

DESCRIPTION

TITLE OF INVENTION: COMPOSITION CONTAINING SESAMIN COMPOUND
AND FERULIC ACID OR SALT THEREOF

5

TECHNICAL FIELD

[0001]

The present invention relates to a composition containing a sesamin-class
compound and ferulic acid or a salt thereof.

10

BACKGROUND ART

[0002]

Energy is required for living organisms to sustain life activities. Most of the
energy is produced in mitochondria, which are a type of organelle. Sugar, lipids,
15 amino acids, and other nutrition sources taken from food are metabolized 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).

[0003]

20 The energy production decreases with aging, disease, and other factors. In
humans, for example, a decline in energy production leads to a decline in cellular
function, physical function, and the like. For this reason, there is a demand for
ingredients suitable for continuous ingestion that have the effect of improving,
promoting, maintaining, or reducing a decline in energy production without concern for
25 side effects. When an ingredient that has the above effect is ingested as a supplement,
preferably, the ingredient is in a form that facilitates continuous ingestion by consumers.
For example, oral formulations such as 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 ingredients, so that
30 it is desirable to use an ingredient that is highly effective even when used in a small
amount or a combination of such ingredients in order to reduce the volume of an oral
formulation.

[0004]

Sesamin is one of main lignan compounds found in sesame. Patent Literature
35 1 discloses that a composition containing a sesamin-class compound and γ -oryzanol has

an anti-fatigue effect. Ferulic acid is a type of polyphenol and is known to have an antioxidant effect.

CITATION LIST

5 - Patent Literature

[0005]

Patent Literature 1: JP 2009-73749 A

SUMMARY OF INVENTION

10 - Technical Problem

[0006]

The present invention aims to provide a composition that can effectively improve, promote, maintain, or reduce a decline in energy production.

15 - Solution to Problem

[0007]

The present inventors conducted extensive studies to solve the problems described above. The inventors found that combined use of a sesamin-class compound and ferulic acid or a salt thereof at a specific ratio significantly increases the effect of improving, promoting, maintaining, or reducing a decline in energy production beyond the predictable range of the effect of using a sesamin-class compound alone and the effect of using ferulic acid or a salt thereof alone.

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[0008]

The present invention encompasses, but is not limited to, compositions below.

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(1) A composition containing: (A) a sesamin-class compound; and (B) ferulic acid or a salt thereof, wherein a ratio of a weight of the ferulic acid or a salt thereof (B) in terms of ferulic acid to a weight of the sesamin-class compound (A) in terms of sesamin is 5 to 100.

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(2) The composition according to (1) above, wherein the sesamin-class compound is at least one of sesamin or episesamin.

(3) The composition according to (1) or (2) above, wherein the composition is an oral composition.

(4) The composition according to any one of (1) to (3) above, wherein the composition is a food or beverage.

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(5) The composition according to (1) or (2) above, wherein the composition is

a cosmetic.

(6) The composition according to any one of (1) to (5) above, which is a composition for improving, promoting, maintaining, or reducing a decline in energy production.

5 (7) The composition according to any one of (1) to (6) above, which is an anti-senescence composition.

(8) The composition according to any one of (1) to (7) above, which is a composition for extending at least one of lifespan or healthy life expectancy.

10 - Advantageous Effects of Invention
[0009]

The present invention can provide a composition that can effectively improve, promote, maintain, or reduce a decline in energy production.

15 BRIEF DESCRIPTION OF DRAWINGS
[0010]

FIG. 1 is a graph showing the effect of a sesamin-class compound and ferulic acid on energy production.

20 FIG. 2 is a graph showing the results of studies on the effect of a combination of a sesamin-class compound and ferulic acid (weight ratio of ferulic acid/sesamin-class compound = 5) on extending the replicative lifespan in yeast.

FIG. 3 is a graph showing the results of studies on the effect of a combination of a sesamin-class compound and ferulic acid (weight ratio of ferulic acid/sesamin-class compound = 11) on extending the replicative lifespan in yeast.

25 FIG. 4 is a graph showing the results of studies on the effect of a combination of a sesamin-class compound and ferulic acid (weight ratio of ferulic acid/sesamin-class compound = 27) on extending the replicative lifespan in yeast.

30 FIG. 5 is a graph showing the results of studies on the effect of a combination of a sesamin-class compound and ferulic acid (weight ratio of ferulic acid/sesamin-class compound = 55) on extending the replicative lifespan in yeast.

DESCRIPTION OF EMBODIMENTS
[0011]

35 The composition of the present invention contains: (A) a sesamin-class compound; and (B) ferulic acid or a salt thereof. In the composition of the present

invention, the ratio of the weight of the ferulic acid or a salt thereof (B) in terms of ferulic acid to the weight of the sesamin-class compound (A) in terms of sesamin is 5 to 100.

[0012]

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. Examples of the sesamin analogs include episesamin and dioxabicyclo[3.3.0]octane derivatives described in JP H04-9331 A.

