

DESCRIPTION

TITLE OF INVENTION: COMPOSITION FOR IMPROVING OR
MAINTAINING ENERGY PRODUCTION OR REDUCING A DECLINE IN
5 ENERGY PRODUCTION

DESCRIPTION

[0001]

10 The present invention relates to a composition for
improving or maintaining energy production or reducing a
decline in energy production. The present invention also
relates to, for example, a method of improving or
maintaining energy production or reducing a decline in
energy production.

15

BACKGROUND ART

[0002]

20 Energy production means production of energy
required by humans and non-human animals to maintain life
activities.

Most of the energy is produced in mitochondria that
are a type of organelles. Sugar, lipids, amino acids, and
other nutrition sources taken from food are metabolized by
glycolysis, pentose phosphate pathway, and citric acid
25 pathway and converted into nicotinamide adenine
dinucleotide (NADH). Then, NADH electrons are transferred
to protein in mitochondrial respiratory chains (electron
transport chains), and energy is produced in the form of
adenosine triphosphate (ATP).

30 A decline in the amount of ATP production is known
to cause various problems. For example, in the case of
humans, such problems include an increase in risk of
developing obesity and diabetes due to reduced metabolic
capacity, muscle strength decline, increase in fatigue,
35 lethargy/decline in concentration, and depression.

[0003]

Maintaining the amount of ATP production is important in fatigue alleviation, maintenance of concentration, muscular exercise, and maintenance of vitality of mind and body.

[0004]

Various agents for increasing energy production have been known which contain substrates required for ATP production such as carbohydrates, amino acids, and lipids. (Patent Literature 1).

[0005]

As described above, the substrates required for ATP production are converted into ATP via mitochondrial electron transport chains. However, a decline in mitochondrial function prevents ATP production regardless of an increase in substrates.

It is known that a decline in mitochondrial function is caused by aging and oxidative stress and results in a decline in the amount of ATP production (Non-Patent Literatures 1 and 2).

[0006]

When a component that reduces a decline in energy production or a decline in mitochondrial function is ingested as a supplement, preferably, the component is in a form that facilitates continuous ingestion by consumers. For example, small tablets and small capsules are desirable particularly for the elderly because swallowing function declines with aging. A supplement tends to be bulky particularly when it contains multiple components, so that it is desirable to use a component that is highly effective even when used in a small amount or a combination of such components in order to reduce the volume of a tablet or capsule.

[0007]

Sesamin is a lignan compound found in sesame and has

been reported as having an antioxidant effect. According to a report using a diabetic mouse model, sesamin has an action that reduces a decline in mitochondrial function by an antioxidant effect (Non-Patent Literature 3). Sesamin
 5 is also known to exert, based on its antioxidant effect, an action that reduces mitochondrial reactive oxygen species production and an action that reduces mitochondrial membrane potential drop (Non-Patent Literature 4). According to another report, sesamin
 10 activates PGC1 α involved in mitochondrial biogenesis (Patent Literature 2).
 [0008]

Astaxanthin is a type of carotenoid and is known to have an antioxidant effect.
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CITATION LIST

- Patent Literature
 [0009]
 Patent Literature 1: JP 2009-215170 A
 20 Patent Literature 2: WO 2018/079719
- Non-Patent Literature
 [0010]
 Non-Patent Literature 1: Conley, Kevin E., et al.
 "Oxidative capacity and ageing in human muscle", The
 25 Journal of physiology 526.1 (2000): 203-210.
- Non-Patent Literature 2: Kudryavtseva, Anna V., et al.
 "Mitochondrial dysfunction and oxidative stress in aging and cancer." Oncotarget 7.29 (2016): 44879.
- Non-Patent Literature 3: Takada, Shingo, et al.
 30 "Sesamin prevents decline in exercise capacity and impairment of skeletal muscle mitochondrial function in mice with high-fat diet-induced diabetes." Experimental physiology 100.11 (2015): 1319-1330.
- Non-Patent Literature 4: Maharjan, Sunita, et al.
 35 "Mitochondrial impairment triggers cytosolic oxidative

stress and cell death following proteasome inhibition."
Scientific reports 4 (2014): 5896.

SUMMARY OF INVENTION

5 - Technical Problem

[0011]

Humans and the like constantly require energy to maintain life activities, so that there is a desire for a highly safe method of promoting production of energy, using a component which can be continuously ingested without concern for side effects. There has been suggested a method of increasing the amount of energy production by ingestion of substrates of energy production, however, its effect is limited in a state of decline in mitochondrial function. While some food components are known to have an action that improves energy production, it is desirable to use a component that exerts its effect even when used in a small amount or to use a combination of such components in terms of easy ingestion and safety for continuous ingestion.

[0012]

The present invention aims to provide a composition effective in improving or maintaining energy production or reducing a decline in energy production, which is highly safe and can be ingested continuously.

- Solution to Problem

[0013]

The present inventors conducted extensive studies to solve the problems described above. They studied components that can be used to improve or maintain energy production or reduce a decline in energy production. As a result, the present inventors found that when a sesamin-class compound and an astaxanthin-class compound are combined at a specific weight ratio, the combination can

improve or maintain energy production or reduce a decline in energy production in a more effective (synergistic) manner than when the sesamin-class compound or the astaxanthin-class compound is used alone.

5 [0014]

The present invention relates to, for example, a composition for improving or maintaining energy production or reducing a decline in energy production described below.

10 (1) A composition for improving or maintaining energy production or reducing a decline in energy production, the composition containing, as active ingredients: a component (A); and a component (B),
the component (A) being a sesamin-class compound,
15 the component (B) being an astaxanthin-class compound,

wherein a weight ratio (A)/(B) of the component (A) in terms of sesamin to the component (B) in terms of astaxanthin is 0.05 to 15.

20 (2) The composition according to (1) above, wherein the composition is for use in suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue.

(3) The composition according to (1) or (2) above,
25 wherein the improving or maintaining energy production or reducing a decline in energy production is mediated by improving or maintaining mitochondrial function or reducing a decline in mitochondrial function.

(4) The composition according to any one of (1) to
30 (3) above, wherein the sesamin-class compound is at least one compound selected from the group consisting of sesamin, episesamin, and metabolites thereof.

(5) The composition according to any one of (1) to
(4) above, wherein the astaxanthin-class compound is at
35 least one compound selected from the group consisting of

astaxanthin and derivatives thereof.

(6) The composition according to any one of (1) to (5) above, wherein the astaxanthin-class compound is derived from a *Haematococcus pluvialis* extract.

5 (7) The composition according to any one of (1) to (6) above, wherein the composition is an oral composition.

(8) The composition according to any one of (1) to (7) above, wherein the composition is a food or beverage.

10 (9) The composition according to any one of (1) to (8) above, wherein the composition is for use on humans with strong feelings of daily fatigue.

(10) The composition according to any one of (1) to (9) above, wherein the composition is for use in combination with exercise.

15 (11) The composition according to any one of (1) to (10) above, wherein the composition is labeled with at least one function claim selected from the group consisting of "facilitating energy production or metabolism", "facilitating cellular energy production or metabolism", "facilitating intracellular mitochondrial
20 energy production or metabolism", "maintaining vigor and vitality", "alleviating age-related fatigue", "alleviating feelings of age-related fatigue", "for those more prone to feelings of fatigue with aging", "alleviating fatigue that is more easily felt with aging", "alleviating fatigue that
25 is felt in daily life", "alleviating feelings of fatigue in daily life", "alleviating general malaise", "alleviating tiredness", "alleviating exhaustion", "alleviating discomfort", "reducing a decline in motivation", and "preventing a decline in muscle
30 function".

