

DESCRIPTION

COMPOSITION FOR SUPPRESSING PHOSPHORUS ABSORPTION

5 [Field of the Invention]

The present invention relates to compositions for suppressing phosphorus absorption, which comprise a fermented dairy product and an oligosaccharide as active ingredients. Further, the present invention relates to compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus.

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[Background of the Invention]

Proton pump inhibitors (PPIs) which are powerful suppressants of gastric acid secretion are one of the most commonly used oral medications, and are considered to be generally safe. Meanwhile, use of PPIs is reported to increase the risk of bone fracture.

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With regard to this, the present inventors have reported that short-term subcutaneous administration of PPIs into rats during development reduces their bone mineral density (BMD) and bone strength (Non-Patent Literature 1 and 2). However, there is no report that long-term subcutaneous administration of a PPI to humans or animals would affect their bone strength.

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Oral intake of milk or fermented dairy products (fermented milk, cheese, etc.) has been reported to be useful for prevention of osteoporosis. With respect to this, the present inventors have reported that short-term oral administration of a lactic acid fermentation product to growing rats during short-term subcutaneous administration of PPIs improves calcium absorption partially, and increases BMD and bone strength

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(Non-Patent Literature 1). Meanwhile, oral administration of galacto-oligosaccharides (GOS) is reported to enhance calcium absorption and increase BMD in growing rats and ovariectomized rats (Non-Patent Literature 3 to 5). GOS is hardly digested in the small intestine, and is an indigestible carbohydrate that becomes fermented in the large intestine. With regard to this, the present inventors have reported that short-term oral

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administration of a lactic acid fermentation product and GOS in combination to growing rats during short-term subcutaneous administration of a PPI improves calcium absorption additively, and increases bone strength (Non-Patent Literature 2).

[Citation List]

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[Non-Patent Literature]

[Non-Patent Literature 1] Takasugi et al., Br. J. Nutr., 2011, 106, 1487-1494

[Non-Patent Literature 2] Takasugi et al., Biol. Trace Elem. Res., 2013, 153, 309-318

[Non-Patent Literature 3] Wearer et al., J. Agric. Food Chem., 2011, 59, 6501-6510

[Non-Patent Literature 4] Chonan et al., J. Nutr. Sci. Vitaminol., 1995, 41, 95-104

[Non-Patent Literature 5] Chonan et al., Biosci. Biotechnol. Biochem., 1995, 59, 236-

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[Summary of the Invention]

As described above, orally administering a combination of a lactic acid fermentation product and GOS to growing rats for a short duration after short-term subcutaneous administration of a PPI improves calcium absorption and increases bone strength. However, administering a PPI to rats over a long period of time has an adverse effect on phosphorus metabolism, and it was unclear whether long-term administration of a lactic acid fermentation product and GOS in combination would have any influence on the worsened phosphorus metabolism. The present inventors then experimentally investigated the influence on this worsened phosphorus metabolism of administering a lactic acid fermentation product and GOS in combination for a long period of time, in a state of reduced gastric acid secretion (elevated gastric acid pH) that results from long-term subcutaneous administration of a PPI.

In other words, an objective of the present invention is to provide compositions for treating or preventing osteoporosis and for improving phosphorus metabolism (specifically, for suppressing excessive incorporation of phosphorus), which comprise a combination of a lactic acid fermentation product (a fermented dairy product) and GOS as active ingredients, which can be taken for a long period of time, and are composed of ingredients (nutrients) that have been proven to be excellent in safety and taste property from a long history of use in foods. Further, an objective of the present invention is to provide compositions for treating or preventing diseases caused by excessive incorporation of phosphorus, which comprise a combination of a lactic acid fermentation product and GOS as active ingredients.

The present inventors conducted intensive research to solve the above issues. Specifically, the present inventors experimentally examined the influence on phosphorus metabolism, calcium metabolism, bone strength and such of orally administering for a long period of time a combination of a lactic acid fermentation product (a fermented dairy product) and GOS to rats in a state of reduced gastric acid secretion that results from PPI administration, and in a normal state without PPI administration. As a result, the present inventors revealed that long-term oral administration of a combination of a fermented dairy product and GOS to rats increases

bone strength both in a state of reduced gastric acid secretion and in a normal state. The present inventors further revealed that the increase of phosphorus absorption is suppressed in a state of reduced gastric acid secretion by orally administering a combination of a fermented dairy product and GOS for a long period of time. The present inventors have thereby discovered the possibility that diseases caused by excessive incorporation of phosphorus can be treated and/or prevented by long-term administration of a fermented dairy product and GOS in combination to ameliorate the abnormality of phosphorus metabolism.

The present invention is based on the above-described findings and provides the subject matter below.

[1] A composition for use in suppressing phosphorus absorption, which comprise a fermented dairy product and an oligosaccharide as active ingredients.

[2] The composition of [1] above, wherein the oligosaccharide is an oligosaccharide that comprises galactose as a constituent sugar.

[3] The composition of [2] above, wherein the oligosaccharide is galacto-oligosaccharide.

[4] The composition of any one of [1] to [3] above, wherein the fermented dairy product is a fermented dairy product obtained using lactic acid bacteria that belong to the genus *Lactobacillus* and/or lactic acid bacteria that belong to the genus *Streptococcus*.

[5] The composition of any one of [1] to [4] above, wherein the fermented dairy product is yogurt and/or unmatured cheese.

[6] The composition of any one of [1] to [5] above, for use in oral administration to a subject with reduced gastric acid secretion and/or elevated gastric acid pH.

[7] The composition of any one of [1] to [6] above, for use in daily oral administration over a period of at least four weeks or more.

[8] The composition of any one of [1] to [7] above, for use as a food additive.

[9] Use of a fermented dairy product and an oligosaccharide in the manufacturing of a composition for use in suppressing phosphorus absorption.

[Effect of the Invention]

The compositions of the present invention can suppress the increase of phosphorus absorption along with the reduction of gastric acid secretion. Accordingly, oral administration (which may also include the concept of enteral administration) of the compositions of the present invention to subjects with reduced gastric acid secretion such as elderly people and such can suppress the increase of phosphorus absorption, ameliorate the abnormality of phosphorus metabolism, and return the excessive

incorporation of phosphorus to a normal range. Further, oral administration of the compositions of the present invention can ameliorate (treat, prevent or such) diseases caused by excessive incorporation of phosphorus. The compositions of the present invention can be orally administered for a long period of time without a side-effect problem because they comprise as active ingredients (main ingredients) a fermented dairy product and an oligosaccharide that have been proven to be excellent in safety and taste property from a long history of use in foods.

[Mode for Carrying Out the Invention]

The present invention provides compositions for use in suppressing phosphorus absorption, which comprise a fermented dairy product and an oligosaccharide as active ingredients. Further, the present invention relates to compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus, which comprise a fermented dairy product and an oligosaccharide as active ingredients. The excessive incorporation of phosphorus into the body results from, for example, increase of pH due to reduction of gastric acid secretion. The compositions of the present invention significantly suppress the excessive incorporation of phosphorus into the body that results from increase of pH due to reduction of gastric acid secretion, and ameliorate the abnormality of phosphorus metabolism.

The compositions for use in suppressing phosphorus absorption of the present invention can be expressed as compositions for suppressing absorption of phosphorus, phosphorus absorption inhibitors, and such. The compositions of the present invention for use in suppressing phosphorus absorption can be orally administered to subjects with reduced gastric acid secretion and/or elevated gastric acid pH. That is, the present invention relates to compositions for use in suppressing phosphorus absorption to be used for administration to subjects with reduced gastric acid secretion and/or elevated gastric acid pH. The compositions of the present invention for use in suppressing phosphorus absorption can also be expressed as “compositions for use in suppressing phosphorus absorption that comprise a fermented dairy product and an oligosaccharide as active ingredients, and which are for use in oral administration to a subject determined to have reduced gastric acid reduction and/or elevated gastric acid pH by a method comprising the step of determining whether the secretion of gastric acid is reduced and/or whether the pH of gastric acid is elevated in the subject to be administered with (to take) the composition”. In the present invention, “administration” and “intake” can be interchangeably used.

Whether gastric acid secretion is reduced can be determined by measuring the pH of gastric acid. That is, when the pH of gastric acid measured is elevated, the secretion of gastric acid is judged to be reduced. In the present invention, the subject with reduced gastric acid secretion and/or elevated gastric acid pH has a gastric pH of preferably 9 to 2, more preferably 8 to 2, and even more preferably 7 to 2, without being limited thereto. Methods of measuring gastric pH are well known to persons skilled in the art, and for example, a measurement method of inserting microwire pH glass electrodes into the stomach intranasally (Pharma. Medica., 2009, 27, 109-15) and such are known. The subject with reduced gastric acid secretion and/or elevated gastric acid pH is, for example, a subject that has been orally administered with a PPI for a long period of time. That is, compositions of the present invention for use in suppressing phosphorus absorption can be used for oral administration to subjects that have been orally administered with a PPI for a long period of time. Further, other subjects with reduced gastric acid secretion and/or elevated gastric acid pH are, for example, elderly people, gastrectomized patients, H₂ blocker-administered patients, and such. In the present invention, a long period of time is, for example, preferably one week or more and 30 years or less, more preferably two weeks or more and 20 years or less, and even more preferably three weeks or more and 10 years or less, without being limited thereto.