10 Specific examples of the sesamin-class compound include sesamin, episesamin, sesaminol, episesaminol, sesamol, and sesamolin. Stereoisomers or racemates of these compounds may be used alone or in mixture. 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

15 in the present invention, as long as they exhibit the effect(s) of the present invention. Examples of the metabolites that can be used as the sesamin-class compound include a compound disclosed in JP 2009-143884 A. Examples of the metabolites of the sesamin-class compound 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)-7,9':7',9-diepoxy lignane-3,3',4,4'-tetraol). The metabolites are preferably metabolites of sesamin, more preferably SC1.

20 [0013]

In the present invention, the sesamin-class compound preferably includes at least one of sesamin or episesamin, and more preferably includes sesamin and episesamin. When sesamin and episesamin are used, the ratio thereof is not limited,

25 but the ratio (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.

[0014]

30 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 sesamin-class compound is sesamin, an extract containing 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). The

35 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)).

[0015]

Ferulic acid is a type of polyphenol found in plants. Ferulic acid or a salt thereof is not limited in any way by its form, production method, or the like. For example, ferulic acid can be extracted from ferulic acid-containing plants or obtained by chemical synthesis. Ferulic acid or a salt thereof may be a chemically synthesized product, or may be extracted and purified from a natural product.

[0016]

Examples of plants containing ferulic acid include corn, barley, wheat, rice, coffee, onion, radish, lemon, *Cnidium officinale*, *Angelica acutiloba*, pine, *Coptis japonica*, *Ferula assa-foetida*, and sweet potato. In the case of rice, ferulic acid is abundantly present in rice bran. Examples of the chemically synthesized ferulic acid include ferulic acid produced by condensation and decarboxylation of vanillin and malonic acid. Ferulic acid or a salt thereof may be extracted and purified from a raw material by any methods, and known methods can be used.

[0017]

The salt of ferulic acid may be any salt that is pharmacologically acceptable or that is acceptable for use in food and beverages. Examples include basic salts.

Examples of the basic salts include alkali metal salts such as sodium salts and potassium salts; and alkaline earth metal salts such as calcium salts and magnesium salts.

[0018]

In the composition of the present invention, the ratio of the weight of the ferulic acid or a salt thereof (B) in terms of ferulic acid to the weight of the sesamin-class compound (A) in terms of sesamin ((B) in terms of ferulic acid/(A) in terms of sesamin) is 5 to 100. The composition of the present invention contains the sesamin-class compound (A) and the ferulic acid or a salt thereof (B) at the weight ratio above.

As shown in EXAMPLES below, combined use of a sesamin-class compound and ferulic acid or a salt thereof at the weight ratio above effectively reduced the decrease in APT production due to hydrogen peroxide (H₂O₂ treatment). The effect of reducing the decrease in APT production achieved by using a sesamin-class compound and ferulic acid or a salt thereof at the weight ratio above was a synergistic effect that was significantly superior to the predictable additive effect of using a sesamin-class compound alone and using ferulic acid or a salt thereof alone.

[0019]

When a sesamin-class compound and ferulic acid or a salt thereof are used in combination at the weight ratio above, a significantly high effect of improving, promoting, maintaining, or reducing a decline in energy production can be achieved beyond the predictable range of the effect of using a sesamin-class compound alone and the effect of using ferulic acid or a salt thereof alone. A composition containing a sesamin-class compound and ferulic acid or a salt thereof at the weight ratio above has an excellent effect of improving, promoting, maintaining, or reducing a decline in energy production. When the composition of the present invention is used, for example, as an active ingredient to improve, promote, maintain, or reduce a decline in energy production, the effect thereof can be achieved even at a low dose of the active ingredient, thereby reducing the required intake of the active ingredient. A reduced intake leads to easy ingestion, resulting in a composition for improving, promoting, maintaining, or reducing a decline in energy production capacity which is more suitable for continuous ingestion, for example.

[0020]

In the present invention, the ratio of the weight of the ferulic acid or a salt thereof (B) in terms of ferulic acid to the weight of the sesamin-class compound (A) in terms of sesamin ($(B) \text{ in terms of ferulic acid} / (A) \text{ in terms of sesamin}$) is preferably 10 or more, more preferably 11 or more, while preferably 70 or less, more preferably 55 or less. In one embodiment, the weight ratio ($(B) \text{ in terms of ferulic acid} / (A) \text{ in terms of sesamin}$) is preferably 10 to 100, more preferably 10 to 70, still more preferably 10 to 55, particularly preferably 11 to 55.

[0021]

Herein, when a sesamin-class compound is sesamin or episesamin, the weight of the sesamin-class compound in terms of sesamin or any expression similar to this means the weight of sesamin or episesamin; and when the sesamin-class compound is a compound other than sesamin or episesamin, the weight of the sesamin-class compound in terms of sesamin or any expression similar to this means a value obtained by multiplying the number of moles of the compound by the molecular weight of sesamin.

When ferulic acid or a salt thereof is ferulic acid, the weight of ferulic acid or a salt thereof in terms of ferulic acid or any expression similar to this means the weight of ferulic acid; and when ferulic acid or a salt thereof is a salt of ferulic acid, the weight of ferulic acid or a salt thereof in terms of ferulic acid or any expression similar to this means a value obtained by multiplying the number of moles of the salt by the molecular weight of ferulic acid.