(12) A method of improving or maintaining energy production or reducing a decline in energy production, the method including:

35 administering a composition containing a component

(A) and a component (B),

the component (A) being a sesamin-class compound and
the component (B) being astaxanthin-class compound,

wherein a weight ratio ((A)/(B)) of the component
5 (A) in terms of sesamin to the component (B) in terms of
astaxanthin is 0.05 to 15.

(13) Use of a composition for improving or
maintaining energy production or reducing a decline in
energy production, the composition containing a component
10 (A) and a component (B),

the component (A) being a sesamin-class compound and
the component (B) being astaxanthin-class compound,

wherein a weight ratio ((A)/(B)) of the component
(A) in terms of sesamin to the component (B) in terms of
15 astaxanthin is 0.05 to 15.

- Advantageous Effects of Invention

[0015]

The present invention can provide a composition
20 effective in improving or maintaining energy production or
reducing a decline in energy production, which is highly
safe and can be ingested continuously.

DESCRIPTION OF EMBODIMENTS

25 [0016]

A composition for improving or maintaining energy
production or reducing a decline in energy production of
the present invention contains a sesamin-class compound as
a component (A) and an astaxanthin-class compound as a
30 component (B). The composition for improving or
maintaining energy production or reducing a decline in
energy production of the present invention contains the
sesamin-class compound and the astaxanthin-class compound
as active ingredients.

35 Energy production means production of energy

required by humans and non-human animals to maintain life activities.

[0017]

(Component (A): Sesamin-class compound)

5 In the present invention, the term "sesamin-class compound" is a collective term for compounds including sesamin and its analogs. The sesamin-class compound may include one compound alone or two or more compounds. Sesamin is one of main lignan compounds found in sesame.

10 Examples of the sesamin analogs include episesamin and dioxabicyclo[3.3.0]octane derivatives described in JP H04-9331 A. Specific examples of the sesamin-class compound include sesamin, episesamin, sesaminol, episesaminol, sesamol, and sesamolin. Stereoisomers or racemates of

15 these compounds may be used alone or in mixture. In addition, metabolites of the sesamin-class compound (e.g., those described in JP 2001-139579 A) are also sesamin analogs included in the sesamin-class compound of the present invention, and can also be used in the present

20 invention, as long as they exhibit the effect(s) of the present invention. In the present invention, sesamin, episesamin, or any metabolite thereof can be suitably used as the sesamin-class compound. When sesamin and episesamin are used, the ratio thereof is not limited, but

25 the weight ratio of sesamin:episesamin is preferably 1:0.1 to 1:9, more preferably 1:0.3 to 1:3, still more preferably 1:0.5 to 1:2. The embodiment in which the weight ratio of sesamin:episesamin is 1:1 is one of preferred embodiments of the present invention.

30 Examples of the metabolites that can be used as the sesamin-class compound include a compound disclosed in JP 2009-143884 A. Preferred metabolites of sesamin are SC1 ((7 α ,7' α ,8 α ,8' α)-3',4'-methylenedioxy-7,9':7',9-diepoxy lignane-3,4-diol) and SC2 ((7 α ,7' α ,8 α ,8' α)-

35 7,9':7',9-diepoxy lignane-3,3',4,4'-tetraol). A more

preferred metabolite of sesamin is SC1.

[0018]

The sesamin-class compound for use in the present invention is not limited in any way by its form, production method, or the like. For example, when the
5 sesamin-class compound is sesamin, sesamin extracted from sesame oil by a known method (e.g., the method described in JP H04-9331 A) can be used (hereinafter, such sesamin is called a sesamin extract or purified sesamin).
10 Commercially available sesame oil (in liquid form) can also be used as is. However, when sesame oil is used, the characteristic flavor of sesame oil is sometimes evaluated as being organoleptically undesirable. Thus, a tasteless and odorless sesamin extract (or purified sesamin) from
15 sesame oil is preferably used. In addition, since sesame oil has a low sesamin content, use of sesame oil to incorporate a desirable amount of sesamin results in excess volume per unit dose of a composition to be prescribed. This sometimes causes inconvenience in terms
20 of ingestion. In particular, in the case where the composition is formulated for oral administration, the preparation (e.g., tablet or capsule) becomes so bulky that it causes trouble in terms of ingestion. Thus, use of a sesamin extract (or purified sesamin) from sesame oil
25 is preferred in terms of low intake. The sesamin-class compound can also be obtained by synthesis. For example, sesamin and episesamin can be synthesized by the method of Beroza et al. (J. Am. Chem. Soc., 78, 1242 (1956)). The sesamin-class compound can also be produced by the method
30 disclosed in JP 2009-143884 A, for example.

[0019]

(Component (B): Astaxanthin-class compound)

In the present invention, the term "astaxanthin-class compound" is a collective term for compounds
35 including astaxanthin and its derivatives. The

astaxanthin-class compound may include one compound alone or two or more compounds.

Astaxanthin (3,3'-dihydroxy- β,β -carotene-4,4'-dione) is a type of carotenoid, and is a red pigment contained in
5 crustaceans such as shrimp and crab, fish such as salmon and sea bream, algae such as green alga *Haematococcus*, and yeasts such as the red yeast *Phaffia*.

Astaxanthin has three types of isomers, 3S, 3'S-form, 3S, 3'R-form (meso form), and 3R, 3'R-form,
10 depending on the steric configuration of the hydroxyl group at position 3(3') of the ring structures at both ends of the molecule. Astaxanthin also has cis and trans geometric isomers of conjugated double bonds at the center of the molecule. Specific examples of the geometric
15 isomers include all-cis-isomers, 9-cis isomers, and 13-cis isomers. Astaxanthin may include any one of these compounds or two or more of these compounds.

[0020]

Derivatives of astaxanthin are not limited as long
20 as they are compounds in which a substituent or the like is bonded to a functional group of astaxanthin. Examples include esters.

The hydroxy group at position 3(3') of astaxanthin can form an ester with a fatty acid. Esters of
25 astaxanthin include monoesters and diesters.

Hydrolysis of an ester of astaxanthin produces astaxanthin.

The fatty acid to form the ester is not limited but preferably has a carbon number of 1 to 30.

30 In the present invention, the astaxanthin-class compound is preferably astaxanthin or an ester of astaxanthin.

[0021]

The astaxanthin-class compound for use in the
35 present invention is not limited in any way by its form,

production method, or the like. Any natural or synthetic astaxanthin-class compound can be used.

Examples of the natural astaxanthin-class compound include astaxanthin-class compound-containing extracts
 5 obtained from algae such as *Haematococcus*; yeasts such as *Phaffia*; crustaceans such as shrimp, krill and crab; cephalopods such as squid and octopus; various fish and shellfish; plants such as *Adonis*; bacteria such as *Paracoccus* sp. N81106, *Brevundimonas* sp. SD212, and
 10 *Erythrobacter* sp. PC6; actinomycetes such as *Gordonia* sp. KANMONKAZ-1129; Labyrinthulomycetes such as *Schizochytrium* sp. KH105; fungi such as *Blakeslea trispora*; genetically modified astaxanthin-producing organisms; and the like. Examples also include
 15 astaxanthin-class compounds suitably purified from such astaxanthin-class compound-containing extracts. Preferred are astaxanthin-class compounds derived from microalgae extracts obtained from microalgae such as *Haematococcus*, and an astaxanthin-class compound derived from fungal
 20 extracts obtained from fungi such as *Blakeslea trispora*. More preferred are astaxanthin-class compounds derived from *Haematococcus pluvialis* extracts obtained from *Haematococcus pluvialis*.

Examples of the synthetic astaxanthin-class compound
 25 include AstaSana (DSM) and Lucantin Pink® (BASF).

Examples of synthetic astaxanthin-class compounds chemically converted from other natural carotenoids include AstaMarine (PIVEG).

