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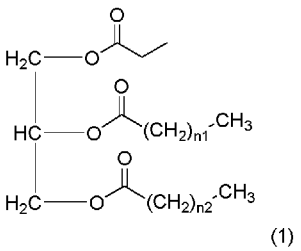
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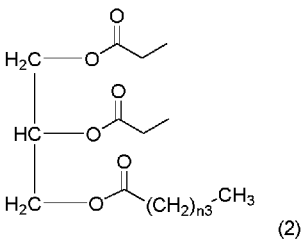
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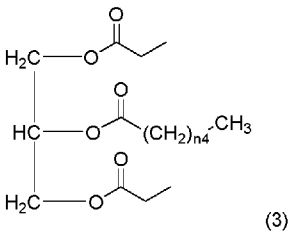
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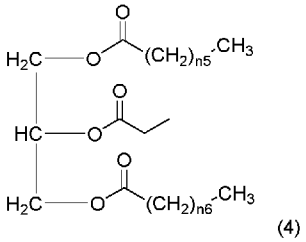
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(57) Abstract: A composition comprising a compound having the formula (1), (2), (3) or (4) or combinations thereof, wherein n1, n2, n3, n4, n5 and n6 are independently 4 to 10.

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DIETARY PROPIONATE

FIELD OF THE INVENTION

The present invention relates to a dietary source of propionic acid containing triglycerides. The present invention also provides propionic acid containing triglycerides that provide a source of ketones.

BACKGROUND TO THE INVENTION

Salts and esters of propionic acid (also referred to as propanoic acid) are known as propionates or propanoates. Propionate is one of the most common short-chain fatty acids (SCFAs) produced by human gut microbiota in response to indigestible dietary fiber in the diet.

To the microbial community, SCFAs are a waste product. However, for humans, SCFAs are important for maintaining a healthy colon. A wide range of pre-clinical evidence supports roles for SCFA as modulators of not only colonic function, but also multiple inflammatory and metabolic processes (Gill, P.A., et al., 2018. Alimentary pharmacology & therapeutics, 48(1), pp.15-34).

SCFAs may play a key role in the prevention and treatment of metabolic syndromes, bowel disorders, and certain types of cancer. In clinical studies, SCFA administration has positively influenced the treatment of ulcerative colitis, Crohn's disease, and antibiotic-associated diarrhea (den Besten, G., et al., 2013. Journal of lipid research, 54(9), pp.2325-2340).

One of the primary uses of SCFAs in tissues is as a source of energy. Propionate acts as a precursor for the production of glucose (gluconeogenesis) in the liver via propionyl-CoA. Alternatively, propionyl-CoA may be converted to β-ketopentanoate-CoA (BKP-CoA) by 3-ketoacyl-CoA thiolase (Deng, S., et al., 2009. Journal of Biological Chemistry, 284(41), pp.27799-27807). This may be further converted to β-ketopentanoate, a 5-carbon ketone body, via C5 ketogenesis.

Ketones may also be produced from medium-chain fatty acids (MCFAs). Octanoate is the most efficient MCFA at making blood ketones in human, via C4 ketogenesis (Vanderberghe et al.; 2017 Curr. Dev. Nutr. 1(4)). However, a high dose intake (>10g) induces diarrhea and stomach cramps, which limits the amount that can be ingested at once.

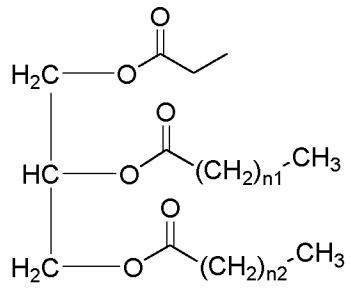
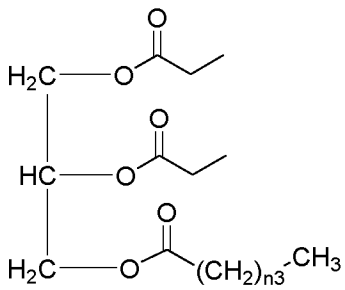
Thus, consumption of MCFAs and SCFAs, including propionic acid, may have beneficial effects. However, propionic acid is associated with negative sensory qualities such as an unpleasant smell and a bitter taste.

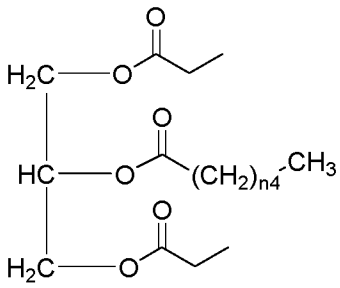
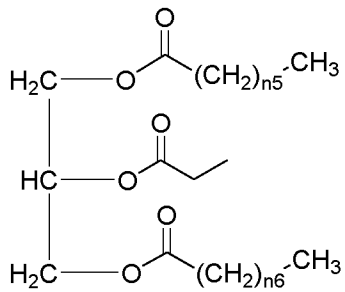
SUMMARY OF THE INVENTION

The present invention provides compounds that are a source of propionate having improved organoleptic properties, and potential for high ketone production after oral or enteral intake in human and other mammals. In particular, the invention provides new triglycerides (TG) composed of a mixture of propionate and medium chain fatty acids (MCFAs). The compounds have improved odor relative to propionic acid. The compounds may be used as a dietary source of propionic acid. The compounds may be used in, for example, nutritional compositions and dietary supplements, and as a source of ketones.

Fatty acids are liberated from triglycerides due to lipases, naturally present in the gastrointestinal tract. Relative to propionate salts, the compounds do not add additional mineral salts to the final formulation.

According to a first aspect of the present invention, there is provided a composition comprising a compound having the formula

(1)  , (2)  ,

(3)  or (4)  ,

or combinations thereof, wherein n1, n2, n3, n4, n5 and n6 are independently 4 to 10.

In one embodiment n1=n2 and/or n5=n6. In a further embodiment n1=n2=n3=n4=n5=n6.

The composition may comprise the compound having formula (1) and the compound having formula (2).

The composition may comprise the compound having formula (1) and the compound having formula (3).

The composition may comprise the compound having formula (1) and the compound having formula (4).

The composition may comprise the compound having formula (2) and the compound having formula (3).

The composition may comprise the compound having formula (2) and the compound having formula (4).

The composition may comprise the compound having formula (3) and the compound having formula (4).

The composition may comprise the compound having formula (1), the compound having formula (2) and the compound having formula (3).

The composition may comprise the compound having formula (1), the compound having formula (2) and the compound having formula (4).

The composition may comprise the compound having formula (1), the compound having formula (3) and the compound having formula (4).

The composition may comprise the compound having formula (2), the compound having formula (3) and the compound having formula (4).

The composition may comprise the compound having formula (1), the compound having formula (2), the compound having formula (3) and the compound having formula (4).

In one embodiment, the compound having formula (1) comprises at least 2%, 5%, 10% or 15% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (1) comprises 2 to 35%, 5 to 30% or 10 to 25% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (2) comprises at least 2%, 5%, 10% or 15% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (2) comprises 2 to 35%, 5 to 30% or 10 to 25% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (3) comprises at least 2%, 5%, 10% or 15% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (3) comprises 2 to 35%, 5 to 30% or 10 to 25% by weight of the total triglycerides of the composition.

