

DESCRIPTION

TITLE OF INVENTION: COMPOSITION FOR PREVENTING, ALLEVIATING, OR
IMPROVING HEAT STROKE OR DEHYDRATION CONTAINING
5 ERGOTHIONEINE OR SALT THEREOF, AND COMPOSITION FOR
REGULATING INTRACELLULAR AND EXTRACELLULAR WATER CONTENT

TECHNICAL FIELD

[0001]

10 The present invention relates to a composition for preventing, alleviating, or
ameliorating heat-related illness. The present invention also relates to a composition for
preventing, alleviating, or ameliorating dehydration. The present invention further
relates to a composition for regulating intracellular and extracellular water. The present
invention further relates to a method for preventing, alleviating, or ameliorating heat-
15 related illness, a method for preventing, alleviating, or ameliorating dehydration, and a
method for regulating intracellular and extracellular water, for example.

BACKGROUND ART

[0002]

20 Water is the most abundant compound among the components of the human
body. Water in the body plays an essential role in sustaining life, including regulating
body temperature and transporting oxygen, nutrients, and waste products. About two-
thirds of the water in the human body exists within various cells as intracellular fluid,
while the remaining one-third exists as extracellular fluid. The extracellular fluid is
25 classified into plasma, interstitial fluid, and lymph.

[0003]

The body water content tends to decrease with age. Both intracellular fluid and
extracellular fluid decrease, but a decrease in intracellular fluid is greater than that in
extracellular fluid and therefore the proportion of extracellular fluid increases. Such an
30 increase in the proportion of extracellular fluid in the body water due to factors such as
aging and the resulting disruption of the balance of intracellular and extracellular water
cause a variety of problems such as a decline in thermoregulatory function. For
example, a decline in thermoregulatory function causes conditions such as heat-related
illness and dehydration. Accordingly, regulating intracellular and extracellular water is

expected to prevent, alleviate, or ameliorate conditions such as heat-related illness and dehydration.

[0004]

Ergothioneine is an amino acid found in, for example, mushrooms. L-
5 ergothioneine is present in nature. L-ergothioneine is known to have physiological
actions such as antioxidant action. With regard to the physiological actions of
ergothioneine, Patent Literature 1 reports an action that promotes the production of
immune response-activating cytokine.

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CITATION LIST

- Patent Literature

[0005]

Patent Literature 1: JP 2017-218431 A

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SUMMARY OF INVENTION

- Technical Problem

[0006]

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The present invention aims to provide a composition that regulates intracellular
and extracellular water and that is useful for preventing, alleviating, or ameliorating
heat-related illness or dehydration.

- Solution to Problem

[0007]

25

The present inventors performed extensive studies to solve the above problem
and thereby found that L-ergothioneine or a salt thereof has an action that decreases the
proportion of the extracellular water content to the total amount of intracellular water
and extracellular water (extracellular water content/(total amount of intracellular water
and extracellular water)). L-ergothioneine or a salt thereof has an action that regulates
intracellular and extracellular water and is useful for preventing, alleviating, or
ameliorating heat-related illness or dehydration.

30

[0008]

35

In other words, the present invention relates to, but is not limited to, for
example, a composition for preventing, alleviating, or ameliorating heat-related illness,
a composition for preventing, alleviating, or ameliorating dehydration, and a
composition for regulating intracellular and extracellular water to be described below.

(1) A composition for preventing, alleviating, or ameliorating heat-related illness, containing L-ergothioneine or a salt thereof.

(2) The composition according to the clause (1), wherein the composition prevents, alleviates, or ameliorates heat-related illness by regulating intracellular and
5 extracellular water.

(3) The composition according to the clause (1) or (2), wherein the composition is labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating heat-related illness”, “preventing worsening of heat-related illness”, “regulating intracellular and extracellular water”, “retaining water”, and
10 “preventing, alleviating, or ameliorating dryness”.

(4) A composition for preventing, alleviating, or ameliorating dehydration, containing L-ergothioneine or a salt thereof.

(5) The composition according to the clause (4), wherein the composition prevents, alleviates, or ameliorates dehydration by regulating intracellular and
15 extracellular water.