[0022]

30 Examples of *Haematococcus pluvialis* from which natural astaxanthin-class compounds are obtainable include *Haematococcus pluvialis*, *Haematococcus lacustris*, *Haematococcus capensis*, *Haematococcus deroebakensis*, and *Haematococcus zimbabweensis*.

35 [0023]

The *Haematococcus pluvialis* may be cultured by any method. A closed culture method is preferred in which there is no risk of contamination by heterogeneous microorganisms or proliferation of heterogeneous microorganisms with only slight contamination by other contaminants. Examples of such a culture method include a culture method that uses a partially open domed, conical, or cylindrical culture device and a medium culture including a gas jet unit freely movable within the device (WO 1999/050384); a method in which dry stress is applied to *Haematococcus pluvialis* to induce cyst formation of the algae, and astaxanthin is extracted from the culture of the algae in the form of cysts (JP H08-103288 A); a method in which a light source is placed in a closed culture device to illuminate the culture medium from the inside; and a method that uses a flat plate-shaped culture tank or a tubular culture tank.

[0024]

The astaxanthin-class compound that can be used in the present invention may be, for example, an astaxanthin-class compound-containing extract obtained by crushing cell walls of the above-described *Haematococcus pluvialis* as needed by a method disclosed in JP H05-068585 A or the like and adding an organic solvent such as acetone, ether, chloroform, or alcohol (e.g., ethanol or methanol) or another extraction solvent or solvent such as carbon dioxide in supercritical state for extraction; or a product obtained by suitably purifying the astaxanthin-class compound-containing extract. Such an astaxanthin-class compound-containing extract or a purified product thereof may be added to the composition. The astaxanthin-class compound content of the astaxanthin-class compound-containing extract is preferably 3 to 40 wt%, more preferably 3 to 12 wt%, still more preferably 5 to 10 wt%.

[0025]

In the present invention, the astaxanthin-class compound may be a commercial product. Examples of the commercial product include AstaReal, Astavita, and Astamate series (all the products are trademark registered; AstaReal, Fuji Chemical Industries Co., Ltd.) such as AstaReal Oil 200SS (a fat-soluble extract from *Haematococcus pluvialis*, containing about 20% astaxanthin-class compound (free base)), AstaReal L10, AstaReal Oil 50F, AstaReal Oil 50FC, AstaReal Oil 5F, AstaReal P2AF, AstaTROL-X, AstaReal Oil 50FC, AstaReal Powder 20F, water-soluble AstaReal liquid, AstaReal WS liquid, AstaReal 10WS liquid, AstaReal ACT, Astavita e, Astavita Sport, and Astamate; ASTOTS series (all the ASTOTS products are trademark registered; FUJIFILM Wako Pure Chemical Corporation) such as ASTOTS-S, ASTOTS-100, ASTOTS-ECS, ASTPTS-2.0PW, and ASTOTS-3.0MB; BioAstin (registered trademark; Cyanotech Corporation); Astazine TM (BGG Japan); astaxanthin powder 1.5%, astaxanthin powder 2.5%, astaxanthin oil 5%, astaxanthin oil 10% (Bio Actives Japan Corporation); astaxanthin (Oryza Co., Ltd.); Sunactive AX (registered trademark; Taiyo Kagaku Co., Ltd.); *Haematococcus* WS30 (Yaegaki Biotechnology, Inc.); and AstaMarine (PIVEG).

[0026]

The sesamin-class compound and the astaxanthin-class compound are found in natural products and food and beverages. They are compounds with a long history of consumption and recognized as being highly safe. Thus, the sesamin-class compound and the astaxanthin-class compound are suitable for continuous ingestion and long-term ingestion.

[0027]

The composition of the present invention contains a sesamin-class compound (component (A)) and an astaxanthin-class compound (component (B)) as active ingredients, and

the weight ratio ((A)/(B)) of the component (A) (in terms of sesamin) to the component (B) (in terms of astaxanthin) is 0.05 to 15.

5 A combination of the sesamin-class compound and the astaxanthin-class compound at the above weight ratio results in a remarkably excellent effect in improving or maintaining energy production or reducing a decline in energy production.

10 The weight ratio of the component (A) (in terms of sesamin) to the component (B) (in terms of astaxanthin) is preferably 0.08 to 12, more preferably 0.1 to 12, still more preferably 0.12 to 10, particularly preferably 0.15 to 9.

15 When the sesamin-class compound is a compound other than sesamin, the amount "in terms of sesamin" means the amount of the compound converted into the amount of sesamin. More specifically, herein, when the sesamin-class compound is sesamin, the amount in terms of sesamin or any expression similar to this means the amount of
20 sesamin; and when the sesamin-class compound is a compound other than sesamin, it means a value obtained by multiplying the molar number of the compound by the molecular weight of sesamin.

25 When the astaxanthin-class compound is a compound other than astaxanthin, the amount "in terms of astaxanthin" means the amount of the compound converted into the amount of astaxanthin. More specifically, herein, when the astaxanthin-class compound is astaxanthin, the amount in terms of astaxanthin or any
30 expression similar to this means the amount of astaxanthin; and when the astaxanthin-class compound is a compound other than astaxanthin, it means a value obtained by multiplying the molar number of the compound by the molecular weight of astaxanthin.

35 The sesamin-class compound content and the

astaxanthin-class compound content of the composition can be measured by high-performance liquid chromatography (HPLC).

When the astaxanthin-class compound is a derivative
5 of astaxanthin, the derivative can be quantified as astaxanthin by subjecting the derivative to hydrolysis or the like.

[0028]

Most of the energy production in living organisms is
10 carried out in mitochondria. Improving or maintaining mitochondrial function or reducing a decline in mitochondrial function results in an effect of improving or maintaining energy production or reducing a decline in energy production.

15 The composition of the present invention for improving or maintaining energy production or reducing a decline in energy production can be used, for example, to improve or maintain energy production or reduce a decline in energy production by improving or maintaining
20 mitochondrial function or reducing a decline in mitochondrial function.

The composition of the present invention can also activate the energy metabolism by improving or maintaining mitochondrial function or reducing a decline in
25 mitochondrial function.

In one embodiment, the composition of the present invention can be used as a composition for improving or maintaining energy production or reducing a decline in energy production, which is mediated by improving or
30 maintaining mitochondrial function or reducing a decline in mitochondrial function. In one embodiment, the composition of the present invention can be used to improve or maintain energy production capacity or reduce a decline in energy production capacity.

35 [0029]

Improving or maintaining mitochondrial function and/or energy production or reducing a decline in mitochondrial function and/or energy production is effective in suppressing, alleviating, or reducing fatigue.

Herein, the term "fatigue" means a decline in physical and/or mental activity capacity due to physical or mental causes (a decline in activity capacity caused by mental and physical overload). Fatigue is usually associated with feelings of fatigue (self-awareness of fatigue, e.g., discomfort and reduced motivation for activities) and the like. The term "anti-fatigue" refers to suppressing, alleviating, or reducing fatigue. The term "suppressing fatigue" encompasses increasing resistance to fatigue, preventing fatigue (including reducing risks in a subject at risk of fatigue), and the like. The term "alleviating fatigue" encompasses alleviating fatigue symptoms (e.g., feelings of fatigue) and the like. The term "reducing fatigue" encompasses helping recovery from fatigue, reducing fatigue symptoms, and the like.

The energy production tends to decrease, particularly with aging. This results in susceptibility to fatigue, slow recovery from fatigue, and constant feelings of fatigue. The composition of the present invention can be preferably used to suppress, alleviate, or reduce age-related fatigue or feelings of age-related fatigue by improving or maintaining mitochondrial function and/or energy production or reducing a decline in mitochondrial function and/or energy production. Examples of the age-related fatigue or feelings of age-related fatigue include fatigue or feelings of fatigue that is more easily felt in daily life with aging. In one embodiment, the composition of the present invention can be preferably used to suppress, alleviate, or reduce

feelings of age-related fatigue.