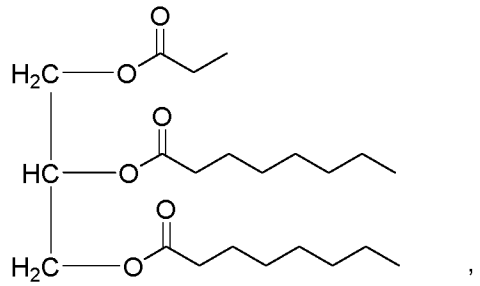
In one embodiment, the compound having formula (4) comprises at least 2%, 5%, 10% or 15% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (4) comprises 2 to 35%, 5 to 30% or 10 to 25% by weight of the total triglycerides of the composition.

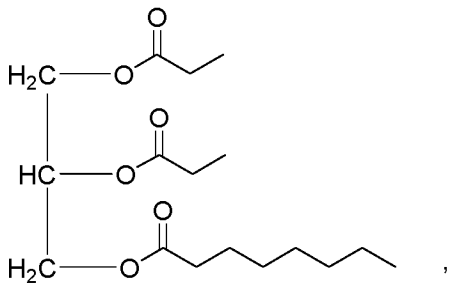
The compounds having formula (1), (2), (3) and (4) may comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total triglycerides of the composition.

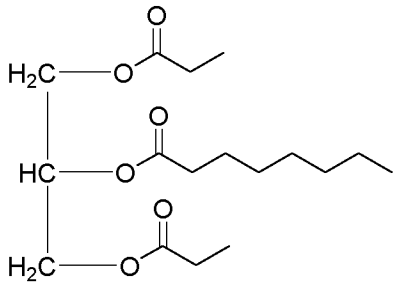
In one embodiment, the compound having formula (1) comprises at least 2%, 5%, 10% or 15% by weight of the total propionate moiety containing triglycerides in the composition, and/or the compound having formula (2) comprises at least 2%, 5%, 10% or 15% by weight of the total propionate moiety containing triglycerides in the composition, and/or the compound having formula (3) comprises at least 2%, 5%, 10% or 15% by weight of the total propionate moiety containing triglycerides in the composition, and/or the compound having formula (4) comprises at least 2%, 5%, 10% or 15% by weight of the total propionate moiety containing triglycerides in the composition.

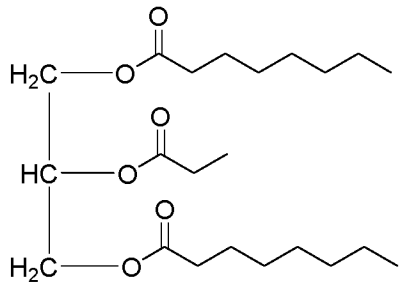
The compounds having formula (1), (2), (3) and (4) may comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total propionate moiety containing triglycerides of the composition and/or comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total medium chain fatty acid moiety containing triglycerides in the composition.

According to one embodiment of the present invention, there is provided a composition comprising a compound having the formula

(5)  ,

(6)  ,

(7)  or

(8)  ,

or combinations thereof.

The composition may comprise the compound having formula (5) and the compound having formula (6).

The composition may comprise the compound having formula (5) and the compound having formula (7).

The composition may comprise the compound having formula (5) and the compound having formula (8).

The composition may comprise the compound having formula (6) and the compound having formula (7).

The composition may comprise the compound having formula (6) and the compound having formula (8).

The composition may comprise the compound having formula (7) and the compound having formula (8).

The composition may comprise the compound having formula (5), the compound having formula (6) and the compound having formula (7).

The composition may comprise the compound having formula (5), the compound having formula (6) and the compound having formula (8).

The composition may comprise the compound having formula (5), the compound having formula (7) and the compound having formula (8).

The composition may comprise the compound having formula (6), the compound having formula (7) and the compound having formula (8).

The composition may comprise the compound having formula (5), the compound having formula (6), the compound having formula (7) and the compound having formula (8). In one embodiment, the compound having formula (5) comprises at least 2%, 5%, 10%, 15%, 20% or 25% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (5) comprises 5 to 35%, 10 to 30%, or 20 to 30% by weight of the total triglycerides of the composition

In one embodiment, the compound having formula (6) comprises at least 2%, 5%, 10%, 15%, 20% or 25% by weight of the total triglycerides of the composition. In one embodiment, the

compound having formula (6) comprises 5 to 35%, 10 to 30%, or 15 to 25% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (7) comprises at least 2%, 5%, 10%, 15%, 20% or 25% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (7) comprises 5 to 35%, 10 to 30%, 10 to 20% or 5 to 15% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (8) comprises at least at least 2%, 5%, 10%, 15%, 20% or 25% by weight of the total triglycerides of the composition. In one embodiment, the compound having formula (8) comprises 5 to 35%, 5 to 20%, or 5 to 15% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (5) comprises at least 5% by weight of the total triglycerides of the composition, the compound having formula (6) comprises at least 5% by weight of the total triglycerides of the composition, the compound having formula (7) comprises at least 5% by weight of the total triglycerides of the composition, and the compound having formula (8) comprises at least 5% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (5) comprises at least 20% by weight of the total triglycerides of the composition, the compound having formula (6) comprises at least 15% by weight of the total triglycerides of the composition, the compound having formula (7) comprises at least 10% by weight of the total triglycerides of the composition, and the compound having formula (8) comprises at least 5% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (5) comprises 20 to 30% by weight of the total triglycerides of the composition, the compound having formula (6) comprises 15 to 25% by weight of the total triglycerides of the composition, the compound having formula (7) comprises 10 to 20% by weight of the total triglycerides of the composition, and the compound having formula (8) comprises 5 to 15% by weight of the total triglycerides of the composition.

The compounds having formula (5), (6), (7) and (8) may comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total triglycerides of the composition.

In one embodiment, the compound having formula (5) comprises at least 5% by weight of the total propionate moiety containing triglycerides in the composition. In one embodiment, the compound having formula (5) comprises at least 10%, 20% or 30% by weight of the total propionate moiety containing triglycerides in the composition.

In one embodiment, the compound having formula (6) comprises at least 5% by weight of the total propionate moiety containing triglycerides in the composition. In one embodiment, the compound having formula (6) comprises at least 10%, 15% or 20% by weight of the total propionate moiety containing triglycerides in the composition.

In one embodiment, the compound having formula (7) comprises at least 5% by weight of the total propionate moiety containing triglycerides in the composition. In one embodiment, the compound having formula (7) comprises at least 5%, 10% or 15% by weight of the total propionate moiety containing triglycerides in the composition.

In one embodiment, the compound having formula (8) comprises at least 5% by weight of the total propionate moiety containing triglycerides in the composition. In one embodiment, the compound having formula (8) comprises at least 2% or 5% by weight of the total propionate moiety containing triglycerides in the composition.

The compounds having formula (5), (6), (7) and (8) may comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total propionate moiety containing triglycerides in the composition, and/or comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total octanoate moiety containing triglycerides in the composition.

In a preferred embodiment, tripropionin comprises less than 10% by weight of the total triglycerides in the composition, preferably less than 8% by weight, more preferable less than 5% by weight of the total triglycerides in the composition.

The composition of the invention may be a nutritional composition.

The composition may be a dietary supplement. The dietary supplement may be in the form of a capsule, tablet, sachet, powder or liquid shot.

According to another aspect, there is provided a composition of the invention for providing a source of propionate with improved organoleptic properties.

According to another aspect, there is provided use of a composition of the invention for providing a source of propionate with improved organoleptic properties.

According to another aspect, there is provided a composition of the invention for use in increasing ketone levels, preferably blood ketone levels.

According to another aspect, there is provided a composition of the invention for use in treating a disease treatable by increasing ketone levels, preferably blood ketone levels. In one

embodiment, there is provided a composition of the invention for treating a disease associated with low ketone levels, preferably low blood ketone levels.