(6) The composition according to the clause (4) or (5), wherein the composition is labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating dehydration”, “preventing worsening of dehydration”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing,
20 alleviating, or ameliorating dryness”.

(7) A composition for regulating intracellular and extracellular water, containing L-ergothioneine or a salt thereof.

(8) The composition according to the clause (7), wherein the composition is used to decrease a proportion of an extracellular water content to a total amount of
25 intracellular water and extracellular water in a human.

(9) The composition according to the clause (7) or (8), wherein the composition is labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating heat-related illness”, “preventing worsening of heat-related illness”, “preventing, alleviating, or ameliorating dehydration”, “preventing worsening of dehydration”, “regulating intracellular and extracellular water”, “retaining water”,
30 and “preventing, alleviating, or ameliorating dryness”.

(10) The composition according to any one of the clauses (1) to (9), wherein the composition is an oral composition.

(11) The composition according to any one of the clauses (1) to (10), wherein
35 the composition is a food or beverage.

(12) A method for preventing, alleviating, or ameliorating heat-related illness, the method including administering L-ergothioneine or a salt thereof.

(13) A method for preventing, alleviating, or ameliorating dehydration, the method including administering L-ergothioneine or a salt thereof.

5 (14) A method for regulating intracellular and extracellular water, the method including administering L-ergothioneine or a salt thereof.

(15) Use of L-ergothioneine or a salt thereof for preventing, alleviating, or ameliorating heat-related illness.

10 (16) Use of L-ergothioneine or a salt thereof for preventing, alleviating, or ameliorating dehydration.

(17) Use of L-ergothioneine or a salt thereof for regulating intracellular and extracellular water.

- Advantageous Effects of Invention

15 [0009]

The present invention can provide a composition that regulates intracellular and extracellular water and that is useful for preventing, alleviating, or ameliorating heat-related illness or dehydration.

20

BRIEF DESCRIPTION OF DRAWINGS

[0010]

FIG. 1 is a graph showing the measured uric acid/urea values in the test food group and the control group.

25 FIG. 2 is a graph showing the changes in uric acid/urea value (Δ uric acid/urea) in the test food group and the control group.

DESCRIPTION OF EMBODIMENTS

[0011]

30 The composition for preventing, alleviating, or ameliorating heat-related illness of the present invention contains L-ergothioneine or a salt thereof. The composition for preventing, alleviating, or ameliorating heat-related illness of the present invention is also referred to as the composition according to a first aspect of the present invention. Heat-related illness refers to a condition in which thermoregulatory function is impaired and heat accumulates in the body due to a high-temperature, high-humidity
35 environment.

[0012]

The composition for preventing, alleviating, or ameliorating dehydration of the present invention contains L-ergothioneine or a salt thereof. The composition for preventing, alleviating, or ameliorating dehydration of the present invention is also referred to as the composition according to a second aspect of the present invention. Dehydration refers to a condition in which body water is insufficient.

[0013]

The composition for regulating intracellular and extracellular water of the present invention contains L-ergothioneine or a salt thereof. The composition for regulating intracellular and extracellular water of the present invention is also referred to as the composition according to a third aspect of the present invention.

The composition according to the first aspect, the composition according to the second aspect, and the composition according to the third aspect of the present invention are also collectively referred to as the composition of the present invention. The composition of the present invention contains L-ergothioneine or a salt thereof as an active ingredient.

[0014]

L-ergothioneine is a type of sulfur-containing amino acid.

The salt of L-ergothioneine is any pharmacologically acceptable salt or a dietary acceptable salt, and may be either an acidic salt or a basic salt. Examples of the acidic salt include inorganic acidic salts such as hydrochloride, sulfate, nitrate, and phosphate; and organic acidic salts such as acetate, citrate, maleate, malate, oxalate, lactate, succinate, fumarate, and propionate. Examples of the basic salt include alkali metal salts such as sodium salt and potassium salt, and alkaline earth metal salts such as calcium salt and magnesium salt.

