

DESCRIPTION

Title of Invention: COMPOSITION FOR PREVENTION AND/OR TREATMENT
OF CANCER

5 Technical Field
 [0001]

 The present invention relates to a composition to be
used for preventing and/or treating cancer.

10 Background Art
 [0002]

 In cancer research in recent years, it has been
revealed that a cancer tissue is not a mass of cells having
properties such as being uniform, but is a mass of cells having
15 properties such as being nonuniform. In addition, it is also
known that the cancer tissue contains cancer stem cells, and
while cancer cells are differentiated from the cancer stem cells,
the cancer stem cells themselves also proliferate.
 [0003]

20 The cancer stem cells can be induced by culturing
induced pluripotent stem cells (iPS cells) through use of a
culture of a cancer-derived cell line. There is known a
technology involving performing screening for an active
ingredient for cancer treatment through use of the cancer stem
25 cells generated by such induction (Patent Literatures 1 and 2).
In addition, in Non-patent Literature 1, there is a disclosure
that a method for induction from embryonic stem cells into cancer
stem cells is the same as the above-mentioned method for
induction from iPS cells into cancer stem cells.

30 [0004]

 Stilbene compounds are compounds contained in plant
bodies such as grapes, which have an experience of being edible
to animals, and there are known, for example, compounds each
exhibiting an antioxidant function, such as resveratrol and
35 pterostilbene. It is known that pterostilbene or a glycoside

thereof exhibits not only the antioxidant function, but also a whitening effect (Patent Literatures 3 and 4) and a hair growth effect (Patent Literature 5).

[0005]

5 Glycosylation technologies aimed at, for example, imparting water solubility to a certain compound have been developed, and for example, a technology for adding a saccharide to a stilbene compound has been developed (Patent Literature 6). However, it is also known that, when a certain compound is
10 glycosylated, physiological activity of the compound before the glycosylation is lost (Non-patent Literature 2). Accordingly, it is understood that, even when a compound is subjected to glycosylation with a desire to, for example, impart water solubility, benefits thereof can be rarely enjoyed.

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Citation List

Patent Literature

[0006]

PTL 1: WO 2014/148562 A1

20 PTL 2: JP 2014-207889 A

PTL 3: JP 6173543 B1

PTL 4: JP 6233826 B1

PTL 5: JP 6364143 B2

PTL 6: JP 6467762 B2

25 Non-patent Literature

[0007]

NPL 1: A. SENO et al., ONCOLOGY LETTERS 18: 2756-2762, 2019

NPL 2: D. Uesugi et al., Bioscience Biotechnology, and Biochemistry, 2017, Vol. 81, No. 2, 226-230

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Summary of Invention

Technical Problem

[0008]

In general, it is realistically difficult to completely
35 cure cancer by administering an existing cancer therapeutic drug

as apparent from the fact that a therapeutic effect is expressed like "5-year survival rate." Existing cancer therapeutic drugs, including molecularly targeted therapeutic drugs, show effects only on specific cancer cells in a cell population contained in a cancer tissue, but do not show drug efficacy against the remaining cancer cells showing nonuniformity or cancer stem cells. Presumably for this reason, cancer has little chance of being completely cured. The inability to completely cure cancer poses serious problems on not only a patient affected by cancer, but also, for example, the family of the patient or a medical institution owing to the prolongation of the treatment period of the cancer and the like. In view of such circumstances, an object of the present invention is to provide a technology for suppressing cancer stem cells.

Solution to Problem

[0009]

In order to investigate the above-mentioned problem, the inventors of the present invention have made extensive investigations, and as a result, have found that pterostilbene and/or a glycoside thereof contained in grapes and the like suppresses induction from iPS cells into cancer stem cells.

[0010]

The present invention has been completed on the basis of such finding, and widely encompasses the following aspects of the invention.

[0011]

I. Composition

I-1 A composition to be used for suppressing induction from stem cells into cancer stem cells, the composition including at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof.

[0012]

I-2 The composition according to the above-mentioned item I-1, wherein the pterostilbene glycoside has a chemical

structure in which pterostilbene and a saccharide have a glycosidic bond therebetween.

[0013]

I-3 The composition according to the above-mentioned
5 item I-2, wherein the glycosidic bond is an O-glycosidic bond.

[0014]

I-4 The composition according to the above-mentioned
item I-3, wherein the O-glycosidic bond is a (1-4)-O-glycosidic
bond.

10 [0015]

I-5 The composition according to the above-mentioned
item I-3 or I-4, wherein the O-glycosidic bond is a β -O-
glycosidic bond.

[0016]

15 I-6 The composition according to any one of the above-
mentioned items I-2 to I-5, wherein the saccharide is a
monosaccharide or a polysaccharide.

[0017]

I-7 The composition according to the above-mentioned
20 item I-6, wherein the monosaccharide is at least one kind of
monosaccharide selected from the group consisting of: an aldose;
a ketose; and oxidation products or reduction products thereof,
which may assume any one structure out of oxyrose ring, oxetose
ring, pyranose ring, furanose ring, septanose ring, and octanose
25 ring structures.

[0018]

I-8 The composition according to the above-mentioned
item I-6, wherein the monosaccharide is glucose.

[0019]

30 I-9 The composition according to any one of the above-
mentioned items I-6 to 1-8, wherein the polysaccharide is a
polysaccharide having a structure in which at least two or more
monosaccharides selected from the group consisting of: an aldose;
a ketose; a deoxy sugar; and oxidation products or reduction
35 products thereof, which may assume any one structure out of

oxyrose ring, oxetose ring, pyranose ring, furanose ring, septanose ring, and octanose ring structures, have a glycosidic bond to each other.