According to another aspect, there is provided a composition of the invention for use in the treatment or prevention of neurological disease, metabolic disease, cancer and/or cardiac ischemia.

According to another aspect, there is provided a composition of the invention for use in the treatment or prevention of one or more diseases selected from the list consisting of: a brain energy deficiency condition, a migraine, memory disorder, age-related memory disorder, brain injury, stroke, amyloid lateral sclerosis, multiple sclerosis, cognitive impairment, cognitive impairment post-intensive care, age-induced cognition impairment, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, inherited metabolic disorders (such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency), depression, schizophrenia, epilepsy, narcolepsy, diabetes, obesity, non-alcoholic fatty liver disease and polycystic ovary syndrome.

In one embodiment, there is provided a composition of the invention for use in the treatment or prevention of epilepsy.

According to another aspect, there is provided a compound having formula (1). In one embodiment n1=n2=6. In this embodiment, a compound having the formula (1) corresponds to a compound having the formula (5).

According to another aspect, there is provided a compound having formula (2). In one embodiment n3=6. In this embodiment, a compound having the formula (2) corresponds to a compound having the formula (6).

According to another aspect, there is provided a compound having formula (3). In one embodiment n4=6. In this embodiment a compound having the formula (3) corresponds to a compound having the formula (7).

According to another aspect, there is provided a compound having formula (4). In one embodiment n5=n6=6. In this embodiment a compound having the formula (4) corresponds to a compound having the formula (8).

According to another aspect, there is provided use of a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for providing a source of propionate with improved organoleptic properties.

According to another aspect, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use in increasing ketone levels, preferably blood ketone levels.

According to another aspect, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use as a medicament.

According to another aspect, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use in treating a disease treatable by increasing ketone levels, preferably blood ketone levels.

According to another aspect, there is provided compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use in treating a disease associated with low ketone levels, preferably low blood ketone levels.

According to another aspect, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use in the prevention or treatment of a neurological disease, metabolic disease, cancer and/or cardiac ischemia.

According to another aspect, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for use in the treatment or prevention of one or more diseases selected from the list consisting of: a brain energy deficiency condition, migraine, memory disorder, age-related memory disorder, brain injury, stroke, amyloid lateral sclerosis, multiple sclerosis, cognitive impairment, cognitive impairment post-intensive care, age-induced cognition impairment, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, inherited metabolic disorders (such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency), depression, schizophrenia, epilepsy, narcolepsy, diabetes, obesity, non-alcoholic fatty liver disease and polycystic ovary syndrome.

In one embodiment, there is provided a compound having the formula (1), (2), (3) or (4) or a combination thereof, preferably a compound having the formula (5), (6), (7) or (8) or a combination thereof, for the treatment of epilepsy.

According to another aspect, there is provided a method of increasing ketone levels, preferably blood ketone levels, comprising administering a compound or composition defined herein to a subject in need thereof.

According to another aspect, there is provided a method of treating a disease treatable by increasing ketone levels, preferably blood ketone levels, comprising administering a compound or composition defined herein to a subject in need thereof.

According to another aspect, there is provided a method of treating or preventing a disease associated with low ketone levels, preferably low blood ketone levels, comprising administering a compound or composition defined herein to a subject in need thereof.

According to another aspect, there is provided a method of treating or preventing a neurological disease, metabolic disease, cancer and/or cardiac ischemia comprising administering a compound or composition defined herein to a subject in need thereof.

In one embodiment, there is provided a method of treating or preventing one or more diseases selected from the list consisting of: a brain energy deficiency condition, a migraine, memory disorder, age-related memory disorder, brain injury, stroke, amyloid lateral sclerosis, multiple sclerosis, cognitive impairment, cognitive impairment post-intensive care, age-induced cognition impairment, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, inherited metabolic disorders (such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency), depression, schizophrenia, epilepsy, narcolepsy, diabetes, obesity, non-alcoholic fatty liver disease and polycystic ovary syndrome, comprising administering a compound or composition defined herein to a subject in need thereof.

According to another aspect, there is provided a method for producing a composition of the invention, or a compound having the formula (1), (2), (3) or (4) as defined herein, comprising interesterification of tripropionin and one or more triglycerides selected from the list consisting of: trihexanoin, triheptanoin, tricaprylin, trinonanoin, tricaprin, triundecanoin and tridodecanoin.

According to one embodiment, there is provided a method for producing a composition of the invention, or a compound having the formula (5), (6), (7) or (8) as defined herein, comprising interesterification of tripropionin and tricaprylin.

DETAILED DESCRIPTION OF THE INVENTION

Triglycerides

A triglyceride (also known as a triacylglycerol) is a triester that is derived from glycerol and three fatty acids.

Fatty acids may be either unsaturated or saturated. Fatty acids which are not attached to other molecules are referred to as free fatty acids (FFA).

The term “fatty acid moiety” refers to the part of the triglyceride that originates from a fatty acid in an esterification reaction with glycerol. The triglycerides of the present invention comprise at least one propionic acid (C3) moiety and at least one medium chain fatty acid moiety.

A medium chain fatty acid moiety may contain between 6 and 12 carbon atoms. Accordingly, a medium chain fatty acid moiety may be hexanoate (caproic acid), heptanoate (enanthic acid), octanoate (caprylic acid), nonanoate (pelargonic acid), decanoate (capric acid), undecanoate (undecylic acid) or dodecanoate (lauric acid).

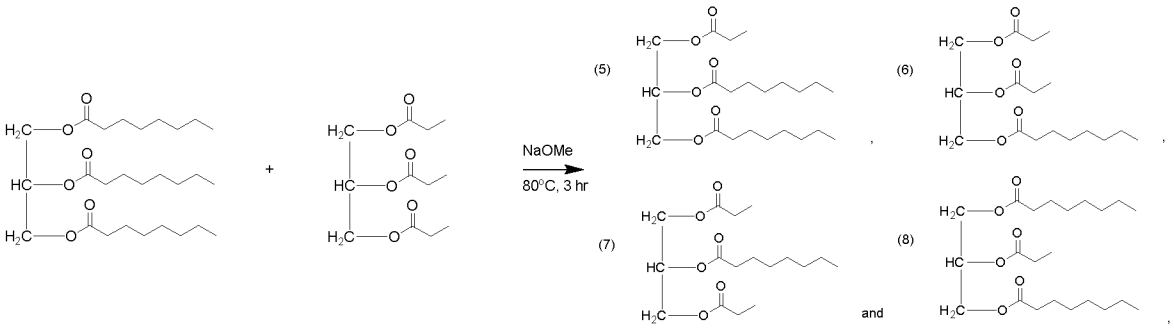
When one or more medium chain fatty acid moiety is present in a triglyceride, the medium chain fatty acid moieties may contain the same or a different number of carbon atoms.

In some embodiments, the one or more medium chain fatty acid moieties contain between 6 and 10 carbon atoms. In a preferred embodiment, the one or more medium chain fatty acid moieties contain 8 carbon atoms (the medium chain fatty acid moieties are octanoate).

The triglycerides of the present invention may be synthesised by, for example, esterification of medium chain FFAs (e.g. hexanoic acid, heptanoic acid, octanoic acid, nonanoic acid, decanoic acid, undecanoic acid, and/or dodecanoic acid) and propionic acid with glycerol. When the medium chain fatty acid moiety is octanoate, the triglyceride may be synthesised by, for example, esterification of octanoic acid and propionic acid with glycerol.

