油提供。在某些实施方案中，总卡路里的约13％至约16％可由大豆油提供。

[0138] 在一些实施方案中，营养组合物还可以包含LCPUFA来源。在一个实施方案中，营养组合物中LCPUFA的量有利地为至少约5 mg/100 Kcal，并且可以从约5 mg/100 Kcal至约100 mg/100 Kcal，更优选地从约10 mg/100 Kcal至约50 mg/100 Kcal变化。LCPUFA的非限制性实例包括但不限于DHA、ARA、亚油酸(18:2 n-6)、γ-亚麻酸(18:3 n-6)、n-6途径中的双高-γ-亚麻酸(20:3 n-6)、α-亚麻酸(18:3 n-3)、亚麻油酸(18:4 n-3)、二十碳四烯酸(20:4 n-3)、二十碳五烯酸(20:5 n-3)和二十二碳五烯酸(22:6 n-3)。

[0139] 在一些实施方案中，包含在营养组合物中的LCPUFA可以包含DHA。在一个实施方案中，营养组合物中DHA的量有利地为至少约17 mg/100 Kcal，并且可以从约5 mg/100 Kcal至约75 mg/100 Kcal，更优选地从约10 mg/100 Kcal至约50 mg/100 Kcal变化。

[0140] 在另一个实施方案中，特别是如果营养组合物是婴儿配方，营养组合物补充有DHA和ARA二者。在该实施方案中，ARA:DHA的重量比可以为约1:3至约9:1。在具体的实施方案中，ARA:DHA的比例为约1:2至约4:1。

[0141] DHA和ARA可以是天然形式，条件是LCPUFA来源的其余部分不会对婴儿产生任何实质性的有害作用。或者，DHA和ARA可以以精制的形式使用。

[0142] 本文所述的公开的营养组合物在一些实施方案中还可以包含β-葡聚糖来源。葡聚糖是多糖，特别是葡萄糖的聚合物，其是天然存在的并且可以在细菌、酵母、真菌和植物的细胞壁中发现。β葡聚糖(β-葡聚糖)本身是葡萄糖聚合物的不同子集，其由通过β型糖苷键连接在一起以形成复杂碳水化合物的葡萄糖单体链组成。

[0143] β-1,3-葡聚糖是从例如酵母、蘑菇、细菌、藻类或谷类中纯化的碳水化合物聚合物(Stone BA, Clarke AE. Chemistry and Biology of (1-3)-Beta-Glucans. London: Portland Press Ltd; 1993)。β-1,3-葡聚糖的化学结构取决于β-1,3-葡聚糖的来源。此外，各种生理化学参数，如溶解度、一级结构、分子量和分支在β-1,3-葡聚糖的生物活性中发挥作用(Yadomae T., *Structure and biological activities of fungal beta-1,3-glucans*. Yakugaku Zasshi. 2000;120:413-431)。

[0144] β-1,3-葡聚糖是天然存在的多糖，具有或不具有在各种植物、酵母、真菌和细菌的

细胞壁中发现的β-1,6-葡萄糖侧链。β-1,3;1,6-葡聚糖是含有具有(1,3)连接的葡萄糖单元的那些,其具有在(1,6)位连接的侧链。β-1,3;1,6葡聚糖是共享结构共性的异质葡萄糖聚合物组,包括通过β-1,3键连接的直链葡萄糖单元的骨架,具有伸出该骨架的β-1,6-连接的葡萄糖分支。虽然这是目前描述的一类β-葡聚糖的基本结构,但可能存在一些变化。例如,某些酵母β-葡聚糖具有伸出β(1,6)分支的额外的β(1,3)支化区域,这进一步增加了它们各自结构的复杂性。

[0145] 衍生自面包酵母酿酒酵母(*Saccharomyces cerevisiae*)的β-葡聚糖由在1和3位连接的D-葡萄糖分子链组成,其具有在1和6位连接的葡萄糖侧链。酵母来源的β-葡聚糖是不溶性纤维状的复杂糖,其具有带有β-1,3骨架的葡萄糖单元直链的一般结构,其中点缀有β-1,6侧链,长度通常为6-8 个葡萄糖单元。更具体而言,源自面包酵母的β-葡聚糖是聚-(1,6)-β-D-吡喃葡萄糖基-(1,3)-β-D-吡喃葡萄糖。