[0022]

In one embodiment, the composition of the present invention can be favorably used to improve, promote, maintain, or reduce a decline in energy production. The composition of the present invention may be a composition for improving, promoting, 5 maintaining, or reducing a decline in energy production that contains a sesamin-class compound and ferulic acid or a salt thereof as active ingredients. The energy production capacity decreases with aging, for example. A decline in energy production leads to declined cellular function, declined organ function, and declined overall bodily functions. Improving, promoting, maintaining, or reducing a decline in energy 10 production is expected to have effects such as maintaining or reducing a decline in cellular function, maintaining or reducing a decline in organ function, and maintaining or reducing a decline in overall bodily functions. Improving, promoting, maintaining, or reducing a decline in energy production is effective, for example, in preventing or reducing senescence (anti-senescence). Senescence includes cellular senescence and 15 individual senescence. The individual is preferably a human.

[0023]

As shown in EXAMPLES below, when a sesamin-class compound and ferulic acid were used in combination at the weight ratio above, an effect of extending replicative lifespan in yeast was obtained. The extension of replicative lifespan can be 20 regarded as extension of the lifespan of an individual or extension of healthy life expectancy of the individual. The extension of replicative lifespan can also be regarded as prevented or reduced senescence. In one embodiment, the composition of the present invention can be used as an anti-senescence composition. The composition of the present invention may be an anti-senescence composition that contains a sesamin- 25 class compound and ferulic acid or a salt thereof as active ingredients.

[0024]

In one embodiment, the composition of the present invention can be used to extend the lifespan of an individual. The composition of the present invention can be used as a composition for extending lifespan. The composition of the present 30 invention is also useful in extending healthy life expectancy. Healthy life expectancy refers to the period during which an individual can live without limitations in daily life due to health problems (Ministry of Health, Labour and Welfare, Annual Health, Labour and Welfare Report 2020, p. 17). In one embodiment, the composition of the present invention can be used as a composition for extending healthy life expectancy. The 35 composition of the present invention can be used as a composition for extending at least

one of lifespan or healthy life expectancy.

[0025]

In one embodiment, the composition of the present invention can be used to prevent or alleviate a condition or disease associated with a decline in energy production. Examples of the condition or disease associated with a decline in energy production include a condition or disease caused by a decline in energy production, and a condition or disease accompanied by a decline in energy production. The condition or disease may be a chronic fatigue syndrome, a muscle disease such as sarcopenia, or a cognitive disorder such as dementia.

The term "preventing" as used herein encompasses preventing onset, delaying onset, reducing the incidence rate, reducing the risk of onset, and the like. The phrase "alleviating conditions or diseases" encompasses helping a subject recover from conditions or diseases, alleviating conditions or disease symptoms, making positive changes in conditions or disease symptoms, delaying or preventing progression of conditions or diseases, and the like.

[0026]

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) are added thereto. Thereby, the energy production can be evaluated. Evaluation items such as ATP production, which is a major index for evaluation of energy production, are analyzed, whereby the energy production can be evaluated.

[0027]

The sesamin-class compound and ferulic acid or a salt thereof are found in natural products and food or beverages. They are compounds with a history of consumption as food. Thus, the sesamin-class compound and ferulic acid or a salt thereof are less likely to cause problems in terms of safety, for example, even if ingested daily. The present invention can provide a composition that contains highly safe substances as active ingredients and has an excellent effect of improving, promoting, maintaining, or reducing a decline in energy production.

[0028]

The composition of the present invention is applicable to both therapeutic use (medical use) and non-therapeutic use (non-medical use). The "non-therapeutic" is a

concept that does not include medical activities, i.e., a concept that does not include methods of surgery, therapy, or diagnosis of humans.

The composition of the present invention can be provided in the form of, but is not limited to, a food or beverage, a cosmetic, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like. The composition of the present invention may be a food or beverage, a cosmetic, a pharmaceutical product, a quasi-pharmaceutical product, feed, or the like by itself; or the composition may be a formulation, material, or the like to be added to these products.

For example, the composition of the present invention may be provided as an agent or the like, but it is not limited thereto. Such an agent may be provided as a composition directly, or as a composition containing the agent. In one embodiment, the composition for improving, promoting, maintaining, or reducing a decline in energy production can be regarded as an agent for improving, promoting, maintaining, or reducing a decline in energy production. The anti-senescence composition can be regarded as an anti-senescence agent. The composition for extending at least one of lifespan or healthy life expectancy can be regarded as an agent for extending at least one of lifespan or healthy life expectancy.

[0029]

The composition of the present invention may be an oral composition or a parenteral composition. In one embodiment, preferably, the composition of the present invention is 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.

In another embodiment, the composition of the present invention can be used as a topical agent for skin (topical composition for skin). The topical agent for skin may be a cosmetic, a pharmaceutical product, a quasi-pharmaceutical product, or the like, and is preferably a cosmetic.