Alternatively, the triglycerides of the present invention may be synthesised by, for example, interesterification between tripropionin and trihexanoin, triheptanoin, tricaprylin, trinonanoin, tricaprin, triundecanoin and/or tridodecanoin. When the medium chain fatty acid moiety is octanoate, the triglyceride may be synthesised by, for example, interesterification between tripropionin and tricaprylin (trioctanoin).

By way of example, a method of obtaining compounds having the formula (5), (6), (7) and (8) is shown below:



A single propionate moiety containing triglyceride may be used herein. Alternatively, a mixture of different propionate moiety containing triglycerides may be used.

Compositions

The present invention provides compositions comprising propionate moiety containing triglycerides referred to herein. The composition may be, for example, a nutritional composition or a dietary supplement.

The expression "nutritional composition" means a composition that nourishes a subject.

In some specific embodiments, the nutritional composition according to the invention is an "enteral nutritional composition" that is to say a foodstuff that involves the gastrointestinal tract for its administration. The gastric introduction may involve the use of a tube through a naso-gastric or oro-gastric tube leading directly to the stomach. This may be used especially in hospitals or clinics.

A "dietary supplement" may be used to complement the nutrition of an individual (it is typically used as such but it might also be added to any kind of compositions intended to be ingested). It may be in the form of tablets, capsules, pastilles or a liquid for example. The supplement may further contain protective hydrocolloids (such as gums, proteins, modified starches), binders, film forming agents, encapsulating agents/materials, wall/shell materials, matrix compounds, coatings, emulsifiers, surface active agents, solubilizing agents (oils, fats, waxes, lecithins etc.), adsorbents, carriers, fillers, co-compounds, dispersing agents, wetting agents, processing aids (solvents), flowing agents, taste masking agents, weighting agents, jellifying agents and gel forming agents. The dietary supplement may also contain conventional pharmaceutical additives and adjuvants, excipients and diluents, including, but not limited to, water, gelatine of any origin, vegetable gums, lignin-sulfonate, talc, sugars, starch, gum arabic, vegetable oils, polyalkylene glycols, flavouring agents, preservatives, stabilizers, emulsifying agents, buffers, lubricants, colorants, wetting agents, fillers, and the like.

When the composition is a supplement, it can be provided in the form of unit doses.

In one embodiment the nutritional composition of the present invention is a fortifier.

The nutritional composition of the invention may contain a protein source, a carbohydrate source and/or a lipid source. In some embodiments however, especially if the composition of the invention is a supplement or a fortifier, there may be only lipids (or a lipid source).

Protein sources based on, for example, whey, casein and mixtures thereof may be used as well as protein sources based on soy. As far as whey proteins are concerned, the protein source may be based on acid whey or sweet whey or mixtures thereof and may include alpha-lactalbumin and beta-lactoglobulin in any desired proportions.

The proteins may be either fully or partially hydrolysed. If hydrolysed proteins are required, the hydrolysis process may be carried out as desired and as is known in the art. For example, whey protein hydrolysates may be prepared by enzymatically hydrolysing the whey fraction in one or more steps.

In one embodiment the proteins of the composition are plant based protein.

The nutritional composition according to the present invention may contain a carbohydrate source. Any carbohydrate source such as lactose, sucrose, saccharose, maltodextrin, starch and mixtures thereof may be used. The nutritional composition of the invention may also contain vitamins and minerals understood to be essential in the daily diet and in nutritionally significant amounts. Minimum requirements have been established for certain vitamins and minerals. Examples of minerals, vitamins and other nutrients optionally present in the composition of the invention include vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B6, vitamin B12, vitamin E, vitamin K, vitamin C, vitamin D, folic acid, inositol, niacin, biotin, pantothenic acid, choline, calcium, phosphorous, iodine, iron, magnesium, copper, zinc, manganese, chlorine, potassium, sodium, selenium, chromium, molybdenum, taurine, and L-carnitine. Minerals are usually added in salt form. The presence and amounts of specific minerals and other vitamins will vary depending on the intended population. If necessary, the nutritional composition of the invention may contain emulsifiers and stabilisers such as soy, lecithin, citric acid esters of mono- and diglycerides, and the like. The nutritional composition of the invention may also contain other substances which may have a beneficial effect such as lactoferrin, osteopontin, TGFbeta, sIgA, glutamine, nucleotides, nucleosides, and the like.

The composition of the invention can further comprise at least one non-digestible oligosaccharide (e.g. prebiotics).

Prebiotics are usually non-digestible in the sense that they are not broken down and absorbed in the stomach or small intestine and thus remain intact when they pass into the colon where

they are selectively fermented by the beneficial bacteria. Examples of prebiotics include certain oligosaccharides, such as fructooligosaccharides (FOS), inulin, xylooligosaccharides (XOS), polydextrose or any mixture thereof. In a particular embodiment, the prebiotics may be fructooligosaccharides and/or inulin. In a specific embodiment, the prebiotics is a combination of FOS with inulin such as in the product sold by BENEO-Orafti under the trademark Orafti® oligofructose (previously Raftilose®) or in the product sold by BENEO-Orafti under the trademark Orafti® inulin (previously Raftiline®). Another example is a combination of 70% short chain fructooligosaccharides and 30% inulin, which is registered by Nestle under the trademark "Prebio 1". The nutritional composition of the invention can also comprise at least one milk oligosaccharide that can be a BMO (bovine milk oligosaccharide) and/or a HMO (human milk oligosaccharide). In a particular embodiment, the nutritional composition according to the invention comprises an oligosaccharide mixture comprising from 0.1 to 4.0 wt% of N-acetylated oligosaccharide(s), from 92.0 to 98.5 wt% of the galacto-oligosaccharide(s) and from 0.3 to 4.0 wt% of sialylated oligosaccharide(s). The composition of the present invention can further comprise at least one probiotic (or probiotic strain), such as a probiotic bacterial strain.

The probiotic microorganisms most commonly used are principally bacteria and yeasts of the following genera: Lactobacillus spp., Streptococcus spp., Enterococcus spp., Bifidobacterium spp. and Saccharomyces spp.

In some particular embodiments, the probiotic is a probiotic bacterial strain. In some specific embodiments, it is Bifidobacteria and/or Lactobacilli.

The composition of the present invention can be in, for example, a solid (e.g. powder), liquid or gelatinous form.

The composition of the present invention can be in, for example, tablet, dragee, capsule, gel cap, powder, granule, solution, emulsion, suspension, coated particle, spray-dried particle, a pill or in the form of a shot e.g., a small serving of liquid that may be consumed quickly, for example in one or more mouthfuls.

The composition may in the form of a pharmaceutical composition and may comprise one or more suitable pharmaceutically acceptable carriers, diluents and/or excipients.

Examples of such suitable excipients for compositions described herein may be found in the “Handbook of Pharmaceutical Excipients”, 2nd Edition, (1994), Edited by A Wade and PJ Weller.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985).

The pharmaceutical compositions may comprise as, or in addition to, the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s) and/or solubilising agent(s). Examples of suitable binders include starch, gelatin, natural sugars such as glucose, anhydrous lactose, free-flow lactose, beta-lactose, corn sweeteners, natural and synthetic gums, such as acacia, tragacanth or sodium alginate, carboxymethyl cellulose and polyethylene glycol.

Examples of suitable lubricants include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Preservatives, stabilisers, dyes and even flavouring agents may be provided in the composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may be also used.

Treatment

It is to be appreciated that all references herein to treatment include curative, palliative and prophylactic treatment. Treatment may also include arresting progression in the severity of a disease.

Both human and veterinary treatments are within the scope of the invention.

Ketones

As discussed above, the compounds and compositions of the invention, which comprise C3 and medium chain fatty acids, are a source of ketones.