In the present invention, suppressing phosphorus absorption refers to reducing the incorporation of phosphorus into the body, and can also be expressed as “improving a state of excessive absorption of phosphorus into the body” or such. Compositions of the present invention for use in suppressing phosphorus absorption can be used to treat or prevent diseases caused by excessive incorporation of phosphorus (diseases caused by enhancement of phosphorus absorption).

Compositions for either or both of treating and preventing diseases caused by excessive absorption of phosphorus which comprise a fermented dairy product and an oligosaccharide as active ingredients can be described as (medicinal) agents for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus. Compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus can be orally administered to subjects with reduced gastric acid secretion and/or elevated gastric acid pH. That is, the present invention relates to compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus, which are used for oral administration to subjects with reduced gastric acid secretion and/or elevated gastric acid pH. Compositions of the present invention for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus can be expressed as

“compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus which comprise a fermented dairy product and an oligosaccharide as active ingredients, and for use in oral administration to a subject determined to have reduced gastric acid reduction and/or elevated gastric acid pH by a method comprising the step of determining whether the secretion of gastric acid is reduced and/or whether the pH of gastric acid is elevated in the subject to be administered with (to take) the composition”. The “disease caused by excessive incorporation of phosphorus” can be expressed as “disease caused by excessive intake of phosphorus”, “disease caused by enhancement of phosphorus absorption” or such. In the present invention, the “disease caused by excessive incorporation of phosphorus” is, for example, a disease that develops as a result of excessive phosphorus absorption due to preferably reduction of gastric acid secretion, elevation of gastric acid pH, long-term (oral) administration of a PPI, or such, without limitations thereto. That is, more specifically, the disease that develops as a result of excessive phosphorus absorption due to reduction of gastric acid secretion, elevation of gastric acid pH, long-term (oral) administration of a PPI, or such is, for example, cardiovascular diseases, ectopic calcification, osteoporosis and such, without being limited thereto.

The present inventors discovered that long-term oral intake of a fermented dairy product and an oligosaccharide can suppress excessive incorporation of phosphorus. Accordingly, the compositions of the present invention can be orally administered daily for a long period of time to subjects in need thereof (in particular, subjects with reduced gastric acid reduction, subjects with elevated gastric acid pH, subjects with long-term PPI administration). That is, the present invention relates to compositions for use in suppressing phosphorus absorption to be used for daily oral administration to subjects in need thereof for a long period of time. The present invention relates to compositions for either or both of treating and preventing diseases caused by excessive incorporation of phosphorus to be used for daily oral administration to subjects in need thereof for a long period of time. In the present invention, a long period of time is, for example, preferably one week or more, more preferably two weeks or more, and even more preferably three weeks or more (for example, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 weeks or more), without being limited thereto. Compositions of the present invention can be taken for a long period of time without a side-effect issue, because they comprise as active ingredients (main ingredients) a fermented dairy product and an oligosaccharide that have been proven to be excellent in safety and taste property from a long history of use in foods. Accordingly, in the present invention, the administration period has no upper limit, but as an example, is

preferably 30 years or less, more preferably 20 years or less, and even more preferably 10 years or less, without being limited thereto.

A portion of the compositions of the present invention is prepared using an oligosaccharide. In the present invention, the oligosaccharide refers to an
 5 oligosaccharide which is a compound of 2-20 glycosidically-linked sugars. In the present invention, the oligosaccharide is, for example, lactosucrose, isomalto-oligosaccharide, fructo-oligosaccharide, galacto-oligosaccharide, xylo-oligosaccharide, soybean oligosaccharide, nigero-oligosaccharide, gentio-oligosaccharide, lactose, sucrose, maltose, trehalose, palatinose, or such, without being limited thereto. When
 10 the compositions of the present invention are acidic, it is preferable to use oligosaccharides that are unlikely to decay due to acid decomposition or such.

In the present invention, it is preferable to use oligosaccharides that comprise galactose as a constituent sugar (for example, galacto-oligosaccharides or such). An oligosaccharide that comprises galactose as a constituent sugar refers to a compound of
 15 2-20 glycosidically-linked sugars, in which one or several galactoses are included in the sugars that constitute this compound. Galacto-oligosaccharides are contained in breast milk and have an effect of increasing bifidobacteria in the intestine, and they are known to be poorly digested and absorbed sugars. According to the codes and standards in the system of foods for specified health use (standardized), galacto-oligosaccharides are
 20 defined as “oligosaccharides that have one or several galactoses glycosidically-linked to the galactose residue of lactose, and which are synthesized from lactose by the action of β -galactosidase (β -D-galactoside galactohydrolase, E.C.3.2.1.23, *Cryptococcus* yeast origin), and have 4'-galactosyl lactose (Gal (β 1-4) Gal (β 1-4) Glc) as the principal component (Food Safety Notice No. 0701007 issued by the Director of Food Safety, the
 25 Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare as of July 1, 2005: codes and regulations accompanied with establishment of the system of foods for specified health use (standardized)). In the present invention, the galacto-oligosaccharides are not particularly limited as long as they fit into this definition.

Without being limited thereto, galacto-oligosaccharides in the present
 30 invention are, for example, oligosaccharides that have a structure in which lactose (Gal(β 1-4)Glc) is the basic structure, to which one to several galactose residues are linked, β -1,3-linked galactose/glucose disaccharide (trans-linked disaccharide), Gal-(Gal)n-Glc (n=1-18), Gal-(Gal)n-Gal (n=1-18), etc.

Galacto-oligosaccharides can be obtained by commercial (industrial)
 35 manufacturing methods. A method of manufacturing galacto-oligosaccharides is, without being limited thereto, for example, a method of reacting lactose with β -

galactosidase that has high galactosyltransferase ability (mainly originated from microbes such as *Cryptococcus laurentii*, *Bacillus circulans* or such) by Yoshito Sawairi (Functions of galacto-oligosaccharides and their application in food; Foodstyle 21, 1998, 2, 76-78).

5 Compositions of the present invention are prepared in part using a fermented dairy product. In the present invention, a fermented dairy product refers to generally anything obtained by fermentation of milk or milk containing an equivalent nonfat milk solid material, using lactic acid bacteria, bifidobacteria, propionic acid bacteria, or such as starter or such. In the present invention, “milk or milk containing an equivalent
10 nonfat milk solid material” is, for example, a combination of one or two types of domesticated milk (whole milk) such as cow milk, buffalo milk, goat milk, sheep milk and horse milk, and their partly-skimmed milk, skim milk, reconstituted whole milk, reconstituted partly-skimmed milk, reconstituted skim milk, whole milk powder, partly-skimmed milk powder, skim milk powder, condensed whole milk, condensed partly-
15 skimmed milk, condensed skim milk, casein, whey, whey protein, whey-related products (whey protein concentrate (WPC), whey protein isolate (WPI) and such), milk protein concentrate (MPC), butter, butter milk, cream and such, without being limited thereto. In the present invention, a fermented dairy product is preferably fermented milk (yogurt or such), cheese (matured cheese, non-aged cheese (fresh cheese),
20 processed cheese and such), cheese food or a milk serum (whey) fermented product; more preferably fermented milk, cheese or such; even more preferably yogurt, non-aged cheese or such; particularly preferably yogurt, without being limited thereto.

A “whey-related product” is, for example, a whey concentrate made by concentrating whey; whey powder made by drying whey; a whey protein concentrate
25 (herein below also referred to as WPC) made by a concentration process such as ultrafiltration (UF) of the main proteins in whey followed by a drying process; a skimmed whey protein concentrate (low fat and high protein) made by removing fat from whey with a microfiltration (MF) method or a ultracentrifugation method, followed by a concentration process using an UF method and then a drying process; a
30 whey protein isolate (herein below also referred to as WPI) made by selectively fractionating the main proteins in whey by an ion-exchange resin method, a gel filtration method or such, followed by a drying process; desalted whey made by a desalting process such as a nanofiltration (NF) method, an electrophoresis method, or such, followed by a drying process; or a whey mineral concentrate made by a
35 sedimentation process of the mineral components from whey, followed by a concentration process using a ultracentrifugation method or such. Similar to WPC or

WPI, the milk protein concentrate (herein below also referred to as MPC) made by a concentration process of skim milk using a MF method or an UF method, followed by a concentration process has a reduced lactose or salt content, and a relatively enhanced casein or whey protein content.

5 In the present invention, fermented milk (yogurt or such) refers to “a paste or liquid made by fermentation of milk or milk containing an equivalent (or more) nonfat milk solid material using lactic acid bacteria or yeast, or a frozen product thereof” (Ministerial Ordinance Article 2(38) on the compositional standards for milk and milk products). There are no particular limitations to the fermented milk in the present
10 invention, as long as they are included in this definition. Further, cheese in the present invention refers to “a product made by fermentation of a liquid milk prepared by one type or a combination of two or more types of milk or milk containing an equivalent (or more) nonfat milk solid material, or adding an enzyme or acid thereto, and then removing milk serum from the resultant curd”. In the present invention, cheese may be
15 either solidified or non-solidified. Further, in the present invention, cheese may be either matured (mature cheese) or unmatured (non-aged cheese).