[0146] 此外,β-葡聚糖耐受良好,并且不会在儿科个体中产生或引起过量的气体、腹胀、肿胀或腹泻。将β-葡聚糖添加至用于儿科个体的营养组合物例如婴儿配方、成长乳或其他儿童营养产品中将通过增加对侵入病原体的抗性而改善个体的免疫应答并因此维持或改善整体健康。

[0147] 在一些实施方案中,β-葡聚糖是β-1,3;1,6-葡聚糖。在一些实施方案中,β-1,3;1,6-葡聚糖源自面包酵母。营养组合物可以包含全葡聚糖颗粒β-葡聚糖、颗粒状β-葡聚糖、PGG-葡聚糖(聚-1,6-β-D-吡喃葡萄糖基-1,3-β-D-吡喃葡萄糖)或其任何混合物。

[0148] 在一些实施方案中,营养组合物中β-葡聚糖的量为约3 mg至约17 mg/100 Kcal。在另一个实施方案中,β-葡聚糖的量为约6 mg至约17 mg/100 Kcal。

[0149] 在一些实施方案中,本文所述的公开的营养组合物还可以包含益生菌来源。术语“益生菌”是指对宿主健康发挥有益作用的微生物。在该实施方案中,本领域已知的任何益生菌可以是可接受的。在具体的实施方案中,益生菌可选自任何乳杆菌种(*Lactobacillus* species),鼠李糖乳杆菌(*Lactobacillus rhamnosus*) GG (ATCC号53103),双歧杆菌种(*Bifidobacterium* species),长双歧杆菌(*Bifidobacterium longum*)BB536 (BL999, ATCC: BAA-999),长双歧杆菌AH1206 (NCIMB: 41382),短双歧杆菌(*Bifidobacterium breve*) AH1205 (NCIMB: 41387),婴儿双歧杆菌(*Bifidobacterium infantis*) 35624 (NCIMB: 41003)和动物双歧杆菌乳亚种(*Bifidobacterium animalis subsp. lactis*) BB-12 (DSM No. 10140)或其任何组合。

[0150] 如果包括,则营养组合物可以包含约1 x 10^4至约1.5 x 10^{10} cfu益生菌/100 Kcal,更优选约1 x 10^6至约1 x 10^9 cfu益生菌/100 Kcal。

[0151] 在一个实施方案中,益生菌可以是活性的或无活性的。如本文所用,术语“活性的”是指活的微生物。术语“无活性的”或“无活性的益生菌”是指非生命益生菌微生物,其细胞组分和/或其代谢物。这种无活性的益生菌可能已被热灭活或以其他方式灭活,但它们保留有利地影响宿主健康的能力。可用于本公开的益生菌可以是天然存在的,合成的或通过生物体的基因操作开发的,无论这种新来源是现在已知的还是以后开发的。

[0152] 本文所述的公开的营养组合物在一些实施方案中还可以包含有效量的铁。铁可以包含包封的铁形式,例如包封的富马酸亚铁或包封的硫酸亚铁或较少反应性的铁形式,如焦磷酸铁或正磷酸铁。

[0153] 一种或多种维生素和/或矿物质也可以以足以供应个体每日营养需求的量加入到营养组合物中。本领域普通技术人员将理解，例如，基于儿童的年龄，维生素和矿物质的需求将会变化。例如，相比一到十三岁的儿童，婴儿可能有不同的维生素和矿物质需求。因此，实施方案并非旨在将营养组合物限制于特定年龄组，而是提供一系列可接受的维生素和矿物质组分。