In the body, ketones are mainly produced by the liver from fatty acids via ketogenesis. In ketogenesis, medium chain fatty acids are enzymatically broken down via β-oxidation to form acetyl-CoA and “ketone bodies” (water-soluble molecules that contain a ketone group). Octanoate is the most efficient medium chain fatty acid at making ketone bodies via C4 ketogenesis. The three primary ketone bodies are acetoacetate, β-hydroxybutyrate and acetone. Thus in some embodiments, the compounds and compositions of the invention are a source of acetoacetate, β-hydroxybutyrate and/or acetone.

Additionally, β-ketopentanoate, a 5-carbon ketone body, can be produced from propionate via C5 ketogenesis. Heptanoate may also produce ketone bodies (β-ketopentanoate and β-

hydroxypentanoate) via C5 ketogenesis. Providing a source of propionate may additionally increase the rate of C5 ketogenesis by reducing the channelling of the propionyl moiety of heptanoate into anaplerosis of the citric acid cycle (Deng, S., et al., 2009. Journal of Biological Chemistry, 284(41), pp.27799-27807). Thus, the compounds and compositions of the invention may be a source of β-hydroxypentanoate, β-ketopentanoate and/or β-ketopentanoate-CoA.

Ketogenesis can occur in response to an unavailability of blood glucose, for instance during fasting, starving, low carbohydrate diets, prolonged exercise and untreated type 1 diabetes mellitus. In particular, ketogenesis is promoted by a low carbohydrate diet, or a "ketogenic diet". In one embodiment, the composition according to the present invention is for use as part of a low carbohydrate or ketogenic diet.

In one embodiment, the compound or composition according to the present invention is for use in providing ketones to a bodily fluid of a subject.

In one embodiment, the compound or composition according to the present invention is for use in increasing blood ketone levels, and/or treating a disease treatable by increasing blood ketone levels.

Ketone bodies are transported from the liver to other tissues, in particular the brain. Ketones can be transported to the brain by, for example, monocarboxylic transporter 1 (MCT1) where they are mainly metabolised by neurones. Ketone bodies are able to provide a source of energy by reconversion to acetyl-CoA. The brain gets a portion of its fuel requirements from ketone bodies when glucose is less available than normal. The heart can also effectively use ketone bodies.

Free fatty acids and ketones produced from triglycerides described herein can provide an alternative energy source to glucose to supplement or replace the energy in cells such as myocytes, cardiomyocytes, or neuronal cells. Thus, in metabolic conditions, such as cancer, trauma and ischemia, ketone bodies may be beneficial by providing an additional energy source to tissue at risk of cell death (Barañano, K.W. and Hartman, A.L., 2008. Current treatment options in neurology, 10(6), p.410.). For instance, a ketogenic diet (one way of promoting production of ketone bodies) is a therapy for drug-resistant epilepsy and may have therapeutic effects for a range of neurological disorders (Gano, L., Patel, M. and Rho, J.M., 2014. Journal of lipid research, pp.jlr-R048975).

Brain tissue consumes a large amount of energy in proportion to its volume. In an average healthy subject, the brain gets most of its energy from oxygen-dependent metabolism of

glucose. Typically, the majority of the brain's energy is used to help neurons or nerve cells send signals and the remaining energy is used for cell-health maintenance. A deficiency in brain energy, for example caused by impairment of glucose utilisation, can result in neuronal hyperactivity, seizures and cognitive impairments.

Accordingly, the compounds and compositions of the invention may be used to treat deficiency in neurological conditions or diseases. The compounds and compositions of the invention may be used to treat deficiency in brain energy and/or conditions associated with said deficiency.

Examples of brain energy deficiency conditions or diseases include: migraine, memory disorder, age-related memory disorder, brain injury, neurorehabilitation, stroke and post-stroke, amyloid lateral sclerosis, multiple sclerosis, cognitive impairment, cognitive impairment post-intensive care, age-induced cognition impairment, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, inherited metabolic disorders (such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency), bipolar disorder, schizophrenia, and/or epilepsy.

A "neurological condition" refers to a disorder of the nervous system. Neurological conditions may result from damage to the brain, spinal column or nerves, caused by illness or injury. Examples of the symptoms of a neurological condition include paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain and altered levels of consciousness. An assessment of the response to touch, pressure, vibration, limb position, heat, cold, and pain as well as reflexes can be carried out to determine whether the nervous system is impaired in a subject.

In one embodiment, the neurological condition is the result of traumatic damage to the brain.

The terms "cognitive impairment" and "cognition impairment" refer to disorders that give rise to impaired cognition, in particular disorders that primarily affect learning, memory, perception, and/or problem solving. Cognitive impairment may occur in a subject after intensive care. Cognitive impairment may occur as part of the ageing process.

The term "cognition" refers to the set of all mental abilities and processes, including knowledge, attention, memory and working memory, judgment and evaluation, reasoning and "computation", problem solving and decision making, comprehension and production of language.

Levels of and improvements in cognition can be readily assessed by the skilled person using any suitable neurological and cognitive tests that are known in the art, including cognitive tests

designed to assess speed of information processing, executive function and memory. Suitable example tests include Mini Mental State Examination (MMSE), Cambridge Neuropsychological Test Automated Battery (CANTAB), Alzheimer's Disease Assessment Scale-cognitive test (ADAScog), Wisconsin Card Sorting Test, Verbal and Figural Fluency Test and Trail Making Test, Wechsler Memory scale (WMS), immediate and delayed Visual Reproduction Test (Trahan et al. Neuropsychology, 1988 19(3) p. 173-89), the Rey Auditory Verbal Learning Test (RAVLT) (Ivnik, RJ. et al. Psychological Assessment: A Journal of Consulting and Clinical Psychology, 1990 (2): p. 304-312), electroencephalography (EEG), magnetoencephalography (MEG), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), functional Magnetic Resonance Imaging (fMRI), computerised tomography and long-term potentiation.

A ketogenic diet may also have therapeutic effects for metabolic diseases such as glucose transporter type 1 (GLUT-1) deficiency, pyruvate dehydrogenase (PDH) deficiency, phosphofructokinase (PFK) deficiency; and glycogen storage disease including McArdle's disease, in addition to cancer (astrocytomas, prostate and gastric) and cardiac ischemia (Barañano, K.W. and Hartman, A.L., 2008. Current treatment options in neurology, 10(6), p.410.). A ketogenic diet has also been shown to be an effective strategy for management of type two diabetes (Azar, S.T., Beydoun, H.M. and Albadri, M.R., 2016. J Obes Eat Disord, 2(2)).

Accordingly, compounds and compositions of the invention may be used to treat glucose transporter type 1 (GLUT-1) deficiency, pyruvate dehydrogenase (PDH) deficiency, phosphofructokinase (PFK) deficiency; and glycogen storage disease including McArdle's disease and diabetes. The compounds and compositions of the invention may also be used to treat cancer and cardiac ischemia.

Administration

Preferably, the compounds and compositions described herein are administered enterally.

Enteral administration may be oral, gastric, and/or rectal.

In general terms, administration of the combination or composition described herein may, for example, be by an oral route or another route into the gastro-intestinal tract, for example the administration may be by tube feeding.

In a preferred embodiment, administration is oral.

The subject may be a mammal such as a human, canine, feline, equine, caprine, bovine, ovine, porcine, cervine and primates. Preferably the subject is a human.

Further preferred features and embodiments of the present invention will now be described by way of non-limiting examples.