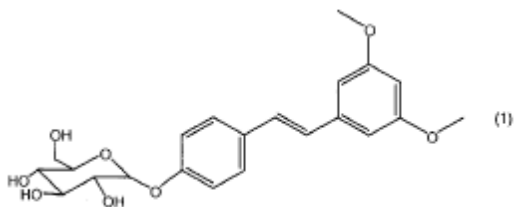
[0020]

- 5 I-10 The composition according to the above-mentioned item I-9, wherein all of the monosaccharides that make up the polysaccharide are glucose.

[0021]

- 10 I-11 The composition according to any one of the above-mentioned items I-1 to I-10, wherein the pterostilbene glycoside is a compound represented by the following formula (1) or (2):

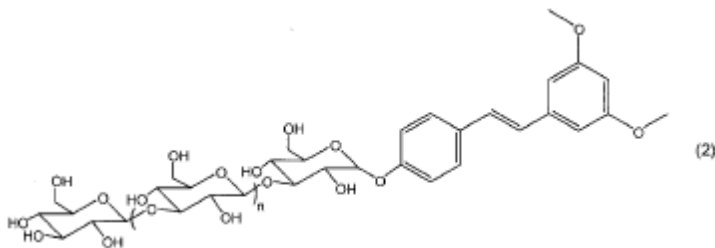
[0022]



[0023]

- 15 where an O-glycosidic bond between glucose and a stilbene skeleton is a β -bond;

[0024]



[0025]

- 20 where an O-glycosidic bond between glucose and a stilbene skeleton is a β -bond, all O-glycosidic bonds between glucose units are α -bonds, and "n" represents an integer of from 0 to 8.

[0026]

- 25 I-12 The composition according to any one of the above-mentioned items I-1 to I-11, wherein the stem cells are any one

of iPS cells, embryonic stem cells, or adult stem cells.
[0027]

II. Food and Beverage Composition

II-1 A food and beverage composition including the
5 composition of any one of the above-mentioned items I-1 to I-12.
[0028]

II-2 The food and beverage composition according to the
above-mentioned item II-1, wherein the food and beverage
composition is used for prevention and/or treatment of cancer.
10 [0029]

III. Pharmaceutical Composition

III-1 A pharmaceutical composition including the
composition of any one of the above-mentioned items I-1 to I-12.
[0030]

15 III-2 The pharmaceutical composition according to the
above-mentioned item III-1, wherein the pharmaceutical
composition is used for prevention and/or treatment of cancer.
[0031]

IV. Medium Composition for Stem Cells

20 IV-1 A medium composition for stem cells, which is used
for inhibiting induction of cancer stem cells, the medium
composition including the composition of any one of the above-
mentioned items I-1 to I-12.
[0032]

25 IV-2 The medium composition for stem cells according to
the above-mentioned item IV-1, wherein the stem cells are any one
of iPS cells, embryonic stem cells, or adult stem cells.
[0033]

V. Prevention and/or Treatment Method

30 V-1 A method of preventing cancer including a step of
administering a composition containing at least one kind selected
from the group consisting of: pterostilbene; and a glycoside
thereof to a living body for which prevention of affection by
cancer is desired.

35 [0034]

V-2 A method of treating cancer including a step of administering a composition containing at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof to a living body affected by cancer.

5

Advantageous Effects of Invention

[0035]

The composition of the present invention contains pterostilbene and/or the glycoside thereof, and exhibits an effect of suppressing induction from stem cells typified by, for example, iPS cells, somatic stem cells, or embryonic stem cells into cancer stem cells.

[0036]

Cancer cells are differentiated from cancer stem cells, and hence the composition of the present invention, which exhibits an effect of inhibiting induction from stem cells into cancer stem cells, exhibits an effect of treating cancer. Such effect is an effect achieved by inhibiting induction into cancer stem cells, which serve as a basis on which cancer cells are differentiated, and hence can be said to be an effect that can even be expected to completely cure cancer. In addition, in view of such mechanism, the composition of the present invention exhibits an effect of keeping cancer cells from occurring, that is, an effect of preventing cancer. In expectation of those effects, the composition of the present invention may be adopted in the field of foods and beverages or pharmaceuticals.

[0037]

The composition of the present invention contains pterostilbene and/or the glycoside thereof as an active ingredient. Pterostilbene and/or the glycoside thereof is a component contained in plant bodies such as grapes, and hence can be said to be a component that living bodies have an experience of ingesting. Accordingly, after the ingestion thereof for the purpose of inhibiting induction from stem cells into cancer stem cells, a living body is extremely unlikely to have such a side

effect as to threaten the life thereof.

[0038]

Stem cells typified by iPS cells are a material that is extremely excellent as a raw material for manufacturing various organs to be used in the field of regenerative medicine, but it is sometimes pointed out that an organ manufactured from stem cells is liable to undergo cancerization. The composition of the present invention may also be used for suppressing the cancerization of various organs to be manufactured using stem cells as a raw material. Accordingly, from this viewpoint, the composition may also be adopted in the field of regenerative medicine.

Brief Description of Drawings

15 [0039]

Fig. 1 shows the results of a cancer stem cell induction suppression test in Example 1. (A) represents a result using pterostilbene (aglycone) as a sample. (B) represents a result using pterostilbene- α -monoglucoside as a sample. (C) represents a result using pterostilbene- β -monoglucoside as a sample. (D) represents a result using pterostilbene diglucoside as a sample. (E) represents a result using pterostilbene triglucoside as a sample. (F) represents a result using a mixture of pterostilbene glycosides as a sample. (G) represents a result using PD0325901 (cancer stem cell induction promoter) as a sample. (H) represents a result using all-trans retinoic acid (ATRA; cancer stem cell induction inhibitor) as a sample. In each of the graphs, the vertical axis represents the relative intensity (%) of GFP, and the horizontal axis represents the concentration ($\mu\text{g/ml}$) of each sample described above.