[0015]

L-ergothioneine or a salt thereof is not limited in any way by, for example, its form or production method. Ergothioneine or a salt thereof may be a chemically synthesized product or may be a purified extract of a natural product. L-ergothioneine is abundantly present in golden/yellow oyster mushrooms (scientific name: *Pleurotus cornucopiae* var. *citrinopileatus*) belonging to the genus *Pleurotus* of the family *Pleurotaceae*. L-ergothioneine is also present in mushrooms such as common mushrooms (scientific name: *Agaricus bisporus*), including white button mushrooms, cremini mushrooms, and portabella mushrooms; grey oyster mushrooms (scientific name: *Pleurotus ostreatus*), shiitake (scientific name: *Lentinula edodes*), hen-of-the-

woods (scientific name: *Grifola Frondosa*), reishi mushrooms (scientific name: *Ganoderma lucidum*), lion's mane mushrooms (scientific name: *Hericium erinaceus*), Yanagi-matsutake (scientific name: *Agrocybe aegerita*), girolles (scientific name: *Cantharellus cibarius*), porcini mushrooms (scientific name: *Boletus edulis*), and common morel mushrooms (scientific name: *Morchella esculenta*). L-ergothioneine obtained from a natural product is preferably extracted from a golden/yellow oyster mushroom, for example. L-ergothioneine or a salt thereof can also be produced by microbial fermentation. L-ergothioneine or a salt thereof may be in an isolated form.

[0016]

L-ergothioneine or a salt thereof is a compound that is present in natural products and food and beverages and that has been consumed. Thus, for example, continuous ingestion of L-ergothioneine or a salt thereof is less likely to cause problems in terms of safety. The present invention can provide a composition for preventing, alleviating, or ameliorating heat-related illness, a composition for preventing, alleviating, or ameliorating dehydration, and a composition for regulating intracellular and extracellular water each of which is highly safe.

[0017]

In an embodiment, the composition according to the first aspect of the present invention can be used to prevent, alleviate, or ameliorate heat-related illness by regulating intracellular and extracellular water. In an embodiment, the composition according to the second aspect of the present invention can be used to prevent, alleviate, or ameliorate dehydration by regulating intracellular and extracellular water.

[0018]

Herein, regulating intracellular and extracellular water refers to regulating the intracellular water content and the extracellular water content. The intracellular water content refers to the amount of water present inside cells (intracellular fluid) out of the water in the body, while the extracellular water content refers to the amount of water present outside cells (extracellular fluid).

An indicator of water distribution in the body is the proportion of the extracellular water content to the total amount of intracellular water and extracellular water (extracellular water content/(total amount of intracellular water and extracellular water)). The total amount of intracellular water and extracellular water corresponds to the total body water content (body water content). The proportion of the extracellular water content to the total amount of intracellular water and extracellular water is also referred to as the extracellular water proportion. Herein, regulating intracellular and

extracellular water encompasses regulating the proportion of the extracellular water content to the total amount of intracellular water and extracellular water (extracellular water proportion).

[0019]

5 Herein, regulating intracellular and extracellular water is preferably decreasing the proportion of the extracellular water content to the total amount of intracellular water and extracellular water (extracellular water proportion). Intracellular fluid serves as a water reservoir; specifically, when extracellular fluid decreases, intracellular fluid moves out of the cells to compensate for the decrease in extracellular fluid. Decreasing
10 the extracellular water proportion can lead to an increase in the intracellular water proportion and, when extracellular fluid decreases, allows the body fluid to immediately move out of intracellular fluid and compensate for the decrease in extracellular fluid. Thus, decreasing the extracellular water proportion is effective in preventing, alleviating, or ameliorating heat-related illness or dehydration. A substance having an
15 action that regulates the extracellular water proportion, in particular an action that decreases the extracellular water proportion, is useful for preventing, alleviating, or ameliorating heat-related illness or dehydration.

[0020]

 Herein, the proportion of the extracellular water content to the total amount of
20 intracellular water and extracellular water (extracellular water proportion) can be evaluated by the ratio of uric acid (mg/dL) to urea (mg/dL) (uric acid/urea) in blood. The blood uric acid level is known to reflect the extracellular water content, while the blood urea level is known to reflect the total body water content (total amount of intracellular water and extracellular water) (e.g., J. Artif. Organs., 2022 Dec 24 (doi:
25 10.1007/s10047-022-01377-6), Kawaguchi Y., “The uric acid-urea distribution volume ratio is a potential marker of hydration status in patients on hemodialysis.”). A decrease in the uric acid/urea value indicates a decrease in the extracellular water proportion.