EXAMPLES

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA and immunology, which are within the capabilities of a person of ordinary skill in the art. Such techniques are explained in the literature. See, for example, J. Sambrook, E. F. Fritsch, and T. Maniatis, 1989, Molecular Cloning: A Laboratory Manual, Second Edition, Books 1-3, Cold Spring Harbor Laboratory Press; Ausubel, F. M. et al. (1995 and periodic supplements; Current Protocols in Molecular Biology, ch. 9, 13, and 16, John Wiley & Sons, New York, N.Y.); B. Roe, J. Crabtree, and A. Kahn, 1996, DNA Isolation and Sequencing: Essential Techniques, John Wiley & Sons; J. M. Polak and James O'D. McGee, 1990, In Situ Hybridization: Principles and Practice; Oxford University Press; M. J. Gait (Editor), 1984, Oligonucleotide Synthesis: A Practical Approach, Irl Press; D. M. J. Lilley and J. E. Dahlberg, 1992, Methods of Enzymology: DNA Structure Part A: Synthesis and Physical Analysis of DNA Methods in Enzymology, Academic Press; and E. M. Shevach and W. Strober, 1992 and periodic supplements, Current Protocols in Immunology, John Wiley & Sons, New York, NY. Each of these general texts is herein incorporated by reference.

Example 1 – Preparation of propionated triglycerides (TAG)

Compositions comprising propionated TAG were generated by chemical interesterification between tripropionin and tricaprylin in the presence of sodium methoxide catalyst.

The following steps were used

Reaction

- The tricaprylin (Neobee 895 from Stepan) and the tripropionin were added successively to a multipurpose reactor L2600 at room temperature. 1 litre of tricaprylin was set aside to promote the addition of sodium methoxide.
- Degassing was performed under agitation with nitrogen.
- The reactor was heated to 60 °C.
- Sodium methoxide suspended in 1 litre of tricaprylin was added (whip agitation before adding).
- The mixture was heated to 80 °C under inert atmosphere (nitrogen) for 3h (time counted from 60 °C).

Work-up

- The mixture was cooled below 60 °C.
- The mixture was washed twice with demineralized salt water (10L + 1kg NaCl) until a neutral pH (elimination of sodium methoxide) and then once with 10L of water
- After the last wash and removal of the aqueous layer, the crude resulting oil was dried under vacuum (60 mBar at 60 °C until there was no water left).

Refining

- Addition of 3% of Tonsil Supreme 110 FF in suspension.
- Agitation and heating at 70 °C under vacuum (60 mbar) for 40 min.
- Nitrogen Compensation.
- Filtration of bleaching lands on büchner (Filtrox 8-20 microns).

Deodorizing

- 8 kg discolored product was added to an L800 deodorizer.
- Heating at 100 °C under 2 mbar with steam injection (V water/h = 30 mL/h) for 1h.
- Cool to 60 °C.
- Nitrogen Compensation.
- Filtration.
- Obtained: 6 kg.

The constituents of the triglycerides are shown below in Table 1. These triglycerides are represented by the three fatty acids they contain. These fatty acids are represented by their lipid number: 3:0 for propionate, 8:0 for caprylic acid.

The fatty acid in the middle is located on the position sn-2 in the triglyceride. As an example, 8:0-3:0-8:0 is a triglyceride having both a propionate in position sn-2 and octanoate in position sn-1 and position sn-3.

TAG profile and regioisomers were analyzed by liquid chromatography coupled to high resolution mass spectrometer. Lipid classes' proportion was evaluated by liquid chromatography coupled to high-resolution mass spectrometer with internal standard.

The C3C8 triglyceride composition had good organoleptic properties (no odour).

Table 1. TAG regioisomer profile [g/100 g]

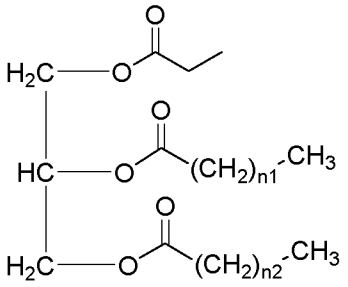
	C3/C8 crude	**C3/C8 after deodo**
TAG	g/100 g TAG	g/100 g TAG
8:0-8:0-3:0	28.55	28.9
8:0-8:0-8:0	19.95	20.6
3:0-3:0-8:0	18.4	18.2

3:0-8:0-3:0	12.57	12.2
8:0-3:0-8:0	9.14	9.4
3:0-3:0-3:0	6.05	5.2
3:0-10:0-8:0	0.91	0.9
3:0-8:0-10:0	0.7	0.7
8:0-3:0-10:0	0.54	0.6
8:0-8:0-10:0	0.53	0.5
3:0-3:0-10:0	0.45	0.5
3:0-10:0-3:0	0.43	0.5
Sum	**98.2**	**98.2**

FA	Total FA	FA	Total FA
8:0	60.6	8:0	61.4
3:0	26.8	3:0	26.0
10:0	1.6	10:0	1.6
4:0	0.5	4:0	0.5
18:1	0.2	18:1	0.3
6:0	0.1	6:0	0.1

CLAIMS

1. A composition comprising a compound having the formula

(1) 

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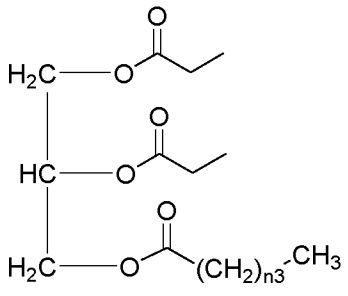
(2) 

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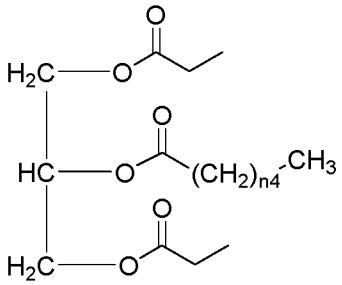
(3) 

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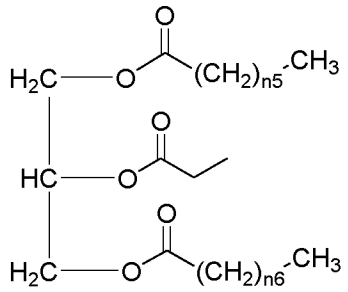
(4) 

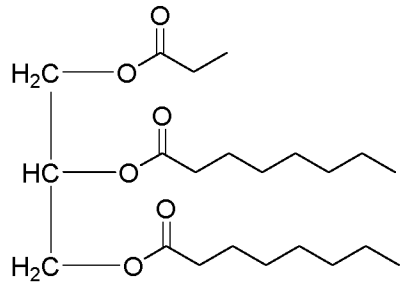
,

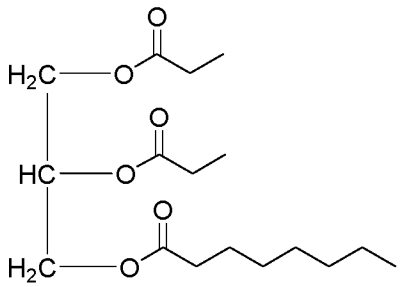
or combinations thereof, wherein n1, n2, n3, n4, n5 and n6 are independently 4 to 10.

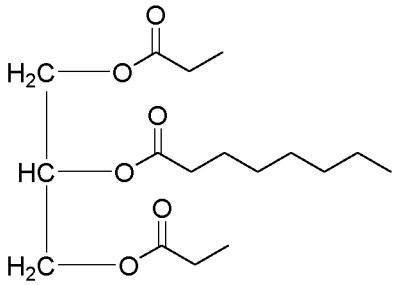
2. A composition according to claim 1, wherein the composition comprises the compound having formula (1), the compound having formula (2), the compound having formula (3) and the compound having formula (4).