Fig. 2 shows the results of MTT assay in Example 2. (A) to (H) beside the graphs respectively represent the same samples as in Fig. 1. In each of the graphs, the vertical axis represents cell viability (%), and the horizontal axis represents the concentration ($\mu\text{g/ml}$) of each sample described above.

Description of Embodiments

[0040]

5 The present invention is described in more detail below. The term "include" or "contain" as used in the following description encompasses the meanings of "consist essentially of" and "consist of". The term "mass" may be read as "weight".

[0041]

1. Composition

10 A composition of the present invention contains at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof. In addition, the composition of the present invention may be used for suppressing induction from stem cells into cancer stem cells.

15 [0042]

Pterostilbene is a stilbene compound that is also called trans-1-(3,5-dimethoxyphenyl)-2-(4-hydroxyphenyl)ethylene or 4'-hydroxy-3,5-dimethoxy-trans-stilbene. Pterostilbene is a polyphenol having a stilbene skeleton, and is contained in grapes and the like.

20 [0043]

The glycoside of pterostilbene contained in the composition of the present invention is not particularly limited to the extent that the effects of the present invention are achieved. An example thereof may be a compound in which pterostilbene and a saccharide have a glycosidic bond therebetween. Such glycoside also encompasses one having a glycosidic bond formed via, for example, a linker having biocompatibility.

25 [0044]

The above-mentioned glycosidic bond is not limited to an O-glycosidic bond, and examples thereof may include a C-glycosidic bond, an N-glycosidic bond, and an S-glycosidic bond. By reason of, for example, easy availability of the above-mentioned saccharide or an ability to glycosylate pterostilbene

35

in a relatively simple manner, it is preferred that the above-mentioned glycosidic bond be an O-glycosidic bond. That is, the glycosidic bond is preferably a glycosidic bond via the hydroxy group of pterostilbene.

5 [0045]

In the above-mentioned glycoside of pterostilbene, the anomeric bond mode of the glycosidic bond between the saccharide and pterostilbene is not particularly limited to the extent that the effects of the present invention are achieved. For example,
10 the anomeric bond mode may be an α -glycosidic bond or a β -glycosidic bond. From the viewpoint that the effects of the present invention can be further exhibited, the above-mentioned anomeric bond mode is preferably a β -glycosidic bond.

[0046]

15 In the above-mentioned glycoside of pterostilbene, the saccharide bonded to pterostilbene is not particularly limited to the extent that the effects of the present invention are achieved. For example, the saccharide may be a monosaccharide or a polysaccharide.

20 [0047]

The above-mentioned monosaccharide is not particularly limited to the extent that the effects of the present invention are achieved. An example thereof may be an aldose or a ketose, which may assume an oxyrose ring, oxetose ring, pyranose ring,
25 furanose ring, septanose ring, or octanose ring structure. Specific examples of such monosaccharide may include glucose, maltose, and galactose. Of those, glucose is preferred. The above-mentioned monosaccharide may also encompass, for example, a uronic acid, an aldonic acid, or an aldaric acid that is an
30 oxidized form of the above-mentioned aldose or ketose, or an alditol or a sugar alcohol that is a reduced form thereof.

[0048]

The stereostructure of the above-mentioned monosaccharide is not particularly limited, and may be, for
35 example, a D-form, an L-form, or a racemate. By reason of, for

example, easy availability of the above-mentioned saccharide or an ability to glycosylate pterostilbene in a relatively simple manner, the stereostructure of the above-mentioned monosaccharide is preferably a D-form.

5 [0049]

The above-mentioned polysaccharide is not particularly limited to the extent that the effects of the present invention are achieved. An example thereof may be a polysaccharide having a structure in which at least two or more monosaccharides selected
10 from aldoses or ketoses, which may assume an oxyrose ring, oxetose ring, pyranose ring, furanose ring, septanose ring, or octanose ring structure, have a glycosidic bond to each other. The monosaccharides that make up such polysaccharide may all be identical to each other, or may be different from each other. By
15 reason of an ability to glycosylate the above-mentioned pterostilbene in a relatively simple manner, it is preferred that the monosaccharides that make up the polysaccharide be all identical to each other.

[0050]

20 The monosaccharides that make up the above-mentioned polysaccharide are not particularly limited to the extent that the effects of the present invention are achieved. Examples thereof may include the same monosaccharides as the examples of the monosaccharide bonded to pterostilbene in the above-mentioned
25 glycoside of pterostilbene.

[0051]

The mode of the glycosidic bond between the two or more monosaccharides in the above-mentioned polysaccharide is not limited to an O-glycosidic bond, and examples thereof may include
30 a C-glycosidic bond, an N-glycosidic bond, and an S-glycosidic bond. By reason of, for example, easy availability of the above-mentioned saccharide or an ability to glycosylate pterostilbene in a relatively simple manner, the mode of the glycosidic bond between the two or more monosaccharides is preferably an O-
35 glycosidic bond. In addition, the modes of those glycosidic bonds

do not all need to be identical to each other, and may be modes different from each other. By reason of, for example, an ability to glycosylate the above-mentioned pterostilbene in a relatively simple manner, it is preferred that the modes of the glycosidic bonds between the two or more monosaccharides described above be all identical to each other.