 In the present invention, for the starter for producing a fermented dairy product, for example, lactic acid bacteria that belong to the genus *Lactobacillus*, genus *Streptococcus*, the genus *Lactococcus*, genus *Leuconostoc*, genus *Pediococcus* or such
20 can be used; and preferably lactic acid bacteria that belong to the genus *Lactobacillus*, genus *Streptococcus*, or the genus *Lactococcus* can be used, and more preferably lactic acid bacteria that belong to the genus *Lactobacillus* and genus *Streptococcus* can be used, without limitations thereto. More specifically, microbes that are generally used in the production of fermented milk, including lactic acid bacteria such as *Lactobacillus*
25 *delbrueckii* subsp. *bulgaricus*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus oris*, *Lactobacillus acidophilus*, *Lactobacillus brevis*, *Lactobacillus mucosae*, *Lactobacillus murinus*, *Streptococcus thermophilus*, *Streptococcus diacetylactis*, *Lactococcus lactis*, *Lactococcus cremoris*, *Enterococcus*
30 *faecium* and *Enterococcus faecalis*; bifidobacteria such as *Bifidobacterium longum*, *Bifidobacterium bifidum* and *Bifidobacterium breve*; or propionic acid bacteria such as *Propionibacterium freudenreichii*, *Propionibacterium thoenii*, *Propionibacterium acidipropionici*, *Propionibacterium jensenii*, *Propionibacterium avidum*, *Propionibacterium acnes*, *Propionibacterium lymphophilum* and *Propionibacterium*
35 *granulosam* can be used. Preferably, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus plantarum*, *Lactobacillus*

casei, *Lactobacillus reuteri*, *Lactobacillus rhamnosus*, *Lactobacillus oris*, *Lactobacillus acidophilus*, *Lactobacillus brevis*, *Streptococcus thermophilus*, *Lactococcus lactis* or *Lactococcus cremoris* can be used; more preferably, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus plantarum*,
 5 *Streptococcus thermophilus*, *Lactococcus lactis* or *Lactococcus cremoris* can be used; even more preferably, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus gasseri*, *Lactobacillus helveticus* or *Streptococcus thermophilus* can be used; and particularly preferably, *Lactobacillus delbrueckii* subsp. *bulgaricus* or *Streptococcus thermophilus* can be used, without limitations thereto. Also, a combination of one or two or more
 10 types of these microbes can be used as the starter.

In the present invention, fermented milk (yogurt and such) can be obtained using a publicly known manufacturing method. Further, in the present invention, cheese can also be obtained using a publicly known manufacturing method. For example, the composition (mass unit) of unmatured cheese is, for example, 17-19 %
 15 total solid, 11-13% protein, 1% or less fat, and 2-8% carbohydrate, without being limited thereto.

Compositions of the present invention are generally prepared as mixtures of an oligosaccharide, a fermented milk product, and other arbitrary components; and can be prepared, for example, in other forms that include the oligosaccharide and the
 20 fermented milk product separately. When a composition of the present invention is prepared in forms that include the oligosaccharide and the fermented milk product separately, it is desirable to (orally) administer the oligosaccharide-containing composition and the fermented milk product-containing composition simultaneously.

For compositions of the present invention, the concentration of
 25 oligosaccharides contained in total solids (100% mass) is preferably 0.1-10 % mass, more preferably 0.2-8 % mass, even more preferably 0.3-6 % mass, and particularly preferably 0.4-6 % mass. For compositions of the present invention, the concentration of the fermented milk product contained in total solids (100% mass) is preferably 5-98 % mass, more preferably 10-97 % mass, even more preferably 15-96 % mass, and
 30 particularly preferably 18-96 % mass. In the present invention, if not indicated otherwise, "total solids" refers to the mass (including the mass of liquid fat) after drying under the 20°C dry atmosphere in a desiccator, and does not mean the mass of a water-containing material such as powdered feeds.

For compositions of the present invention, the daily amount of
 35 oligosaccharide administration (intake) is preferably 0.1 mg-2 g, more preferably 0.5 mg-1.5 g, even more preferably 1 mg-1 g, and particularly preferably 5 mg-0.5 g in

solid content per kilogram of body weight. For compositions of the present invention, the daily amount of administration (intake) of a fermented dairy product is preferably 100 mg-10 g, more preferably 200 mg-7.5 g, even more preferably 300 mg-5 g, and particularly preferably 500 mg-2.5 g in solid content per kilogram of body weight.

5 For compositions of the present invention, the daily amount of oligosaccharide administered to a human is preferably 0.01 g-20 g, more preferably 0.05 g-15 g, even more preferably 0.1 g-10 g, and particularly preferably 0.5 g-5 g in solid content. For compositions of the present invention, the daily amount of a fermented dairy product administered to a human is preferably 1 g-100 g, more preferably 2 g-75 g, even more
10 preferably 3 g-50 g, and particularly preferably 5 g-25 g in solid content. Compositions of the present invention can be appropriately administered to subjects (patients or such) in need of administration before meal, after meal, between meals and/or before bed collectively or separately. The amount of a composition of the present invention administered to subjects (patients or such) in need of administration can be determined
15 individually according to their age, body weight, and purpose of administration; and the amount is not limited to the numerical ranges described above.

In the present invention, the mass ratio (value in terms of solid content) of a fermented dairy product / oligosaccharide is preferably 1-49, more preferably 1-30, even more preferably 2-9, and particularly preferably 3-8.

20 Compositions of the present invention can be used in any form of pharmaceuticals (pharmaceutical composition, nutritional pharmaceutical composition, medicinal agent, enteral nutrient preparation, pharmaceutical additive and such), food or drink (food or drink composition, nutritional composition, special-use food, nutritional functional food, health food, food additive composition (food additive) and such), and
25 cosmetics. Further, compositions of the present invention can be added to (mixed with) pharmaceuticals, foods or drinks, cosmetics or such for use, and/or can be used in combination with pharmaceuticals, foods or drinks, cosmetics or such. As a result, the pharmaceuticals, foods or drinks, cosmetics or such can be conferred with an effect of suppressing phosphorus absorption or an effect of treating and/or preventing a disease
30 caused by excessive incorporation of phosphorus.

When a composition of the present invention is used as a pharmaceutical (in the form of a pharmaceutical), it can be administered in various different forms. The form of administration is, for example, oral administration or enteral administration (intranasal tube, gastric fistula, intestinal fistula or such) of an enteral nutrient
35 preparation, liquid agent or such. In this case, the composition of the present invention can be administered after being processed into a formulation such as tablet, capsule,

granule, powder or syrup. These various formulations can be manufactured according to conventional methods by using an adjuvant already known in the technical field of pharmaceutical formulations, such as excipient, binding agent, disintegrator, lubricant, corrigent, solubilizing agent, suspending agent, coating agent, solvent, tonicity agent or such to the principal agent, without limitations thereto. Further, these various formulations may comprise a suitable amount of calcium, and additionally a suitable amount of vitamins, minerals, organic acids, sugars, amino acids, peptides.

When a composition of the present invention is used as a pharmaceutical, the amount and method of administration can be appropriately selected according to the age, body weight, purpose of administration (symptoms) and such of the subject in need of the administration. For compositions of the present invention, the effective dose per kilogram of body weight at each administration can be appropriately selected from, for example, 5 mg-1500 mg, preferably 10 mg-1000 mg, more preferably 20 mg-750 mg, even more preferably 30 mg-500 mg, and particularly preferably 50 mg-250 mg. For compositions of the present invention, the effective dose for a patient at each administration can be appropriately selected from, for example, 0.5 g-150 g, preferably 1 g-100 g, more preferably 2 g-75 g, even more preferably 3 g-50 g, and particularly preferably 5 g-25 g. For compositions of the present invention, the effective dose is, for example, 5 mg-1500 mg, preferably 10 mg-1000 mg, more preferably 20 mg-750 mg, even more preferably 30 mg-500 mg, and particularly preferably 50 mg-250 mg per kilogram of body weight at each administration; and the method of administration is, for example, one to six times a day, preferably one to five times a day, more preferably one to four times a day, and even more preferably one to three times a day, and for example, for one week or more, preferably one week to twelve months, more preferably two weeks to six months, even more preferably three weeks to four months, and particularly preferably four weeks to two months. Further, compositions of the present invention can be appropriately administered to subjects (patients or such) in need of administration before meal, after meal, between meals and/or before bed collectively or separately. The effective number of times a composition of the present invention is administered can be adjusted individually according to the conditions of each subject with observation of the conditions and trends of blood tests after actual administration to the subjects.

When a composition of the present invention is used as a food or drink (in the form of a food or drink), it can be administered in various different forms. The form of administration is, for example, oral administration or enteral administration (intranasal tube, gastric fistula, intestinal fistula or such) of a food or drink such as a dairy product,

liquid food or such. In this case, the composition of the present invention can be consumed after being processed into a food or drink such as in a liquid, paste, solid or powder form, and in fact can be consumed after being added to (mixed with) various foods or drinks and/or in combination with various foods or drinks. These foods or drinks are preferably water, drinks, sweets (including desserts or such), dairy products, liquid foods (including foods or drinks with high nutritional values), infant formula milk, and instant foods; more preferably water, drinks, sweets, dairy products, liquid foods, and infant formula milk; even more preferably sweets, dairy products, and liquid foods; and particularly preferably dairy products, without being limited thereto. More specific examples are cow milk, refreshing drink, fermented milk, yogurt, cheese, bread, biscuit, cracker, pudding, jelly, ice cream, pizza crust, modified milk powder, liquid food, food for patients, nutritional food, frozen food, food composition, processed food, and any other commercially available food. These various types of foods or drinks can be provided as meals in various schools, nursing facilities, and welfare facilities.