[0030]

The composition of the present invention may contain optional additives and optional ingredients, in addition to the sesamin-class compound and ferulic acid or a salt thereof, as long as the effect of the present invention is not impaired. Such additives and ingredients may be selected depending on the form of the composition, for example, and those generally usable in food or beverages, cosmetics, 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 cosmetic, a pharmaceutical

product, a quasi-pharmaceutical product, feed, or the like, any common method can be used for the production. In one embodiment, the composition of the present invention may consist of a sesamin-class compound and ferulic acid or a salt thereof.

[0031]

5 For example, when the composition of the present invention is provided as a food or beverage, an ingredient usable in food and beverages (e.g., a food material or an optional food additive) can be added to the sesamin-class compound and ferulic acid or a salt thereof to provide various types of foods or beverages. The food or beverage is not limited. Examples thereof include general food or beverages, health foods, health
10 supplements, health drinks, foods with function claims, foods for specified health uses, and foods for the sick. The health foods, health supplements, foods with function claims, foods for specified health uses, foods for the sick, and the like can be used in various forms of formulations such as fine granules, tablets, granules, powders, capsules, chewable tablets, dry syrups, syrups, liquid agents, beverages, energy drinks,
15 and liquid foods.

[0032]

When the composition of the present invention is provided as a cosmetic, ingredients usable in cosmetics (e.g., cosmetically acceptable carriers and additives) can be added to the sesamin-class compound and ferulic acid or a salt thereof to provide
20 various cosmetics. The cosmetics may be provided in any product form. Examples thereof include skin care cosmetics such as skin lotions, essence lotions, face packs, emulsions, creams, and sunscreen lotions.

[0033]

When the composition of the present invention is provided as a pharmaceutical
25 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 ferulic acid or a salt thereof to provide various dosage forms of pharmaceutical products or quasi-pharmaceutical products. Such a carrier, additive, or the like may be any pharmacologically acceptable one that can be used in pharmaceutical products or
30 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 the quasi-pharmaceutical product may be oral or parenteral (e.g., transdermal, transmucosal, enteral, or injection) administration. In one embodiment, when the
35 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 form for oral administration include liquids, tablets, powders, fine granules, granules, sugar-coated tablets, capsules, suspensions, emulsions, and chewable tablets.

5 In another embodiment, preferably, the pharmaceutical product or the quasi-pharmaceutical product is a topical agent for skin. The dosage form and the like of the topical agent for skin are not limited. The topical agent for skin can be provided in any form, such as a solution, an emulsion, a cream, a gel, a powder, an aerosol, a mist, a capsule, or a sheet.

10 The pharmaceutical product may be for non-human animals.
[0034]

 When the composition of the present invention is provided as feed, the sesamin-class compound and ferulic acid or a salt thereof are simply added to feed. The feed includes feed additives. Examples of the feed include feed for farm animals
15 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.
[0035]

 The amount of the sesamin-class compound in the composition of the present invention is not limited and can be set according to the form of the composition or the
20 like. The amount of the sesamin-class compound (in terms of sesamin, for example) in the composition of the present invention is preferably 0.001 wt% or more, more preferably 0.01 wt% or more, still more preferably 0.05 wt% or more, while preferably 10 wt% or less, more preferably 5 wt% or less. In one embodiment, the amount of the sesamin-class compound (in terms of sesamin) is preferably 0.001 to 10 wt%, more
25 preferably 0.01 to 5 wt%, still more preferably 0.05 to 5 wt%. When the composition contains two or more sesamin-class compounds, the amount is the sum of the amounts of these compounds. The amount of the sesamin-class compound in the composition can be measured by high-performance liquid chromatography (HPLC).
[0036]

30 The amount of ferulic acid or a salt thereof in the composition of the present invention is not limited and can be set according to the form of the composition or the like. The amount of ferulic acid or a salt thereof in the composition of the present invention, for example, in terms of ferulic acid in the composition, is preferably 0.01 wt% or more, more preferably 0.1 wt% or more, still more preferably 1 wt% or more,
35 while preferably 90 wt% or less, more preferably 55 wt% or less. In one embodiment,

the amount of ferulic acid or a salt thereof in the composition of the present invention in terms of ferulic acid is preferably 0.01 to 90 wt%, more preferably 0.1 to 55 wt%, still more preferably 1 to 55 wt%. The amount of ferulic acid or a salt thereof in the composition can be measured by HPLC.

5 [0037]

The composition of the present invention can be ingested or administered using various methods known per se, depending on the form or dosage form thereof. In one embodiment, preferably, the composition of the present invention is orally ingested (orally administered). In another embodiment, when the composition of the present
10 invention is provided as a topical agent for skin, the composition is applicable to the skin.

The administration amount (intake) of the composition of the present invention is not limited. In one embodiment, the administration amount of the composition of the present invention may be, for example, an amount that has the effect of improving,
15 promoting, maintaining, or reducing a decline in energy production or the anti-senescence effect, and may be appropriately set depending on the dosage form, administration method, subject body weight, and the like.