[0052]

The anomeric bond mode of the glycosidic bond between the two or more monosaccharides in the above-mentioned polysaccharide is not particularly limited to the extent that the effects of the present invention are achieved. For example, the anomeric bond mode may be an α -glycosidic bond or a β -glycosidic bond. By reason of, for example, an ability to glycosylate the above-mentioned pterostilbene in a relatively simple manner, it is preferred that the anomeric bond mode of the glycosidic bond between the two or more monosaccharides be an α -glycosidic bond. In addition, those anomeric bond modes do not all need to be identical to each other, and may be anomeric bond modes different from each other. By reason of, for example, an ability to glycosylate the above-mentioned pterostilbene in a relatively simple manner, it is preferred that the anomeric bond modes of the glycosidic bonds between the two or more monosaccharides in the above-mentioned polysaccharide be all identical to each other.

[0053]

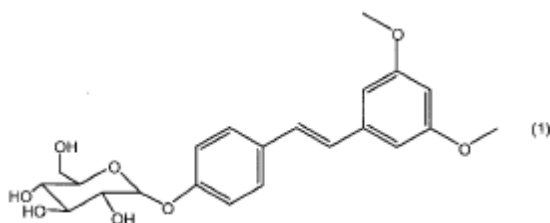
A bonding mode between carbon numbers of monosaccharides in the glycosidic bond between the two or more monosaccharides in the above-mentioned polysaccharide is not particularly limited to the extent that the effects of the present invention are achieved. Examples thereof may include a (1-1) glycosidic bond, a (1-2) glycosidic bond, a (1-3) glycosidic bond, a (1-4) glycosidic bond, and a (1-6) glycosidic bond. By reason of, for example, easy availability of the above-mentioned saccharide or an ability to glycosylate pterostilbene in a relatively simple manner, a (1-4) glycosidic bond is

preferred. In addition, those bonding modes do not all need to be identical to each other, and the bonding modes between carbon numbers of monosaccharides may be different from each other. With a view to simply glycosylating the above-mentioned pterostilbene, it is preferred that the bonding modes between carbon numbers of monosaccharides in the glycosidic bond between the two or more monosaccharides be all identical to each other.

[0054]

As a preferred mode of the above-mentioned pterostilbene, there may be given, for example, a compound represented by the following formula (1) or (2):

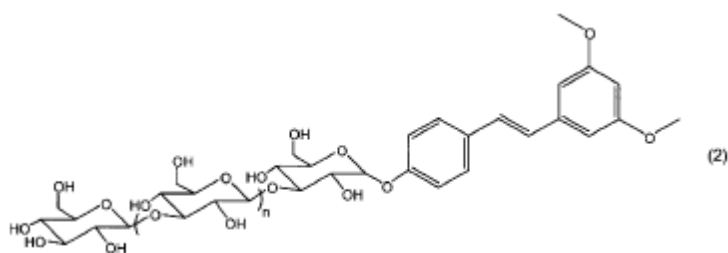
[0055]



[0056]

where an O-glycosidic bond between glucose and a stilbene skeleton is an α -bond or a β -bond;

[0057]



[0058]

where an O-glycosidic bond between glucose and a stilbene skeleton is an α -bond or a β -bond, all O-glycosidic bonds between glucose units are α -bonds, and "n" represents an integer of from 0 to 8.

[0059]

In the compound represented by the formula (1), it is more preferred that the O-glycosidic bond be a β -bond.

[0060]

When the composition of the present invention contains the compound represented by the formula (2), the compound may be contained as a mixture made up of compounds having different
5 integers as "n". The content ratios of the compounds each represented by the formula (2) that make up such mixture are not particularly limited. For example, a compound in which "n" represents a larger integer may tend to have a lower content ratio. In addition, when the composition of the present invention
10 contains the above-mentioned mixture, the composition may also contain the compound represented by the formula (1).

[0061]

Such glycoside of pterostilbene may be obtained from the market, or may be prepared by adopting a method described in,
15 for example, any of Patent Literatures 1 to 4.

[0062]

The stem cells to be targeted for the suppression of induction into cancer stem cells by the composition containing pterostilbene and/or the glycoside thereof of the present
20 invention are not particularly limited. Such stem cells are preferably stem cells retained in a living body (in particular, a mammal). Specific examples thereof may include embryonic stem cells and adult stem cells. Such adult stem cells are also called somatic stem cells or tissue stem cells, and are not particularly
25 limited as long as the cells are stem cells known to have an ability to be induced into cancer stem cells. Specific examples thereof may include hematopoietic stem cells, satellite cells, gut stem cells, hair follicle stem cells, mammary stem cells, mesenchymal stem cells, neurospheres, endothelial stem cells,
30 olfactory stem cells, neural crest stem cells, and testicular cells.

[0063]

The amount of pterostilbene and/or the glycoside thereof contained in the composition of the present invention is
35 not particularly limited to the extent that the effects of the

present invention are achieved. Specifically, the content of pterostilbene and/or the glycoside thereof with respect to 100 mass% of the composition may be set to from about 0.001 mass% to about 100 mass%.

5 [0064]

Pterostilbene and the glycoside thereof contained in the composition of the present invention each exhibit an effect of inhibiting induction from iPS cells into cancer stem cells. Cancer cells are differentiated from cancer stem cells, and hence
10 the composition of the present invention exhibits an effect of preventing and/or treating cancer. In expectation of the exhibition of such effect, the composition of the present invention may be used, for example, in the field of foods and beverages or pharmaceuticals.

15 [0065]

In the manufacture of, for example, cells, tissues, and organs for regenerative medicine using stem cells typified by iPS cells as a raw material, cancerization of those cells and the like is perceived as a problem. In order to solve such problem,
20 the composition of the present invention may also be used for suppressing cancerization during induction of stem cells into, for example, cells, a tissue, or an organ. More specifically, for example, the composition may be added in the form of, for example, a buffer to a medium to be used in the manufacture of
25 cells and the like for regenerative medicine using stem cells as a raw material.