[0154] 在为儿童提供营养组合物的实施方案中，组合物可以任选地包括但不限于一种或多种以下维生素或其衍生物：维生素B_1（硫胺素，焦磷酸硫胺素，TPP，三磷酸硫胺素，TTP，盐酸硫胺素，硝酸硫胺素），维生素B_2（核黄素，黄素单核苷酸，FMN，黄素腺嘌呤二核苷酸，FAD，乳黄素，卵黄素），维生素B_3（尼克酸，烟酸，烟碱，烟酰胺，烟酰胺腺嘌呤二核苷酸，NAD，烟酸单核苷酸，NicMN，吡啶-3-甲酸），维生素B_3-前体色氨酸，维生素B_6（吡哆醇，吡哆醛，吡哆胺，盐酸吡哆醇），泛酸（泛酸盐，泛醇），叶酸盐（叶酸（folic acid），叶酸（folacin），蝶酰谷氨酸），维生素B_{12}（钴胺素，甲基钴胺素，脱氧腺苷钴胺素，氰钴胺素，羟钴胺素，腺苷钴胺素），生物素，维生素C（抗坏血酸），维生素A（视黄醇，醋酸视黄酯，棕榈酸视黄酯，与其他长链脂肪酸的视黄酯，视黄醛，视黄酸，视黄醇酯），维生素D（钙化醇，胆钙化醇，维生素D_3，1,25,-二羟基维生素D），维生素E（α-生育酚，α-生育酚乙酸酯，α-生育酚琥珀酸酯，α-生育酚烟酸酯，α-生育酚），维生素K（维生素K_1，叶绿醌，萘醌，维生素K_2，甲基萘醌-7，维生素K_3，甲基萘醌-4，甲萘醌，甲基萘醌-8，甲基萘醌-8H，甲基萘醌-9，甲基萘醌-9H，甲基萘醌-10，甲基萘醌-11，甲基萘醌-12，甲基萘醌-13），胆碱，肌醇，β-胡萝卜素及其任何组合。

[0155] 在提供儿童营养产品例如成长乳的实施方案中，组合物可以任选地包括但不限于一种或多种以下矿物质或其衍生物：硼、钙、乙酸钙、葡萄糖酸钙、氯化钙、乳酸钙、磷酸钙、硫酸钙、氯离子、铬、氯化铬、吡啶甲酸铬、铜、硫酸铜、葡萄糖酸铜、硫酸铜、氟离子、铁、羰基铁、三价铁、富马酸亚铁、正磷酸铁、铁研磨物、多糖铁、碘离子、碘、镁、碳酸镁、氢氧化镁、氧化镁、硬脂酸镁、硫酸镁、锰、钼、磷、钾、磷酸钾、碘化钾、氯化钾、乙酸钾、硒、硫、钠、多库酯钠、氯化钠、硒酸钠、钼酸钠、锌、氧化锌、硫酸锌及其混合物。无机化合物的非限制性示例性衍生物包括任何无机化合物的盐、碱性盐、酯和螯合物。

[0156] 矿物质可以以盐的形式例如磷酸钙、甘油磷酸钙、柠檬酸钠、氯化钾、磷酸钾、磷酸镁、硫酸亚铁、硫酸锌、硫酸铜、硫酸锰和亚硒酸钠添加到成长乳或其它儿童营养组合物中。如本领域已知的，可以添加额外的维生素和矿物质。

[0157] 本公开的营养组合物可以任选地包含一种或多种以下调味剂，包括但不限于调味提取物、挥发油、可可或巧克力调味剂、花生酱调味剂、曲奇碎屑、香草或任何商购的调味剂。有用的调味剂的实例包括但不限于纯茴香提取物、仿香蕉提取物、仿樱桃提取物、巧克力提取物、纯柠檬提取物、纯橙提取物、纯薄荷提取物、蜂蜜、仿菠萝提取物、仿朗姆酒提取物、仿草莓提取物或香草提取物；或挥发油如香脂油、月桂油、佛手柑油、雪松木油、樱桃油、肉桂油、丁香油或薄荷油；花生酱、巧克力调味剂、香草曲奇碎屑、奶油糖果、太妃糖及其混合物。调味剂的量可以根据所使用的调味剂而有很大的变化。如本领域已知的，可以选择调味剂的类型和量。

[0158] 本公开的营养组合物可以任选地包含一种或多种可为了最终产品的稳定性而添加的乳化剂。合适的乳化剂的实例包括但不限于卵磷脂（例如来自蛋或大豆）、α-乳白蛋白

和/或甘油单酯和甘油二酯及其混合物。其他乳化剂对于本领域技术人员来说是显而易见的，并且选择合适的乳化剂将部分取决于制剂和最终产品。

[0159] 本公开的营养组合物可以任选地包含一种或多种防腐剂，其也可以被添加以延长产品保质期。合适的防腐剂包括但不限于山梨酸钾、山梨酸钠、苯甲酸钾、苯甲酸钠、EDTA二钠钙及其混合物。