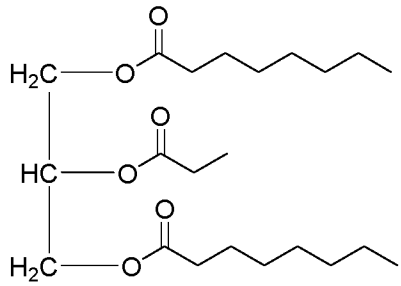
3. A composition according to claims 1 or 2, wherein the compounds having formula (1), (2), (3) and (4), comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total triglycerides of the composition.

4. A composition according to claim 1 comprising a compound having the formula

(5)  ,

(6)  ,

(7)  or

(8)  ,

or combinations thereof.

5. A composition according to claim 4, wherein the composition comprises the compound having formula (5), the compound having formula (6), the compound having formula (7) and the compound having formula (8).

6. A composition according to any one of claims 1 to 5, wherein the compound having formula (5) comprises 20 to 30% by weight of the total triglycerides of the composition, the compound having formula (6) comprises 15 to 25% by weight of the total triglycerides of the composition, the compound having formula (7) comprises 10 to 20% by weight of the total triglycerides of the composition, and the compound having formula (8) comprises 5 to 15% by weight of the total triglycerides of the composition.

7. A composition according to any one of claims 4 to 6, wherein the compounds having formula (5), (6), (7) and (8), comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total triglycerides of the composition, and/or comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99 by weight of the total propionate moiety containing triglycerides in the composition, and/or comprise at least 50%, 60%, 70%, 80%, 90%, 95% or 99% by weight of the total octanoate moiety containing triglycerides in the composition.

8. A composition according to any one of claims 1 to 7 wherein tripropionin comprises less than 10% by weight of the total triglycerides in the composition, preferably less than 8% by weight, more preferable less than 5% by weight of the total triglycerides in the composition.

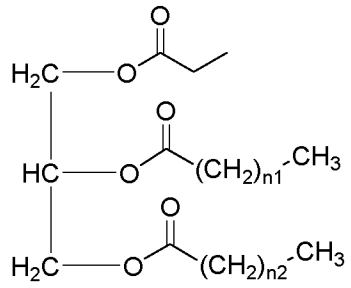
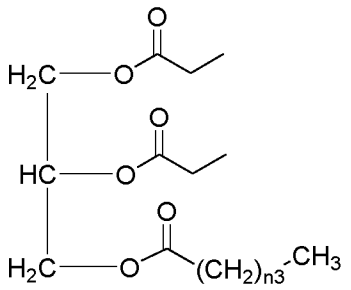
9. A composition according to any one of claims 1 to 8 wherein the composition is a nutritional composition, preferably wherein the composition is a dietary supplement,

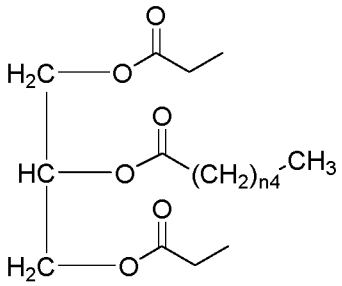
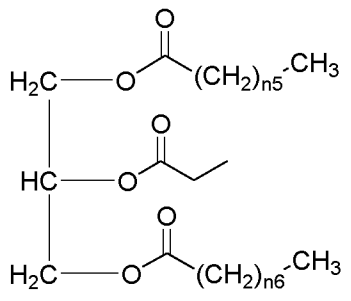
optionally wherein the dietary supplement is in the form of a capsule, tablet, sachet, powder or liquid shot.

10. A composition according to any one of claims 1 to 9 for increasing blood ketone levels, and/or treating a disease treatable by increasing blood ketone levels, preferably wherein the disease is selected from the list consisting of: a brain energy deficiency condition, a neurological condition, migraine, memory disorder, age-related memory disorder, brain injury, stroke, amyloid lateral sclerosis, multiple sclerosis, cognitive impairment, cognitive impairment post-intensive care, age-induced cognition impairment, Alzheimer's disease, Parkinson's disease, Huntingdon's disease, inherited metabolic disorders (such as glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency), depression, schizophrenia, epilepsy, narcolepsy, diabetes, obesity, non-alcoholic fatty liver disease and polycystic ovary syndrome..

11. A composition according to any one of claims 1 to 9 for use in the treatment or prevention of a neurological disease, a metabolic disease, cancer and/or cardiac ischemia.

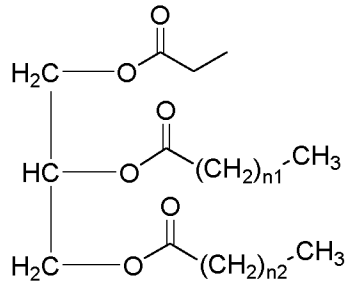
12. A compound having the formula

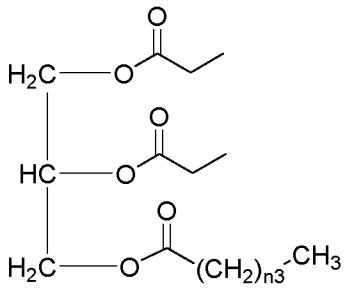
(1)  , (2)  ,

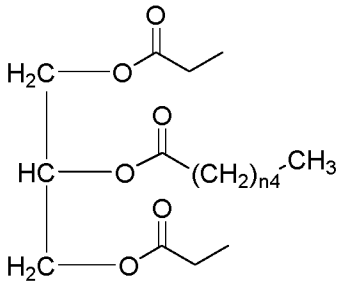
(3)  or (4)  ,

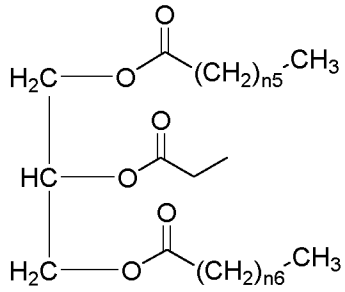
or combinations thereof, for use in increasing blood ketone levels, wherein n1, n2, n3, n4, n5 and n6 are independently 4 to 10.

13. A compound having the formula

(1)  ,

(2)  ,

(3)  or

(4)  ,

or combinations thereof, for use as a medicament, preferably for use in the prevention or treatment of neurological disease, metabolic disease, cancer and/or cardiac ischemia, wherein n1, n2, n3, n4, n5 and n6 are independently 4 to 10.