[0066]

2. Food and Beverage Composition

An active ingredient contained in a food and beverage
30 composition of the present invention is pterostilbene and/or the glycoside thereof contained in the composition of the present invention described above. Pterostilbene and/or the glycoside thereof exhibits an effect of inhibiting induction from stem cells into cancer stem cells, and hence the food and beverage
35 composition of the present invention can serve as a food and

beverage composition exhibiting an effect of keeping cancer stem cells from being produced. Cancer cells are differentiated from cancer stem cells, and hence the food and beverage composition of the present invention may be used for prevention and/or treatment
5 of cancer, preferably for prevention of cancer.

[0067]

The amount of the active ingredient contained in the food and beverage composition of the present invention is not particularly limited to the extent that the effects of the
10 present invention are achieved. Specifically, the content of the active ingredient with respect to 100 mass% of the food and beverage composition may be set to from about 0.001 mass% to about 100 mass%.

[0068]

15 The food and beverage composition of the present invention may encompass all of the following: foods (including beverages) with health claims, such as a food for specified health use, a food with function claims, and a food with nutrient function claims; a dietary supplement, a health supplement, a
20 nutritionally balanced food, and the like; and general foods (including beverages). In addition, the food and beverage composition of the present invention may also encompass feed, including feed for livestock, feed for fish farming, and feed for pet animals such as a pet food. Such food and beverage
25 composition only needs to have the shape of a common food or beverage, and may have the form of, for example, a general food or beverage (obvious food) as well as a food for specified health use or a food with function claims which may be touted to achieve an effect of suppressing induction from stem cells into cancer
30 stem cells as a function of the food and beverage. Specifically, the food and beverage composition of the present invention may be touted, for example, as follows: "health maintenance", "energizing", "energize your everyday life", "power to eliminate bad oxygen", or "for people concerned about cancer".

35 [0069]

The shape of the food and beverage composition of the present invention is not particularly limited to the extent that the effects of the present invention are achieved. Examples thereof may include: beverages, such as a refreshing beverage, a carbonated beverage, a nutritional beverage, a fruit beverage, 5 and a lactic beverage; frozen desserts, such as ice cream and shaved ice; sweets, such as gum, chocolate, a candy, a tablet, snack, jelly, jam, cream, and a gummy candy; noodles, such as a buckwheat noodle, a wheat noodle, an instant noodle, and a Chinese noodle; fish or animal processed foods, such as boiled 10 fish paste, a ham, and a sausage; dairy products, such as processed milk and fermented milk; oils and fats, or oil and fat processed foods, such as salad oil, mayonnaise, whipped cream, and dressing; seasonings, such as sauce and baste; and soup, 15 salad, a prepared food, a pickle food, bread, or cereal.

[0070]

The food and beverage composition of the present invention may be prepared into a formulation that is generally provided as a supplement, for example, a solid formulation, such 20 as a powder, a granule, a capsule, a troche, or a tablet; or a liquid formulation, such as a syrup or a drink.

[0071]

A target to be allowed to ingest the food and beverage composition of the present invention is not particularly limited 25 as long as the target is a living body which retains stem cells capable of being induced into cancer stem cells, and for which the suppression of induction from stem cells into cancer stem cells is desired.

[0072]

30 Examples thereof may include, in addition to humans: livestock, such as cattle, pigs, boars, sheep, horses, goats, donkeys, bears, reindeers, rabbits, and frogs; poultry, such as chickens, ducks, geese, turkeys, Muscovy ducks, quails, ostriches, doves, pheasants, canards, and cormorants; farmed 35 seafood, such as fish, crustacean, and mollusk; commercially

grown insects, such as bees and silkworms; and pet animals, such as dogs, cats, rodents, rabbits, monkeys, pigs, parrots, parakeets, snakes, alligators, turtles, salamanders, aquarium fish (e.g., goldfish and tropical fish), rhinoceros beetles, stag
5 beetles, spiders, and scorpions.
[0073]

The ingestion amount of the food and beverage composition of the present invention may be appropriately set on the basis of, for example, the sex and age of the application
10 target, the application form of the food and beverage composition, and the desired degree of effect, and is not particularly limited. For example, a mouse having a body weight of 50 g may be allowed to ingest the active ingredient of the food and beverage composition of the present invention in an
15 amount of from about 0.1 mg to about 1,000 mg per day. An ingestion amount for a target other than a mouse may be appropriately set on the basis of the above-mentioned numerical range in consideration of the body weight of the target and the like.

20 [0074]

An interval at which the food and beverage composition of the present invention is ingested may also be appropriately set on the basis of, for example, the sex and age of the application target, the application form of the food and beverage
25 composition, and the desired degree of effect, and is not particularly limited. For example, the above-mentioned food and beverage composition of the present invention may be ingested once a day, or may be ingested in a plurality of divided portions, specifically two or three divided portions at an
30 interval. In addition, the food and beverage composition may be ingested at an interval of once every several days to several weeks.