The composition of the present invention can be used to suppress, alleviate, or reduce physical and/or mental fatigue that is more easily felt with aging; to suppress,
5 alleviate, or reduce feelings of physical and/or mental fatigue that is more easily felt with aging; and to suppress, alleviate, or reduce fatigue that is more easily felt in daily life with aging. In particular, the composition can be preferably used to suppress, alleviate,
10 or reduce fatigue and/or feelings of fatigue that is more easily felt in daily life with aging.

[0030]

Use of the sesamin-class compound and the astaxanthin-class compound at the above weight ratio can
15 synergistically enhance the action that improves or maintains energy production or reduces a decline in energy production or the action that improves or maintains mitochondrial function or reduces a decline in mitochondrial function. When the sesamin-class compound
20 and the astaxanthin-class compound in combination at the above weight ratio are used as active ingredients for improving or maintaining energy production or reducing a decline in energy production or as active ingredients for suppressing, alleviating, or reducing age-related fatigue
25 or feelings of age-related fatigue, the above actions can be exerted even when the active ingredients are used in low doses. Thus, the intake of the active ingredients can be reduced. A reduction in intake leads to easy ingestion, making it possible to obtain, for example, an
30 anti-fatigue composition that further facilitates continuous ingestion and a composition for improving or maintaining energy production or reducing a decline in energy production.

[0031]

35 Herein, the energy production may be evaluated by

any method as long as it is evaluated based on common knowledge in the technical field to which the present invention belongs to. For example, an extracellular flux analyzer may be used to continuously measure the measurement target, i.e., the oxygen consumption rate (OCR) of mitochondria during ATP synthesis in cells, while ATP synthase inhibitors (e.g., oligomycin and rotenone) and an uncoupler (e.g., carbonyl cyanide-p-trifluoromethoxy phenylhydrazone (FCCP)) are added thereto. Thereby, the energy production can be evaluated. Evaluation items such as basal respiration, ATP production, and maximal respiration, which are major indices for evaluation of energy production, are analyzed, whereby the energy production can be evaluated. The above evaluation can also be used to evaluate mitochondrial function.

[0032]

The composition of the present invention can be provided in the form of a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like. The composition of the present invention may be a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like by itself for improving or maintaining energy production or reducing a decline in energy production or for suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue; or the composition of the present invention may be a material, a preparation, or the like that is added thereto.

For example, the composition of the present invention may be provided as an agent or the like, but it is not limited thereto. The agent can be directly provided as a composition or can be provided as a composition containing the agent.

The composition of the present invention may be an

oral composition or a parenteral composition, preferably an oral composition. The oral composition may be a food or beverage, an oral pharmaceutical product, an oral quasi-pharmaceutical product, or feed, preferably a food or beverage or an oral pharmaceutical product, more preferably a food or beverage.

[0033]

The composition of the present invention may contain optional additives and optional components, in addition to the sesamin-class compound and the astaxanthin-class compound, as long as the effect(s) of the present invention is not impaired. Such additives and components can be selected according to the composition form or the like. Those that can be generally used in foods, beverages, pharmaceutical products, quasi-pharmaceutical products, feed, and the like can be used. When the composition of the present invention is provided as a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like, any common method can be used for production.

[0034]

For example, when the composition of the present invention is provided as a food or beverage, a component usable in food and beverages (e.g., a food material or an optional food additive) can be added to at the sesamin-class compound and the astaxanthin-class compound to provide various types of foods or beverages. Non-limiting examples of the foods or beverages include general foods and beverages, health foods, health beverages, foods with function claims, foods for specified health uses, health supplements, and foods and beverages for the sick. The health foods, the foods with function claims, the foods for specified health uses, the health supplements, and the like can be used, for example, in various forms of preparations such as fine granules, tablets, granules,

powders, capsules, chewable tablets, dry syrups, syrups, liquids, beverages, and liquid foods.

[0035]

When the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, for example, a pharmacologically acceptable carrier, an optional additive, or the like can be added to the sesamin-class compound and the astaxanthin-class compound to provide various dosage forms of pharmaceutical products or quasi-pharmaceutical products. Such a carrier, an additive, or the like may be any pharmacologically acceptable one that can be used in pharmaceutical products or quasi-pharmaceutical products. Examples thereof include excipients, binders, disintegrants, lubricants, antioxidants, and colorants. One or more of these can be used. The form of administration (ingestion) of the pharmaceutical product or quasi-pharmaceutical product may be an oral or parenteral (transdermal, transmucosal, or enteral administration, injection, or the like). When the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, it is preferably an oral pharmaceutical product or an oral quasi-pharmaceutical product. Examples of the dosage forms of preparations for oral administration include liquids, tablets, powders, fine granules, granules, sugar-coated tablets, capsules, suspensions, emulsions, and chewable tablets. The pharmaceutical product may be for non-human animals.

[0036]

When the composition of the present invention is provided as feed, the sesamin-class compound and the astaxanthin-class compound are simply added to feed. The feed includes feed additives. Examples of the feed include livestock feed for animals such as cows, pigs,

chickens, sheep, and horses; feed for small animals such as rabbits, rats, and mice; and pet food for animals such as dogs, cats, and birds.

[0037]

5 The sesamin-class compound of the composition of the present invention is not limited and can be set according to the form of the composition or the like.

 The total sesamin-class compound content (in terms of sesamin) of the composition of the present invention is
10 preferably 0.001 wt% or more, more preferably 0.01 wt% or more, still more preferably 0.05 wt% or more, and is preferably 10 wt% or less, more preferably 5 wt% or less.

 In one embodiment, the total sesamin-class compound content (in terms of sesamin) is preferably 0.001 to 10
15 wt%, more preferably 0.01 to 10 wt%, still more preferably 0.05 to 5 wt%.

[0038]

 The total astaxanthin-class compound of the composition of the present invention is not limited and
20 can be set according to the form of the composition or the like.

 The total astaxanthin-class compound content (in terms of astaxanthin) of the composition of the present invention is preferably 0.001 wt% or more, more preferably
25 0.01 wt% or more, still more preferably 0.05 wt% or more, and is preferably 10 wt% or less, more preferably 5 wt% or less.

 In one embodiment, the total astaxanthin-class compound content (in terms of astaxanthin) is preferably
30 0.001 to 10 wt%, more preferably 0.01 to 10 wt%, still more preferably 0.05 to 5 wt%.

[0039]

 Preferably, the composition of the present invention is orally ingested (orally administered). The
35 administration amount (intake) of the composition of the

present invention is not limited. The administration amount of the composition of the present invention may be any amount that produces an effect of improving or maintaining energy production or reducing a decline in
5 energy production, an effect of improving or maintaining mitochondrial function or reducing a decline in mitochondrial function, and/or an effect of suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue. The administration amount may be
10 appropriately set according to the administration form, administration method, body weight of a subject, and the like.

[0040]

In one embodiment, when a human (adult) is subjected
15 to oral ingestion or administration of the composition of the present invention, the total administration amount of the sesamin-class compound in terms of sesamin is preferably 0.5 mg or more, more preferably 1 mg or more, still more preferably 3 mg or more, and is preferably 200
20 mg or less, more preferably 100 mg or less, still more preferably 80 mg or less per 60 kg body weight per day. The total administration amount of the astaxanthin-class compound in terms of astaxanthin is preferably 0.5 mg or more, more preferably 1 mg or more, still more preferably
25 3 mg or more, and is preferably 200 mg or less, more preferably 100 mg or less, still more preferably 80 mg or less per 60 kg body weight per day.