[0160] 本公开的营养组合物可以任选地包含一种或多种稳定剂。用于实践本公开的营养组合物的合适的稳定剂包括但不限于阿拉伯胶、印度树胶、刺梧桐树胶、黄蓍胶、琼脂、红藻胶、瓜尔豆胶、结冷胶、刺槐豆胶、果胶、低甲氧基果胶、明胶、微晶纤维素、CMC (羧甲基纤维素钠)、甲基纤维素羟丙基甲基纤维素、羟丙基纤维素、DATEM (甘油一酯和甘油二酯的二乙酰酒石酸酯)、葡聚糖、角叉菜胶及其混合物。

[0161] 本公开的营养组合物可以提供最小的、部分的或全部的营养支持。该组合物可以是营养补充剂或膳食代替品。该组合物可以但不必是营养完全的。在一个实施方案中，本公开的营养组合物是营养完全的并且含有合适类型和量的脂质、碳水化合物、蛋白质、维生素和矿物质。脂质或脂肪的量通常可以从约1至约25 g/100 Kcal变化。蛋白质的量通常可以从约1至约7 g/100 Kcal变化。碳水化合物的量通常可以从约6至约22 g/100 Kcal变化。

[0162] 在一个实施方案中，每份儿童营养组合物可以包含用于任何给定国家的最大饮食建议的约10％至约50％的维生素A、C和E、锌、铁、碘、硒和胆碱，或者用于一组国家的平均饮食建议的约10％至约50％的维生素A、C和E、锌、铁、碘、硒和胆碱。在另一个实施方案中，每份儿童营养组合物可以提供用于任何给定国家的最大饮食建议的约10-30％的B-维生素，或者用于一组国家的平均饮食建议的约10-30％的B-维生素。在又一个实施方案中，儿童营养产品中维生素D、钙、镁、磷和钾的水平可以与乳中发现的平均水平相对应。在其他实施方案中，每份儿童营养组合物中的其他营养物可以用于任何给定国家的最大饮食建议的约20％，或者用于一组国家的平均饮食建议的约20％存在。

[0163] 在一些实施方案中，营养组合物是婴儿配方。婴儿配方是用于婴儿的强化营养组合物。婴儿配方的含量由联邦法规规定，该法规界定了常量营养素、维生素、矿物质和其他成分水平，以试图模拟人母乳的营养和其他性质。设计婴儿配方以支持儿科人类个体例如婴儿或儿童的整体健康和发育。

[0164] 在一些实施方案中，本公开的营养组合物是成长乳。成长乳是意图用于1岁以上(通常1-3岁，4至6岁或1至6岁)的儿童的强化乳基饮料。它们不是医学食品，也不是意图作为膳食代替品或补充剂以解决特定营养缺陷。相反，成长乳的设计旨在作为多元饮食的补充，以提供额外的保险，使儿童实现持续不断地每日摄取所有必需维生素和矿物质，常量营养素和其他功能性膳食组分，例如具有宣称的促进健康特性的非必需营养物。

[0165] 根据本公开的成长乳或其他营养组合物的确切组成可以因市场而异，取决于地方性法规和目标群体的饮食摄入信息。在一些实施方案中，根据本公开的营养组合物由乳蛋白来源(例如全脂或脱脂乳)加上为实现期望的感觉特性而添加的糖和甜味剂以及添加的维生素和矿物质组成。脂肪组合物包含源自乳的富集脂质级分。可以靶向总蛋白质以匹配人乳、牛乳或下限值的总蛋白质。通常靶向总碳水化合物以提供尽可能少的添加糖，如蔗糖或果糖，以获得可接受的味道。典型地，维生素A、钙和维生素D以与地区牛乳的营养贡献相匹配的水平添加。否则，在一些实施方案中，维生素和矿物质可以以每份提供膳食参考摄入

量(DRI)的约20％或每日价值(DV)的20％的水平添加。此外，不同市场之间的营养价值可能会有所不同，取决于目标人群的鉴定的营养需求，原料贡献和区域法规。

[0166] 所公开的营养组合物可以以本领域已知的任何形式提供，例如粉末、凝胶、悬浮液、糊剂、固体、液体、液体浓缩物、可重构的粉状乳替代品或即用型产品。在某些实施方案中，营养组合物可以包含为婴儿或儿科个体设计的营养补充剂、儿童营养产品、婴儿配方、人乳强化剂、成长乳或任何其他营养组合物。本公开的营养组合物包括例如口服可摄取促进健康的物质，包括例如食物、饮料、片剂、胶囊和粉末。此外，本公开的营养组合物可以被标准化为具体的卡路里含量，其可以作为即用型产品提供，或者其可以以浓缩形式提供。在一些实施方案中，营养组合物为粉末形式，其粒度范围为5 μm至1500 μm，更优选的范围为10 μm至300 μm。