When a composition of the present invention is used as a food or drink, the amount of intake and method of intake can be appropriately selected according to the age, body weight, purpose of intake and such of the subject in need of the intake; and it is preferable if its active ingredient can be directly consumed orally as it is. In this case, the composition of the present invention is in the form of a dairy product, liquid food or such, and for example, can be a fresh juice-type beverage, a milkshake-type beverage or such, or powdered food that can be dissolved and dispersed in water before intake. For compositions of the present invention, the daily effective amount of intake is, for example, 0.5 g-150 g, preferably 1 g-100 g, more preferably 2 g-75 g, even more preferably 3 g-50 g, and particularly preferably 5 g-25 g in solid content. Compositions of the present invention can be appropriately administered to subjects (patients or such) in need of the intake before meal, after meal, between meals and/or before bed collectively or separately. Further, compositions of the present invention can be used to replace meals, and can be used as a dietary supplement.

When a composition of the present invention is used as a pharmaceutical or a food or drink, it can be manufactured using methods well known to skilled persons in the art. A skilled artisan would appropriately select and combine a preparation process that mixes a composition of the present invention or its processed product with other ingredients, a sterilization process, a fermentation process, a concentration process, a molding process, a burning process, a drying process, a cooling process, a granulation process, and a packaging process to produce the desirable pharmaceutical or food or

drink. When a composition of the present invention is used as a pharmaceutical or a food or drink, its pH can be set to, for example, 2-6 and preferably 3-5.

When compositions of the present invention are used as various types of dairy products, they can be manufactured using methods well known to skilled persons in the art. For example, yogurt can be produced by a method that involves a step of preparing the starter by culturing lactic acid bacteria; a step of preparing raw milk by, as needed, including in combination (adding) galacto-oligosaccharides and mixing it with a milk constituent; a fermentation step where, after the starter is mixed with the raw milk, the mixture is maintained at a certain temperature; a cooling step that lowers the fermented milk to a certain temperature; a mixing step of combining the fermented milk with galacto-oligosaccharides after crushing or pulverizing as needed; a flavoring step that includes spices or flavoring substances in combination as needed; a filling step, etc. For the starter, for example, a mixture of lactic acid bacteria belonging to the genus *Lactobacillus* and lactic acid bacteria belonging to the genus *Streptococcus* can be used, and preferably a mixture of *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* can be used. Further, cheese can be manufactured by a method that involves the above-mentioned step of starter preparation, the above-mentioned step of raw milk preparation, the above-mentioned fermentation step, a step of generating cheese curds by including rennet in combination, a step of cutting cheese curds, a step of draining cheese whey, a salt addition step, a maturing step and such. In this case, for the starter, for example, lactic acid bacteria belonging to the genus *Lactobacillus* can be used, and preferably *Lactobacillus delbrueckii* subsp. *bulgaricus* or *Lactobacillus helveticus* can be used.

When a composition of the present invention is used as a pharmaceutical or a food or drink, the nutritional composition can be adjusted by further combining it with additional nutrients. In the present invention, for additional nutrients, proteins, sugars, lipids, peptides, amino acids, dietary fibers, vitamins, minerals, organic acids, organic bases, fruit juice, flavors, artificial sweeteners (for example, aspartame) and such can be used. In this case, for proteins, for example, various milk-derived ingredients such as whole milk powder, skim milk powder, partly-skimmed milk powder, condensed whole milk, condensed skim milk, condensed partly-skimmed milk, casein, whey powder, whey protein, whey protein concentrate, whey protein isolate, α -casein, β -casein, κ -casein, β -lactoglobulin, α -lactoalbumin, lactoferrin, soybean protein, hen's egg protein, meat protein, and such, and degradation products thereof, butter, cream, whey, milk serum mineral, non-protein nitrogen, sialic acid, phospholipid, and lactose can be used. Peptides such as casein phosphopeptide and amino acids such as arginine, lysine and such

can also be used. For sugars, for example, sugars such as sucrose, glucose, fructose and honey; processed starches (in addition to dextrin (maltodextrin, indigestible dextrin or such), soluble starches, British starches, oxidized starches, starch esters, starch ethers and such); dietary fibers and such can be used. For lipids, for example, animal fats such as lards, fish oils and such, and fractionated oils, hydrogenated oils, and interesterified oils thereof; vegetable oils such as palm oil, safflower oil, corn oil, canola oil, coconut oil, and fractionated oils, hydrogenated oils, and interesterified oils thereof; and such can be used.

When using a composition of the present invention as a pharmaceutical or a food or drink, one may include in combination (add) a champignon extract which has an effect of reducing fecal malodor, for example, at 0.005-0.5 weight %, or a carotenoid preparation which has a nutrient-enriching effect (including, for example, α -carotene, β -carotene, lycopene and lutein), for example, at 0.00001-0.0002 weight %. Catechin, polyphenol or such can be included in combination as an antioxidant. Further, carnitine which has an effect of enhancing lipid metabolism can also be included in combination. Carnitine is a minor component in the body made from lysine and methionine in the liver and kidney, and its production level is known to decrease with age. Carnitine demonstrates an important function in the metabolism of nutrients by transferring long-chain fatty acids to muscle cells.

Dietary fibers are classified into water-soluble dietary fibers and insoluble dietary fibers, and either one can be used. For water-soluble dietary fibers, lactulose of indigestible oligosaccharides, lactitol and raffinose can be used. A physiological function of indigestible oligosaccharides is an effect of improving the intestinal environment by reaching the large intestine as an undigested material and activating intestinal bifidobacteria or contributing to their proliferation. Lactulose is a disaccharide synthesized from galactose and fructose, and is used as a basic medicinal agent for treatment of hyperammonemia (Bircher, J. et al., Lancet i: 890, 1965). Chronic relapsing hepatic encephalopathy due to chronic hepatic dysfunction respond well to administration of lactulose, specialized amino acid infusion (Fischer solution) for liver failure, and such. Lactitol (β -galactosyl-sorbitol) is viewed as second-generated lactulose; and its clinical effect on chronic hepatic encephalopathy is equivalent to that of lactulose (Lanthier, PL. and Morgan, M., Gut, 26: 415, 1985; Uribe, M., et al., Dig. Dis. Sci., 32: 1345, 1987; Heredia, D. et al., J. Hepatol, 7: 106, 1988; Riggio, O., et al., Dig. Dis. Sci., 34: 823, 1989), and it is used as a medicinal agent for treatment of hyperammonemia.

For water-soluble dietary fibers, pectin (protopectin, pectinic acid, pectic acid) which has improving effects on lipid metabolism (an effect of reducing cholesterol and an effect of reducing neutral fat), guar gum enzyme degradation products, tamarind seed gum or such can be used. The guar gum enzyme degradation products have an effect of suppressing elevation of the blood sugar level and an effect of economizing insulin (Kazuhiko Yamatodani, et al., Journal of Japan Society of Nutrition and Food Science, 46:199, 1993). Further, for water-soluble dietary fibers, konjac glucomannan, alginic acid, low-molecular-weight alginic acid, psyllium, gum arabic, seaweed polysaccharides (cellulose, lignin-like substance, agar, carrageenan, alginic acid, fucoidan, laminarin), microbial gum (wellan gum, curdlan, xanthan gum, gellan gum, dextran, pullulan, rhamsan gum), and other gums (seed-derived locust bean gum, tamarind gum, tara gum, tree sap-derived karaya gum, tragacanth gum) can be used as high-molecular-weight water-soluble dietary fibers; and polydextrose, indigestible dextrin, maltitol, and such can be used as low-molecular-weight water-soluble dietary fibers.

Meanwhile, for insoluble dietary fibers, cellulose, hemicellulose, lignin, chitin, chitosan, soybean dietary fiber, wheat bran, pine fiber, corn fiber, beet fiber, and such can be used. A physiological function of insoluble dietary fibers is an effect of increasing the number of bowel movements to increase the stool output, by increasing the volume of indigestible materials in the large intestine and shortening their passage time.

For vitamins, for example, vitamin A, carotene, B-complex vitamins, vitamin C, vitamin D family, vitamin E, vitamin K family, vitamin P, vitamin Q, niacin, nicotinic acid, pantothenic acid, biotin, inositol, choline, folic acid and such can be used. Thirteen types of vitamins are known.

For minerals, for example, calcium, potassium, magnesium, sodium, copper, iron, manganese, zinc, selenium and such can be used. Trace elements derived from natural products, for example, mineral yeast copper, zinc, selenium, manganese, chromium, copper gluconate, zinc gluconate and such can be used. For organic acids, for example, malic acid, citric acid, lactic acid, tartaric acid and such can be used. In the management of body fluids, the generally problematic electrolytes are sodium, chlorine, potassium, phosphorus, calcium and magnesium. In adjusting a mineral prescription, one should consider (1) whether the intracellularly incorporated mineral is sufficiently distributed, (2) whether the endocrine environment of the patient can sufficiently accommodate the amount and type of nutrient substrate administered, and (3) whether the amount of water administered for estimating the loading of osmotic substances to the kidney and maintaining an appropriate urine osmolarity is adequate.