In one embodiment, in the case of a human (adult), the total administration amount of the sesamin-class
30 compound in terms of sesamin is preferably 0.5 to 200 mg, more preferably 1 to 100 mg, still more preferably 3 to 80 mg per 60 kg body weight per day. In one embodiment, preferably, sesamin and/or episesamin in the total administration amount of preferably 0.5 to 200 mg, more
35 preferably 1 to 100 mg, still more preferably 3 to 80 mg

per 60 kg body weight per day is orally ingested by or administered to a human (adult).

In the case of a human (adult), the total administration amount of the astaxanthin-class compound in
5 terms of astaxanthin is preferably 0.5 to 200 mg, more preferably 1 to 100 mg, still more preferably 3 to 80 mg per 60 kg body weight per day.

Preferably, the compounds in the above amounts are ingested or administered in one or more portions per day,
10 for example, in one to several portions (e.g., two or three portions) per day.

In one embodiment, preferably, the sesamin-class compound and the astaxanthin-class compound in the above amounts are orally ingested by or administered to a human.

15 In one embodiment, the composition of the present invention can be used to subject a human to ingestion or administration of the sesamin-class compound and the astaxanthin-class compound in the above amounts per 60 kg body weight per day.

20 When the composition contains two or more sesamin-class compounds, the total administration amount of the sesamin-class compound means the total amount of these compounds. When the composition contains two or more astaxanthin-class compounds, the total administration
25 amount of the astaxanthin-class compound means the total amount of these compounds.

[0041]

Preferably, the composition of the present invention is continuously ingested or administered. The above
30 effect(s) is likely to be enhanced when the sesamin-class compound and the astaxanthin-class compound are continuously ingested or administered. In one embodiment, preferably, the composition of the present invention is continuously ingested or administered for preferably one
35 week or more, more preferably four weeks or more, still

more preferably eight weeks or more, particularly preferably 12 weeks or more.

[0042]

The subject (administration subject) subjected to
5 ingestion or administration of the composition of the present invention is not limited. Examples include humans and non-human animals. Examples of the non-human animals include industrial animals, pets, and laboratory animals. Specifically, the term "industrial animals" refers to
10 animals that are bred for industrial purposes. Examples include farm animals such as cows, horses, pigs, goats, and sheep; poultry such as chickens, ducks, quails, turkeys, and ostriches; and fish such as yellowtail, young yellowtail, red seabream, Japanese horse mackerel, carp,
15 rainbow trout, and eel. The term "pets" refers to pet animals or companion animals such as dogs, cats, common marmosets, birds, and hamsters. The term "laboratory animals" refers to mice, rats, guinea pigs, beagles, miniature pigs, rhesus monkeys, crab-eating monkeys, and
20 other animals that are used in research in fields of medicine, biology, agronomy, pharmacy, and the like.

[0043]

The administration subject of the composition of the present invention is preferably a human or non-human
25 mammal, more preferably a human.

In one embodiment, examples of the administration subject include those needing or wanting to improve or maintain energy production or reduce a decline in energy production, those needing or wanting to improve or
30 maintain mitochondrial function or reduce a decline in mitochondrial function, those needing or wanting to suppress, alleviate, or reduce age-related fatigue or feelings of age-related fatigue, those with feelings of age-related fatigue, those more prone to feelings of
35 fatigue with aging, those feeling general malaise,

tiredness, or exhaustion, and those with strong feelings of daily fatigue. As described above, aging is known to cause a decline in mitochondrial function and a decline in energy production. In one embodiment, preferably, subjects of the composition of the present invention are middle-aged people. The composition of the present invention may be an anti-fatigue composition for middle-aged people (preferably, the elderly) for age-related fatigue or feelings of age-related fatigue, a composition for suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue, or a composition for improving or maintaining energy production or reducing a decline in energy production. The middle-aged people may be people who are 40 years old and older, for example. The term "middle-aged people" encompasses the elderly. The elderly may be people who are 60 years old and older or 65 years old and older. The composition of the present invention can also be used on healthy people, for example, in order to produce the effect of improving or maintaining mitochondrial function or reducing a decline in mitochondrial function, the effect of improving or maintaining energy production or reducing a decline in energy production, or the effect of suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue. In one embodiment, the composition of the present invention is preferably used on humans with strong feelings of daily fatigue.

[0044]

Use of the composition of the present invention in combination with adequate exercise further enhances the effect of suppressing, alleviating, or reducing fatigue or feelings of fatigue. In one embodiment, the composition of the present invention is preferably used in combination with exercise.

[0045]

To the composition of the present invention may be attached one or more labels indicating, for example, "facilitating energy production or metabolism", "facilitating cellular energy production or metabolism",
5 "facilitating intracellular mitochondrial energy production or metabolism", "maintaining vigor and vitality", "alleviating age-related fatigue", "alleviating feelings of age-related fatigue", "for those more prone to feelings of fatigue with aging", "alleviating fatigue that
10 is more easily felt with aging", "alleviating fatigue that is felt in daily life", "alleviating feelings of fatigue in daily life ", "alleviating general malaise", "alleviating tiredness", "alleviating exhaustion", "alleviating discomfort", "reducing a decline in
15 motivation", and "preventing a decline in muscle function". The energy production may be intracellular or mitochondrial energy production. In one embodiment of the present invention, preferably, the composition of the present invention is a food or beverage to which one or
20 more labels described above are attached. The labels may indicate use for obtaining these functions. The labels may be attached to the composition itself or to a container or package of the composition.

[0046]

25 The present invention also encompasses use of a sesamin-class compound and an astaxanthin-class compound to produce a composition for improving or maintaining energy production or reducing a decline in energy production. In the use, the weight ratio of the sesamin-
30 class compound (in terms of sesamin) to the astaxanthin-class compound (in terms of astaxanthin) is 0.05 to 15.

[0047]

The present invention also encompasses the following methods:

35 a method of suppressing, alleviating, or reducing

fatigue; and a method of improving or maintaining energy production or reducing a decline in energy production, each method including:

administering a composition containing a component
5 (A) and a component (B), the component (A) being a
sesamin-class compound and the component (B) being
astaxanthin-class compound, wherein a weight ratio
((A)/(B)) of the component (A) in terms of sesamin to the
component (B) in terms of astaxanthin is 0.05 to 15.
10 [0048]

The present invention also encompasses the following
uses:

use of the following composition for improving or
maintaining energy production or reducing a decline in
15 energy production; and use of the following composition
for suppressing, alleviating, or reducing age-related
fatigue or feelings of age-related fatigue,

the composition containing a component (A) and a
component (B),

20 the component (A) being a sesamin-class compound and
the component (B) being astaxanthin-class compound,
wherein a weight ratio ((A)/(B)) of the component (A) in
terms of sesamin to the component (B) in terms of
astaxanthin is 0.05 to 15.

25 The above methods and uses may be therapeutic or
non-therapeutic.

Administering the above composition to a subject can
improve or maintain mitochondrial function or reduce a
decline in mitochondrial function. Administering the
30 above composition to the subject results in an effect of
improving or maintaining energy production or reducing a
decline in energy production or an effect of suppressing,
alleviating, or reducing age-related fatigue or feelings
of age-related fatigue.

35 [0049]

In the above uses and methods, the sesamin-class compound, the astaxanthin-class compound, and preferred embodiments thereof including features such as the ratio thereof are as described above for the composition of the present invention.

The composition of the present invention may include one or more sesamin-class compounds and one or more astaxanthin-class compounds.

In the above uses, preferably, the composition is administered to (ingested by) the subject at least once a day, for example, one to several times (e.g., two to three times) a day. In the uses, preferably, the composition is orally administered (orally ingested). The above uses are preferably for humans or non-human mammals, more preferably for humans.

