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(54) Title: NUTRITIONAL COMPOSITION COMPRISING ANTHOCYANIDIN(S) AND RELATED METHODS

(57) Abstract: Provided herein are methods for reducing the risk of developing type 2 diabetes in an individual or for improving the insulin resistance of an individual and related nutritional compositions. The nutritional compositions include at least one anthocyanidin. In certain of the embodiments provided herein, the anthocyanidin is cyanidin and consumption of the anthocyanidin results in the reduction of at least one risk factor associated with type 2 diabetes. In certain embodiments provided herein, use of a composition comprising an anthocyanidin for improving the insulin resistance of an individual and/or for reducing the risk of type 2 diabetes in an individual.

NUTRITIONAL COMPOSITION COMPRISING ANTHOCYANIDIN(S) AND RELATED METHODS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and the benefit of U.S. Provisional Application No. 61/823,550, filed May 15, 2013, the entire content of which is incorporated herein by reference.

TECHNICAL FIELD

[0002] Disclosed embodiments are in the field of nutritional compositions (and related methods) and more particularly in the field of methods and nutritional compositions that provide benefits related to the risk of developing diabetes.

BACKGROUND

[0003] Diabetes mellitus is a group of metabolic disorders with one common manifestation: hyperglycemia. Chronic hyperglycemia causes damage to the eyes, kidneys, nerves, heart and blood vessels. The etiology and pathophysiology leading to the hyperglycemia, however, are markedly different among patients with diabetes mellitus, dictating different prevention strategies, diagnostic screening methods and treatments. Helseth S., Am Fam Physician. 1997;56:471–80.

[0004] Type 2 diabetes is the most common form of diabetes. Once known as adult-onset or noninsulin-dependent diabetes, Type 2 diabetes is a chronic condition that affects the way the body metabolizes glucose in the blood. Williams: Textbook of Endocrinology, (12th ed.), 1371–1435. With type 2 diabetes, the body either resists the effects of insulin, or doesn't produce enough insulin to maintain a normal glucose level. Untreated, type 2 diabetes can be life-threatening and even with treatment the disease often has a significant impact on the quality of life of those afflicted with it.

[0005] The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors. Ripsin C.M. Am Fam Physician 79 (1): 29–36. While some are under an individual's control, such as diet and obesity, others, such as increasing age, female gender, and genetic susceptibility, are not. Williams: Textbook of Endocrinology, (12th ed.), 1371–1435.

SUMMARY

[0006] Nutritional compositions and methods useful for reducing the risk of developing type 2 diabetes in an individual are provided herein. The nutritional compositions include protein, carbohydrates, anthocyanidins and, in certain embodiments, fat. In certain embodiments, the anthocyanidins are plum-sourced and the predominant anthocyanidin is cyanidin. The methods provided herein (utilizing the nutritional compositions) are also useful for reducing one or more risk factors associated with the development of type 2 diabetes in an individual, such as insulin resistance.

[0007] In a first embodiment, a method for improving the insulin response of an individual is provided. The method comprises administering to an individual in need thereof a nutritional composition comprising a therapeutically effective amount of anthocyanidins.

[0008] In a second embodiment, a method for reducing the risk of developing type 2 diabetes in an individual is provided. The method includes administering to an individual in need thereof a nutritional composition comprising: protein in an amount sufficient to provide 9 to 25% of calories from protein; fat in an amount sufficient to provide 10 to 50% of calories from fat; carbohydrates in an amount sufficient to provide 30 to 65% of calories from carbohydrates; and anthocyanidins in an amount sufficient to provide a therapeutically effective amount of cyanidin. The nutritional composition has a glycemic index of between 10 and 69. The individual's risk of developing type 2 diabetes is reduced by consumption of the nutritional composition.

[0009] In a third embodiment, a solid nutritional composition is provided. The nutritional composition comprises anthocyanidins in an amount sufficient to provide from 15 to 450 mg of anthocyanidins per kg of the solid nutritional composition, 10 to 30% by weight of the solid nutritional composition from protein, 1 to 10% by weight of the solid nutritional composition from fat, 30 to 70 % by weight of the solid nutritional composition from carbohydrates, wherein the carbohydrates include at least one source of low glycemic index carbohydrate, and at least one source of high glycemic index carbohydrate. Further, the weight ratio of low glycemic index carbohydrates to high glycemic index carbohydrates in the nutritional composition is from 0.1:1 to 0.5:1.

[00010] In a fourth embodiment, a liquid nutritional composition is provided. The liquid nutritional composition comprises: 500 to 900 g/kg water; no more than 1 % of the calories within the liquid nutritional composition from fat; protein in an amount sufficient to provide 5 to 30% of the calories within the liquid nutritional composition; carbohydrates in an amount sufficient to provide 70 to 95% of the calories within the liquid nutritional composition; and from 1 to 110 mg of anthocyanidins per kg of the liquid nutritional composition. The carbohydrates include at least one source of low glycemic index carbohydrate. The liquid nutritional composition has a pH of between 2 and 5; and a glycemic index between 10 and 69.

[00011] In addition, the general inventive concepts contemplate the use of the nutritional compositions for improving the insulin response of an individual, and for reducing the risk of type 2 diabetes in an individual. In certain embodiments, the use contemplated includes a nutritional composition comprising: protein in an amount sufficient to provide 9 to 25% of calories from protein; fat in an amount sufficient to provide 10 to 50% of calories from fat; carbohydrates in an amount sufficient to provide 30 to 65% of calories from carbohydrates; and anthocyanidins in an amount sufficient to provide a therapeutically effective amount of cyanidin; wherein the nutritional composition has a glycemic index of between 10 and 69, and whereby consumption of the nutritional composition results in a reduction of the risk of developing type 2 diabetes for the individual.

DETAILED DESCRIPTION

[00012] Nutritional compositions and methods useful for reducing the risk of developing type 2 diabetes in an individual are provided herein. The nutritional compositions include protein, carbohydrates, anthocyanidins and, in certain embodiments, fat. In certain embodiments, the anthocyanidins are plum-sourced and the predominant anthocyanidin is cyanidin. The methods provided herein (utilizing the nutritional compositions) are useful for reducing one or more risk factors associated with the development of type 2 diabetes in an individual, such as insulin resistance.

Definitions

[00013] The terminology as set forth herein is for description of the embodiments only and should not be construed as limiting the invention as a whole.

[00014] As used herein, the term "serving" is intended to be construed as any amount which is intended to be consumed in one sitting or within one hour or less.

[00015] The term "individual" or "individual in need thereof" as used herein, refers to a mammal, including companion animals, livestock, laboratory animals, working animals, sport animals, and humans. In certain embodiments, it is contemplated that the individual is a human. In certain embodiments, it is contemplated that the individual is an adult. In certain embodiments it is further contemplated that the individual is elderly. In certain embodiments it is further contemplated that the individual has impaired glucose tolerance. In certain embodiments, it is contemplated that the individual is diagnosed with insulin resistance. In certain embodiments, it is contemplated that the individual display one or more risk factors for developing type 2 diabetes. In certain embodiments it is further contemplated that the individual has been diagnosed with diabetes.

[00016] The term "adult," as used herein, refers to an individual of at least 18 years of age.

[00017] The term "elderly," as used herein, refers to an individual of at least 45 years of age, including at least 50 years of age, at least 55 years of age, at least 60 years of age, at least 65 years of age, at least 70 years of age, at least 75 years of age, and including at least 80 years or age or greater. The term "elderly" also includes the groups of from about 45 years of age to about 95 years of age, and the group of from about 55 years of age to about 80 + years of age.

[00018] In a first embodiment, a method for improving the insulin response of an individual is provided. The method comprising administering to an individual in need thereof a nutritional composition comprising a therapeutically effective amount of anthocyanidins.

[00019] In a second embodiment, a method for reducing the risk of developing type 2 diabetes in an individual is provided. The method includes administering to an individual in need thereof a nutritional composition comprising: protein in an amount sufficient to provide 9 to 25 % of calories from protein; fat in an amount sufficient to provide 10 to 50% of calories from fat; carbohydrates in an amount sufficient to provide 30 to 65% of calories from carbohydrates; and

anthocyanidins in an amount sufficient to provide a therapeutically effective amount of cyanidin. The nutritional composition has a glycemic index of between 10 and 69. The individual's risk of developing type 2 diabetes is reduced by consumption of the nutritional composition.

[00020] In a third embodiment, a solid nutritional composition is provided. The nutritional composition comprises anthocyanidins in an amount sufficient to provide from 15 to 450 mg of anthocyanidins per kg of the solid nutritional composition, 10 to 30% by weight of the solid nutritional composition from protein, 1 to 10% by weight of the solid nutritional composition from fat, 30 to 70% by weight of the solid nutritional composition from carbohydrates, wherein the carbohydrates include at least one source of low glycemic index carbohydrate, and at least one source of high glycemic index carbohydrate. Further, the weight ratio of low glycemic index carbohydrates to high glycemic index carbohydrates in the nutritional composition is from 0.1:1 to 0.5:1.