For these additional nutrients, either chemically synthesized ingredients or natural product-derived ingredients can be used. Further, food products that contain the ingredient of interest can also be used in combination as raw material. These ingredients can be used in combination of at least one type or two types or more.

5 For compositions of the present invention, the osmotic pressure is, for example, 300-1000 mOsm/L, and preferably 300-750 mOsm/L. Further, the viscosity of compositions of the present invention when measured at room temperature (25 °C) is, for example, 1-40 cp (mPa x s) and preferably 3-20 cp. The calorie of compositions of the present invention is, for example, 0.5-3 kcal/mL, preferably 1-2.5 kcal/mL, and
10 more preferably 1-2 kcal/mL. The compositions of the present invention may be in a solid form, liquid form, gel form or semi-solid form.

Compositions of the present invention can be manufactured by known methods in the fields of beverages, dairy products, liquid diets, and enteral nutrients. For example, when a composition of the present invention is used in a liquid form, a
15 method of heat sterilizing the composition (raw solution) in advance, and as needed filling it into a container aseptically after cooling (for example, a method that combines an ultra-high-temperature (UHT) sterilization method (for example, 130-145°C for 1-10 seconds) or a high-temperature short-time (HTST) sterilization method (for example, 100-130°C for 1-60 seconds), with an aseptic filling (packaging) method). When a
20 composition of the present invention is used in a liquid form, a method of filling the composition (raw solution) into a container, and heat sterilizing it together with the container (for example, retort method, autoclave method) can be used. That is, when a composition of the present invention is used in a liquid form, a method of aseptically filling a homogenous compound (homogenized raw solution or sterilized solution)
25 based on the composition after heat sterilization (for example, UHT or HTST sterilization method) followed by cooling as needed, or a method of filling the composition into a can container or soft bag and heat sterilizing it together with the container can be used. When a composition of the present invention is used in a powder form, a method of concentrating a homogenous compound based on the composition by,
30 for example, vacuum evaporation or freezing as needed, followed by spray drying or freeze drying, for example, can be used.

Compositions of the present invention can be expressed as in (1) to (11) below.
(1) A method for suppressing phosphorus absorption, which comprise a step of (orally administering (delivering) a fermented dairy product and an oligosaccharide, or a
35 composition comprising thereof, to a subject.

- (2) A fermented dairy product and an oligosaccharide for use in suppressing phosphorus absorption.
- (3) A method of manufacturing a composition for suppressing phosphorus absorption, comprising combining a pharmaceutically acceptable carrier with a fermented dairy product and an oligosaccharide.
- (4) A composition comprising a fermented dairy product and an oligosaccharide, which is used for addition to a pharmaceutical (pharmaceutical composition) or a food or drink (food or drink composition) and for suppression of phosphorus absorption.
- (5) A method of conferring a phosphorus absorption-suppressing effect to a pharmaceutical composition, nutritional pharmaceutical composition, pharmaceutical, medicinal agent, food or drink composition, food or drink, nutritional composition, special-use food, nutritional functional food, health food, or such, which comprises adding (combining) a fermented dairy product and an oligosaccharide, or a composition comprising thereof, to (with) a pharmaceutical composition, nutritional pharmaceutical composition, pharmaceutical, medicinal agent, food or drink composition, food or drink, nutritional composition, special-use food, nutritional functional food, health food, or such.
- (6) A method for either or both of treating and preventing a disease caused by excessive incorporation of phosphorus, which comprises administering to a subject a fermented dairy product and an oligosaccharide, or a composition comprising thereof.
- (7) Use of a fermented dairy product and an oligosaccharide in the manufacturing of a composition for either or both of treating and preventing a disease caused by excessive incorporation of phosphorus.
- (8) A fermented dairy product and an oligosaccharide for use in either or both of treating and preventing a disease caused by excessive incorporation of phosphorus.
- (9) A method of manufacturing a composition for either or both of treating and preventing a disease caused by excessive incorporation of phosphorus, which comprises combining a pharmaceutically acceptable carrier with a fermented dairy product and an oligosaccharide.
- (10) A composition comprising a fermented dairy product and an oligosaccharide, which is used for addition to a pharmaceutical or a food or drink and for either or both of treating and preventing a disease caused by excessive incorporation of phosphorus.
- (11) A method of conferring an effect of either or both of treating and preventing a disease caused by excessive incorporation of phosphorus to a pharmaceutical composition, nutritional pharmaceutical composition, pharmaceutical, medicinal agent, food or drink composition, food or drink, nutritional composition, special-use food,

nutritional functional food, health food, or such, which comprises adding a fermented dairy product and an oligosaccharide, or a composition comprising thereof, to a pharmaceutical composition, nutritional pharmaceutical composition, pharmaceutical, medicinal agent, food or drink composition, food or drink, nutritional composition, special-use food, nutritional functional food, health food, or such.

All prior art documents cited herein are incorporated into this specification by reference.

[Examples]

1. Test materials and methods

1.1. Feeds

For fermented milk, lactic acid bacteria (*Lactobacillus bulgaricus* and *Streptococcus thermophilus* isolated from the Meiji Bulgaria plain yogurt) are cultured using skim milk as a medium, and the obtained culture was freeze dried. This freeze-dried fermented milk was prepared (produced) by electron beam sterilization with 10-kGy. In the galacto-oligosaccharide (GOS) raw material (Cup-Oligo), the GOS content was 73 wt. %.

For the control diet, AIN93M (Ca content: 0.5 wt. %, phosphorus content: 0.3 wt. %) was used. For the test diet of the fermented milk product and GOS raw material (YG diet), a diet produced by substituting a portion of casein with the freeze-dried fermented milk product, and substituting a portion of sucrose (5 wt. %) with GOS was used. The control diet and test diet (YG diet) were adjusted so that their Ca, phosphorus and crude protein concentrations are equivalent. The crude protein concentration was calculated by multiplying the nitrogen content measured by the Kjeldahl method by 6.38.

Compositions of the test diet of the fermented milk product and GOS raw material (YG diet) and control diet are shown in Table 1.

[Table 1]

	Control feed (AIN-93M)	YG feed (fermented milk +GOS)
composition (g/kg feeds)		
corn starch	447.1	333.03
α -corn starch	155	155
casein	140	46.67
freeze-dried fermented milk	0	220.5
sucrose	100	32.25
soybean oil	40	40
cellulose powder	50	50
AIN-93M mineral premix that does not contain calcium and phosphorus	35	35
calcium carbonate	12.41	5.54
potassium phosphate	8.69	2.46
AIN-93 vitamin premix containing choline bitartrate	10	10
L-cystine	1.8	1.8
GOS raw material	0	67.75
calculated value (g/kg feeds)		
crude protein	118.7	118.7
calcium	5	5
phosphorus	3	3
GOS	0	50

Compositions of “AIN-93M mineral premix that does not contain calcium and phosphorus” in Table 1 are shown in Table 2.

[Table 2]

tri-Potassium citrate monohydrate	28.00
Sodium chloride	74.00
Potassium sulphate	46.60
Magnesium oxide	24.00
Iron citrate	6.06
Zinc carbonate	1.65
Manganese carbonate	0.63
Copper carbonate	0.30
Potassium iodate	0.01
Sodium selenate anhydride	0.01025
Ammonium paramolybdate tetrahydrate	0.00795
Sodium metasilicate nonahydrate	1.45
Chromic potassium sulfate dodecahydrate	0.275
Lithium chloride	0.0174
Boric acid	0.0815
Sodium fluoride	0.0635
Nickel carbonate	0.0318
Ammonium metavanadate	0.0066
Sucrose	774.026

5

Compositions of “AIN-93 vitamin premix containing choline bitartrate” in Table 1 are shown in Table 3.

[Table 3]

Nicotinic acid	3.000
Calcium pantothenate	1.600
Pyridoxine hydrochloride	0.700
Thiamine hydrochloride	0.600
Riboflavin	0.600
Folic acid	0.200
D-biotin	0.020
Cyanocobalamin	2.500
All-rac- α -tocopherol acetate	15.000
All-trans-retinol palmitate	0.800
Cholecalciferol	0.250
Phylloquinone	0.075
Choline bitartrate	250.000
Sucrose	724.655

1.2. Animals

- 5 Thirty-two 11-week-old male Wistar rats (purchased from SLC Japan) were used. These rats were placed in a room with a 12-hour light-dark cycle at room temperature (25°C), and bred individually in stainless metabolism cages. After these rats were domesticated for one week, they were divided into the following four groups with eight rats in each, so that there was no intergroup difference in body weights. The
- 10 PPI was omeprazole sodium (Omepral Injection 20, AstraZeneca).
- Control group (feeding with the control diet and administration of solvent)
 - PPI group (feeding with the control diet and administration of PPI)
 - YG group (feeding with the YG diet and administration of solvent)
 - YG+PPI group (feeding with the YG diet and administration of PPI)

1.3. Test methods

In all groups (control group, PPI group, YG group, and YG+PPI group), the control diet or YG diet (test feeds) was given for 12 weeks only during the dark period.