[0021]

 To be described in Examples below, L-ergothioneine has an action that
30 decreases the ratio of uric acid concentration to urea concentration (uric acid/urea) in blood. Thus, L-ergothioneine or a salt thereof has an action that regulates intracellular and extracellular water. L-ergothioneine or a salt thereof can be used to decrease the proportion of the extracellular water content to the total amount of intracellular water and extracellular water. The composition of the present invention containing L-
35 ergothioneine or a salt thereof is useful as a novel way of preventing, alleviating, or

ameliorating heat-related illness or dehydration in addition to supplement of water and salt, which is a conventional way of preventing, alleviating, or ameliorating heat-related illness or dehydration.

[0022]

5 L-ergothioneine or a salt thereof can be used to decrease the ratio of uric acid concentration to urea concentration (uric acid/urea) in blood. L-ergothioneine or a salt thereof can be used as an active ingredient for decreasing the ratio of uric acid concentration to urea concentration (uric acid/urea) in blood. The present invention also encompasses a composition for decreasing the ratio of uric acid concentration to urea
10 concentration (uric acid/urea) in blood, containing L-ergothioneine or a salt thereof.

[0023]

 The composition of the present invention can be used to prevent, alleviate, or ameliorate a condition or disease which can be effectively prevented, alleviated, or ameliorated by regulating extracellular water. The composition of the present invention
15 can be favorably used to prevent, alleviate, or ameliorate a condition or disease which can be effectively prevented, alleviated, or ameliorated by decreasing the extracellular water proportion.

 Preventing a condition or disease encompasses preventing the onset, delaying the onset, reducing the incidence rate, and reducing the risk of onset. Alleviating a
20 condition or disease encompasses alleviating a symptom of a condition or disease. Ameliorating a condition or disease encompasses facilitating recovery of a subject from a condition or disease, favorably changing a symptom of a condition or a disease, and delaying or inhibiting the progress of a condition or disease. The recovery encompasses partial recovery.

25 [0024]

 The composition of the present invention is applicable to either therapeutic use (medical use) or non-therapeutic use (non-medical use). The non-therapeutic is a concept that does not include medical activities, i.e., surgery, therapy, or diagnosis of humans.

30 In an example, the composition of the present invention can be provided in the form of an agent, but is not limited thereto. This agent can be provided as a composition as it is or can be provided as a composition containing the agent. In an embodiment, the composition according to the first aspect of the present invention can also be referred to as a preventing, alleviating, or ameliorating agent for heat-related
35 illness. The composition according to the second aspect of the present invention can

also be referred to as a preventing, alleviating, or ameliorating agent for dehydration. The composition according to the third aspect of the present invention can also be referred to as a regulating agent for intracellular and extracellular water.

[0025]

5 The composition of the present invention may be either an oral composition or a parenteral composition, and is preferably an oral composition. The oral composition may specifically be a food or beverage, an oral pharmaceutical product, an oral quasi-pharmaceutical product, or feed, for example, and is preferably a food or beverage or an oral pharmaceutical product, more preferably a food or beverage. The composition of
10 the present invention may be a material or preparation to be added to a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, or feed, for example.

[0026]

 The composition of the present invention may contain optional additives and
15 optional components in addition to L-ergothioneine or a salt thereof as long as the effect of the present invention is not impaired. These additives and components can be selected according to the form of the composition, for example. In the case where the composition of the present invention is provided as an oral composition, the composition may contain any additive that can be commonly used for oral compositions
20 such as food and beverages, pharmaceutical products, quasi-pharmaceutical products, and feed.

[0027]

 In the case where the composition of the present invention is provided as a food or beverage, a pharmaceutical product, a quasi-pharmaceutical product, or feed, for
25 example, the composition may be produced by any method and may be produced by a common method.

 The oral composition of the present invention may be in any form such as solid (e.g., powder, granules, or tablet), liquid, or paste.