[0167] 本公开的营养组合物可以在合适的容器系统中提供。例如，合适的容器系统的非限制性实例包括塑料容器、金属容器、箔袋、塑料袋、多层袋及其组合。在某些实施方案中，营养组合物可以是包含在塑料容器内的粉末状组合物。在某些其他实施方案中，营养组合物可以包含在位于塑料容器内的塑料袋内。

[0168] 在一些实施方案中，本文所述的营养组合物在个体中有利地降低过敏反应的发生率并且改善对牛乳过敏的耐受性。此外，在一些实施方案中，营养组合物有利地减少个体中由过敏引起的炎性反应。因此，本公开涉及改善个体中对牛乳过敏的耐受性的方法。此外，本公开涉及通过施用如本文所公开的包含PDX/GOS和膳食丁酸的营养组合物来在个体中降低过敏反应的发生率并降低由过敏引起的炎性反应的方法。

[0169] 在一些实施方案中，该方法包括使目标个体经历牛乳并随后将包含PDX/GOS和膳食丁酸的本文公开的营养组合物提供给目标个体的步骤。在某些实施方案中，在目标个体经历牛乳后，可向目标个体提供本文公开的包含PDX/GOS和膳食丁酸和蛋白质等价物来源的营养组合物。在某些实施方案中，在暴露于牛乳或其他过敏原后，可以对目标个体施用包含PDX/GOS和膳食丁酸和蛋白质等价物来源的营养组合物。在某些实施方案中，蛋白质等价物来源可以基本上不含全蛋白和/或完整蛋白质。在某些其他实施方案中，蛋白质等价物来源可以包含水解蛋白、氨基酸、本文公开的肽组分及其组合。在一些实施方案中，营养组合物包含蛋白质等价物来源，其包含氨基酸且不含水解或全蛋白/完整蛋白质。

[0170] 在一些实施方案中，在施用营养组合物之前目标个体不经历牛乳或过敏原。因此，在一些实施方案中，所述方法涉及通过向目标个体提供包含膳食丁酸的本文公开的营养组合物并且随后将目标个体暴露于牛乳或其他过敏原来减少目标个体中的过敏反应。

[0171] 在一些实施方案中，本文所述的营养组合物有利地减少个体的炎性反应。因此，本公开涉及通过向个体施用含有本文所述的蛋白质等价物来源与PDX/GOS和膳食丁酸的组合的营养组合物来降低个体中的促炎反应的方法。例如，本发明的方法可以减少个体中促炎细胞因子的产生。

[0172] 在一些实施方案中，用于降低个体炎性反应的方法包括向个体施用包含碳水化合物来源、蛋白质等价物来源、脂肪来源、PDX/GOS和膳食丁酸的营养组合物，其中蛋白质等价物来源包含肽组分，所述肽组分包含SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63。在一些实施方案中，肽组分可以包含表1中公开的另

外的肽。例如，组合物可以包含表1中公开的至少10个另外的肽。在一些实施方案中，20％至80％的蛋白质等价物来源包含肽成分，并且20％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白及其组合。

[0173] 在另一个实施方案中，该方法包括向个体施用营养组合物，其中20％至80％的蛋白质等价物来源包含肽组分，其包含选自SEQ ID NO 4、SEQ ID NO 13、SEQ ID NO 17、SEQ ID NO 21、SEQ ID NO 24、SEQ ID NO 30、SEQ ID NO 31、SEQ ID NO 32、SEQ ID NO 51、SEQ ID NO 57、SEQ ID NO 60和SEQ ID NO 63的至少3个肽，和选自表1的至少5个另外的肽；并且其中20％至80％的蛋白质等价物来源包含完整蛋白质、部分水解蛋白或其组合。

[0174] 在其他实施方案中，用于减少炎性反应的方法包括提供包含来自表1的肽组分的营养组合物，其中所述肽组分源自摩尔质量分布为500道尔顿以上的酪蛋白水解物。在一些实施方案中，酪蛋白水解物的摩尔质量分布在500至2000道尔顿的范围内。在其他实施方案中，用于减少炎性反应的方法包括提供包含本文所述肽组分的营养组合物，其中所述肽组分源自酪蛋白水解物，其不包含摩尔质量分布小于200道尔顿的肽。