[00021] In a fourth embodiment, a liquid nutritional composition is provided. The liquid nutritional composition comprises: 500 to 900 g/kg water; no more than 1 % of the calories within the liquid nutritional composition from fat; protein in an amount sufficient to provide 5 to 30% of the calories within the liquid nutritional composition; carbohydrates in an amount sufficient to provide 70 to 95% of the calories within the liquid nutritional composition; and from 1 to 110 mg of anthocyanidins per kg of the liquid nutritional composition. The carbohydrates include at least one source of low glycemic index carbohydrate. The liquid nutritional composition has a pH of between 2 and 5; and a glycemic index of between 10 and 69.

[00022] It is intended that when discussing the nutritional compositions disclosed herein, that the discussion is equally applicable to nutritional compositions useful in the presented methods.

[00023] As previously mentioned, embodiments according to the first and second embodiments include administering to an individual in need thereof nutritional compositions which include anthocyanidins, and embodiments according to the third and fourth embodiments comprise nutritional compositions which include anthocyanidins. Anthocyanidins are common plant pigments, and are the sugar-free counterparts of anthocyanins based on the flavylium ion or 2-phenylchromenylium. Anthocyanidins also fall into the category of molecules called

polyphenols. In certain embodiments according to the first, second, third and fourth embodiments, the nutritional composition includes one or more polyphenols such as fruit sourced polyphenols. Fruit sourced polyphenols include flavanols (also known as flavan-3-ols or proanthocyanidins), hydroxycinnamic acids (*e.g.*, chlorogenic acid), anthocyanidins (*e.g.*, cyanidin), and flavonols (*e.g.*, quercetin, rutin). In certain embodiments of the first, second, third and fourth embodiments disclosed herein, the nutritional compositions include particular anthocyanidins, such as, cyanidin, rutin and hydroxycinnamic acids. Cyanidin is a major component of fruit sourced anthocyanidins. Generally, suitable polyphenols for use in the methods and nutritional compositions of the first, second, third and fourth embodiments include anthocyanidins, hydroxycinnamic acid (*e.g.*, chlorogenic acid), flavonols (*e.g.*, quercetin, rutin and derivatives thereof), flavan-3-ols, procyanidins, and combinations thereof.

[00024] As previously discussed, according to the first embodiment, a therapeutically effective amount of anthocyanidins is provided to an individual via a nutritional composition, and according to the second embodiment anthocyanidins are provided to an individual in an amount sufficient to provide a therapeutically effective amount of cyanidin via a nutritional composition. "Therapeutically effective" as used herein is intended to qualify the amount of the ingredient (anthocyanidins or cyanidin) needed to effect a desired result, such as, for example improving an individual's insulin response or reducing the risk of developing type 2 diabetes, including effecting a reduction in one or more risk factors associated with the disease.

[00025] In accordance with the methods disclosed herein, compositions including an effective amount of anthocyanidins, can be administered to an individual in need thereof, in one or more doses, or servings, over a period of time. In certain embodiments according to the first and second embodiments, an effective amount of anthocyanidins is administered to an individual in need thereof in two servings per day. In other embodiments according to the first and second embodiments, an effective amount of anthocyanidins is administered in two, three, four or more servings per day.

[00026] In accordance with the methods of the first and second embodiments, the effective amount of anthocyanidins can be administered, to an individual in need thereof, one or more times per day for a period suitable to achieve the desired result. For example, a nutritional composition comprising a therapeutically effective amount of anthocyanidin can be administered

to an individual in need thereof every day for at least a week, two weeks, every day for a month, every day for six months, or every day for a year or more. As another example, a nutritional composition comprising a therapeutically effective amount of anthocyanidin can be administered to an individual in need thereof twice a day for at least a week, two weeks, a month, twice a day for six months, or twice a day for a year or more. Within the context of administering a therapeutically effective amount of anthocyanidins to an individual, every day is intended to reflect an individual who has been instructed to be administered anthocyanidins (or nutritional compositions comprising anthocyanidins) everyday, and who actually is administered the anthocyanidins for at least 70% (*i.e.*, 70 to 100%) of the days during the desired period of instruction.

[00027] In certain embodiments, the therapeutically effective amount of anthocyanidins (or a composition comprising the anthocyanidins) is chronically administered. Chronically administering refers to regular administration which is continued indefinitely. In other embodiments, the term refers to regular administration over a significant period of time. For example, in certain embodiments according to the methods of the first and second embodiments, chronic administration can include regular administration for at least one month, six weeks, two months, 3 months, 4 months, 5 months, 6 months, or regular administration for at least 9 months. In certain embodiments, chronic administration refers to regular administration for at least 1 year, 1.5 years, 2 years, or regular administration for more than 2 years. "Regular administration" refers to administration according to a schedule where it is intended that the individual in need thereof will receive anthocyanidins (or a nutritional composition comprising anthocyanidins) at regular intervals.

[00028] As used herein, "regular intervals" refers to administration in a repeating, periodic fashion where the time between administrations is approximately the same. In certain of the first and second embodiments, administration at regular intervals includes daily administration or weekly administration. In other embodiments, the administration at regular intervals includes 1-2 times per week, administration 1-3 times per week, administration 2-3 times per week, administration 1-4 times per week, administration 1-5 times per week, administration 2-5 times per week, administration 3-5 times per week, administration every day of the week, administration 1-2 times per day, administration 1-3 times per day, administration 1-4 times per

day, administration 2-3 times per day, administration 2-4 times per day, administration 3-4 times per day, administration 2-5 times per day, administration 3-5 times per day, or administration 4-5 times per day.

[00029] In embodiments according to the fourth embodiment, and in certain embodiments according to the first and second embodiments, the amount of anthocyanidins contained within the nutritional composition can be expressed in terms of mg/liter and are present in an amount of 1 mg/liter to 110 mg/liter. In certain embodiments according to the first, second and fourth embodiments the amount of anthocyanidins is expressed in a per serving basis, and in such instances the amount is roughly 1-25 mg in a 240 mL serving of the nutritional composition when it is in liquid form. In certain embodiments according to the first, second and fourth embodiments, the anthocyanidins are present in an amount of 4 to 100 mg/liter, including 6 to 60 mg/liter and including 10 to 30 mg/liter when in liquid form. As discussed further herein, a serving of nutritional compositions according to the first, second and fourth embodiments disclosed herein is in no way limited to a 240 mL (approximately 8 fluid ounces) serving size.

[00030] In embodiments according to the third embodiment, and optionally, in embodiments according to the first and second embodiments, the amount of anthocyanidins contained within the nutritional composition can be expressed in terms of mg of anthocyanidins per kg of nutritional composition and is 15-450 mg/kg (such a concentration would roughly equate to 1-25 mg of anthocyanidin in a 58 g solid nutritional composition), including 20 to 220 mg of anthocyanidins per kg, and including 20 to 110 mg of anthocyanidins per kg of the solid nutritional composition.

[00031] In certain embodiments according to the methods of the first and second embodiments, the individual is administered 1 to 50 mg per day of anthocyanidins. In certain embodiments according to the first embodiment, the individual is administered 2.8 to 50 mg of anthocyanidins per day. In other embodiments according to the first and second embodiments, the individual is administered 3 to 40 mg per day of anthocyanidins. This range equates to roughly between 20 and 300 mg of anthocyanidins per week to the individual, assuming daily consumption. Further, in certain embodiments, the individual is administered 3 to 40 mg per day of anthocyanidins, including 3 to 20 mg per day, including 3 to 10 mg per day, and including 3 to 7 mg per day of anthocyanidins.

[00032] In certain embodiments, the anthocyanidins utilized in embodiments according to the first, second, third and fourth embodiments comprise between 50 and 90% cyanidin. Cyanidin is a particular anthocyanidin with the IUPAC name 2-(3,4-Dihydroxyphenyl) chromenylium-3,5,7-triol. It is found in many fruits and has a characteristic reddish-orange color. In certain embodiments according to the first embodiment, the individual is administered between 1 and 25 mg per day of cyanidin.

[00033] In embodiments according to the fourth embodiment, and in certain embodiments according to the first and second embodiments, the amount of cyanidin contained within the nutritional composition can be expressed in terms of mg/liter and is present in an amount of 1 mg/liter to 90 mg/liter, including 3 to 75 mg of cyanidin per liter, 3-50 mg of cyanidin per liter or 5 to 27 mg of cyanidin per liter of the liquid nutritional composition. In certain embodiments according to the first, second and fourth embodiments the amount of anthocyanidins is expressed in a per serving basis, and in such instances the amount is roughly 1-20 mg in a 240 mL serving of the nutritional composition when it is in liquid form. In certain embodiments according to the first, second and fourth embodiments, the anthocyanidins are present in an amount of 4 to 100 mg/liter, including 6 to 60 mg/liter and including 10 to 30 mg/liter when in liquid form.