[0050]

The above uses only require use of at least one sesamin-class compound and at least one astaxanthin-class compound in amounts (effective amounts) that produce a desirable effect(s). Preferred administration amounts, administration subjects, and the like of the sesamin-class compound and the astaxanthin-class compound are as described above for the composition of the present invention.

[0051]

Herein, in each numerical range defined by the lower limit and the upper limit, i.e., "the lower limit to the upper limit", the lower limit and the upper limit are inclusive. For example, the range defined by "1 to 2" means 1 or more and 2 or less, with 1 and 2 being inclusive. Herein, the range may be any combination of any upper limit and any lower limit.

All the academic literature and patent literature described in this description are incorporated herein by reference.

EXAMPLES

[0052]

The present invention is more specifically described
5 below with reference to examples. The present invention
is not limited to these examples.

[0053]

<Evaluation test on energy production by sesamin
metabolite and astaxanthin>

10 A sesamin metabolite, SC1 ($(7\alpha, 7'\alpha, 8\alpha, 8'\alpha)-3', 4'$ -
methylenedioxy-7,9':7',9-diepoxy lignane-3,4-diol), was
used as the sesamin-class compound.

Blakeslea trispora-derived astaxanthin (Sigma-
Aldrich) was used as the astaxanthin.

15 A culture medium of TIG-3 cells (human fetal
pulmonary fibroblasts) was prepared by adding 10% fetal
bovine serum (SIGMA, 172012-500 mL) and 1% antibiotic-
antimycotic mixed stock solution (Nacalai Tesque, Inc.,
02892-54) to MEM high glucose (Nacalai Tesque, Inc.,
20 08458-45), unless otherwise specified.

[0054]

(Example 1)

In order to study actions on energy production, TIG-
3 cells were seeded onto a 6-well plate and cultured at
25 37°C with CO₂ (5%) for three weeks in a medium containing
250 nM sesamin metabolite (hereinafter also described as
SC1) and 890 nM astaxanthin (hereinafter also described as
Asta). TIG-3 cells were seeded at 2.0×10^5 cells/well
when passaged on day 3 after the start of culturing, or at
30 1.0×10^5 cells/well when passaged on day 4 after the
start of culturing and cultured for three weeks. After
three weeks, the cells were seeded onto a plate for XF
analyzer and cultured at 37°C with CO₂ (5%) for 24 hours.
Subsequently, the medium was replaced by a medium for
35 analysis, and the oxygen consumption rate (pmol/min) was

analyzed using an analyzer (XF analyzer, Agilent). After analysis, the nuclei were stained with Hoechst He. The cells were photographed by a fluorescence microscope "BZ-x" (Keyence Corporation), and the number of cells was counted by image analysis. The amount of ATP production, which indicates mitochondrial function, can be evaluated by measuring the amount of decrease in oxygen consumption rate of the living cells by the XF analyzer.

Specifically, an ATP synthase inhibitor (oligomycin) was added to the wells after the oxygen consumption rate of basal respiration of the living cells in the wells was measured. Then, the amount of decrease in oxygen consumption rate (pmol/min/ 10^2 cells) due to addition of oligomycin was measured. The result was regarded as the amount of ATP production. The basal respiration indicates cellular energy demand at baseline. A part of the basal respiration is used for ATP production. The amount of decrease in oxygen consumption rate by addition of oligomycin indicates the amount of ATP production. Table 1 shows the results. The weight ratio of SC1 in terms of sesamin to the astaxanthin in the medium used in Example 1 (hereinafter also described as the weight ratio of SC1 in terms of sesamin/astaxanthin) was 0.17.

[0055]

(Comparative Example 1)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had a sesamin metabolite (SC1) concentration of 250 nM and contained no astaxanthin. Table 1 shows the results.

[0056]

(Comparative Example 2)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had an astaxanthin concentration of 890 nM and contained no sesamin metabolite (SC1). Table 1 shows the results.

[0057]

(Example 2)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had a sesamin metabolite (SC1) concentration of 1 μ M and an astaxanthin concentration of 350 nM. Table 2 shows the results. The weight ratio of SC1 in terms of sesamin/astaxanthin in the medium used in Example 2 was 1.7.

10 [0058]

(Comparative Example 3)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had a sesamin metabolite (SC1) concentration of 1 μ M and contained no astaxanthin. Table 2 shows the results.

[0059]

(Comparative Example 4)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had an astaxanthin concentration of 350 nM and contained no sesamin metabolite (SC1). Table 2 shows the results.

[0060]

(Examples 3)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had a sesamin metabolite (SC1) concentration of 3 μ M and an astaxanthin concentration of 214 nM. Table 3 shows the results. The weight ratio of SC1 in terms of sesamin/astaxanthin in the medium used in Example 3 was 8.3.

30 [0061]

(Comparative Example 5)

The amount of ATP production was measured as in Example 1, except that the culture medium of TIG-3 cells had a sesamin metabolite (SC1) concentration of 3 nM and

contained no astaxanthin. Table 3 shows the results.

[0062]

(Comparative Example 6)

5 The amount of ATP production was measured as in
Example 1, except that the culture medium of TIG-3 cells
had an astaxanthin concentration of 214 nM and contained
no sesamin metabolite (SC1). Table 3 shows the results.

[0063]

(Comparative Example 7)

10 The amount of ATP production was measured as in
Example 1, except that the culture medium of TIG-3 cells
had a sesamin metabolite (SC1) concentration of 3 μ M and
contained no astaxanthin. Table 4 shows the results.

[0064]

15 (Comparative Example 8)

The amount of ATP production was measured as in
Example 1, except that the culture medium of TIG-3 cells
had an astaxanthin concentration of 107 nM and contained
no sesamin metabolite (SC1). Table 4 shows the results.

20 [0065]

(Comparative Example 9)

The amount of ATP production was measured as in
Example 1, except that the medium had a sesamin metabolite
(SC1) concentration of 3 μ M and an astaxanthin
25 concentration of 107 nM. Table 4 shows the results. The
weight ratio of SC1 in terms of sesamin/astaxanthin in the
medium used in Comparative Example 8 was 16.7.

[0066]

(Reference Example 1)

30 The amount of ATP production was measured as in
Example 1, except that the culture medium of TIG-3 cells
contained no sesamin metabolite (SC1) and no astaxanthin.
Tables 1, 3, and 4 show the results of this example as
control (CTL) of Examples 1 and 3 and Comparative Examples
35 1, 2, and 5 to 9.

[0067]

(Reference Example 2)

The amount of ATP production was measured as in
Example 1, except that the culture medium of TIG-3 cells
5 contained no sesamin metabolite (SC1) and no astaxanthin.
Table 2 shows the results of this example as control (CTL)
of Example 2 and Comparative Examples 3 and 4.