[0038]

In one embodiment, when a human (adult) is subjected to ingestion or
20 administration of the composition of the present invention, the 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, while preferably 200 mg or less, more preferably 100 mg or less, still more preferably 80 mg or less per day. In one embodiment, in the case of a human (adult), the administration amount of the
25 sesamin-class 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 day. When the composition contains two or more sesamin-class compounds, the administration amount of the sesamin-class compound means the total amount of these compounds. In one
30 embodiment, preferably, sesamin and/or episesamin of preferably 0.5 to 200 mg, more preferably 1 to 100 mg, still more preferably 3 to 80 mg per day is orally ingested by or administered to a human (adult).

[0039]

In one embodiment, when a human (adult) is subjected to ingestion or
administration of the composition of the present invention, the administration amount of
35 ferulic acid or a salt thereof in terms of ferulic acid is preferably 5 mg or more, more

preferably 10 mg or more, still more preferably 35 mg or more, while preferably 2000 mg or less, more preferably 1200 mg or less, still more preferably 900 mg or less per day. In one embodiment, when a human (adult) is subjected to ingestion or administration, the administration amount of ferulic acid or a salt thereof in terms of
5 ferulic acid is preferably 5 to 2000 mg, more preferably 10 to 1200 mg, still more preferably 35 to 900 mg per day.

In one embodiment, preferably, the sesamin-class compound and ferulic acid or a salt thereof in the above amounts are orally ingested by or administered to a human per day. Preferably, the sesamin-class compound and ferulic acid or a salt thereof in
10 the above amounts are ingested or administered in one or more portions per day, for example, in one to several portions (e.g., two or three portions) per day. The administration amounts above may be administration amounts per 60 kg body weight.

When the composition of the present invention is used to achieve the effect of improving, promoting, maintaining, or reducing a decline in energy production in a
15 human, the administration amounts of the sesamin-class compound and ferulic acid or a salt thereof are preferably set to fall within the respective ranges above. Also when the composition is used to achieve the anti-senescence effect or the effect of extending lifespan or healthy life expectancy in a human, the administration amounts of the sesamin-class compound and ferulic acid or a salt thereof are preferably set to fall
20 within the respective ranges above.

In one embodiment, the composition of the present invention can be used to allow the sesamin-class compound and ferulic acid or a salt thereof in the above amounts to be ingested by or administered to a human per day.

[0040]

25 The composition of the present invention contains the sesamin-class compound in an amount in terms of sesamin of preferably 0.5 to 200 mg, more preferably 1 to 100 mg, still more preferably 3 to 80 mg per daily intake for an adult.

The composition of the present invention contains ferulic acid or a salt thereof in an amount in terms of ferulic acid of preferably 5 to 2000 mg, more preferably 10 to
30 1200 mg, still more preferably 35 to 900 mg per daily intake for an adult.

[0041]

Preferably, the composition of the present invention is continuously ingested or administered. In one embodiment, the composition of the present invention is continuously ingested or administered for preferably one week or more, more preferably
35 four weeks or more, still more preferably eight weeks or more, particularly preferably

12 weeks or more.

[0042]

The subject (administration subject) subjected to ingestion or administration of the composition of the present invention is not limited. The administration subject is preferably a human or non-human mammal, more preferably a human.

In one embodiment, the administration subject may be one needing or wanting to improve, promote, maintain, or reduce a decline in energy production, or one needing or wanting to prevent or alleviate symptoms of senescence. Examples of such a subject include middle-aged and older people. In one embodiment, the composition of the present invention is suitable as a composition for improving, promoting, maintaining, or reducing a decline in energy production in middle-aged and older people or an anti-senescence composition for middle-aged and older people. The middle-aged and older people may be those who are 40 years old and older, for example. In one embodiment, the elderly are preferred subjects among the middle-aged and older people. The elderly may be people who are 60 years old and older or 65 years old and older, for example. The composition of the present invention can also be used on healthy people to prevent or alleviate a condition or disease that can be prevented or alleviated by, for example, improving, promoting, maintaining, or reducing a decline in energy production.

[0043]

To the composition of the present invention may be attached one or two or more labels indicating, for example, "facilitating energy production or metabolism", "facilitating cellular energy production or metabolism", "facilitating intracellular mitochondrial energy production or metabolism", "maintaining and enhancing vigor and vitality", "maintaining and enhancing physical strength and performance", "reducing cellular senescence", "extending healthy life expectancy", and "healthy longevity".

In one embodiment, preferably, the composition of the present invention is a food or beverage labeled with one or more function claims described above. The label may be one indicating use for obtaining one or more of these functions. The label may be attached to the composition itself or may be attached to a container or package of the composition.

[0044]

The present invention also encompasses the following method:
a method for improving, promoting, maintaining, or reducing a decline in energy production, including administering the composition of the present invention.

Administering the composition of the present invention to a subject enables effective improvement, promotion, maintenance, or reduction of a decline in energy production in the subject. The method may be a therapeutic or non-therapeutic method. The preferred embodiments of the composition of the present invention
5 include those as described above.

[0045]

The present invention also encompasses the following use:

use of the composition of the present invention for improving, promoting, maintaining, or reducing a decline in energy production.