[0075]

3. Pharmaceutical Composition

35 An active ingredient contained in a pharmaceutical

composition of the present invention is pterostilbene and/or the glycoside thereof contained in the composition of the present invention described above. Pterostilbene and/or the glycoside thereof exhibits an effect of inhibiting induction from stem
5 cells into cancer stem cells, and hence the pharmaceutical composition of the present invention can serve as a pharmaceutical composition exhibiting an effect of keeping cancer stem cells from being produced. Cancer cells are differentiated from cancer stem cells, and hence the pharmaceutical composition
10 of the present invention may be used for prevention and/or treatment of cancer, preferably for prevention of cancer.
[0076]

The amount of the active ingredient contained in the pharmaceutical composition of the present invention is not
15 particularly limited to the extent that the effects of the present invention are achieved. Specifically, the content of the active ingredient with respect to 100 mass% of the pharmaceutical composition may be set to from about 0.001 mass% to about 100 mass%.
20 [0077]

The pharmaceutical composition of the present invention may be manufactured by blending the above-mentioned active ingredient with a pharmaceutically acceptable known carrier or additive to be used in the manufacture of a composition in the
25 field of pharmacy. Such carrier or additive is not particularly limited to the extent that the effects of the present invention are achieved. Examples thereof may include any carrier, diluent, excipient, suspending agent, lubricating agent, adjuvant, vehicle, delivery system, emulsifier, disintegrant, absorbent,
30 preservative, surfactant, colorant, flavorant, and sweetener.
[0078]

The pharmaceutical composition of the present invention may be prepared into various dosage forms in appropriate combination with the above-mentioned carrier or additive.
35 Accordingly, the dosage form of the pharmaceutical composition of

the present invention is not particularly limited to the extent that the effects of the present invention are achieved. Specific examples thereof may include: injections, such as infusions, implants/pellets, microneedles, or prolonged-release injections; dialysis agents, such as peritoneal dialysis agents or hemodialysis agents; tablets, such as orally disintegrating tablets, chewable tablets, effervescent tablets, dispersible tablets, or soluble tablets; capsules, such as hard capsules or soft capsules; granules containing effervescent granules, sustained-release granules, enteric granules, or the like; powders; liquids and solutions for oral administration, such as elixirs, suspensions, emulsions, or lemonades; syrups; jellies for oral administration; tablets for oro-mucosal application, such as troches, sublingual tablets, buccal tablets, mucoadhesive tablets, or medicated chewing gums; sprays for oro-mucosal application; semi-solid preparations for oro-mucosal application; preparations for gargles; inhalations, such as inhalation powders, inhalation solutions, or inhalation aerosols; ophthalmic preparations such as ophthalmic ointments; ear preparations; nasal preparations, such as nasal powder or nasal solutions; suppositories; semi-solid preparations for rectal application; enemas for rectal application; tablets for vaginal use; suppositories for vaginal use; solid dosage forms for cutaneous application, such as powders for cutaneous application; liquids and solutions for cutaneous application, such as liniments or lotions; sprays, such as aerosols for cutaneous application or pump sprays; ointments, creams, gels; and patches, such as tapes or cataplasms.

[0079]

An administration method for the pharmaceutical composition of the present invention is not particularly limited as long as the administration method is a known administration method optimized for each of the above-mentioned dosage forms. Specific examples thereof may include oral administration, intramuscular administration, intravenous administration,

intraarterial administration, intrathecal administration,
intradermal administration, intraperitoneal administration,
intranasal administration, pulmonary administration, intraocular
administration, intravaginal administration, intracervical
5 administration, intrarectal administration, and subcutaneous
administration.

[0080]

The administration target of the pharmaceutical
composition of the present invention is not particularly limited
10 as long as the target is a living body retaining stem cells
capable of being induced into cancer stem cells (living body
having the possibility of being affected by cancer), and is a
living body for which the suppression of induction from stem
cells into cancer stem cells is desired (living body for which
15 the prevention and/or treatment of cancer is desired).
Specifically, the target may be similar to the target to be
allowed to ingest the above-mentioned food and beverage
composition.

[0081]

20 The dose of the pharmaceutical composition of the
present invention is not particularly limited to the extent that
the effects of the present invention are achieved. Specifically,
the dose may be appropriately set on the basis of, for example,
the sex and age of the application target, the application form
25 of the pharmaceutical composition, and the desired degree of
effect. For example, a mouse having a body weight of 50 g may be
administered the active ingredient of the pharmaceutical
composition of the present invention in an amount of from about
0.1 mg to about 1,000 mg per day. A dose for a target other than
30 a mouse may be appropriately set on the basis of the above-
mentioned numerical range in consideration of the body weight of
the target and the like.

[0082]

The administration interval of the food and beverage
35 composition of the present invention may also be appropriately

set on the basis of, for example, the sex and age of the application target, the application form of the food and beverage composition, and the desired degree of effect, and is not particularly limited. For example, the above-mentioned food and beverage composition of the present invention may be administered once a day, or may be administered in a plurality of divided portions, specifically two or three divided portions at an interval. In addition, the food and beverage composition may be administered at an interval of once every several days to several weeks.

[0083]

4. Medium Composition for Stem Cells

An active ingredient contained in a medium composition for stem cells of the present invention is pterostilbene and/or the glycoside thereof contained in the composition of the present invention described above. Pterostilbene and/or the glycoside thereof exhibits an effect of inhibiting induction from stem cells into cancer stem cells, and hence the medium composition for stem cells of the present invention can serve as a medium composition for stem cells exhibiting an effect of keeping cancer stem cells from being produced. Cancer cells are differentiated from cancer stem cells, and hence the medium composition for stem cells of the present invention may be used for preventing cancerization of, for example, various cells, tissues, or organs to be manufactured using stem cells as a raw material.

[0084]

The above-mentioned stem cells are not particularly limited. Examples thereof may include iPS cells, embryonic stem cells, and adult stem cells. For the adult stem cells, reference may be made to the foregoing description of 1. Composition.

[0085]

The amount of the active ingredient contained in the medium composition for stem cells of the present invention is not particularly limited to the extent that the effects of the present invention are achieved. Specifically, the content of the

active ingredient with respect to 100 mass% of the medium supplement for stem cells may be set to from about 0.001 mass% to about 100 mass%.

[0086]

5 In addition to the above-mentioned active ingredient, the medium composition for stem cells of the present invention may contain a component contained in a medium for differentiation or proliferation to be generally used for obtaining various organs through culture using stem cells as a raw material in the
10 field of regenerative medicine. Such component contained in a medium for differentiation or proliferation is not particularly limited. Specifically, the component may be appropriately decided in view of, for example, what cells, tissue, or organ the culture is aimed at differentiating or the kind of stem cells to be
15 cultured.