5 For the control group and PPI group, a pair feeding method was used, and the amount of intake was matched with that of test feeds in the YG group and YG+PPI group. Then, in the PPI group and YG+PPI group, one hour before the beginning of the dark period, a dose of 20 mg/kg body weight of PPI was subcutaneously administered to the above rats daily. As a preliminary experiment, the 20 mg/kg body weight dose of PPI showed
10 significantly high values when subcutaneously administered to mature rats; in contrast to the baseline gastric acid pH of 1.8 ± 0.2 , the pH two to five hours after subcutaneous administration was 7.0 ± 0.2 , and the pH nine to twelve hours post-administration was 2.5 ± 0.3 . Further, the same method was used in the control group and YG group, and one hour before the beginning of the dark period, a dose of 20 mg/kg body weight of
15 physiological saline was subcutaneously administered to the above rats daily. All of the groups were allowed to freely consume ion-exchanged water during the test period.

Four and twelve weeks after beginning of the experiment, feces and urine were collected from each rat for three days, and used for measurement of calcium and phosphorus. When the experiment ended, blood was collected from the abdominal
20 aorta under pentobarbital anesthesia, and the rats were sacrificed. After the rats were sacrificed, right femur was extirpated from each rat, conserved in 70% ethanol, and used for X-ray CT measurement, μ CT measurement, and bone strength measurement.

Measurement of femur bone mineral density (BMD) and bone strength by X-ray CT
25 (Latheta CT imaging):

A CT device for animals, Latheta (LCT-100 M, Hitachi-Aloka Medical), was used to photograph images of the right femur of each rat at 1 mm intervals. The Latheta software (version 1.31) was used to analyze these photographed images to calculate the cortical bone mineral density, trabecular bone mineral density, total bone mineral
30 density, cortical bone width, minimum moment of inertia of cross-sectional area (MMICA), and polar moment of inertia of cross-sectional area (PMICA). Starting with the femur, bones are made of generally two types of structural parts called “cortical bone” and “trabecular bone”, and the ratio of these two types of structures differs depending on the bone type. The cortical bone is a hard and elaborate structure
35 covering the surface of bone. Meanwhile, the trabecular bone is a netlike structure of intricately combined small fine bones. Further, “cortical bone mineral density” is the

partial bone mineral density (bone mass per unit volume (unit area)) of cortical bone, and “trabecular bone density” is the partial bone mineral density (bone mass per unit volume (unit area)) of trabecular bone. “Total bone mineral density” is the bone mineral density (bone mass per unit volume (unit area)) of the above “cortical bone”

5 portion and the above “trabecular bone” portion in combination. Any of them can serve as an indicator of bone strength. Also, “cortical bone width” is the thickness of cortical bone. If the bone diameter is the same, cortical bones with a thicker width tend to have a higher mechanical strength. Further, minimum moment of inertia of cross-sectional area (MMICA) is an indicator of the cross-sectional intensity which represents the
10 strength against bending. When a load was applied to cause bending of a round-bar-like component, it serves as an indicator of the strength against the bending load. The larger the moment of inertia of cross-sectional area is, the stronger it is against bending. That is, comparison of the minimum moment of inertia of cross-sectional area among multiple bones allows comparison of their relative strengths against bending.
15 Meanwhile, polar moment of inertia of cross-sectional area (PMICA) is an indicator of the cross-sectional intensity that represents the strength against torsion. When a load was applied to cause torsion of a round-bar component (in the state of one fixed end and the opposite end rotated), it serves as an indicator of the strength against the torsion load. In fact, the moment of inertia of cross-sectional area is determined according to the
20 cross-sectional diameter of the component and the size of the applied load. The larger the moment of inertia of cross-sectional area is, the stronger it is against torsion. That is, by setting the applied load to the same conditions, the relative strengths of multiple bones against torsion can be compared by comparing the moment of inertia of cross-sectional area.

25

Measurement of bone microarchitecture of the distal shaft of femur by μ CT (μ CT imaging):

Images were taken at sites 0.5 mm away from the growth plate (2 mm in length) of the right femur of each rat using μ CT (ScanXmate-L080, Comscantecno Co.,
30 Ltd.). Compared to conventional CT, μ CT has a narrower field of filming, and a higher resolution (the minimum size that can be ultimately recognized). In μ CT, the inner structure of the test material in a non-disrupted stated can be observed in detail, and depending on the actual conditions, 1-10 μ m shape can be determined. The imaging conditions are tube voltage: 80 kV, tube current: 100 μ A, magnification: 6.96, and voxel
35 size: 14.368 x 14.368 x 14.368 μ m. In order to reduce the beam hardening effect, brass plate filters of 0.1 mm thickness were used. The TRI/3D-BON software (Ratoc System

Engineering Co., Ltd.) was used to calculate trabecular bone mineral density (BV/TV, %), trabecular width (Tb.Th, μm), number of trabeculae (Tb.N, mm^{-1}), trabecular space (Tb.Sp, μm), and star volume of the bone-marrow space ($V^*\text{m.space}$, mm^3), trabecular star volume ($V^*\text{tr}$, mm^3), number of nodes (Nd: three or more points of union in bone trabeculae) per volume of tissue (N.Nd/TV), number of termini (Tm: terminal points at which there is no binding with other trabeculae) per volume of tissue (N.Tm/TV), number of cortices (Ct: points of binding with trabeculae) per volume of tissue (N.Ct/TV), total length of the skeletal line of the analyzed portion of the bone per volume of tissue (TSL/TV), total volume (Tt.V, mm^3), cortical bone volume (Ct.V, mm^3), ratio of cortical bone volume (Ct.V/Tt.V, %), average cortical bone width (Ct.Th, mm), minimum moment of inertia of cross-sectional area (I_{min} , mm^5), density-weighted minimum moment of inertia of cross-sectional area ($I_{\text{min Dn}}$, $\text{mm} (\text{mm}^2)$)). Here, “trabecula” is a basic unit in the trabecular bone, and is the sponge-shaped portion that stretches vertically and horizontally like a mesh. Compared to cortical bone, its bone metabolism is more active. “Bone marrow” is the space among trabeculae, and this is where red blood cells, white blood cells, platelets and such are generated. “Trabecular width” is the thickness of trabeculae, and the “number of trabeculae” is the number of trabeculae per unit length. “Trabecular space” is the width of space between two trabeculae. Any of them can serve as an indicator of the strength of trabecular bone. Their respective numerical values can be quantitatively calculated by, for example, analyzing the three-dimensional structure of trabeculae from tomographic images of the bone obtained by μCT . Further, “star volume” is an indicator of osteoporosis, and is a volume of the field of vision not blocked in all directions from any arbitrary site. For example, if the linear continuity of bone-marrow space is maintained, the star volume of the bone-marrow space becomes larger. Further, if the linear continuity of trabeculae is maintained, the star volume of the trabeculae becomes larger. That is, in star volume analysis, the star volume of the bone-marrow space and the star volume of trabeculae are determined, and these numerical values can be used as an indicator of osteoporosis. The node-strut analysis is a method for evaluating the trabecular structure by viewing the trabecular structure as a structural body of only points and lines, and is expressed two-dimensionally by image processing of the trabecular image and converting the trabecular structure into skeletal patterns. Next, nodes (three or more points of union in bone trabeculae), termini (terminal points at which there is no binding with other trabeculae), cortices (points of binding between trabecula and cortical bone) are determined, and the nodes, termini and cortex are jointed to determine the total length of

the skeletal line. These respective numerical values are used as an indicator of the changes in the inner structure of trabeculae.

Three-point bending test:

- 5 A three-point bending test was performed on a bone strength tester device (Bone Strength Tester model TK-252, Muromachi Kikai Co., Ltd.) using the right femur that had been photographed by Latheta CT and μ CT. The right femur was placed on top of a supporting apparatus (space: 15 mm), and a force was applied at the constant speed of 5 mm/min perpendicularly to the center of the femur until the bone fractured.
- 10 The breaking energy, stiffness, and maximum load were calculated. The “breaking energy” in a three-point bending test refers to the total energy required until a test material breaks when a load is applied to the test material. “Stiffness” is the level of difficulty for the shape to change against the force of bending or torsion. When there is a small change in the shape against the force, the stiffness is increased; and when there
- 15 is a big change in the shape, the stiffness is reduced. Any of them can serve as an indicator of the strength of the test material.

Balance of calcium and phosphorus:

- 20 The test feeds, feces and urine were incinerated in the presence of concentrated nitric acid using a wet ashing device (Multiwave3000, Perkin Elmer), and calcium and phosphorus were measured using an ICP device (ICP-S7500, Shimadzu Corporation). The apparent amount of calcium absorption (mg/3 days) was calculated according to [amount of Ca intake] - [amount of fecal Ca excretion], and the percentage of calcium absorption (%) was calculated by [amount of Ca intake] - [amount of fecal Ca
- 25 excretion] / [amount of Ca intake] x 100. The amount of calcium accumulation (mg/3 days) was calculated by [apparent amount of Ca absorption] - [amount of urinary Ca excretion], and the percentage of calcium accumulation (%) was calculated by ([apparent amount of Ca absorption] - [amount of urinary Ca excretion]) / [amount of Ca intake] x 100. Parameters for phosphorus were calculated in the same manner as
- 30 calcium.