10 The use may be therapeutic or non-therapeutic use. The preferred embodiments of the composition of the present invention include those described above. The composition of the present invention described above can also be used to prevent or reduce senescence. The composition of the present invention described above can also be used to extend at least one of lifespan or healthy life expectancy.

15 [0046]

In the above methods and 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. The administration method is preferably oral administration (ingestion). The above use is preferably for humans or non-human mammals, more
20 preferably for humans.

[0047]

The above method and use only require use of the composition of the present invention in an amount that achieves a desired effect (such an amount can also be referred to as "effective amount"). Preferred administration amounts, administration
25 subjects, or the like of the sesamin-class compound and ferulic acid or a salt thereof are as described above for the composition of the present invention.

[0048]

The present invention encompasses use of the sesamin-class compound (A) and the ferulic acid or a salt thereof (B) for production of a composition for improving, promoting, maintaining, or reducing a decline in energy production. The present
30 invention also encompasses use of the sesamin-class compound (A) and the ferulic acid or a salt thereof (B) for production of an anti-senescence composition or a composition for extending at least one of lifespan or healthy life expectancy. In the above use, the sesamin-class compound (A) and the ferulic acid or a salt thereof (B) are used such that
35 the ratio of the weight of the ferulic acid or a salt thereof (B) in terms of ferulic acid to

the weight of the sesamin-class compound (A) in terms of sesamin in the composition is 5 to 100. The compositions and the preferred embodiments of the compositions are as described above for the composition of the present invention.

[0049]

5 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 included. Herein, the range may be any combination of any upper limit and any lower limit.

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

EXAMPLES

[0050]

15 The present invention is described in further detail below with reference to examples. The present invention is not limited to these examples.

[0051]

20 In EXAMPLES, a mixture of sesamin and episesamin (sesamin:episesamin (weight ratio) = 1:1) was used as the sesamin-class compound. This mixture of sesamin and episesamin is hereinafter referred to as a sesamin-class mixture.

Ferulic acid used was ferulic acid available from Oryza Co., Ltd.

[0052]

<Examples 1 and 2>

25 TIG-3 cells (fetal lung-derived cells) were seeded on a dedicated plate at 5.5×10^3 cells/well and cultured for 24 hours under conditions of 37°C and CO₂ (5%) (first culture). The medium used was prepared by adding 10% Fetal Bovine Serum (Sigma-Aldrich, 500 mL) and 1% Antibiotic Antimycotic Mixed Stock Solution (100×) (Nacalai Tesque, Inc., product code: 02892-54) to DMEM high Glucose (Nacalai Tesque, Inc., product code: 08458-45). After 24 hours of culture, the sesamin-class mixture and the ferulic acid were added to the medium in the wells at the concentrations shown in the following Table 1 and cultured for 24 hours (second culture). The medium containing the sesamin-class mixture and the ferulic acid was removed, and the cells in the wells were treated with a medium containing H₂O₂ (500 μM) (H₂O₂ treatment). Subsequently, the medium was replaced with an analysis medium, and the oxygen consumption rate (pmol/min) was analyzed using an analyzer (XF analyzer,

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Agilent Technologies Japan, Ltd.). After analysis, the nuclei were stained with Hoechst. 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/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 due to addition of oligomycin indicates the amount of ATP production. Table 1 shows the results obtained.

[0053]

15 In the medium used for the second culture in Example 1, the weight ratio (FA/SE) of the ferulic acid (FA) to the sesamin-class compound (SE) was 11, and the mole ratio (FA/SE) was 20. In the medium used for the second culture in Example 2, the weight ratio (FA/SE) of the ferulic acid to the sesamin-class compound was 55, and the mole ratio (FA/SE) was 100.

20 [0054]

<Reference Example 1>

In Reference Example 1, the second culture was carried out in a medium not containing the sesamin-class mixture or the ferulic acid, and no H₂O₂ treatment was performed. Specifically, the culture was carried out and the amount of ATP production was examined by the following method.

25 TIG-3 cells were seeded on a dedicated plate at 5.5×10^3 cells/well and cultured for 24 hours under conditions of 37°C and CO₂ (5%) (first culture). After 24 hours of culture, the cells were further cultured for 26 hours (second culture). Thereafter, the medium was replaced with an analysis medium, followed by counting the number of cells and measuring the oxygen consumption rate and the amount of decrease in oxygen consumption rate by the same methods as in Example 1. Table 1 shows the results.

[0055]

<Comparative Example 1>

35 In Comparative Example 1, cell culture and H₂O₂ treatment were performed in the same manner as in Example 1, except that the second culture was carried out in a

medium that did not contain the sesamin-class mixture or the ferulic acid. Specifically, the culture was carried out and the amount of ATP production was measured by the method below.

5 TIG-3 cells were seeded on a dedicated plate at 5.5×10^3 cells/well and cultured for 24 hours under conditions of 37°C and CO₂ (5%) (first culture), and the cells were further cultured for 24 hours (second culture). The medium was removed, and the cells in the wells were treated with a medium containing H₂O₂ (500 μM) for two hours (H₂O₂ treatment). Thereafter, the medium was replaced with an analysis medium, followed by counting the number of cells and measuring the oxygen consumption rate and the amount of decrease in oxygen consumption rate by the same methods as in
10 Example 1. Table 1 shows the results.