[00034] In certain embodiments according to the fourth embodiment, the liquid nutritional compositions comprise between 1 and 20 mg of cyanidin per serving. In certain embodiments according to the fourth embodiment, the nutritional compositions comprise 3 to 90 mg of cyanidin per liter including 3 to 75 mg of cyanidin per liter, 3-50 mg of cyanidin per liter or 5 to 27 mg of cyanidin per liter of the liquid nutritional composition. In certain embodiments according to the first, second, third and fourth embodiments, the anthocyanidins utilized comprise between 50 and 90% cyanidin by weight, including between 50 and 85%, between 60 and 85% and between 70 and 90 % by weight cyanidin. In embodiments according to the third embodiment, and optionally, in embodiments according to the first and second embodiments, the amount of cyanidins contained within the nutritional composition can be expressed in terms of mg of cyanidins per kg of nutritional composition and is 9 to 400 mg/kg (such a concentration would roughly equate to 1-20 mg of anthocyanidin in a 58 g solid nutritional composition), including 10 to 200 mg of cyanidin per kg, and including 10 to 100 mg of cyanidin per kg of the solid nutritional composition.

[00035] As previously mentioned, anthocyanidins, including cyanidin, are found in fruits. In certain embodiments according to the first, second third and fourth embodiments, the source of anthocyanidins (or cyanidin) is a fruit or a fruit extract. Particularly useful fruits and fruit extracts may be selected from the group including: plum/prune, apple, pear, strawberry, blueberry, raspberry, cherry, and combinations thereof. Further, in certain embodiments of the first, second, third and fourth embodiments, the source of the anthocyanidins in the nutritional compositions is a plum or prune extract. Commercially available examples of suitable plum/prune extract are available from the P.L. Thomas Company under product names "PE-50" and "PE-60." The polyphenol distribution of PE-50 is provided in Table 1 below.

Table 1
Plum Extract PE-50

Polyphenol	Concentration
Chlorogenic acids	25 g/kg
Rutin + Quercetin (flavonols)	18 g/kg
Anthocyanidins	2.36 g/kg
Proanthocyanidins (flavanols)	490 g/kg
Gallic acid	3.7 g/kg
Total Phenolic Content (TPC), gallic acid equivalents	536 g/kg
Antioxidant activity, microEq Trolox/100 g	420,000

[00036] The polyphenol distribution of PE-60 is provided in Table 2 below.

Table 2
Plum Extract PE-60

Polyphenol	Concentration	Flavanoid Type	Predominant Individual Flavanoid
Anthocyanidins (total)	2.1 g/kg	Anthocyanidin	Cyanidin, peonidin

Chlorogenic acid	19	Hydroxycinnamic acid	3-,4-, and 5-chlorogenic acids
Procyanidins	500-700	Flavan-3-ol	Catechin, epicatechin, epigallocatechin, epigallocatechin-3-gallate
Rutin	12	Flavanol	quercetin
Quercetin	7.2	Flavanol	

[00037] In Table 3, the concentrations of anthocyanidins and cyanidin in PE-50 are compared to those reported for a number of fresh fruits in the USDA Flavonoid database (2011).

Table 3

Fruit (USDA NDB No.)	Anthocyanidins (mg/100 g)	Cyanidin, mg/100 g	Cyanidin, % of anthocyanidins, w/w
PE-50, P.L. Thomas lot PE5010-2607	236	189	@ 80% of total
Blueberries, highbush, raw (09050)	141.03	7.10	5%
Blueberries, rabbiteye, raw (99653)	139.98	21.60	15%
Blackberries, raw (09042)	90.64	90.49	> 99%
Cranberries, raw (09078)	85.52	37.74	44%
Grapes, Concord, raw (99650)	67.61	13.16	19%
Plum, Davidson's, raw (99621)	48.96	28.42	58%
Grapes, red, raw (97074)	43.97	0.95	2%
Raspberries, raw (09302)	40.63	36.74	90%
Plum, black diamond, raw (97077)	39.70	39.68	> 99%
Cherries, sweet, raw	29.05	27.45	94%

(09070)			
Strawberries, raw (09316)	27.76	1.63	6%
Pears, raw (09252)	12.18	12.18	100%
Plum, red, raw (97043)	6.98	4.73	68%

[00038] From the data in Table 3, it is clear that among the fresh fruits listed, blackberries, cranberries, plum/prune, pear, raspberry and cherry have the most significant percentages of cyanidin as a component of the anthocyanidins present. Accordingly, in certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the anthocyanidins (or cyanidins) utilized in the nutritional composition are in the form of fruit-sourced extract from a fruit selected from the group consisting of blackberry, cranberry, plum/prune, pear, raspberry, cherry, and combinations thereof. In certain embodiments, according to the first, second, third and fourth embodiments disclosed herein, the anthocyanidins (or cyanidins) utilized in the nutritional composition are in the form of fruit-sourced extract from plum/prune.

[00039] In certain embodiments according to the first, second embodiments, the anthocyanidin-containing nutritional compositions are administered to an individual who is at risk of developing or who has one or more of the following conditions: diabetes mellitus, insulin resistance, obesity, metabolic syndrome, sarcopenia, heart disease and atherosclerosis. Further, in certain embodiments disclosed herein, it is contemplated that the nutritional compositions according to the third and fourth embodiments may be administered to similar such individuals. In certain embodiments according to the first embodiment disclosed herein, the individual in need thereof is an individual who is at risk of developing or who has one or more of the following conditions: diabetes mellitus, insulin resistance, obesity, metabolic syndrome, sarcopenia, heart disease. In certain embodiments according to the second embodiment disclosed herein, the individual in need thereof is an individual who is at risk of developing, or who has, one or more of the following conditions: diabetes mellitus, insulin resistance, obesity, metabolic syndrome, sarcopenia, heart disease.

[00040] As previously mentioned, the methods according first embodiment improve the insulin response of an individual. As used herein, the terms “improving,” “improvement,” “enhancement” or “enhancing” insulin response can refer to a decrease in measured insulin resistance, a decrease in measured glucose tolerance, or both. In another embodiment, the terms

refer to a decrease in a measured fasting insulin level for the individual. In another embodiment, the term refers to an improved value in a glucose clamp test or an oral glucose tolerance test. Furthermore, it should be understood, that when discussing insulin response herein, the term generally refers to insulin response after consumption of food by the individual.

[00041] In certain embodiments, the terms "improving" or "enhancing" insulin response refers to effecting a 10% improvement thereof (or more). In another embodiment, the term refers to effecting a 20% improvement thereof (or more). In another embodiment, the term refers to effecting a 30% improvement thereof (or more). In another embodiment, the term refers to effecting a 40% improvement thereof (or more). In another embodiment, the term refers to effecting a 50% improvement thereof (or more). In another embodiment, the term refers to effecting a 10-50% improvement thereof. In another embodiment, the term refers to effecting a 20-50% improvement thereof. In another embodiment, the term refers to effecting a 30-50% improvement thereof. In another embodiment, the term refers to effecting a 40-50% improvement thereof. As discussed further herein, in certain embodiments, an improvement or enhancement in insulin response is measured using a glucose test. An improvement in insulin response of 10% or more can be measured by a reduction in the blood glucose levels of an individual that occurs in the 2 hour interval after administration of glucose during a glucose test (*e.g.*, a blood glucose level after 2 hours of 12 mmol/L before treatment compared to a blood glucose level after 2 hours of 10.7 mmol/L after treatment).

[00042] In certain embodiments according to the first embodiment, improving the insulin response is assessed relative to an untreated individual, such as, in an animal study or human control. For example, a study may comprise administration of anthocyanidins (or nutritional compositions comprising anthocyanidins) to a first group of test individuals coupled with administration of a control to a second group of test individuals, followed by subsequent assessment of the insulin response of the two groups. In another embodiment, improvement or enhancement of insulin response is assessed according to a standardized criterion or test such as, for example, the euglycemic insulin clamp, HOMA, insulin tolerance test, *etc* (Ref.: Ferrannini, E., Mari, A., How to measure insulin sensitivity, J. Hypertens. 1998, 16(7): 895-906.

[00043] As previously mentioned, methods according to the second embodiment reduce the risk of developing type 2 diabetes in an individual. As used herein, "reducing" or "reduction"

of the risk of developing type 2 diabetes can refer to a reduction in one or more risk factors associated with type 2 diabetes. A non-exhaustive list of risk factors includes: obesity, impaired glucose tolerance, weight, hip-to-waist ratio, impaired fasting glucose level, insulin resistance, high blood pressure, and sedentary lifestyle. In another embodiment, the term refers to a reduction in measured glucose tolerance. In certain embodiments, the reduction in the risk of developing type 2 diabetes refers to an improvement in glucose tolerance.

[00044] In certain embodiments, the term "reducing" or "reduction" of the risk of developing type 2 diabetes refers to effecting a 10% reduction thereof (or more). In another embodiment, the term refers to effecting a 20% reduction thereof (or more). In another embodiment, the term refers to effecting a 30% reduction thereof (or more). In another embodiment, the term refers to effecting a 40% reduction thereof (or more). In another embodiment, the term refers to effecting a 50% reduction thereof (or more). In another embodiment, the term refers to effecting a 10-50% reduction thereof. In another embodiment, the term refers to effecting a 20-50% improvement thereof. In another embodiment, the term refers to effecting a 30-50% improvement thereof. In another embodiment, the term refers to effecting a 40-50% improvement thereof. As discussed above, in certain embodiments, the reduction in the risk of developing type 2 diabetes refers to an improvement (*i.e.*, a reduction) in glucose tolerance; in certain such embodiments, the improvement in glucose tolerance can be measured using a glucose test.