[0028]

30 For example, in the case where the composition of the present invention is provided as a food or beverage, L-ergothioneine or a salt thereof may be combined with a component usable in foods and beverages (e.g., a food material or an optional food additive) to provide various types of foods and beverages. Examples of the food or beverage include, but are not limited to, general foods and beverages, health foods,
35 health 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, and the like can be used in various forms of preparations such as fine granules, tablets, granules, powders, capsules, chewable tablets, dry syrups, syrups, liquid agents, beverages, energy drinks, and liquid foods.

5 [0029]

In the case where the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, for example, L-ergothioneine or a salt thereof can be combined with a pharmacologically acceptable carrier or an optional additive to provide pharmaceutical products or quasi-pharmaceutical products in various dosage forms. Such a carrier or additive 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 two or more of these may be used. The form of administration (ingestion) of a pharmaceutical product or a quasi-pharmaceutical product may be oral or parenteral (e.g., transdermal, transmucosal, enteral, or injection) administration. In the case where the composition of the present invention is provided as a pharmaceutical product or a quasi-pharmaceutical product, the composition is preferably provided as an oral pharmaceutical product or an oral quasi-pharmaceutical product. Examples of dosage forms for oral administration of a pharmaceutical product or a quasi-pharmaceutical product include liquids, tablets, powders, fine granules, granules, sugar-coated tablets, capsules, suspensions, emulsions, and chewable tablets. Examples of dosage forms for parenteral administration include injections, intravenous agents, ointments, lotions, adhesive skin patches, suppositories, nasal agents, and transpulmonary agents (inhalants). The pharmaceutical product may be medicine for non-human animals.

[0030]

In the case where the composition of the present invention is provided as feed, L-ergothioneine or a salt thereof is simply added to feed. The feed includes feed additives. Examples of the feed include feed for farm 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.

[0031]

The composition of the present invention may be ingested by or administered to any subject (administration subject). The subject is preferably a human or non-human mammal, more preferably a human.

In an embodiment, the administration subject may be, for example, a subject in need of or desirous of preventing, alleviating, or ameliorating heat-related illness; a subject in need of or desirous of preventing, alleviating, or ameliorating dehydration; a subject in need of or desirous of regulating intracellular and extracellular water; or a
5 subject in need of or desirous of preventing, alleviating, or ameliorating a condition or disease which can be effectively prevented, alleviated, or ameliorated by regulating intracellular and extracellular water. Examples of the subject include middle-aged and older people. The middle-aged and older people include the elderly. The middle-aged and older people may be those who are 40 years old and older, for example. In an
10 embodiment, the elderly are preferred subjects among the middle-aged and older people. This is because heat-related illness and dehydration tend to occur especially in the elderly. The elderly may be people who are 60 years old and older or 65 years old and older, for example. The administration subject may be a healthy person. For example, the composition of the present invention can be used in healthy people for
15 purposes such as preventing heat-related illness or preventing dehydration.
[0032]

In an embodiment, the composition of the present invention can be favorably used to decrease the proportion of the extracellular water content to the total amount of intracellular water and extracellular water in a human.
20 [0033]

The amount of L-ergothioneine 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, for example.

The amount of L-ergothioneine or a salt thereof in the composition of the
25 present invention in terms of L-ergothioneine is, for example, preferably 0.0001% by weight or more, more preferably 0.001% by weight or more, while preferably 90% by weight or less, more preferably 50% by weight or less. In an embodiment, the amount of L-ergothioneine or a salt thereof in the composition of the present invention in terms of L-ergothioneine is preferably 0.0001 to 90% by weight, more preferably 0.001 to
30 50% by weight. The amount of L-ergothioneine or a salt thereof can be determined by high-performance liquid chromatography (HPLC).
[0034]

Herein, the amount in terms of L-ergothioneine or an expression similar thereto refers to the amount of L-ergothioneine or a salt thereof as L-ergothioneine.
35 Specifically, in the case of L-ergothioneine, the amount in terms of L-ergothioneine or

an expression similar thereto refers to the amount of L-ergothioneine itself; in the case of a salt of L-ergothioneine, the amount in terms of L-ergothioneine or an expression similar thereto refers to a value obtained by multiplying the number of moles of the salt by the molecular weight of L-ergothioneine.