[0068]

[Table 1]

		Amount of ATP production (pmol/min/10 ² cells)					Standard error of measured values	Improvement rate (%)	p Value
		Measured value			Average				
		1	2	3					
Reference Example 1	CTL	2.82	2.54	2.64	2.67	0.14	—	—	
Comparative Example 1	SC1 alone	2.94	2.51	2.13	2.53	0.41	-5	0.957	
Comparative Example 2	Asta alone	3.80	3.03	2.55	3.13	0.63	17	0.461	
Example 1	SC1 in terms of sesamin:Asta = 1:6 (weight ratio)	4.71	4.09	4.82	4.54	0.39	70	0.002	

[0069]

[Table 2]

		Amount of ATP production (pmol/min/10 ² cells)				Standard error of measured values	Improvement rate (%)	p Value
		Measured value			Average			
		1	2	3				
Reference Example 2	CTL	2.26	2.20	1.91	2.12	0.18	—	—
Comparative Example 3	SC1 alone	2.00	2.40	2.29	2.23	0.21	5	0.971
Comparative Example 4	Asta alone	1.81	2.34	3.19	2.45	0.69	15	0.606
Example 2	SC1 in terms of sesamin:Asta = 10:6 (weight ratio)	2.92	3.00	2.97	2.97	0.04	40	0.059

[0070]

[Table 3]

		Amount of ATP production (pmol/min/10 ² cells)				Standard error of measured values	Improvement rate (%)	p Value
		Measured value			Average			
		1	2	3				
Reference Example 1	CTL	2.82	2.54	2.64	2.67	0.14	—	—
Comparative Example 5	SC1 alone	2.94	3.07	3.06	3.02	0.07	13	0.498
Comparative Example 6	Asta alone	3.75	4.62	3.29	3.89	0.68	46	0.007
Example 3	SC1 in terms of sesamin:Asta =50:6 (weight ratio)	4.33	4.43	4.28	4.35	0.08	63	0.001

[0071]

[Table 4]

		Amount of ATP production (pmol/min/10 ² cells)				Standard error of measured values	Improvement rate (%)	p Value
		Measured value			Average			
Reference Example 1	CTL	2.82	2.54	2.64	2.67	0.14	—	—
Comparative Example 7	SC1 alone	2.94	3.07	3.06	3.02	0.07	13	0.463
Comparative Example 8	Asta alone	2.59	3.70	2.60	2.96	0.63	11	0.583
Comparative Example 9	SC1 in terms of sesamin:Asta = 100:6 (weight ratio)	2.56	2.52	2.74	2.61	0.12	-2	0.992

[0072]

In Tables 1 to 4, values in "Measured value"
5 (pmol/min/10² cells) show the amount of ATP production

(the amount of decrease in oxygen consumption rate due to the ATP synthase inhibitor) determined above (n = 3).

The improvement rates shown in Tables 1 to 4 were each obtained by subtracting 100 (%) from "Relative value (%) " of the amount of ATP production in each of Examples 1 to 3 and Comparative Examples 1 to 9, taking an average amount of ATP production in control (CTL) as 100 (%).

The obtained results were tested by Dunnett's test. Tables 1 to 4 show p values.

10 [0073]

As shown in Tables 1 to 4, the amount of ATP production increased relative to the control group (Reference Example 1) when the cells were treated with SC1 or Asta alone in Comparative Examples 2 to 8. This confirmed the effect of improving or maintaining energy production or reducing a decline in energy production.

As shown in Table 1, the improvement rate in Example 1 in which SC1 (in terms of sesamin) and Asta were combined at a weight ratio of 1:6 was higher than the total improvement rate of Comparative Example 1 and Comparative Example 2 in which the cells were treated with SC1 and Asta at the same concentrations as they were as in Example 1. Similarly, as shown in Table 2, the improvement rate in Example 2 in which SC1 (in terms of sesamin) and Asta were combined at a weight ratio of 10:6 was higher than the total improvement rate of Comparative Example 3 and Comparative Example 4.

Similarly, as shown in Table 3, the improvement rate in Example 3 in which SC1 (in terms of sesamin) and Asta were combined at a weight ratio of 50:6 was also higher than the total improvement rate of Comparative Example 5 and Comparative Example 6.

In contrast, as shown in Table 4, when SC1 (in terms of sesamin) and Asta were combined at a weight ratio of 100:6 (Comparative Example 9), the amount of ATP

production decreased relative to the control group (Reference Example 1), producing no effect from the combination of SC1 and Asta.

These results confirmed that in Examples 1 to 3,
5 the amount of ATP production was not simply additively increased by being treated with SC1 and Asta but was synergistically increased because SC1 and Asta were combined at a predetermined ratio. In other words, the composition containing SC1 and Asta at a predetermined
10 ratio exhibits a synergistic effect of increasing or maintaining the amount of ATP production or reducing a decrease in the amount of ATP production, owing to the presence of SC1 and Asta, so that the composition was confirmed to exert the effect(s) even at low doses.

15 [0074]

The above clearly shows that the combination of the sesamin-class compound and the astaxanthin-class compound produces a synergistic effect of increasing or maintaining the amount of ATP production or reducing a decline in the
20 amount of ATP production. This confirmed that the composition containing the sesamin-class compound and the astaxanthin-class compound at a specific ratio can effectively improve or maintain mitochondrial function or reduce a decline in mitochondrial function. Use of the
25 sesamin-class compound and the astaxanthin-class compound in combination can improve or maintain energy production or reduce a decline in energy production. This produces, for example, the effect of suppressing, alleviating, or reducing age-related fatigue or feelings of age-related
30 fatigue.

[0075]

(Examples 4)

<Evaluation of energy production in humans>

(Evaluation sample)

35 A test food (in the form of soft capsules)

containing 10 mg of a sesamin-class compound (in terms of sesamin) and 6 mg of an astaxanthin-class compound (in terms of astaxanthin) per three capsules was produced.

5 The weight ratio of the sesamin-class compound (in terms of sesamin) to the astaxanthin-class compound (in terms of astaxanthin) in the test food was 1.7.

The sesamin-class compound was a mixture of sesamin and episesamin in which the weight ratio of sesamin:episesamin was about 1:1, and the astaxanthin-
10 class compound was one derived from a *Haematococcus pluvialis* extract.

The same materials used in the test food were used to produce a food as a control food, except without using the sesamin-class compound and the astaxanthin-class
15 compound.

The test food and the control food were the same in terms of calories, protein content, lipid content, and carbohydrate content per three capsules, and these foods were indistinguishable from the appearance and the like.
20 (Evaluation method)

The metabolism of oxygen consumption was measured by a near-infrared spectroscopy device to evaluate the energy production and metabolism before and after six weeks of ingestion of the test food or the control food. The test
25 was carried out in accordance with the method described in Dynamic Medicine 2004, 3:2. A specific test method is described below.

(1) Subjects

Seventy-seven healthy male adults (37 subjects in
30 the test food group; 35 subjects in the control food group) were subjected to analysis.

(2) Test food or control food ingestion method

The test food (three capsules per day) was ingested by the subjects in the test food group. The control food
35 (three capsules per day) was ingested by the subjects in

the control food group.

The test food and the control food were orally ingested once a day for six weeks.

(3) Evaluation of energy production

Before and after six weeks of ingestion of the food, a near-infrared spectroscopy device was used to determine, as the muscle oxygen consumption, the rate of decrease in the concentration of muscle tissue oxygen of the non-dominant arm while blood flow was blocked immediately after exercise. Changes in muscle oxygen consumption obtained in six minutes were calculated from a mono-exponential model to determine the recovery rate (recovery time constant). Table 5 shows the amount of change before and after six weeks of ingestion.

[0076]

[Table 5]

Evaluation	Group	Summary item	Amount of change
Recovery rate of muscle oxygen consumption (sec)	Control food (<i>N</i> = 35)	Average $\pm$ standard deviation	2.5 ± 20.8
	Test food (<i>N</i> = 37)	Average $\pm$ standard deviation	-7.7 ± 22.9
	<i>P</i> value (Mann-Whitney's <i>U</i> -test)		0.04

[0077]

As shown in Table 5, the subjects who ingested the test food showed a significant increase in the recovery rate of the muscle oxygen consumption, as compared to the subjects who ingested the control food. Presumably, this action was resulted from the effect of improving energy production by the food containing the sesamin-class compound and the astaxanthin-class compound at a specific weight ratio.

[0078]

(Example 5)

<Evaluation of anti-fatigue in humans>

(Evaluation method)

The test food (three capsules per day) or the
 5 control food (three capsules per day) were ingested for
 eight weeks by male and female subjects of 40 years or
 older and younger than 65 years old (136 subjects in the
 test food group; 136 subjects in the control food group)
 who felt fatigue with aging and also felt fatigue in daily
 10 life. Examinations were scheduled at the beginning of the
 ingestion, week 4 of the ingestion, and week 8 of the
 ingestion. On the day of examination, the feelings of
 fatigue were measured on waking up.