[00045] One commonly used method of diagnosing whether an individual has diabetes is a glucose tolerance test. During a glucose tolerance test, a fasting individual takes a 75 gram oral dose of glucose. Blood glucose levels are then measured over the following 2 hours. After 2 hours a glycemia (blood glucose level) less than 7.8 mmol/L (140 mg/dl) is considered normal, a glycemia of between 7.8 to 11.0 mmol/L (140 to 197 mg/dl) is considered indicative of impaired glucose tolerance and a glycemia of greater than or equal to 11.1 mmol/L (200 mg/dl) is considered indicative of diabetes mellitus.

[00046] As discussed above, the blood glucose test may be utilized to measure a reduction in an individual's risk of developing type 2 diabetes, an improvement in an individual's glucose tolerance, an improvement in an individual's insulin response, and combinations thereof. In certain embodiments, the risk of developing type 2 diabetes in an individual is reduced by

effecting a 10% decrease (or more) in the individual's glucose tolerance. In certain other embodiments, the risk of developing type 2 diabetes in an individual is reduced by effecting a 20% decrease (or more) in the individual's glucose tolerance, including effecting a 30% decrease (or more) in the individual's glucose tolerance, effecting a 40% decrease (or more) in the individual's glucose tolerance, and including effecting a 50% decrease (or more) in the individual's glucose tolerance. In another embodiment, the risk of developing type 2 diabetes in an individual is reduced by effecting a 10 to 50% decrease in the individual's glucose tolerance. In certain of the foregoing embodiments, the improvement in glucose tolerance can be measured using a glucose test. An improvement in glucose tolerance can be measured by a reduction in the blood glucose levels of an individual that occur in the 2 hour internal after administration of glucose during a glucose test (*e.g.*, a blood glucose level after 2 hours of 12 mmol/L before treatment and a blood glucose level after 2 hours of 10.7 mmol/L after treatment).

[00047] Another method of diagnosing whether an individual has diabetes is to assess the individual relative to the National Diabetes Data Group criteria. The criteria include 1) one or more classic symptoms (excessive thirst, polyuria, weight loss, and hunger) plus elevated glucose concentrations (fasting concentrations of 126 mg/dL (7.0 mmol/L), random plasma glucose concentrations of 200 mg/dL (11.1 mmol/L), and concentrations of 200 mg/dL after 2 hours shown during oral-glucose-tolerance testing), 2) elevated plasma glucose concentrations on 2 different occasions in the absence of symptoms, or 3) treatment with hypoglycemic medication (insulin or oral hypoglycemic agent).

[00048] As previously discussed, the nutritional composition according to the second embodiment and according to certain embodiments of the first, third and fourth embodiments, have a glycemic index of between 10 and 69. In certain other embodiments according to the first, second, third and fourth embodiments, the nutritional compositions have a glycemic index of between 10 and 55; including between 20 and 50; and 30 and 45. The term "glycemic index" when referring to the nutritional compositions described herein is intended to describe the glycemic index of the nutritional compositions as a whole, absent context to the contrary.

[00049] The glycemic index (GI) provides a measure of how quickly blood sugar levels (*i.e.* levels of glucose in the blood) rise after eating a particular type of food. The effects that different foods have on blood sugar levels vary considerably. The glycemic index estimates how

much each gram of available carbohydrate (total carbohydrate minus fiber) in a food raises a person's blood glucose level following consumption of the food, relative to consumption of pure glucose.

[00050] The glycemic index of a food is defined as the incremental area under the two-hour blood glucose response curve (AUC) following a 12-hour fast and ingestion of a food with a certain quantity of available carbohydrate (usually 50 g). The AUC of the test food is divided by the AUC of the standard (glucose, the standard, has a GI of 100) and multiplied by 100. The average GI value is calculated from data collected in 10 human subjects. Both the standard and test food must contain an equal amount of available carbohydrate. The result gives a relative ranking for each tested food. Glycemic index charts often give only one value per food, but variations are possible due to variety, ripeness, cooking methods, processing, and the length of storage. Potatoes are a notable example, ranging from moderate to very high GI even within the same variety. Thus, while absolute values for certain products or ingredients are presented herein, some variability is to be expected. However, tables reporting commonly accepted GI values for a variety of foods are available including the international GI database maintained by the University of Sydney, and available on the internet at: www.glycemicindex.com.

[00051] Carbohydrates are classified as low, medium or high GI based on their glycemic index score. Generally, carbohydrates below 55 on the GI are classified as low GI carbohydrates, carbohydrates between 56 and 69 are classified as medium, and carbohydrates with a score above 70 are classified as high GI carbohydrates.

[00052] As previously discussed, the nutritional compositions according to the third embodiment and in certain embodiments according to the fourth embodiment, the nutritional compositions comprise at least one source of low glycemic index carbohydrates (low glycemic index carbohydrates having a GI score of 55 or below). Non-limiting examples of low glycemic index carbohydrates useful in the nutritional compositions disclosed herein include: sucromalt, Fibersol™ (inulin), maltodextrins having a dextrose equivalence (DE) of less than 15, rice syrup having a dextrose equivalence of less than 15, fructooligosaccharides, resistant starches, starches, fruit sourced fibers, vegetable sourced fibers, whole grains, beta-glucans, soy fibers, oat fibers, locust bean gum, konjac flour, hydroxypropyl methylcellulose, gum acacia, chitosan,

arabinogalactans, xanthan gum, alginate, low and high methoxy pectin, carrageenan, psyllium, isomaltulose, glycerine and sugar alcohols.

[00053] As previously discussed, according to the third and fourth embodiments, the nutritional compositions comprise at least one source of high glycemic index carbohydrates (high glycemic index carbohydrates having a GI score of 70 or above). Non-limiting examples of high glycemic index carbohydrates useful in the nutritional compositions disclosed herein include: simple sugars, sucrose, glucose, galactose, corn syrup solids, maltodextrins having a dextrose equivalence of more than 15, and rice syrup (having a dextrose equivalence of more than 15).

[00054] As previously discussed, in nutritional compositions according to the third embodiment, the weight ratio of low glycemic index carbohydrates to high glycemic index carbohydrates is between 0.1:1 and 0.5:1. In certain embodiments according to the third embodiment, the ratio of low glycemic index carbohydrates to high glycemic index carbohydrates is between 0.1:1 and 0.4:1, including between 0.1:1 to 0.3:1 and between 0.2:1 and 0.4:1.

[00055] As previously discussed, the nutritional compositions according to the second, third and fourth embodiments contain carbohydrates or a source of carbohydrates. Similarly, in certain embodiments according to the first embodiment, the nutritional composition contains carbohydrates or a source of carbohydrates. In certain embodiments according to the first, second, third and fourth embodiments, the carbohydrates are from more than one source. As previously discussed, the nutritional compositions according the second embodiment include carbohydrates in an amount sufficient to provide 30 to 65 % of calories from carbohydrates, and in embodiments according to the fourth embodiment, carbohydrates are present in an amount sufficient to provide 70 to 95% of the calories in the nutritional composition. Within these parameters, the particular amount of carbohydrate present in the nutritional compositions may vary widely. In other embodiments disclosed herein, the carbohydrates comprise 30-80%, 30-70%, 30-60%, 50 to 65% or 40-50% of the total calories of the nutritional composition. Similarly, in embodiments according to the third embodiment, the amount of carbohydrates may be expressed in terms of weight % (wt/wt) of the nutritional compositions. In such embodiments, carbohydrates comprise 30 to 70 weight % of the nutritional compositions, including 30 to 60 weight %, including 30 to 50 weight %.

[00056] The source(s) of carbohydrates suitable for use in certain embodiments of the nutritional compositions disclosed herein may be simple, complex, or variations or combinations thereof. Generally, any source of carbohydrates may be used so long as it is suitable for use in oral nutritional compositions and is otherwise compatible with any other selected ingredients or features present in the nutritional composition, including those discussed above. Non-limiting examples of a source of carbohydrates suitable for use in the nutritional compositions described herein include maltodextrin, hydrolyzed or modified starch or cornstarch, glucose polymers, corn syrup, corn syrup solids, rice-derived carbohydrates, sucrose, glucose, fructose, lactose, high fructose corn syrup, honey, sugar alcohols (*e.g.*, maltitol, erythritol, sorbitol, *etc.*), isomaltulose, sucromalt, pullulan, potato starch, slowly-digested carbohydrates, dietary fibers including, but not limited to, oat fiber, soy fiber, gum arabic, sodium carboxymethylcellulose, methylcellulose, guar gum, gellan gum, locust bean gum, konjac flour, hydroxypropyl methylcellulose, tragacanth gum, karaya gum, gum acacia, chitosan, arabinogalactans, glucomannan, xanthan gum, alginate, pectin, low and high methoxy pectin, cereal beta-glucans (*i.e.*, oat beta-glucan, barley beta-glucan), carrageenan and psyllium, Fibersol™, other resistant starches, and combinations thereof.