5 [0035]

The composition of the present invention can be ingested or administered by a method appropriate to the form thereof. In an embodiment, preferably, the composition of the present invention is orally ingested (orally administered). The administration amount of the composition of the present invention (also referred to as intake) may be
10 any amount that can provide an effect of preventing, alleviating, or ameliorating heat-related illness, an effect of preventing, alleviating, or ameliorating dehydration, or an effect of regulating intracellular and extracellular water, and may be set as appropriate according to, for example, the administration form, administration method, and the body weight of the subject.

15 [0036]

In an embodiment where the composition of the present invention is orally ingested by or administered to a human (adult) as a subject, the administration amount of L-ergothioneine or a salt thereof in terms of L-ergothioneine per day is preferably 2 mg or more, more preferably 5 mg or more, still more preferably 7 mg or more, while
20 preferably 50 mg or less, more preferably 25 mg or less, still more preferably 20 mg or less. In an embodiment, the administration amount of the composition of the present invention as the administration amount of L-ergothioneine or a salt thereof in terms of L-ergothioneine to a human (adult) per day is preferably 2 to 50 mg, more preferably 5 to 25 mg, still more preferably 5 to 20 mg, further more preferably 7 to 20 mg.
25 Preferably, the compound in the above amount is 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. In an embodiment, preferably, L-ergothioneine or a salt thereof in the above amount is orally ingested by or administered to a human. The above administration amount may be an administration amount per 60 kg body weight. In an
30 embodiment, the composition of the present invention can be used to enable daily ingestion or administration of L-ergothioneine or a salt thereof in the above amount by or to a human per 60 kg body weight, for example.

[0037]

The amount of L-ergothioneine or a salt thereof in the composition of the
35 present invention per adult daily intake is preferably 2 to 50 mg, more preferably 5 to 25

mg, still more preferably 5 to 20 mg, particularly preferably 7 to 20 mg, in terms of L-ergothioneine.

[0038]

5 The composition of the present invention may be labeled with a function of regulating intracellular and extracellular water or a function resulting from regulating intracellular and extracellular water.

10 The composition according to the first aspect of the present invention may be labeled with a function of preventing, alleviating, or ameliorating heat-related illness, for example. The composition according to the first aspect of the present invention may be labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating heat-related illness”, “preventing worsening of heat-related illness”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating dryness”.

[0039]

15 The composition according to the second aspect of the present invention may be labeled with a function of preventing, alleviating, or ameliorating dehydration, for example. The composition according to the second aspect of the present invention may be labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating dehydration”, “preventing worsening of dehydration”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating dryness”.

[0040]

25 The composition according to the third aspect of the present invention may be labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating heat-related illness”, “preventing worsening of heat-related illness”, “preventing, alleviating, or ameliorating dehydration”, “preventing worsening of dehydration”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating dryness”.

[0041]

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

35 [0042]

The present invention also encompasses the following methods:

a method for preventing, alleviating, or ameliorating heat-related illness, the method including administering L-ergothioneine or a salt thereof;

5 a method for preventing, alleviating, or ameliorating dehydration, the method including administering L-ergothioneine or a salt thereof;

a method for regulating intracellular and extracellular water, the method including administering L-ergothioneine or a salt thereof; and

10 a method for decreasing the ratio of uric acid concentration to urea concentration (uric acid/urea) in blood, the method including administering L-ergothioneine or a salt thereof.

The methods each may be a therapeutic method or may be a non-therapeutic method.

[0043]

The present invention also encompasses the following uses:

15 use of L-ergothioneine or a salt thereof for preventing, alleviating, or ameliorating heat-related illness;

use of L-ergothioneine or a salt thereof for preventing, alleviating, or ameliorating dehydration;

20 use of L-ergothioneine or a salt thereof for regulating intracellular and extracellular water; and

use of L-ergothioneine or a salt thereof for decreasing the ratio of uric acid concentration to urea concentration (uric acid/urea) in blood.

The uses each may be therapeutic use or may be non-therapeutic use.

25 Administering L-ergothioneine or a salt thereof enables regulating intracellular and extracellular water in a subject.