[0056]

<Comparative Examples 2 to 4>

15 In each of Comparative Examples 2 to 4, the amount of ATP production was evaluated in cells treated with the sesamin-class mixture alone or cells treated with the ferulic acid alone. Specifically, the culture was carried out and the amount of ATP production was measured by the method below.

TIG-3 cells were seeded on a dedicated plate at 5.5×10^3 cells/well and cultured for 24 hours under conditions of 37°C and CO₂ (5%) (first culture). After 24 hours of
20 culture, the sesamin-class mixture (Comparative Example 2) or the ferulic acid (Comparative Examples 3 and 4) was added to the medium in the wells at the concentration shown in the following Table 1, and the cells were further cultured for 24 hours (second culture). The medium containing the sesamin-class mixture or the ferulic acid was removed, and the cells in the wells were treated with a medium
25 containing H₂O₂ (500 μM) for two hours (H₂O₂ treatment). Thereafter, the medium was replaced with an analysis medium, followed by counting the number of cells and measuring the oxygen consumption rate and the amount of decrease in oxygen consumption rate by the same methods as in Example 1. Table 1 shows the results.

[0057]

30 [Table 1]

	H ₂ O ₂ treatment	Concentration (μM)		FA/SE (weight ratio)	ATP production (10 ⁻² pmol/min/cell)		Improvement rate relative to Comparative Example 1 (%)
		SE	FA		Average	SD	
Reference Example 1	—	—	—	—	1.93	0.12	—
Comparative Example 1	+	—	—	—	1.45	0.13	-
Comparative Example 2	+	1	—	0	1.54	0.07	6.1
Comparative Example 3	+	—	20	—	1.44	0.19	-0.7
Comparative Example 4	+	—	100	—	1.52	0.18	4.8
Example 1	+	1	20	11	1.67	0.18	15.2
Example 2	+	1	100	55	1.65	0.19	13.8

[0058]

In Table 1, SE indicates the sesamin-class compound, and FA indicates the ferulic acid.

5 The “ATP production (10⁻² pmol/min/cell)” indicates the average and standard deviation (SD) (n = 4) of the amounts of ATP production (amounts of decrease in oxygen consumption rate due to ATP synthase inhibition) determined above. The “Improvement rate relative to Comparative Example 1” was calculated from the amount of ATP production (10⁻² pmol/min/cell) shown in Table 1 by the following method.

10 Improvement rate relative to Comparative Example 1 (%) = 100 × ((amount of ATP production of example or comparative example) - (amount of ATP production of Comparative Example 1))/(amount of ATP production of Comparative Example 1)

[0059]

15 Comparison between Reference Example 1 and Comparative Example 1 shows that the amount of ATP production was decreased by the hydrogen peroxide treatment. A greater improvement rate relative to Comparative Example 1 (hereinbelow, referred to simply as “improvement rate”) means that the decrease in amount of ATP production was more reduced. FIG. 1 is a graph showing the effect of the sesamin-class compound and the ferulic acid on energy production. The vertical axis (improvement rate) of the graph in FIG. 1 indicates the improvement rate relative to Comparative Example 1. FIG. 1 also shows the value (sum) obtained by adding the improvement rates of Comparative Examples 2 and 3 and the value (sum) obtained by adding the improvement rates of Comparative Examples 2 and 4.

20

Comparative Example 2 (sesamin-class compound concentration: 1 μ M) showed an improvement rate of 6.1%. Comparative Example 3 (ferulic acid concentration: 20 μ M) showed an improvement rate of -0.7%.

Example 1 (sesamin-class compound concentration: 1 μ M, ferulic acid concentration: 20 μ M) showed an improvement rate of 15.2%. This improvement rate of Example 1 was significantly higher than the value (5.4%) obtained by adding the improvement rate (6.1%) of Comparative Example 2 in which the sesamin-class compound concentration was the same and the improvement rate (-0.7%) of Comparative Example 3 in which the ferulic acid concentration was the same.

The improvement rate of Example 2 was also higher than the value ($6.1 + 4.8 = 10.9\%$) obtained by adding the improvement rates of Comparative Examples 2 and 4. [0060]

As shown in FIG. 1, the improvement rates of Examples 1 and 2 were higher than the sum of the improvement rate resulting from treatment with the sesamin-class compound alone and the improvement rate resulting from treatment with the ferulic acid alone. In other words, the decrease in amount of ATP production was not simply reduced additively by the sesamin-class compound and the ferulic acid, but was reduced synergistically by the combined use of the sesamin-class compound and the ferulic acid. The composition containing both the sesamin-class compound and the ferulic acid or a salt thereof was determined to exert a synergistic effect of improving, promoting, maintaining, or reducing a decline in energy production. [0061]