[00057] As previously discussed, the nutritional compositions according to the second, third and fourth embodiments disclosed herein contain protein. In embodiments according to the second embodiment, the amount of protein is between 9 and 25 % of the total calories of the nutritional composition, including 12 to 18 % of the total calories of the nutritional composition. Similarly, protein is present in an amount sufficient to provide 5 to 30% of the calories of the nutritional composition according to the fourth embodiment. In embodiments according to the third embodiment, protein comprises 10 to 30% by weight of the nutritional compositions. In certain embodiments according to the first embodiment, the nutritional compositions contain protein; in certain such instances the amount of protein is between 5 and 30% of the total calories. Within these ranges, the particular amount of protein that is present in a nutritional composition according to the embodiments disclosed herein may vary depending upon the nutritional needs of the intended individual.

[00058] Generally, the protein in the nutritional compositions according to the first, second, third and fourth embodiments may be provided by one source or type of protein or by a

combination of source or types of proteins, including, but not limited to, intact, hydrolyzed, and partially hydrolyzed protein, which may be derived from any known or otherwise suitable source such as milk (*e.g.*, casein, whey), animal (*e.g.*, meat, fish, earthworm), cereal (*e.g.*, rice, corn), vegetable (*e.g.*, soy, potato, pea), insect (*e.g.*, locust) and combinations thereof. Non-limiting examples of the source of protein include whey protein concentrates, whey protein isolates, whey protein hydrolysates, acid caseins, sodium caseinates, calcium caseinates, potassium caseinates, casein hydrolysates, milk protein concentrates, milk protein isolates, milk protein hydrolysates, nonfat dry milk, condensed skim milk, soy protein concentrates, soy protein isolates, soy protein hydrolysates, pea protein concentrates, pea protein isolates, pea protein hydrolysates, collagen proteins, and combinations thereof. It should be understood that certain protein sources are more or less suitable for use depending upon the pH of the nutritional composition when in liquid form. Whey protein, commercially available soluble soy protein isolates, hydrolyzed soy protein, hydrolyzed whey protein, hydrolyzed pea protein, hydrolyzed soy protein, hydrolyzed casein protein and hydrolyzed collagen protein are generally more suitable for use in nutritional compositions having a pH of 2 to 5.

[00059] When soy protein is included in a nutritional composition according to the first, second, third or fourth embodiments disclosed herein, the soy protein may be provided by one or more than one source. Common forms of soy protein include soy protein concentrates and soy protein isolates. In certain embodiments, the amount of soy protein utilized in the nutritional compositions according to the third embodiment is up to 100 weight % of the total protein (*i.e.*, 0-100 weight %), including between 50 and 100% soy protein, and in other embodiments 5-10 weight %, 5-90 weight % or even 30-90 weight % of the total protein. In certain embodiments according to the first, second, third and fourth embodiments, the soy protein is soy protein concentrate. Commercial sources of soy protein are well known in the nutrition art, some non-limiting examples of which include soy protein isolates distributed by The Archer Daniels Midland Company. As previously discussed, soy protein may be utilized in combination with one or more other proteins such as whey protein, other milk-sourced proteins, or both.

[00060] When whey protein is included in a nutritional composition according to the first, second, third and fourth embodiments disclosed herein, the whey may be provided by one or more than one source. Common forms of whey protein include whey protein concentrate and

whey protein isolate. In certain embodiments according to the first, second, third and fourth embodiments, the whey protein is present as a whey protein concentrate. Various commercial sources of whey protein exist, containing varying concentrations of protein such as about 75 weight % protein (w/w, based on the total weight of the protein source). As previously discussed, in certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the amount of whey protein utilized in the nutritional compositions can be up to 100 weight % (*i.e.*, 0-100 weight %) of the total protein in certain embodiments. In certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the amount of whey protein is up to 10 weight %, up to 50 weight %, 10-50 weight %, up to 90 weight %, 10-90 weight %, or even 100 weight % of the total protein.

[00061] In addition to the protein sources specifically discussed above, the nutritional compositions according to the first, second, third and fourth embodiments may also contain protein from one or more other sources, in amounts in accord with the amount of protein discussed above. Exemplary sources of protein are discussed above. The additional protein sources can also include free amino acids known for use in nutritional compositions, non-limiting examples of which include L-tryptophan, L-glutamine, L-tyrosine, L-methionine, L-cystine, taurine, L-arginine, L-carnitine, and combinations thereof.

[00062] As previously discussed, in embodiments according to the third embodiment, 1-10% of the weight of the nutritional composition is provided by fat. Fat is an optional component of the nutritional compositions according to the first, and fourth embodiments. As previously discussed, according to embodiments of the second embodiment, fat is present in an amount sufficient to provide 10 to 50% of calories in the nutritional composition, including 10 to 30% of the calories in the nutritional composition. As previously discussed, in embodiments according to the fourth embodiment, fat is present in an amount of no more than 1% of the calories in the liquid nutritional compositions. Within these ranges, the particular amount of fat that is present in a nutritional composition according to the embodiments disclosed herein may vary depending upon the nutritional needs of the intended individual.

[00063] Various commercial sources of fat exist and may be utilized in certain embodiments according to the first, second and third embodiments. (Generally, any fat present in the liquid nutritional compositions according to the fourth embodiment is present as a residual

in another ingredient and is not intentionally added by itself as a source of fat.) Non-limiting examples of suitable fats or sources thereof for use in the nutritional compositions disclosed herein include coconut oil, fractionated coconut oil, soy oil, corn oil, olive oil, safflower oil, high oleic safflower oil, MCT oil (medium chain triglycerides), sunflower oil, high oleic sunflower oil, palm and palm kernel oils, palm olein, canola oil, marine oils, cottonseed oils and combinations thereof.

[00064] In accordance with the embodiments disclosed herein, the anthocyanidin-containing nutritional compositions can be administered in a form suitable for the chosen route of administration. Any solid, liquid, semi-solid, semi-liquid or powder form, including combinations or variations thereof, is suitable for use herein, provided that such forms allow for safe and effective oral administration to the individual of the nutritional composition disclosed herein. Oral administration, as used herein, refers to any form of administration in which the anthocyanidins pass through the esophagus of the individual.

[00065] Generally, the nutritional compositions according to the first, second, third and fourth embodiments are intended to deliver some amount of nutrition to consumers of the nutritional composition (*i.e.,* the nutritional compositions contain one or more macronutrients). In certain embodiments according to the first and second embodiments disclosed herein, the nutritional compositions may be provided in the form of a solid nutritional composition, a liquid nutritional composition or as a reconstitutable powder. As previously discussed, the nutritional compositions according to the first, second, third and fourth embodiments are often or generally provided or consumed in the form of one to two servings daily, in one or two or more divided doses daily. In certain embodiments according to the first, second and fourth embodiments, when the nutritional composition is a liquid, the serving is within a range of 30 milliliters to 500 milliliters (~1 fl oz to ~17 fl oz). In certain other embodiments according to the first, second and fourth embodiments, when the nutritional composition is a liquid, the serving is 237 milliliters (~8 fl oz). In other embodiments according to the first, second and fourth embodiments, when the nutritional composition is a liquid, the serving is 177 milliliters to 417 milliliters (~6 fl oz to ~14 fl oz). In yet other embodiments according to the first, second and fourth embodiments, when the nutritional composition is a liquid, the serving is 207 milliliters to 296 milliliters (~7 fl oz to ~10 fl oz). In still other embodiments according to the first, second and fourth

embodiments, when the nutritional composition is a liquid, the serving is 30 milliliters to 75 milliliters (~1 fl oz to ~ 2.5 fl oz).

[00066] As previously discussed, the liquid nutritional compositions according to the fourth embodiment disclosed herein have a pH of 2 to 5, similarly, in certain embodiments according to the first and second embodiments, when in liquid form, may have a pH of 2 to 5. In certain such embodiments, the pH of the liquid nutritional composition is 2.5 to 4.5, including a pH of 3 to 3.5. In certain other embodiments according to the first and second embodiments, the nutritional composition has a pH ranging from 2 to 8; in other such embodiments, the nutritional composition has a pH in a range of from 3 to 8, including from 6 to 8, and also including from 6.5 to 7.5. Generally, when the anthocyanidin-containing nutritional composition is a liquid, it will be beneficial to maintain the pH of the liquid nutritional composition at less than or equal to 5 in order to prevent destabilization and destruction of the anthocyanidins.

[00067] The nutritional compositions according to the first, second, third and fourth embodiments disclosed herein can have widely varying calorie contents. One way to express the calorie content of a nutritional composition is on a kilocalorie per serving basis. Generally, the nutritional compositions according to the first, second, third and fourth embodiments disclosed herein have an amount of calories of 35-1000 kilocalories per serving. In certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the nutritional compositions have a calorie content of 35-500 kilocalorie (kcal) per serving, including 35-450 kcal per serving, including 35-350 kcal per serving, including 100-450 kcal per serving, and including 150-350 kcal per serving.