[0044]

In the above methods and uses, preferred embodiments of L-ergothioneine or a salt thereof are the same as described above for the composition of the present invention. In the above methods and uses, preferably, L-ergothioneine or a salt thereof
30 is administered to (ingested by) a subject at least once a day, for example, one to several times (e.g., two or three times) a day. In the above methods and uses, preferably, L-ergothioneine or a salt thereof is orally administered (ingested). The above uses are preferably uses for a human or non-human mammal, more preferably for a human.

[0045]

In the above methods and uses, L-ergothioneine or a salt thereof is used in an amount sufficient to achieve a desired effect (effective amount). A preferred administration amount of L-ergothioneine or a salt thereof, a preferred administration subject, and the like are as described above for the composition of the present invention.

5 L-ergothioneine or a salt thereof may be administered directly or may be administered in the form of a composition containing L-ergothioneine or a salt thereof. For example, the composition of the present invention described above may be used.

[0046]

The present invention also encompasses use of L-ergothioneine or a salt thereof

10 for producing a composition for preventing, alleviating, or ameliorating heat-related illness (also referred to as a composition for prevention, alleviation, or amelioration of heat-related illness). The present invention also encompasses use of L-ergothioneine or a salt thereof for producing a composition for preventing, alleviating, or ameliorating dehydration (also referred to as a composition for prevention, alleviation, or

15 amelioration of dehydration). The present invention also encompasses use of L-ergothioneine or a salt thereof for producing a composition for regulating intracellular and extracellular water (also referred to as a composition for regulation of intracellular and extracellular water). The present invention also encompasses use of L-ergothioneine or a salt thereof for producing a composition for decreasing the ratio of

20 uric acid concentration to urea concentration (uric acid/urea) in blood.

[0047]

Herein, the numerical ranges each defined by the lower limit and the upper limit, i.e., “the lower limit to the upper limit”, include the lower limit and the upper limit. For example, the range defined by “1 to 2” means 1 or more and 2 or less, with 1

25 and 2 being included. Herein, the upper limits and the lower limits may be used in any combination to form a range.

The academic literature and patent literature mentioned herein are incorporated herein by reference.

30 EXAMPLES

[0048]

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

[0049]

35 <Example 1>

(Evaluation testing of blood marker for ratio of intracellular water and extracellular water on human subject)

In order to evaluate the influence of supplements containing ergothioneine on the blood marker value for the ratio of intracellular water and extracellular water of a human, a placebo-controlled, randomized, double-blind, parallel-group study was performed on male and female adult subjects (46 subjects in a test food group; 46 subjects in a control food group; 92 subjects in total), each of whom was instructed to take one capsule containing 20 mg ergothioneine (test food) or one capsule not containing ergothioneine (control food) per day for four weeks. Before the start of the study (i.e., before the start of ingestion of the test food or control food), the participants were subjected to preliminary assessment in which the blood marker value for the ratio of intracellular water and extracellular water was measured. After 4-week ingestion of the test food or the control food, the blood marker value for the ratio of intracellular water and extracellular water of each participant was measured again (Week 4 assessment). The marker for the ratio of intracellular water and extracellular water measured was the ratio of uric acid and urea (uric acid/urea) in blood. The measured value of the marker for the ratio of intracellular water and extracellular water was determined from the measured values of uric acid concentration (mg/dL) and urea concentration (mg/dL) in blood. The between-group significance was tested using a two-sample t-test (vs. control food group).

[0050]

(Evaluation foods)

Two types of evaluation foods were prepared, which were designed to be indistinguishable in factors such as appearance and flavor. The participants in the test-food group ingested the test food, while the participants in the control group ingested the control food.

- Test food: capsule containing a test substance (20 mg L-ergothioneine)

- Control food: capsule without the test substance

The raw materials of each evaluation food include dextrin, hydroxypropyl cellulose, carrageenan, potassium chloride, and titanium oxide in addition to the test substance. The control food was produced using the same ingredients as the test food except for the absence of the test substance (L-ergothioneine).