Statistical analysis:

- 35 All the data are presented mean value $\pm$ standard deviation. All the data were verified for equality of variance by Bartlett’s test. When equality of variance was confirmed, a two way factorial analysis of variance was performed with the two factors of PPI and diet. In the two way factorial analysis of variance, when the interaction was

significant (the value of interaction was less than 0.05), the Tukey-Kramer multiple comparisons test was performed. When equality of variance was not confirmed in the data, the Kruskal-Wallis test was performed followed by the Steel-Dwass multiple comparisons test. $P < 0.05$ was considered statistically significant. The statistical analysis was performed using Excel Statistics 2012 (Social Survey Research Information Co., Ltd.). In Table 7 and Table 8, the “a”, “b” or “c” symbol was used to denote statistically significant difference between different types of symbols.

2. Test results

2.1. Body weights

When the experiment ended, the body weight of the control group was 340.6 ± 5.2 g, the body weight of the PPI group was 347.3 ± 4.2 g, the body weight of the YG group was 348.5 ± 4.1 g, and the body weight of the YG+PPI group was 348.6 ± 5.5 g. A significant difference in the body weight was not observed among these groups.

Total femur bone density and bone strength:

The results of measuring the bone mineral density and bone strength of femur by X-ray CT and the measurement results of the three-point bending test are shown in Table 4. The total bone mineral density, cortical bone mineral density, trabecular bone mineral density, cortical bone thickness of the femur were significantly reduced by PPI. The P value (PPI) in the two way factorial analysis of variance when the control group and the PPI group were compared and when the YG group and the YG+PPI group were compared (Table 2), was 0.0008-0.0113, and less than 5% in both comparisons, showing a significant reduction. The total bone mineral density, cortical bone mineral density, trabecular bone mineral density, cortical bone thickness of the femur were significantly increased by the YG diet. The P value (feeds) in the two way factorial analysis of variance when the control group and the YG group were compared and when the PPI group and the YG+PPI group were compared (Table 2), was 0.0001 or less, and less than 5% in both comparisons, showing a significant increase. The PPI administration significantly reduced the polar moment of inertia of cross-sectional area, demonstrating a trend of reducing the polar moment of inertia of cross-sectional area (p value: 0.0623). Meanwhile, the YG diet feeding significantly increased the minimum moment of inertia of cross-sectional area and the polar moment of inertia of cross-sectional area. Further, in the three-point bending test, the PPI administration significantly reduced the stiffness and maximum load of the femur, but did not affect the breaking energy. Meanwhile, the YG diet feeding significantly increased the

breaking energy and the maximum load, and showed a tendency of increasing the femur stiffness (p value: 0.0576). Comparison of the control group (310 ± 11) and the PPI group (274 ± 4) showed that femur stiffness was reduced by the PPI administration, and comparison of the YG group (311 ± 11) and the YG+PPI group (309 ± 8) showed that

5 femur stiffness was not changed by the PPI administration. That is, femur stiffness is originally reduced by PPI, but the YG diet increased femur stiffness, and thus the influence of PPI in the YG+PPI diet feeding tended to be cancelled out (value of interaction: 0.0611). These results clearly showed that the YG diet improves (increases)

10 bone strength both in a healthy state with no PPI administration, and in a state of reduced bone strength with PPI administration.

[Table 4]

	Control group	PPI group	YG group	YG+PPI group	P value by two way factorial analysis of variance		
					pPI	Feeds	Interaction
Total BMD (mg/cm ³)	718 ± 6	695 ± 8	789 ± 6	768 ± 5	0.0013	<0.0001	0.911
: Total bone mineral density							
Cortical BMD (mg/cm ³)	1147 ± 3	1134 ± 4	1178 ± 3	1167 ± 3	0.0012	<0.0001	0.7937
: Cortical bone mineral density							
Trabecular BMD (mg/cm ³)	403 ± 5	386 ± 6	456 ± 4	438 ± 4	0.0008	<0.0001	0.9456
: Trabecular bone mineral density							
Cortical thickness (mm)	0.454 ± 0.005	0.439 ± 0.005	0.506 ± 0.006	0.493 ± 0.004	0.0113	<0.0001	0.7915
Minimum moment of inertia (mg•cm)							
: Minimum moment of inertia of cross-sectional area (strength against bending)	1.239 ± 0.028	1.190 ± 0.023	1.358 ± 0.036	1.277 ± 0.025	0.0312	0.0014	0.5805
Polar moment of inertia (mg•cm)							
: Polar moment of inertia of cross-sectional area (strength against torsion)	3.765 ± 0.097	3.669 ± 0.071	4.206 ± 0.114	3.946 ± 0.083	0.0623	0.0007	0.3843
Three-point bending test							
Breaking energy (mJ)	66 ± 4	73 ± 4	87 ± 4	84 ± 4	0.6387	0.0004	0.2165
Stiffness (N/mm)	310 ± 10	274 ± 4	311 ± 11	309 ± 8	0.0432	0.0576	0.0611
Maximum load (N)	172 ± 3	168 ± 5	192 ± 5	178 ± 4	0.0466	0.0014	0.2529

The bone microarchitecture of the distal shaft of femur:

Results of measuring the microarchitecture of the femur by μ CT are shown in Table 5. While the PPI administration had no influence on the bone mineral density of the trabecular bone, the number of trabeculae, and trabecular space, it showed a
5 tendency of reducing the trabecular bone width (p value: 0.0549). Meanwhile, the YG diet feeding significantly improved (increased) the bone mineral density of the trabecular bone, the number of trabeculae, and trabecular space, but did not affect the trabecular bone width. In star volume analysis, PPI administration had no influence on either the star volume of the bone-marrow space or the star volume of trabeculae. The
10 YG diet feeding significantly reduced the star volume of the bone-marrow space and significantly increased the star volume of trabeculae. Further, in node-strut analysis, the PPI administration showed no influence on either of these indicators. Meanwhile, the YG diet feeding significantly increased the number of nodes, the number of cortices, and the total length of the skeletal line, and showed a tendency of reducing the number
15 of termini (p value: 0.0955). These results clearly showed that the YG diet improves the bone structure of the trabecular bone of femur both in a healthy state with no PPI administration, and in a state of reduced bone strength with PPI administration. This suggests that the compositions of the present invention can be effectively used to treat or prevent diseases with degenerated bone structure such as osteoporosis.

[Table 5]

	Control group	PPI group	YG group	YG+PPI group	P value by two way factorial analysis of variance		
					PPI	Feeds	Interaction
BV/TV (%)	16.2 ±0.9	14.8 ±1.7	21.8 ±1.8	20.7 ±1.2	0.4201	0.0006	0.9353
: Bone mineral density							
Tb.Th (µm)	96.0 ±1.9	95.3 ±1.6	105.7 ±0.9	100.9 ±1.0	0.0549	<0.0001	0.1455
: Trabecular width							
Tb.N (1/mm)	1.17 ±0.07	1.05 ±0.09	1.35 ±0.12	1.37 ±0.07	0.553	0.0103	0.4365
: Number of trabeculae							
Tb.Sp (µm)	216 ±10	213 ±10	193 ±9	208 ±7	0.5196	0.1312	0.3043
: Trabecular space							
Star volume analysis							
: Indicator of the level of osteoporosis							
V* m.space (mm ³)	1.25 ±0.10	1.50 ±0.12	0.89 ±0.14	0.86 ±0.06	0.3132	<0.0001	0.2263
: Star volume of the bone-marrow space							
V* tr (mm ³)	0.036 ±0.002	0.038 ±0.003	0.049 ±0.003	0.042 ±0.003	0.3375	0.0061	0.1167
: Star volume of trabecula (average volume of the field from the central point of the trabecula to the periphery of the trabecula in all directions							
Node-strut analysis							
: Indicator for classification of skeletal lines extracted from the network of skeletal lines of trabeculae							
N.Nd/TV (1/mm ³)	54.0 ±3.4	45.3 ±4.0	63.2 ±6.8	68.5 ±4.0	0.7238	0.0024	0.1591
: Number of Nd (point of union in trabeculae) in total volume							
N.Tm/TV (1/mm ³)	2.60 ±0.19	2.57 ±0.15	2.32 ±0.14	2.31 ±0.15	0.8656	0.0955	0.9576
: Number of Tm (terminal point without binding with other trabeculae) in total volume							
N.Ct/TV (1/mm ³)	17.9 ±0.6	16.2 ±1.0	19.9 ±1.3	20.1 ±0.9	0.4371	0.0075	0.3408
: Number of Ct (point of binding to cortical bone) in total volume							
TSL/TV (1/mm ³)	19.2 ±1.0	17.0 ±1.5	23.2 ±2.2	24.1 ±1.3	0.6868	0.0022	0.3373
: Total length of skeletal line in total volume							

Results of measuring the morphology of the cortical bone of femur by μ CT are shown in Table 6. In the measurement of the cortical bone morphology, the PPI administration significantly reduced the cortical bone volume, ratio of the cortical bone volume, average cortical bone width, minimum moment of inertia of cross-sectional area, and density-weighted minimum moment of inertia of cross-sectional area. Meanwhile, the YG diet feeding significantly increased the cortical bone volume, ratio of the cortical bone volume, average cortical bone width, minimum moment of inertia of cross-sectional area, and density-weighted minimum moment of inertia of cross-sectional area. These results clearly showed that the YG diet enhances (increases) the bone density of the cortical bone, and improves the bone structure of the trabecular bone of femur both in a healthy state with no PPI administration, and in a state of reduced bone strength with PPI administration.