[00068] In certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the nutritional compositions contain other ingredients, non-limiting examples of which include preservatives, antioxidants, emulsifying agents, buffers, pharmaceutical actives, additional nutrients, colorants, flavors, thickening agents and stabilizers.

[00069] In certain other embodiments according to the first, second, third, and fourth embodiments, the nutritional composition may further comprise any of a variety of vitamins or related nutrients, non-limiting examples of which include vitamin A, vitamin E, vitamin D2, vitamin D3, vitamin A palmitate, vitamin E acetate, vitamin C palmitate (ascorbyl palmitate), vitamin K, thiamine, riboflavin, pyridoxine, vitamin B12, carotenoids (*e.g.*, beta-carotene,

zeaxanthin, lutein, lycopene), niacin, folic acid, pantothenic acid, vitamin C, choline, inositol, salts and derivatives thereof, and combinations thereof.

[00070] In yet other embodiments according to the first, second, third, and fourth embodiments, the nutritional composition comprises any of a variety of additional minerals (either in combination with vitamins or alone), non-limiting examples of which include calcium, selenium, potassium, iodine, phosphorus, magnesium, iron, zinc, manganese, copper, sodium, molybdenum, chromium, chloride, and combinations thereof.

[00071] In certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the nutritional compositions also optionally include one or more masking agents to reduce or otherwise obscure the development of any residual bitter flavors and after taste in the nutritional compositions over time. Suitable masking agents include natural and artificial sweeteners, sodium sources such as sodium chloride, and hydrocolloids, such as guar gum, xanthan gum, carrageenan, gellan gum, and combinations thereof. The amount of masking agent in the nutritional emulsion may vary depending upon the particular masking agent selected, other ingredients in the formulation, and other formulation or product target variables. Such amounts, however, most typically range from at least about 0.1%, including form about 0.15% to about 3.0%, and also including from about 0.18% to about 2.5%, by weight of the nutritional emulsion.

Examples

[00072] The following examples illustrate specific and exemplary embodiments and features of nutritional compositions according to the third and fourth embodiments and suitable for use according to the methods of the first and second embodiments disclosed herein, as relevant from the product forms identified in the particular examples. The examples are provided solely for the purposes of illustration and should not be construed as limitations of the present disclosure. Numerous variations over these specific examples are possible without departing from the spirit and scope of the presently disclosed nutritional compositions. All amounts indicated within the tables below are weight percentages based upon the total weight of the composition, unless indicated otherwise.

[00073] **Examples 1-5:** Table 4A shows five exemplary nutritional compositions according to certain embodiments of the first, second and third embodiments disclosed herein, where the nutritional composition is a bar, with plum-sourced polyphenols present in varying amounts (using PE-50 plum extract).

Table 4A

Ingredient, % w/w	Example 1	Example 2	Example 3	Example 4	Example 5
Coating	10.12	10.12	10.12	10.12	10.12
High fructose corn syrup	3.20	3.20	3.20	3.20	3.20
Corn syrup	1.78	1.78	1.78	1.78	1.78
Soy protein isolate	12.11	12.11	12.11	12.11	12.11
Soy crisp	8.09	8.09	8.09	8.09	8.09
Sorbitol, 70%	1.05	1.05	1.05	1.05	1.05
FOS	8.00	8.00	8.00	8.00	0.00
XOS	0.00	0.00	0.00	0.00	8.00
PE-50	1.00	2.00	4.00	6.00	15.0
CaHMB.H2O	6.20	6.20	6.20	6.20	6.20
DCP	1.77	1.77	1.77	1.77	1.77
Fructose	1.15	1.15	1.15	1.15	1.15
Rice syrup	39.00	38.00	36.00	34.00	25.00
Vitamin/mineral premix	0.52	0.52	0.52	0.52	0.52
Ground flaxseed	6.01	6.01	6.01	6.01	6.01
TOTAL	100.00	100.00	100.00	100.00	100.00

[00074] The bars according to Examples 1-5 contain protein, fat, carbohydrates, and anthocyanidins in the amounts indicated in Table 4B. Additionally, the weight ratio of low glycemic index carbohydrates (LGIC) to high glycemic index carbohydrates (HGIC) is provided in Table 3B. The glycemic index of each of the bars is estimated to be between 56 and 69.

Table 4B					
	Example 1	**Example 2**	**Example 3**	**Example 4**	**Example 5**
protein (weight %)	12	13	14	17	20
fat (weight %)	17	16	15	12	9
carbohydrates (weight %)	61	62	63	64	61
anthocyanidins (mg/kg)	17	30	60	120	425
weight ratio LGIC:HGIC	0.28:1	0.29:1	0.31:1	0.32:1	0.42:1

[00075] **Examples 6-11:** Table 5A shows exemplary nutritional compositions according to certain embodiments of the first, second and fourth embodiments disclosed herein, representing a liquid nutritional composition containing protein, a minimum of fat, and plum-sourced polyphenols (using PE-50 plum extract)) in varying amounts.

Table 5A						
Ingredient, kg/1000 kg	**6**	**7**	**8**	**9**	**10**	**11**
Water	Q.S.	Q.S	Q.S.	Q.S.	Q.S.	Q.S.
Sucrose	109	109	109	109	109	109
Maltodextrin	95.5	95.5	95.5	95.5	95.5	95.5
PE-50	12	24	36	48	60	130
Whey protein isolate	42.9	42.9	42.9	42.9	42.9	42.9
Flavoring	1.5	1.5	1.5	1.5	1.5	1.5
Ascorbic acid	0.535	0.535	0.535	0.535	0.535	0.535
UTM/TM premix	0.230	0.230	0.230	0.230	0.230	0.230
ADEK premix	0.178	0.178	0.178	0.178	0.178	0.178
Antifoam	0.060	0.060	0.060	0.060	0.060	0.060
WSV premix	0.0379	0.0379	0.0379	0.0379	0.0379	0.0379
Folic acid	0.0013	0.0013	0.0013	0.0013	0.0013	0.0013

Potassium iodide	0.000204	0.000204	0.000204	0.000204	0.000204	0.000204
TOTAL	1000	1000	1000	1000	1000	1000

[00076] The liquid nutritional compositions according to Examples 6-11 contain protein, fat, carbohydrates, and anthocyanidins in the amounts indicated in Table 5B. Additionally, the weight ratio of low glycemic index carbohydrates (LGIC) to high glycemic index carbohydrates (HGIC) is provided in Table 5B. The glycemic index of each of the compositions is estimated to be between 56 and 69.

Table 5B

	Example 6	**Example 7**	**Example 8**	**Example 9**	**Example 10**	**Example 11**
protein (% total calories)	30	25	20	15	10	5
fat (% total calories)	0	5	15	20	30	50
carbohydrates (% total calories)	70	75	65	65	60	45
anthocyanidins (mg/kg)	6	20	30	50	60	80
weight ratio LGIC:HGIC	0.47:1	0.47:1	0.47:1	0.47:1	0.47:1	0.47:1

[00077] **Example 12:** Table 6 shows exemplary liquid nutritional compositions according to certain embodiments of the first, second and fourth embodiments disclosed herein, including PE-50 plum/prune extract. The extract provides anthocyanidins and cyanidin in amounts in accordance with the disclosed embodiments.

Table 6

	Minimum PE-50 fortification	**Maximum PE-50 fortification**
Serving size	8 oz.	

Servings per day	2 x 8 oz.	
Servings per week	14 x 8 oz.	
PE-50 per serving	0.58 g per 8 oz.	8.6 g per 8 oz.
anthocyanidins per serving	1.4 mg	21 mg
PE-50 anthocyanidins per week	19 mg	284 mg
PE-50 cyanidin per week	15 mg	238 mg

[00078] **Example 13:** Table 7 shows exemplary solid nutritional compositions according to certain embodiments of the first, second and third embodiments disclosed herein. The solid nutritional compositions comprise PE-50 plum/prune extract and provide anthocyanidins and cyanidin in amounts in amounts in accordance with the disclosed embodiments.

Table 7

	Minimum PE-50 fortification	**Maximum PE-50 fortification**
Serving size	58 g (1 bar)	
Servings per day	2 x 58 g	
Servings per week	14 x 58 g	
PE-50 per serving	0.58 g per 58-g bar	8.6 g per 58-g bar
anthocyanidins per serving	1.4 mg	21 mg
cyanidins per serving	1.1 mg	17 mg
PE-50 anthocyanidins per week	19 mg	284 mg
PE-50 cyanidin per week	15 mg	238 mg

[00079] **Example 14**: Table 8 shows exemplary pediatric liquid nutritional compositions according to certain embodiments of the first, second and fourth embodiments disclosed herein. The nutritional compositions comprise PE-50 plum/prune extract and provide anthocyanidins and cyanidin in amounts in accordance with the disclosed embodiments.

Table 8

	Minimum PE-50 fortification	**Maximum PE-50 fortification**
Serving size	8 oz.	
Servings per day	2 x 8 oz.	