[0051]

FIG. 1 and FIG. 2 show the measured uric acid/urea values at the preliminary assessment and Week 4 assessment and the changes in the values between the

assessments. The changes were calculated as follows: for each participant, the measured uric acid/urea value at the preliminary assessment was subtracted from the measured uric acid/urea value at the Week 4 assessment (measured value at Week 4 assessment - measured value at preliminary assessment), whereby the Δ value (change in uric acid/urea value) was calculated. The change in uric acid/urea value at the preliminary assessment was defined as 0. The results shown in FIG. 1 and FIG. 2 are expressed by mean $\pm$ standard error in each group. The between-group significance was tested using a two-sample t-test (vs. control food group).

[0052]

FIG. 1 is a graph showing the measured uric acid/urea value in the test food group and the control group. In FIG. 1 and FIG. 2, the black squares and solid lines represent the test food group, while the white squares ($\square$) and dotted lines represent the control food group.

[0053]

FIG. 2 is a graph showing the changes in uric acid/urea value (Δ uric acid/urea) in the test food group and the control group. The results show that the uric acid/urea value more decreased in the test food group than in the control food group.

[0054]

The above results demonstrate that L-ergothioneine or a salt thereof has an action that decreases the uric acid/urea value. The blood uric acid level and the blood urea level are known to reflect the extracellular water content and the total body water content (total amount of intracellular water and extracellular water), respectively, so that the uric acid/urea value serves as an indicator of the balance of intracellular and extracellular water. A decrease in the uric acid/urea value indicates a decrease in the proportion of the extracellular water content to the total amount of intracellular water and extracellular water. Therefore, L-ergothioneine exhibits an effect of regulating the balance of intracellular and extracellular water.

CLAIMS

[Claim 1] A composition for preventing, alleviating, or ameliorating heat-related illness, comprising L-ergothioneine or a salt thereof.

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[Claim 2] The composition according to claim 1,
wherein the composition prevents, alleviates, or ameliorates heat-related illness by regulating intracellular and extracellular water.

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[Claim 3] The composition according to claim 1 or 2,
wherein the composition is labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating heat-related illness”, “preventing worsening of heat-related illness”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating dryness”.

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[Claim 4] A composition for preventing, alleviating, or ameliorating dehydration, comprising L-ergothioneine or a salt thereof.

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[Claim 5] The composition according to claim 4,
wherein the composition prevents, alleviates, or ameliorates dehydration by regulating intracellular and extracellular water.

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[Claim 6] The composition according to claim 4 or 5,
wherein the composition is labeled with at least one function selected from the group consisting of “preventing, alleviating, or ameliorating dehydration”, “preventing worsening of dehydration”, “regulating intracellular and extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating dryness”.

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[Claim 7] A composition for regulating intracellular and extracellular water, comprising L-ergothioneine or a salt thereof.

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[Claim 8] The composition according to claim 7,
wherein the composition is used to decrease a proportion of an extracellular water content to a total amount of intracellular water and extracellular water in a human.

[Claim 9] The composition according to claim 7 or 8,
wherein the composition is labeled with at least one function selected from the
group consisting of “preventing, alleviating, or ameliorating heat-related illness”,
5 “preventing worsening of heat-related illness”, “preventing, alleviating, or ameliorating
dehydration”, “preventing worsening of dehydration”, “regulating intracellular and
extracellular water”, “retaining water”, and “preventing, alleviating, or ameliorating
dryness”.

10 [Claim 10] The composition according to any one of claims 1, 4, and 7,
wherein the composition is an oral composition.

[Claim 11] The composition according to claim 10,
wherein the composition is a food or beverage.

15 [Claim 12] A method for preventing, alleviating, or ameliorating heat-related
illness, the method comprising administering L-ergothioneine or a salt thereof.

[Claim 13] A method for preventing, alleviating, or ameliorating dehydration,
20 the method comprising administering L-ergothioneine or a salt thereof.

[Claim 14] A method for regulating intracellular and extracellular water, the
method comprising administering L-ergothioneine or a salt thereof.

25 [Claim 15] Use of L-ergothioneine or a salt thereof for preventing, alleviating,
or ameliorating heat-related illness.

[Claim 16] Use of L-ergothioneine or a salt thereof for preventing, alleviating,
or ameliorating dehydration.

30 [Claim 17] Use of L-ergothioneine or a salt thereof for regulating intracellular
and extracellular water.