The feelings of fatigue were evaluated using Visual
 15 Analogue Scale (VAS). Specifically, each subject
 indicated the level of feelings of fatigue by marking on a
 100-mm straight line with "Feeling the best without any
 feelings of fatigue" at the left end (0 mm) and "Feeling
 the worst and too fatigued to do anything" at the right
 20 end (100 mm). The distance (mm) of the mark from the left
 end on the 100-mm straight line was measured as a measured
 value of the feelings of fatigue. The amount of change in
 feelings of fatigue at week 4 of ingestion and at week 8
 of ingestion was calculated from the following formulas
 25 (i) and (ii).

Amount of change in feelings of fatigue = (Feelings of
 fatigue at week 4 of ingestion) - (Feelings of fatigue at
 week 0) formula (i)

Amount of change in feelings of fatigue = (Feelings of
 30 fatigue at week 8 of ingestion) - (Feelings of fatigue at
 week 0) formula (ii)

[0079]

(Analysis 1: Analysis on subject of effectiveness
 analysis)

35 Analysis was performed on subjects excluding those

who stopped or declined the test, those who violated the compliance with administrative rules, and those who met exclusion criteria (25 subjects in the test food group; 22 subjects in the control food group). Table 6 shows the results of the amount of change in feelings of fatigue. Significance between the groups was tested by unpaired t-test (significance between the groups (relative to the feelings of fatigue in the control food group) *: $p < 0.05$, #: $p < 0.10$).

[0080]

[Table 6]

Timing	Test food group n = 111	Control food group n = 114
Week 4 of ingestion	-13.2 ± 17.2*	-8.6 ± 15.2
Week 8 of ingestion	-18.0 ± 18.5#	-13.8 ± 19.5

[0081]

(Analysis 2: Subgroup analysis)

Each group was divided into two levels: those whose VAS values at screening visit were lower than the overall median (60 mm); and those whose VAS values at screening visit were equal to or higher than the overall median. Table 7 shows the results (the amount of change in feelings of fatigue) of analysis based on the formulas (i) and (ii). Significance was tested by unpaired t-test (significance between the groups (relative to the feelings of fatigue in the control food group) #: $p < 0.10$).

[0082]

[Table 7]

Subgroup	Timing	Test food group n = 57	Control food group n = 59
VAS 60 mm or more	Week 4 of ingestion	-15.7 ± 16.9#	-10 ± 15.2
	Week 8 of ingestion	-21.9 ± 18.6#	-15.4 ± 18
Subgroup	Timing	Test food group n = 54	Control food group n = 55
VAS less than 60 mm	Week 4 of ingestion	-10.6 ± 17.4	-7.3 ± 15.3
	Week 8 of ingestion	-14.0 ± 17.5	-12.0 ± 21.1

[0083]

The group with higher VAS values at screening visit and a higher level of feelings of fatigue showed a
 5 tendency of lower values due to the ingestion of the test food at week 4 of ingestion and at week 8 of ingestion than the group with lower VAS values at screening visit and a lower level of feelings of fatigue.

This shows that the effect of the sesamin-class
 10 compound and the astaxanthin-class compound is likely to be particularly high among people with a high level of feelings of daily fatigue.

[0084]

(Analysis 3: Subgroup analysis)

15 Each group was divided into two levels depending on the exercise frequency at screening visit: those who exercise almost zero to a few times a month; and those who exercise at least once a week to everyday. Table 8 shows the results (the amount of change in feelings of fatigue)
 20 of analysis based on the formulas (i) and (ii). Significance was tested by unpaired t-test (significance between the groups (relative to the feelings of fatigue in the control food group) *: $p < 0.05$).

[0085]

25 [Table 8]

Subgroup	Timing	Test food group n = 28	Control food group n = 34
At least once a week to everyday	Week 4 of ingestion	-14.9 ± 12.3*	-6.9 ± 15.8
	Week 8 of ingestion	-18.9 ± 16.8	-11.1 ± 22.9
Subgroup	Timing	Test food group n = 83	Control food group n = 80
Almost zero to a few times a month	Week 4 of ingestion	-12.7 ± 18.6	-9.4 ± 15.0
	Week 8 of ingestion	-17.8 ± 19.1	-14.9 ± 18.0

[0086]

The group with a high exercise frequency ("At least once a week to everyday") showed a significant decrease at week 4 of ingestion.

This indicates that the combination of the ingestion with adequate exercise can possibly promote the effect of alleviating feelings of fatigue by the sesamin-class compound and the astaxanthin-class compound.

CLAIMS

Claim 1. A composition for improving or maintaining energy production or reducing a decline in energy production, the composition comprising, as active ingredients:

a component (A); and
a component (B),
the component (A) being a sesamin-class compound,
the component (B) being an astaxanthin-class compound,
wherein a weight ratio (A)/(B) of the component (A) in terms of sesamin to the component (B) in terms of astaxanthin is 0.05 to 15.

Claim 2. The composition according to claim 1, wherein the composition is for use in suppressing, alleviating, or reducing age-related fatigue or feelings of age-related fatigue.

Claim 3. The composition according to claim 1 or 2, wherein the improving or maintaining energy production or reducing a decline in energy production is mediated by improving or maintaining mitochondrial function or reducing a decline in mitochondrial function.

Claim 4. The composition according to claim 1 or 2, wherein the sesamin-class compound is at least one compound selected from the group consisting of sesamin, episesamin, and metabolites thereof.

Claim 5. The composition according to claim 1 or 2, wherein the astaxanthin-class compound is at least one compound selected from the group consisting of astaxanthin and derivatives thereof.

Claim 6. The composition according to claim 1 or 2,
wherein the astaxanthin-class compound is derived
from a *Haematococcus pluvialis* extract.

5

Claim 7. The composition according to claim 1 or 2,
wherein the composition is an oral composition.

10

Claim 8. The composition according to claim 1 or 2,
wherein the composition is a food or beverage.

Claim 9. The composition according to claim 1 or 2,
wherein the composition is for use on humans with
strong feelings of daily fatigue.

15

Claim 10. The composition according to claim 1 or 2,
wherein the composition is for use in combination
with exercise.

20

Claim 11. The composition according to claim 1 or 2,
wherein the composition is labeled with at least one
function claim selected from the group consisting of
"facilitating energy production or metabolism",
"facilitating cellular energy production or metabolism",
25 "facilitating intracellular mitochondrial energy
production or metabolism", "maintaining vigor and
vitality", "alleviating age-related fatigue", "alleviating
feelings of age-related fatigue", "for those more prone to
feelings of fatigue with aging", "alleviating fatigue that
30 is more easily felt with aging", "alleviating fatigue that
is felt in daily life", "alleviating feelings of fatigue
in daily life", "alleviating general malaise",
"alleviating tiredness", "alleviating exhaustion",
"alleviating discomfort", "reducing a decline in
35 motivation", and "preventing a decline in muscle

function".

Claim 12. A method of improving or maintaining
energy production or reducing a decline in energy
5 production, the method comprising:

administering a composition containing a component
(A) and a component (B),

the component (A) being a sesamin-class compound and
the component (B) being astaxanthin-class compound,

10 wherein a weight ratio (A)/(B) of the component (A)
in terms of sesamin to the component (B) in terms of
astaxanthin is 0.05 to 15.

Claim 13. Use of a composition for improving or
15 maintaining energy production or reducing a decline in
energy production,

the composition comprising a component (A) and a
component (B),

the component (A) being a sesamin-class compound and
20 the component (B) being astaxanthin-class compound,

wherein a weight ratio (A)/(B) of the component (A)
in terms of sesamin to the component (B) in terms of
astaxanthin is 0.05 to 15.