14. A compound or combinations for use according to claims 12 or 13, wherein n1=6, n2=6, n3=6, n4=6, n5=6, and n6=6.

15. A method for producing a composition of any one of claims 1 to 14, or a compound having the formula (1), (2), (3), (4), (5), (6), (7) or (8) as defined therein, comprising interesterification of tripropionin and one or more triglycerides selected from the list consisting of: trihexanoin, triheptanoin, tricaprylin, trinonanoin, tricaprin, triundecanoin and tridodecanoin, preferably wherein the triglyceride is tricaprylin.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/085520

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L33/12 A61K31/215 A61K31/23 C11C3/04 C11C3/10
C07C69/30 A23D9/00
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 A61K C11C C07C A23D

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 380 544 A (KLEMANN LAWRENCE P [US] ET AL) 10 January 1995 (1995-01-10) examples 2-6	1
X	US 5 434 278 A (PELLOSO TURIDDU A [US] ET AL) 18 July 1995 (1995-07-18) column 3, lines 45-48; example 3	1

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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 :

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

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"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
12 February 2020	21/02/2020

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

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

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JANA ORSAVOVA ET AL: "Fatty Acids Composition of Vegetable Oils and Its Contribution to Dietary Energy Intake and Dependence of Cardiovascular Mortality on Dietary Intake of Fatty Acids", INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES, vol. 16, no. 12, 5 June 2015 (2015-06-05), pages 12871-12890, XP055572713, DOI: 10.3390/ijms160612871 table 1	1
Y	Katrin Augustin ET AL: "Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders", The Lancet Neurology, 1 January 2018 (2018-01-01), pages 84-93, XP055572279, England DOI: 10.1016/S1474-4422(17)30408-8 Retrieved from the Internet: URL:https://www.thelancet.com/pdfs/journals/laneur/PIIS1474-4422(17)30408-8.pdf the whole document	1-15
Y	US 2018/036274 A1 (HENDERSON SAMUEL T [US]) 8 February 2018 (2018-02-08) the whole document	1-15
Y	US 2018/353455 A1 (CUENOUD BERNARD [CH] ET AL) 13 December 2018 (2018-12-13) the whole document	1-15
Y	CAMILLE VANDENBERGHE ET AL: "Tricaprylin Alone Increases Plasma Ketone Response More Than Coconut Oil or Other Medium-Chain Triglycerides: An Acute Crossover Study in Healthy Adults", CURRENT DEVELOPMENTS IN NUTRITION, vol. 1, no. 4, 1 April 2017 (2017-04-01), page e000257, XP055571966, DOI: 10.3945/cdn.116.000257 cited in the application the whole document	1-15
Y	Anonymous: "CAPTEX MCT FOOD FOR THOUGHT", , 1 November 2017 (2017-11-01), XP055573601, Retrieved from the Internet: URL:https://www.abiteccorp.com/media/3167/cognition-brochure-new.pdf [retrieved on 2019-03-25] the whole document	1-15

1 -/--

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CLIFF J. D C. HARVEY ET AL: "The Effect of Medium Chain Triglycerides on Time to Nutritional Ketosis and Symptoms of Keto-Induction in Healthy Adults: A Randomised Controlled Clinical Trial", JOURNAL OF NUTRITION AND METABOLISM, vol. 2018, 1 January 2018 (2018-01-01), pages 1-9, XP055572286, US ISSN: 2090-0724, DOI: 10.1155/2018/2630565 the whole document	1-15
Y	US 2016/374980 A1 (MOCHEL FANNY [FR] ET AL) 29 December 2016 (2016-12-29) paragraph [0050]; claims 1-34	1-15
Y	ALI KHATIBJOO ET AL: "Effects of dietary short- and medium-chain fatty acids on performance, carcass traits, jejunum morphology, and serum parameters of broiler chickens", JOURNAL OF APPLIED ANIMAL RESEARCH, vol. 46, no. 1, 6 July 2017 (2017-07-06), pages 492-498, XP055572379, IN ISSN: 0971-2119, DOI: 10.1080/09712119.2017.1345741 tables 1-7	1-15
Y	TRAN VAN HUNG ET AL: "Short-Chain Fatty Acids Suppress Inflammatory Reactions in Caco-2 Cells and Mouse Colons", JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, vol. 66, no. 1, 26 December 2017 (2017-12-26), pages 108-117, XP055572474, US ISSN: 0021-8561, DOI: 10.1021/acs.jafc.7b04233 the whole document	1-15
A	HENDERSON ET AL: "Ketone Bodies as a Therapeutic for Alzheimer's Disease", NEUROTHERAPEUTICS, ELSEVIER INC, US, vol. 5, no. 3, 1 July 2008 (2008-07-01), pages 470-480, XP023438787, ISSN: 1933-7213, DOI: 10.1016/J.NURT.2008.05.004 [retrieved on 2008-07-12] the whole document	1-15

-/--

1

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 560 944 A1 (NABISCO INC [US]) 22 September 1993 (1993-09-22) paragraphs [0056] - [0058]; claims 1-22; examples 2, 5	1-15
Y	Anonymous: "Salatrim", , 1 January 1997 (1997-01-01), XP055572612, Retrieved from the Internet: URL:http://www.fao.org/3/w6355e/w6355e0w.h tm [retrieved on 2019-03-21] the whole document	1-15
Y	B.L.A. PRABHAVATHI DEVI ET AL: "Enzymatic synthesis of designer lipids", O.C.L. OLEAGINEUX CORPS GRAS LIPIDES., vol. 15, no. 3, 1 May 2008 (2008-05-01), pages 189-195, XP055345460, FR ISSN: 1258-8210, DOI: 10.1051/ocl.2008.0194 the whole document	1-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/085520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5380544 A	10-01-1995	AU 671205 B2	15-08-1996
		BR 9407892 A	19-11-1996
		CA 2156612 A1	15-09-1994
		EP 0687145 A1	20-12-1995
		FI 954144 A	27-09-1995
		IL 108813 A	05-04-1998
		JP H08507566 A	13-08-1996
		KR 960700631 A	24-02-1996
		NZ 262703 A	26-05-1997
		PH 30298 A	20-02-1997
		TW 279788 B	01-07-1996
		US 5380544 A	10-01-1995
		WO 9419961 A1	15-09-1994
US 5434278 A	18-07-1995	AU 670187 B2	04-07-1996
		BR 9405681 A	21-11-1995
		CA 2153411 A1	18-08-1994
		EP 0682689 A1	22-11-1995
		FI 953685 A	30-08-1995
		JP H08506607 A	16-07-1996
		KR 960701180 A	24-02-1996
		NZ 261791 A	24-03-1997
		TW 408107 B	11-10-2000
		US 5434278 A	18-07-1995
		WO 9418290 A1	18-08-1994
US 2018036274 A1	08-02-2018	US 6835750 B1	28-12-2004
		US 8445535 B1	21-05-2013
		US 2013225682 A1	29-08-2013
		US 2018036274 A1	08-02-2018
US 2018353455 A1	13-12-2018	AU 2016363771 A1	26-04-2018
		BR 112018009288 A2	06-11-2018
		CA 3004986 A1	08-06-2017
		CN 108348496 A	31-07-2018
		EP 3383383 A1	10-10-2018
		JP 2018537091 A	20-12-2018
		US 2018353455 A1	13-12-2018
		WO 2017093449 A1	08-06-2017
US 2016374980 A1	29-12-2016	AU 2013358951 A1	02-07-2015
		AU 2018202336 A1	26-04-2018
		BR 112015013349 A2	11-07-2017
		CA 2894456 A1	19-06-2014
		CN 104955450 A	30-09-2015
		EP 2931269 A1	21-10-2015
		ES 2728727 T3	28-10-2019
		HK 1216717 A1	02-12-2016
		IL 239330 A	31-05-2018
		JP 2016504323 A	12-02-2016
		JP 2018131470 A	23-08-2018
		KR 20150095704 A	21-08-2015
		US 2014221482 A1	07-08-2014
		US 2016374980 A1	29-12-2016
		US 2019290610 A1	26-09-2019
		WO 2014093901 A1	19-06-2014
EP 0560944 A1	22-09-1993	AT 181210 T	15-07-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2019/085520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		CA 2097800 A1	08-06-1992
		DE 69131354 D1	22-07-1999
		DE 69131354 T2	27-01-2000
		DK 0560944 T3	10-01-2000
		EP 0560944 A1	22-09-1993
		ES 2136081 T3	16-11-1999
		GR 3031199 T3	31-12-1999
		JP 3504260 B2	08-03-2004
		JP H06506106 A	14-07-1994
		WO 9210105 A1	25-06-1992