[0087]

 The shape of the medium composition for stem cells of the present invention is not particularly limited to the extent that the effects of the present invention are achieved. Specific
20 examples thereof may include liquid medium, solid medium, semisolid medium, and bilayer medium.

[0088]

5. Prevention and/or Treatment Method

 A prevention method of the present invention is a
25 method of preventing cancer including a step of bringing a composition containing at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof into contact with a living body for which the prevention of affection by cancer is desired.

30 [0089]

 A treatment method of the present invention is a method of treating cancer including a step of bringing a composition containing at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof into contact with a
35 living body affected by cancer.

[0090]

For the composition containing at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof, reference may be made to the foregoing
5 description of 1. Composition.

[0091]

For specific prevention and treatment methods of the present invention, reference may be made to the foregoing descriptions of 1. Composition, 2. Food and Beverage Composition,
10 and 3. Pharmaceutical Composition.

Examples

[0092]

Examples for describing the present invention in more
15 detail are given below. Needless to say, the present invention is not limited to an invention as described in the following Examples.

[0093]

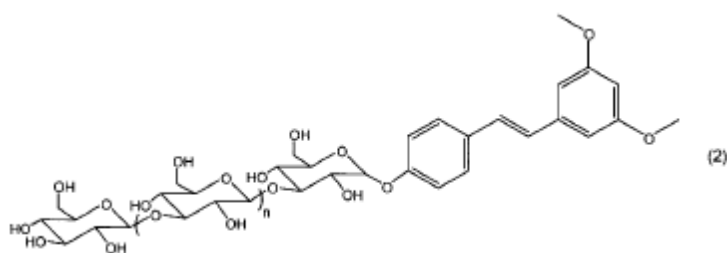
Pterostilbene or glycosides thereof used as samples in
20 the Examples are the following six kinds of compounds. All of these compounds were obtained from Meisterbio Co., Ltd.

[0094]

(Samples)

1. Pterostilbene (aglycone)
- 25 2. Pterostilbene- α -monoglucoside
3. Pterostilbene- β -monoglucoside
4. Pterostilbene diglucoside (n=0) represented by the following formula (2)
5. Pterostilbene triglucoside (n=1) represented by the following
30 formula (2)
6. Mixture of pterostilbene- β -monoglucoside represented by the following formula (1) and pterostilbene polyglucoside (n=0 to 8) represented by the following formula (2):

[0095]



[0096]

where an O-glycosidic bond between glucose and a stilbene skeleton is a β -bond, and all O-glycosidic bonds between glucose units are α -bonds.

Mouse iPS cells adapted to feeder-free culture (iPS-MEF-NG-20D-17; RIKEN BRC) were suspended in a cancer stem cell induction medium and seeded into a 96-well plate in an amount of 1,000 cells per well. The "cancer stem cell induction medium" is a mixed medium of: a culture supernatant of a Lewis lung carcinoma cell line (JCRB Cell Bank); and LIF-free medium for mouse iPS cells (DMEM high glucose (FUJIFILM Wako Pure Chemical Corporation), 15% FBS, 0.1 mM NEAA, 2 mM L-Glutamine, 50 U/ml Pen/Strep, 0.1 mM 2-mercaptoethanol).

[0097]

A cancer stem cell induction medium containing 50 $\mu\text{g/ml}$ of each sample was prepared and then diluted in a 2-fold series, and the diluted products were exposed to the cells seeded in the wells. From the next day to the 6th day, the culture supernatant of each well was half-changed using a medium containing the same sample concentration.

[0098]

As a control experiment, there was performed an experiment in which 0.05% of DMSO was added to the above-mentioned cancer stem cell induction medium. In addition, there was also performed an experiment using media obtained by supplementing 0.8 $\mu\text{g/mL}$ to 50 $\mu\text{g/mL}$ of PD0325901 (cancer stem cell induction-promoting agent; Stemgent) or 0.8 $\mu\text{g/mL}$ to 50 $\mu\text{g/mL}$ of all-trans-retinoic acid (ATRA: cancer stem cell induction-suppressing agent; Stemgent), each of which was used by

being added at diluted final concentrations in the same manner as the above-mentioned samples.

[0099]

5 (Example 1) Evaluation of Cancer Stem Cell Induction
 Suppression by Fluorescence Intensity Measurement

 Mouse iPS cells (iPS-MEF-Ng-20D-17) are cells expressing a nucleic acid having a GFP gene arranged downstream of a promoter of a Nanog gene, and hence, when the cells are in an undifferentiated state, strong GFP fluorescence is detected.
10 Through utilization of this, on the 7th day after exposure of each sample to the cells, 1.0% of Tween 20 was added to lyse the cells in each case, and a relative GFP fluorescence intensity in each well was measured to evaluate what degree of stemness the cells in each case showed.

15 [0100]

 When mouse iPS cells are continuously cultured in a cancer stem cell induction medium, cancer stem cells are induced. The cancer stem cells are undifferentiated cells. Accordingly, the relative GFP fluorescence is maintained along with the
20 expression of the Nanog gene in the cells, and the GFP fluorescence intensity to be measured tends to become stronger until the 7th day as compared to that on the first day. The relative GFP fluorescence intensity for each sample is shown in Fig. 1.

25 [0101]

 Graphs shown in Fig. 1 show numerical values obtained by calculating relative GFP fluorescence intensities obtained at various concentrations of the above-mentioned samples with respect to relative GFP fluorescence intensities obtained in the
30 case of adding DMSO serving as a control.