[0175] 在一些实施方案中，目标个体可以是儿科个体。此外，在一个实施方案中，提供给儿科个体的营养组合物可以是婴儿配方。本文鉴定的肽组分、PDX/GOS和本文公开的膳食丁酸可以添加到婴儿配方中，并且进一步地，每种可以选自特定的来源，并且可以调节其浓度以使健康益处最大化。在该方法的另一个实施方案中，包含本文公开的肽组分、PDX/GOS和膳食丁酸的营养组合物是成长乳。

[0176] 在营养组合物为婴儿配方的实施方案中，所述组合物可以有利地降低婴儿中的促炎反应，从而降低炎性疾病的发生率。此外，炎性疾病的减少可能持续整个童年并持续到成年。类似地，当营养组合物是成长乳时，摄取成长乳的儿童可能在成年以及儿童时期经历炎性疾病发生率的降低。

[0177] 在某些实施方案中，本公开涉及通过向目标个体提供或施用包含PDX/GOS和膳食丁酸的本文公开的营养组合物来改善目标个体中丁酸的吸收的方法。在一些实施方案中，目标个体是儿科个体或婴儿。在一些实施方案中，营养组合物是婴儿配方或成长乳。

[0178] 除非另外指明或通过其中提及组合的上下文明确暗示相反，否则如本文所用的方法或工艺步骤的所有组合可以以任何顺序执行。

[0179] 本公开的方法和组合物，包括其组分，可以包含下列、由下列组成、或基本由下列组成：本文所述的实施方案的基本要素和限制，以及本文所述或另外用于营养组合物中的任何另外的或任选的成分、组分或限制。

[0180] 提供制剂实施例以例示本公开的营养组合物的一些实施方案，但不应解释为对其的任何限制。考虑到本文公开的营养组合物或方法的说明或实践，在本文权利要求范围内的其他实施方案对于本领域技术人员而言将是显而易见的。意图是说明书与实施例一起被认为仅是示例性的，本公开的范围和精神由实施例后面的权利要求指示。

[0181] 制剂实施例

表3提供了包含来自表1的8个肽的肽组分的实施例实施方案。

[0182] 表3．实施例肽组分

用于肽组分的所选肽的实施例
SEQ ID NO 5

SEQ ID NO 24
SEQ ID NO 33
SEQ ID NO 56
SEQ ID NO 64
SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60

[0183] 表4提供了包含来自表1的某些肽的肽组分的实施例实施方案。

[0184] 表4．实施例肽组分

用于肽组分的所选肽的实施例
SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60
SEQ ID NO 5
SEQ ID NO 11
SEQ ID NO 22
SEQ ID NO 25
SEQ ID NO 33
SEQ ID NO 45
SEQ ID NO 46
SEQ ID NO 47
SEQ ID NO 48
SEQ ID NO 52
SEQ ID NO 34
SEQ ID NO 36
SEQ ID NO 61
SEQ ID NO 62
SEQ ID NO 64

[0185] 表2提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表2中公开的氨基酸的量是以蛋白质等价物来源中的总氨基酸为基础，以w/w %计。

[0186] 表2．实施例蛋白质等价物来源

氨基酸	基于总氨基酸的w/w %量
L-亮氨酸	9.94
L-赖氨酸	7.93
L-缬氨酸	9.21
L-异亮氨酸	5.48
L-苏氨酸	4.95
L-酪氨酸	4.38
L-苯丙氨酸	4.05

L-组氨酸	2.12
L-胱氨酸	2.12
L-色氨酸	1.93
L-甲硫氨酸	1.87

[0187] 表3提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表3中公开的氨基酸的量是以蛋白质等价物来源中的总氨基酸为基础,以w/w %计。

[0188] 表3. 实施例蛋白质等价物来源

氨基酸	基于总氨基酸的w/w %量
L-天冬氨酸	16.16
L-脯氨酸	8.05
L-丙氨酸	7.87
谷氨酸一钠	5.54
L-丝氨酸	4.95
L-精氨酸	4.27
甘氨酸	2.12

[0189] 表4提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表4中公开的氨基酸的量基于克每100 Kcal营养组合物。