Servings per week	14 x 8 oz.	
PE-50 per serving	0.58 g per 8 oz.	8.6 g per 8 oz.
anthocyanidins per serving	1.4 mg	21 mg
cyanidins per serving	1.1 mg	17 mg
PE-50 anthocyanidins per week	19 mg	284 mg
PE-50 cyanidin per week	15 mg	238 mg

[00080] **Example 15**: An exemplary liquid nutritional composition suitable for use in certain embodiments of the first, second and fourth embodiments disclosed herein. The liquid nutritional composition according to Table 9 is particularly suitable for administration of anthocyanidins to individuals having or at a high risk for diabetes. The estimated glycemic index of the liquid nutritional composition according to Table 9 is approximately 55, and the composition has a weight ratio of LGIC:HGIC of 0.1:1 to 0.5:1.

Table 9

	UNIT	per 8 fl oz
Nutrient Density	Cal/ml	0.93
Protein	% Cal	18
Carbohydrate	% Cal	47
Fat	% Cal	35
Osmolality	mOsm/L	86
Viscosity		Thin
Protein	g	9.9
Carbohydrate	g	29.3
Fat	g	8.6
Water	g	200
Ca-HMB	g	1.5
VITAMINS		
Vitamin A (Palmitate)	IU	1750
Vitamin A (B-Carotene)	mg	0.5
Vitamin D	IU	100
Vitamin E	IU	30
Vitamin K	mcg	20
Vitamin C	mg	60
Folic Acid	mcg	200
Vitamin B_1	mg	0.38
Vitamin B_2	mg	0.43

Vitamin B_6	mg	1.0
Vitamin B_{12}	mcg	3.0
Niacin	mg	5.0
Pantothenate	mg	2.5
Biotin	mcg	75
L-carnitine	mg	43
Choline	mg	100
MINERALS		
Sodium	mg	210
Potassium	mg	370
Chloride	mg	355
Calcium	mg	250
Phosphorus	mg	250
Magnesium	mg	100
Iron	mg	4.5
Zinc	mg	3.8
Manganese	mg	1.0
Copper	mg	0.50
Iodine	mcg	38
Selenium	Mcg	18
Chromium	Mcg	120
Molybdenum	Mcg	38

[00081] The liquid nutritional composition described in Table 9 includes Water, Corn Maltodextrin, Sodium & Calcium Caseinates, Maltitol Syrup, High Oleic Safflower Oil, Fructose, Soy Protein Isolate, Soy Fiber, Short-Chain Fructooligosaccharides, Canola Oil, Calcium Phosphate, Magnesium Chloride, Soy Lecithin, Artificial Flavor, Sodium Citrate, Magnesium Phosphate, Potassium Citrate, Potassium Chloride, Potassium Phosphate, Ascorbic Acid, Choline Chloride, dl-Alpha- Tocopheryl Acetate, Gellan Gum, Acesulfame Potassium, Ferrous Sulfate, Zinc Sulfate, Niacinamide, Manganese Sulfate, Calcium Pantothenate, Cupric Sulfate, Sucralose, Pyridoxine Hydrochloride, Thiamine Chloride Hydrochloride, Vitamin A Palmitate, Riboflavin, Chromium Chloride, Beta-Carotene, Folic Acid, Biotin, Sodium Molybdate, Potassium Iodide, Sodium Selenate, Phylloquinone, Cyanocobalamin, and Vitamin D3.

[00082] **Example 16:** In this Example, the effect of a composition including a combination of Prune Extract + Ca-HMB for reducing blood glucose levels was analyzed.

[00083] The effect on fasted blood glucose levels is tested over time in aged Sprague Dawley rats (20 months at start of study). Animals were divided into two groups: a control group and a Test feed group. Initially, fasted blood glucose levels of the rats from each group were recorded. The control group was chronically fed, *ad libitum*, a purified rodent diet AIN-93M over an 8-week period. The test study group of rats was fed a composition including AIN-93M supplemented with a combination of Ca-HMB at 340 mg/kg body weight and Prune Extract (PE-60) at 500 mg/kg body weight. Fasted blood glucose levels are then tested again at the end of the 8-week study. The change in blood glucose levels is shown in the Table 10 below.

Table 10

Rat Group	Week 0	End of Study (Week 8)
Control (AIN-93M)	88.89	85.11
Standard Deviation	7.80	7.25
AIN-93M + Prune Extract + Ca-HMB	89.89	80.11*
Standard Deviation	10.60	7.74

* statistically significant decrease compared to control (p=0.04)

[00084] Chronic feeding of the combination of Prune Extract and HMB over a period of 8 weeks is surprisingly found to significantly lower blood glucose levels as compared to the control. Prune Extract and HMB act synergistically to reduce blood glucose levels.

[00085] **Example 17**: In this Example, the effect of Prune Extract (PE-60) for reducing acute blood glucose levels is analyzed.

[00086] The effect on acute blood glucose levels was tested in Zucker obese diabetic rats at the age of approximately 10 weeks. The average weight of the rats was about 363 grams. Initially, after fasting overnight, blood glucose levels of the rats were recorded. The rats were divided into four groups: one control group and three test groups. The control group was fed a composition including 2.0 g/kg of body weight maltodextrin (commercially available as Maltrin-100) and water by gavage at a volume of 10 ml/kg of body weight. A first test group was fed the maltodextrin composition supplemented with 500 mg/kg body weight Prune Extract (PE-60).

Blood glucose levels were then tested using the Precision G blood glucose testing system (available from Medisense, Alameda, Georgia) after 30 minutes, 60 minutes, 90 minutes, and 120 minutes. The change in blood glucose levels is shown in the Table 11 below. As can be seen from the data, the PE-60 group showed reduced acute blood glucose levels compared to the control.

Table 11

		Post-meal Glucose Levels			
Rat Group	**Pre-meal Glucose Levels**	**30 minutes**	**60 minutes**	**90 minutes**	**120 minutes**
Control (Maltrin-100)	106.11	211.67	204.56	170.44	154.44
Standard Deviation	8.62	29.80	30.86	36.31	22.73
Maltrin-100 + Prune Extract	103.89	153.78*	169.89*	166.11	157.11
Standard Deviation	7.64	19.52	25.56	22.29	23.91

*significantly lower compared to control

[00087] As previously mentioned, the nutritional compositions according to the fourth embodiment and in certain embodiments according to the first and second embodiments are in liquid form. Liquid nutritional compositions suitable for use in such embodiments can be manufactured by any process or suitable method for making nutritional emulsions. In one suitable manufacturing process, at least three separate slurries are prepared. These slurries include: a protein-in-fat (PIF) slurry, a carbohydrate-mineral (CHO-MIN) slurry and a protein-in-water (PIW) slurry. The PIF slurry is formed by heating and mixing any oils that are selected for the fat component (when present) and then adding an emulsifier (*e.g.*, lecithin), fat-soluble vitamins and a portion of the total protein with continued heat and agitation. The CHO-MIN slurry is formed by adding to water (with heat and agitation), minerals (*e.g.*, potassium citrate, dipotassium phosphate, sodium citrate, *etc.*), trace and ultra trace minerals (often as pre-mix(es)), thickening-type or suspending agents (*e.g.*, Avicel, gellan, carragenan). The CHO-MIN slurry

that results is held for 10 minutes with continued heat and agitation and then additional minerals may be added (*e.g.*, potassium chloride, magnesium carbonate, potassium iodide, *etc.*) and/or carbohydrates (*e.g.*, fructooligosaccharides, sucrose, corn syrup, *etc.*). The PIW slurry is formed by mixing the remaining protein (*i.e.*, sodium caseinate, soy protein, why protein, *etc.*) into water.

[00088] The three slurries are blended together with heat and agitation and the pH is adjusted to the desired range (typically near neutral, around 6.6-7), after which the composition is subjected to high-temperature short-time (HTST) processing during which time the composition is heat treated, emulsified and homogenized and allowed to cool. Water soluble vitamins and ascorbic acid are added (if applicable), the pH is again adjusted (if necessary), flavors are added and any additional water can be added to adjust the solids content to the desired range.

[00089] A composition suitable for use in certain embodiments according to the first and second disclosed herein, and optionally as a reconstitutable powder form of certain embodiments according to the fourth embodiment, such as a spray dried nutritional powder or dryblended nutritional powder, may be prepared by any collection of known or otherwise effective technique, suitable for making and formulating a nutritional powder. For example, when the nutritional powder is a spray dried nutritional powder, the spray drying step may likewise include any spray drying technique that is known for or otherwise suitable for use in the production of nutritional powders. Many different spray drying methods and techniques are known for use in the nutrition field, all of which are suitable for use in the manufacture of the spray dried nutritional powders herein.

[00090] One method of preparing a spray dried nutritional powder comprises forming and homogenizing an aqueous slurry or liquid comprising predigested fat, and optionally protein, carbohydrate, and other sources of fat, and then spray drying the slurry or liquid to produce a spray dried nutritional powder. The method may further comprise the step of spray drying, dryblending, or otherwise adding additional nutritional ingredients, including any one or more of the ingredients described herein, to the spray dried nutritional powder.