<Example 3>

The effect of the sesamin-class compound and the ferulic acid on extending the replicative lifespan was examined. Daughter yeast cells of yeast strain K6001 do not undergo division, so that the replicative lifespan of the parent cell can be measured by counting the number of daughter cells that bud from the parent cell. In this test, the yeast strain K6001 was cultured until it reached the stationary phase in a YP galactose liquid medium (2% galactose, 1% yeast extract, 2% peptone), and a portion of the yeast was collected and washed twice with water. The washed yeast was seeded onto a YP glucose agar medium (2% galactose, 1% yeast extract, 2% peptone) containing the sesamin-class mixture and the ferulic acid, and cultured at 30°C for two days. Subsequently, daughter cells were counted under a microscope. The concentration of the sesamin-class mixture in the medium was 1 μ M. The concentration of the ferulic acid in the medium was 10 μ M, 20 μ M, 50 μ M, or 100 μ M. The weight ratio (FA/SE)

of the ferulic acid (FA) to the sesamin-class compound (SE) in the medium was 5 in a medium containing 10 μ M ferulic acid. The weight ratio (FA/SE) was 11 in a medium containing 20 μ M ferulic acid, 27 in a medium containing 50 μ M ferulic acid, and 55 in a medium containing 100 μ M ferulic acid.

5 [0062]

In the control group, the yeast strain K6001 was cultured until it reached the stationary phase in the same manner as described above, washed with water, and then seeded into a YP galactose liquid medium not containing the sesamin-class mixture or the ferulic acid, followed by culture at 30°C for two days. Thereafter, daughter cells
10 were counted under a microscope.

[0063]

<Results>

FIG. 2, FIG. 3, FIG. 4, and FIG. 5 are each a graph showing the results of studies on the effect of a combination of a sesamin-class compound and the ferulic acid
15 on extending the replicative lifespan in yeast. The horizontal axis of the graph in each of FIG. 2, FIG. 3, FIG. 4, and FIG. 5 indicates the generation (number) of daughter cells that bud from one parent cell. The vertical axis, labeled as "Dividing cells (%)", indicates the percentage (%) of parent cells that produced daughter cells up to the generation shown on the horizontal axis, relative to the total number of parent cells
20 (100%) (reference: Jarolim et al. "A novel assay for replicative lifespan in *Saccharomyces cerevisiae*." FEMS yeast research 5.2 (2004): 169-177). For example, when five daughter cells (first to fifth generations) budded from a parent cell, the parent cell (dividing cell) is included in the count for each of the first to fifth generations. In FIG. 2, FIG. 3, FIG. 4, and FIG. 5, the white circles (○) represent the control yeast
25 (CTL), and the black circles (●) represent the yeast cultured in a medium containing the sesamin-class compound (SE) and the ferulic acid (FA). In FIG. 2, FIG. 3, FIG. 4, and FIG. 5, the concentration of the sesamin-class mixture in the medium is 1 μ M. The concentration of the ferulic acid is 10 μ M in FIG. 2, 20 μ M in FIG. 3, 50 μ M in FIG. 4, and 100 μ M in FIG. 5.

30 [0064]

The weight ratio (FA/SE) of the ferulic acid to the sesamin-class compound in a medium containing the sesamin-class compound (SE) and the ferulic acid (FA) is 5 in FIG. 2, 11 in FIG. 3, 27 in FIG. 4, and 55 in FIG. 5. As shown in FIG. 2, FIG. 3, FIG. 4, and FIG. 5, the number of daughter yeast cells was increased by the sesamin-class
35 compound and the ferulic acid as compared with the control. Combined use of the

sesamin-class compound and the ferulic acid demonstrated the effect of extending replicative lifespan in yeast. The extension of replicative lifespan can be interpreted as extension of lifespan or healthy life expectancy in individuals. The extension of replicative lifespan can be interpreted also as prevention or reduction of senescence.

- 5 The results demonstrated that the effect of extending lifespan and the like can be achieved by a composition containing the sesamin-class compound (A) and the ferulic acid or a salt thereof (B) at a ratio of the weight of (B) in terms of ferulic acid to the weight of (A) in terms of sesamin ((B) in terms of ferulic acid/(A) in terms of sesamin) of 5 to 100.

CLAIMS

- 5 Claim 1. A composition comprising:
 (A) a sesamin-class compound; and
 (B) ferulic acid or a salt thereof,
 wherein a ratio of a weight of the ferulic acid or a salt thereof (B) in terms of
ferulic acid to a weight of the sesamin-class compound (A) in terms of sesamin is 5 to
100.
- 10 Claim 2. The composition according to claim 1,
 wherein the sesamin-class compound is at least one of sesamin or episesamin.
- Claim 3. The composition according to claim 1 or 2,
 wherein the composition is an oral composition.
- 15 Claim 4. The composition according to claim 1 or 2,
 wherein the composition is a food or beverage.
- Claim 5. The composition according to claim 1 or 2,
20 wherein the composition is a cosmetic.
- Claim 6. The composition according to claim 1 or 2, which is a composition for
improving, promoting, maintaining, or reducing a decline in energy production.
- 25 Claim 7. The composition according to claim 1 or 2, which is an anti-
senescence composition.
- Claim 8. The composition according to claim 1 or 2, which is a composition for
extending at least one of lifespan or healthy life expectancy.