[0190] 表4. 实施例蛋白质等价物来源

氨基酸(g)	每100 Kcal
L-亮氨酸	0.25
L-赖氨酸	0.20
L-缬氨酸	0.23
L-异亮氨酸	0.14
L-苏氨酸	0.12
L-酪氨酸	0.11
L-苯丙氨酸	0.10
L-组氨酸	0.053
L-胱氨酸	0.053
L-色氨酸	0.049
L-甲硫氨酸	0.047

[0191] 表5提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表5中公开的氨基酸的量基于克每100 Kcal营养组合物。

[0192] 表5. 实施例蛋白质等价物来源

氨基酸(g)	每100 Kcal
L-亮氨酸	0.31
L-赖氨酸	0.24
L-缬氨酸	0.28
L-异亮氨酸	0.17
L-苏氨酸	0.15

L-酪氨酸	0.13
L-苯丙氨酸	0.12
L-组氨酸	0.07
L-胱氨酸	0.07
L-色氨酸	0.06
L-甲硫氨酸	0.06

[0193] 表6提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表6中公开的氨基酸的量基于克每100 Kcal营养组合物。

[0194] 表6. 实施例蛋白质等价物来源

氨基酸(g)	每100 Kcal
L-天冬氨酸	0.41
L-脯氨酸	0.20
L-丙氨酸	0.20
谷氨酸一钠	0.14
L-丝氨酸	0.13
L-精氨酸	0.11
甘氨酸	0.05

[0195] 表7提供了可包含在本文公开的营养组合物中的蛋白质等价物来源的实施例实施方案。表7中公开的氨基酸的量基于克每100 Kcal营养组合物。

[0196] 表7. 实施例蛋白质等价物来源

氨基酸(g)	每100 Kcal
L-天冬氨酸	0.50
L-脯氨酸	0.28
L-丙氨酸	0.24
谷氨酸一钠	0.17
L-丝氨酸	0.15
L-精氨酸	0.13
甘氨酸	0.07

[0197] 以下例示的表8提供了包含PDX/GOS和膳食丁酸的营养组合物的营养概况的实施例实施方案,并且描述了每100 Kcal份营养组合物所包含的每种成分的量。

[0198] 表8. 包含膳食丁酸的实施例营养组合物的营养概况

	每 100 Kcal	
营养物		
	最小值	最大值
蛋白质等价物来源(g)	1.0	7.0
膳食丁酸 (mg)	22	280
鼠李糖乳杆菌 *GG* (cfu)	$1x10^4$	$1.5x10^{12}$
碳水化合物(g)	6	22
脂肪(g)	1.3	7.2
益生元(g)	0.3	1.2
DHA (g)	4	22
β 葡聚糖(mg)	2.9	17
益生菌(cfu)	0.5	5.0
维生素 A (IU)	9.60×10^5	3.80×10^8
维生素 D (IU)	134	921
维生素 E (IU)	22	126
维生素 K (mcg)	0.8	5.4
硫胺素(mcg)	2.9	18
核黄素(mcg)	63	328
维生素 B6 (mcg)	68	420
维生素 B12 (mcg)	52	397
烟酸(mcg)	0.2	0.9
叶酸(mcg)	690	5881
泛酸(mcg)	8	66
生物素(mcg)	232	1211
维生素 C (mg)	1.4	5.5
胆碱(mg)	4.9	24
钙(mg)	4.9	43
磷(mg)	68	297
镁(mg)	54	210

钠(mg)	4.9	34
钾(mg)	24	88
氯(mg)	82	346
碘(mcg)	53	237
铁(mg)	8.9	79
锌(mg)	0.7	2.8
锰(mcg)	0.7	2.4
铜(mcg)	7.2	41

[0199] 本说明书中引用的所有参考文献，包括但不限于所有论文、出版物、专利、专利申请、演示文稿、文本、报告、手稿、小册子、书籍、网络发帖、期刊文章、期刊等以其整体特此通过引用并入本说明书。本文对参考文献的讨论仅仅是为了总结他们作者的主张，并不承认任何参考文献构成现有技术。申请人保留质疑所引用参考文献的准确性和针对性的权利。

[0200] 尽管已经使用特定的术语、设备和方法描述了本公开的实施方案，但是这样的描述仅用于说明的目的。所用的词语是描述性词语而非限制性词语。应该理解，在不脱离下面的权利要求中列出的本公开的精神或范围的情况下，本领域普通技术人员可以进行改变和变化。另外，应该理解，各种实施方案的方面可以全部或部分互换。因此，所附权利要求的精神和范围不应限于其中包含的版本的描述。

序列表

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