[0102]

 PD0325901, capable of promoting the induction of cancer stem cells, maintained an undifferentiated state of cancer stem cells, and hence enhanced the relative GFP fluorescence intensity
35 to 100% or more even in an addition amount of 19.4 µg/ml or less.

In addition, even when the addition amount was smaller than the foregoing, specifically 0.8 µg/ml, the relative GFP fluorescence intensity was more than 70%. Meanwhile, the relative GFP fluorescence intensity of ATRA, capable of inhibiting the induction of cancer stem cells, did not exceed 100% even when the addition amount was as low a concentration as 0.8 µg/ml, and the relative GFP fluorescence intensity indicating the retention of stemness tended to reduce as the addition amount became a higher concentration. However, the intensity did not exceed 50%, and hence it is conceived that few cells died.

[0103]

On the basis of the results shown in the graphs of Figure 1, a concentration at which a relative GFP fluorescence intensity of 100% was shown (100% point) and a concentration at which a relative GFP fluorescence intensity of 50% was shown (50% point) were calculated for each sample. The results are shown in Table 1 below.

[0104]

Table 1

µg/ml	1	2	3	4	5	6	PD0325901	ATRA
100% point	<1.6	<1.6	<1.6	10.5	5.6	26.6	19.4	<0.8
50% point	5.3	17.6	6.1	20.2	10.4	44.5	>50	48.8

[0105]

From the results shown in Table 1, it was revealed that pterostilbene and the glycosides thereof serving as the samples generally suppressed induction from iPS cells into cancer stem cells. Of those, the aglycone of pterostilbene (sample 1), pterostilbene-α-monoglucoside (sample 2), pterostilbene-β-monoglucoside (sample 3), pterostilbene diglucoside (sample 4), and pterostilbene triglucoside (sample 5) were found to have more excellent effects.

[0106]

(Example 2) Evaluation of Cancer Stem Cell Induction

Suppression by Proliferation Suppression Measurement

Mouse iPS cells cultured under the same conditions as in Example 1 for 7 days were subjected to MTT assay. The results are shown in Fig. 2, and IC₅₀ values calculated from the results are shown in Table 2.

[0107]

Table 2

μg/ml	1	2	3	4	5	6	PD0325901	ATRA
IC ₅₀ value	22.2	40.3	16.3	28.0	32.9	-	22.5	9.3

[0108]

According to the experimental results shown in Example 1, all of the above-mentioned samples showed differentiation induction abilities like ATRA, and did not show a tendency to kill iPS cells. In view of this, the results of the MTT assay may be interpreted to show the degree of suppression of proliferation through differentiation of cells. Specifically, as the IC₅₀ value becomes lower, it may be judged that the proliferation of mouse iPS cells is suppressed more, that is, the effect of suppressing induction into cancer stem cells is higher.

[0109]

Thus, it was revealed that pterostilbene and the glycosides thereof serving as the samples generally exhibited effects of suppressing induction from iPS cells into cancer stem cells. Of those, the aglycone of pterostilbene (sample 1), pterostilbene-β-monoglucoside (sample 3), and pterostilbene diglucoside (sample 4) were found to have more excellent effects.

CLAIMS

[Claim 1]

A cancer-preventing composition to be used for suppressing induction from stem cells into cancer stem cells, the
5 cancer-preventing composition comprising at least one kind selected from the group consisting of: pterostilbene; and a glycoside thereof.

[Claim 2]

10 A cancer-preventing composition to be used for suppressing induction from stem cells into cancer stem cells, the cancer-preventing composition comprising a pterostilbene glycoside.

[Claim 3]

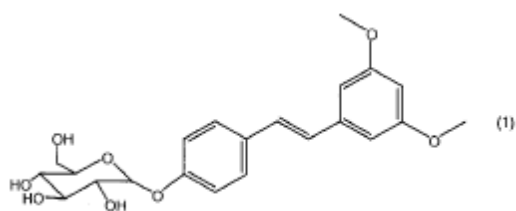
15 The cancer-preventing composition according to claim 2, wherein the pterostilbene glycoside has a structure in which pterostilbene and a saccharide have an O-glycosidic bond therebetween.

[Claim 4]

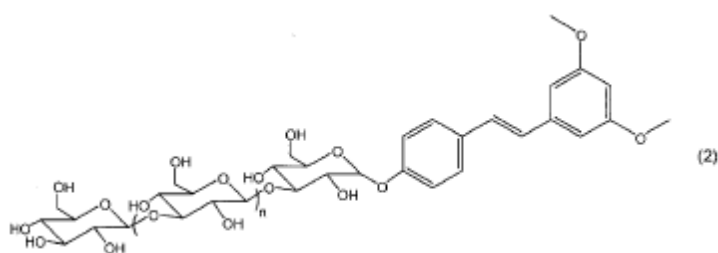
20 The cancer-preventing composition according to claim 3, wherein the O-glycosidic bond is a β -glycosidic bond.

[Claim 5]

25 The cancer-preventing composition according to any one of claims 2 to 4, wherein the pterostilbene glycoside is represented by the following formula (1) or (2):



30 where an O-glycosidic bond between glucose and a stilbene skeleton is a β -bond;



where an O-glycosidic bond between glucose and a stilbene skeleton is a β -bond, all O-glycosidic bonds between glucose units are α -bonds, and "n" represents an integer of from 0 to 8.

5

[Claim 6]

The cancer-preventing composition according to any one of the claims 1 to 5, wherein the stem cells are iPS cells, embryonic stem cells, or adult stem cells.

10

[Claim 7]

The cancer-preventing composition according to any one of the claims 1 to 5, wherein the cancer-preventing composition is a pharmaceutical composition or a food and beverage

15

composition.