[00091] In certain embodiments according to the first, second, third and fourth embodiments disclosed herein, the nutritional compositions and methods herein may also be free

of any optional or other ingredient or feature described herein provided that the remaining composition still contains the requisite ingredients or features as described herein. In this context, the term "free" means the selected composition or method contains or is directed to less than a functional amount of the ingredient or feature, typically less than 0.1 % by weight, and also including zero percent by weight, of such ingredient or feature.

[00092] In certain embodiments according to the first and second embodiments disclosed herein, the nutritional compositions provided herein may also be formulated in product forms such as liquids (*e.g.*, suspensions, solutions, emulsions, clear solutions), semi-solids, yogurts, gels, powders or other particulates, and so forth. These product forms generally contain only the ingredients as described herein, optionally in combination with other actives, processing aids or other dosage form excipients.

[00093] Any combination of method or process steps as used herein may be performed in any order, unless otherwise specifically or clearly implied to the contrary by the context in which the referenced combination is made.

[00094] To the extent that the term "includes" or "including" is used in the specification or the claims, it is intended to be inclusive in a manner similar to the term "comprising" as that term is interpreted when employed as a transitional word in a claim. Furthermore, to the extent that the term "or" is employed (*e.g.*, A or B) it is intended to mean "A or B or both." When the applicants intend to indicate "only A or B but not both" then the term "only A or B but not both" will be employed. Thus, use of the term "or" herein is the inclusive, and not the exclusive use. *See* Bryan A. Garner, *A Dictionary of Modern Legal Usage* 624 (2d. Ed. 1995). Also, to the extent that the terms "in" or "into" are used in the specification or the claims, it is intended to additionally mean "on" or "onto." Furthermore, to the extent the term "connect" is used in the specification or claims, it is intended to mean not only "directly connected to," but also "indirectly connected to" such as connected through another component or components.

[00095] While the present application has been illustrated by the description of embodiments thereof, and while the embodiments have been described in considerable detail, it is not the intention of the applicants to restrict or in any way limit the scope of the appended claims to such detail. Additional advantages and modifications will readily appear to those skilled in the art. Therefore, the application, in its broader aspects, is not limited to the specific

details, the representative apparatus, and illustrative examples shown and described. Accordingly, departures may be made from such details without departing from the spirit or scope of the applicant's general inventive concept.

What is claimed is:

Claim 1. A method for improving the insulin response of an individual, the method comprising administering to an individual in need thereof a nutritional composition comprising a therapeutically effective amount of anthocyanidins.

Claim 2. The method of claim 1 wherein the anthocyanidins comprise between 50 and 90% cyanidin.

Claim 3. The method of claim 1 or 2 wherein the individual is administered the nutritional composition in an amount sufficient to provide 2.8 to 50 mg per day of anthocyanidin.

Claim 4. The method according to any preceding claim wherein the individual is administered the nutritional composition in an amount sufficient to provide between 1 and 25 mg per day of cyanidin.

Claim 5. The method of any one of claims 1 to 4, wherein the anthocyanidins are derived from a fruit selected from the group consisting of plum/prune, apple, pear, strawberry, blueberry, raspberry, cherry, and combinations thereof.

Claim 6. The method according to any one of claims 1-4 wherein the anthocyanidins are provided by plum extract.

Claim 7. The method according to claim 6 wherein the anthocyanidins comprise cyanidin.

Claim 8. The method according to any one of claims 1-4 wherein the nutritional composition has a total glycemic index of between 10 and 55.

Claim 9. A method for reducing the risk of developing type 2 diabetes in an individual, comprising:

administering to an individual in need thereof a nutritional composition comprising:

protein in an amount sufficient to provide 9 to 25% of calories from protein;

fat in an amount sufficient to provide 10 to 50% of calories from fat;

carbohydrates in an amount sufficient to provide 30 to 65% of calories from carbohydrates; and

anthocyanidins in an amount sufficient to provide a therapeutically effective amount of cyanidin;

wherein the nutritional composition has a glycemic index of between 10 and 69, and

whereby consumption of the nutritional composition results in a reduction of the risk of developing type 2 diabetes for the individual.

Claim 10. The method according to claim 9, wherein the risk is reduced by improving the insulin response of the individual.

Claim 11. A solid nutritional composition comprising:

anthocyanidins in an amount sufficient to provide from 15 to 450 mg of anthocyanidins per kg of the nutritional composition;

10 to 30% by weight of the solid nutritional composition from protein;

1 to 10% by weight of the solid nutritional composition from fat;

30 to 70% by weight of the solid nutritional composition from carbohydrates, wherein the carbohydrates include

at least one source of low glycemic index carbohydrate;

at least one source of high glycemic index carbohydrate; and

wherein the weight ratio of low glycemic index carbohydrates to high glycemic index carbohydrates is from 0.1:1 to 0.5:1.

Claim 12. The solid nutritional composition of claim 11, wherein the anthocyanidins are sourced from one or more of blueberries, blackberries, cranberries, grapes, cherries, plums, strawberries and pears.

Claim 13. The solid nutritional composition of claim 11, wherein the source of anthocyanidins is plums.

Claim 14. The solid nutritional composition of claim 11, wherein the anthocyanidins comprise between 50 and 90% cyanidin.

Claim 15. The solid nutritional composition of any one of claims 11-14, wherein consumption of the solid nutritional composition by an individual results in a reduction of the risk of type 2 diabetes for the individual.

Claim 16. The solid nutritional composition of claims 11 to 14 wherein the anthocyanidins comprise between 50 and 90% cyanidin.

Claim 17. The solid nutritional composition of any one of claims 11-14, wherein the glycemic index of the solid nutritional composition is between 10 and 69.

Claim 18. The solid nutritional composition of any one of claims 11 to 14, wherein the protein is between 50 and 100% soy protein.

Claim 19. The solid nutritional composition of any one of claims 11-14 further comprising at least one of: cysteine, cystine, glutathione soy protein and whey protein.

Claim 20. A liquid nutritional composition comprising:

500-900 g/kg water;

no more than 1 % of the calories within the liquid nutritional composition from fat;

protein in an amount sufficient to provide 5 to 30% of the calories within the liquid nutritional composition;

carbohydrates in an amount sufficient to provide 70 to 95% of the calories within the liquid nutritional composition;

from 1 to 110 mg of anthocyanidins per liter of the liquid nutritional composition;

at least one source of low glycemic index carbohydrate;

wherein the liquid nutritional composition has a pH of between 2 and 5; and wherein the glycemic index of the liquid nutritional composition is between 10 and 69.

Claim 21. The liquid nutritional composition of claim 20, wherein the liquid nutritional composition is heated at a temperature of 200 F for a time sufficient to produce a sterilized liquid nutritional composition.

Claim 22. The liquid nutritional composition of claim 20 or 21, wherein the source of anthocyanidins is selected from the group comprising: blueberries, blackberries, cranberries, grapes, cherries, plums, strawberries and pears.

Claim 23. The liquid nutritional composition of claim 20, wherein the source of anthocyanidins is a plum extract.

Claim 24. The liquid nutritional composition of any one of claims 20-23 wherein the anthocyanidins comprise between 50 and 90% cyanidin.

Claim 25. The liquid nutritional composition of any one of claims 20-23 wherein consumption of the liquid nutritional composition by an individual results in a reduction of the risk of type 2 diabetes for the individual.

Claim 26. The liquid nutritional composition of any one of claims 20-23 wherein the liquid nutritional composition comprises cyanidin in an amount from 1 to 20 mg per serving.

Claim 27. The liquid nutritional composition of any one of claims 20-23 further comprising at least one of: cysteine, cystine, glutathione and whey protein.

Claim 28. The liquid nutritional composition of any one of claims 20-23 wherein the glycemic index of the liquid nutritional composition is between 10 and 55.

Claim 29. Use of a composition according to any one of claims 11-28 for improving the insulin response of an individual.

Claim 30. Use of a composition according to any one of claims 11-28 for reducing the risk of type 2 diabetes in an individual.

Claim 31. The use according to claim 29 or 30, the composition comprising:

protein in an amount sufficient to provide 9 to 25% of calories from protein;

fat in an amount sufficient to provide 10 to 50% of calories from fat;

carbohydrates in an amount sufficient to provide 30 to 65% of calories from carbohydrates; and

anthocyanidins in an amount sufficient to provide a therapeutically effective amount of cyanidin;

wherein the nutritional composition has a glycemic index of between 10 and 69, and

whereby consumption of the nutritional composition results in a reduction of the risk of developing type 2 diabetes for the individual.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/037862

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/30
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

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, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/097064 A1 (ABBOTT LAB [US]; PEREIRA SUZETTE L [US]; JOHNS PAUL W [US]; EDENS NEIL) 19 July 2012 (2012-07-19) paragraphs [0001] - [0010], [0046] - [0083] examples	1-31
X	US 2007/060533 A1 (YOSHIKAWA MASAYUKI [JP] ET AL) 15 March 2007 (2007-03-15) paragraphs [0001], [0003], [0008] - [0052]	1-31
X	US 2011/268825 A1 (BURGOS RAFAEL [CL] ET AL) 3 November 2011 (2011-11-03) paragraphs [0002] - [0045]	1-31

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
18 August 2014	26/08/2014

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2014/037862

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2014/037862

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