[Table 6]

	P value by two way factorial analysis of variance				
	Control group	PPI group	YG group	YG+PPI group	PP1 Feeds Interaction
Tt.V (mm ³)	28.2 ±0.3	27.9 ±0.5	28.9 ±0.6	28.6 ±0.3	0.525 0.1352 0.9639
:Total volume of analyzed portion of bone					
Ct.V (mm ³)	10.2 ±0.1	9.7 ±0.1	11.0 ±0.2	10.5 ±0.1	0.0005 <0.0001 0.8849
: Cortical bone volume					
Ct.V/Tt.V (μm)	36.1 ±0.5	34.6 ±0.5	38.3 ±1.0	36.7 ±0.6	0.0267 0.0036 0.9126
: Ratio of the cortical bone volume					
Ct.Th (μm)	393 ±6	373 ±5	425 ±10	402 ±6	0.0049 0.0002 0.8408
: cortical bone width					
Imin (mm ⁵)	19.5 ±0.3	17.9 ±0.4	20.8 ±0.5	19.7 ±0.3	0.0028 0.0012 0.5715
: Minimum moment of inertia of cross-sectional area					
Imin Dn [mg(mm) ²]					
: Density-weighted minimum moment of inertia of cross-sectional area	36.6 ±0.7	33.4 ±0.8	39.0 ±1.0	36.6 ±0.6	0.0014 0.0011 0.5966

Balance of calcium and phosphorus:

Results of the calcium balance are shown in Table 7, and results of the phosphorus balance are shown in Table 8. The PPI administration did not have a significant influence on calcium balance. Meanwhile, the YG diet feeding significantly increased the week 4 calcium absorption, and the week 4 and week 12 urinary calcium excretion. In the PPI group, the amount of phosphorus absorption and percentage of phosphorus absorption at the 4th week were significantly increased. Meanwhile, in the YG group, there was no significant increase in the amount of phosphorus absorption or the percentage of phosphorus absorption at the 4th week. In the YG+PPI group, the amount of phosphorus absorption and percentage of phosphorus absorption were significantly reduced when compared to those for the PPI group. Thus, it became clear that the YG diet has no influence on phosphorus balance in a healthy state; however, when the gastric acid is reduced as a result of PPI administration, the YG diet reduces phosphorus absorption. The same trend was observed in the amount of phosphorus absorption and percentage of phosphorus absorption at the 12th week, and the amount of urinary phosphorus excretion at the 4th and 12th weeks. These results revealed that the YG diet feeding has an effect of reducing phosphorus absorption, and an effect of normalizing phosphorus absorption when phosphorus absorption is abnormally increased.

The above results showed that compositions comprising a combination of a fermented dairy product and an oligosaccharide have an effect of improving bone strength, an effect of improving bone mineral density, and an effect of suppressing phosphorus absorption (effect of normalizing phosphorus metabolism). Until now, it was completely unknown as to how combinations of a fermented dairy product and an oligosaccharide would affect phosphorus metabolism. For the first time, the long-term effect was evaluated and verified in the present invention by oral administration (oral intake) of a fermented dairy product and an oligosaccharide to 11-week-old elderly rats for twelve weeks. As a result, it was discovered for the first time that combinations of a fermented dairy product and an oligosaccharide have an effect of normalizing the abnormality of phosphorus metabolism (excessive incorporation of phosphorus) when gastric acid is reduced. In addition, it was discovered for the first time by the present invention that combinations of a fermented dairy product and an oligosaccharide have a particularly excellent effect in improving bone strength and a particularly excellent effect of improving bone mineral density. Accordingly, it was revealed that it is possible to normalize the abnormality of phosphorus metabolism and improve bone strength or bone mineral density by oral administration of a composition of the present

invention, which has a highly beneficial effect for subjects with reduced gastric acid, in particular.

[Table 7]

	P value by two way factorial analysis of variance				
	Control group	PPI group	YG group	YG+PPI group	PPI Feeds Interaction
4th week					
Amount of calcium intake (mg/3 day)	215.4 ±4.7	215.4 ±4.7	206.2 ±9.0	226.4 ±6.0	0.1242 0.8980 0.1242
Amount of fecal calcium excretion (mg/3 day)	160.4 ±8.0	156.6 ±6.0	131.4 ±7.3	152.3 ±6.6	0.2324 0.0246 0.0883
Amount of calcium absorption (mg/3 day)	55.1 ±7.2	58.9 ±2.5	74.8 ±5.9	74.1 ±5.6	0.7856 0.0042 0.6864
Percentage of calcium absorption (%)	25.6 ±3.3	27.5 ±1.5	36.3 ±2.1	32.7 ±2.4	0.7332 0.0026 0.2643
Amount of urinary calcium excretion (mg/3 day)	1.8 ±0.1 a	1.5 ±0.2 a	13.0 ±1.8 b	6.7 ±1.2 b	$P_{\text{Kruskal Wallis}} = 0.0001$
Amount of calcium accumulation (mg/3 day)	53.2 ±7.2	57.4 ±2.6	61.9 ±5.9	67.4 ±6.3	0.4104 0.1174 0.9057
Percentage of calcium accumulation (%)	24.7 ±3.3	26.8 ±1.5	30.1 ±2.5	29.8 ±2.7	0.7438 0.1174 0.6433
12th week					
Amount of calcium intake (mg/3 day)	210.4 ±3.7	210.4 ±3.7	211.1 ±6.6	222.7 ±9.0	0.3539 0.3025 0.3539
Amount of fecal calcium excretion (mg/3 day)	173.4 ±9.9	160.3 ±8.1	166.7 ±10.7	168.0 ±7.1	0.5206 0.9558 0.4334
Amount of calcium absorption (mg/3 day)	37.0 ±8.7	50.1 ±5.9	44.3 ±9.0	54.6 ±11.0	0.1949 0.5040 0.8758
Percentage of calcium absorption (%)	17.7 ±4.1	24.0 ±3.0	21.1 ±4.3	23.7 ±4.7	0.2775 0.7029 0.6587
Amount of urinary calcium excretion (mg/3 day)	2.6 ±0.5 a	1.7 ±0.1 a	19.1 ±1.4 c	8.3 ±1.2 b	$P_{\text{Kruskal Wallis}} < 0.0001$
Amount of calcium accumulation (mg/3 day)	34.3 ±8.6	48.3 ±5.9	25.2 ±9.4	46.4 ±10.9	0.0574 0.5391 0.6900
Percentage of calcium accumulation (%)	16.4 ±4.0	23.2 ±2.9	11.9 ±4.5	20.0 ±4.8	0.0827 0.3648 0.8716

[Table 8]

	Control group				P value by two way factorial analysis of variance			
	Control group	PPI group	YG group	YG+PPI group	PPI	Feeds	Interaction	
4 th week								
Amount of phosphorus intake (mg/3 day)	132.7 ±2.9	132.7±2.9	130.0 ±5.7	142.7±3.8	0.1220	0.3716	0.1220	
Amount of fecal phosphorus excretion (mg/3 day)	80.2 ±4.0 a	29.7 ±2.0 b	73.6 ±4.0 a	67.7 ±3.0 a	<0.0001	0.0001	<0.0001	
Amount of phosphorus absorption (mg/3 day)	52.5 ±3.9 a	103.0 ±1.3 c	56.4 ±4.1 a	75.0 ±3.4 b	<0.0001	0.0012	0.0001	
Percentage of phosphorus absorption (%)	39.6 ±2.8 a	77.8 ±1.1 c	43.3 ±2.0 a	52.6 ±1.9 b	<0.0001	<0.0001	<0.0001	
Amount of urinary phosphorus excretion(mg/3 day)	20.3 ±0.9 a	47.6 ±2.8 b	20.6 ±1.5 a	28.3 ±3.6 a	$P_{\text{Kruskal Wallis}} = 0.0002$			
Amount of phosphorus accumulation (mg/3 day)	32.2 ±4.2	55.4 ±3.4	35.8 ±3.9	46.7 ±5.3	0.0004	0.5543	0.1628	
Percentage of phosphorus accumulation (%)	24.2 ±3.0 a	41.7 ±2.5 b	27.4 ±2.4 a	32.8 ±3.7 ab	0.0006	0.3445	0.0479	
12 th week								
Amount of phosphorus intake (mg/3 day)	129.6 ±2.3	129.6 ±2.3	133.1 ±4.2	140.4 ±5.7	0.3520	0.0768	0.3520	
Amount of fecal phosphorus excretion (mg/3 day)	83.9 ±4.9 a	35.7 ±2.5 b	87.0 ±5.6 a	73.8 ±3.3 a	<0.0001	<0.0001	0.0003	
Amount of phosphorus absorption (mg/3 day)	45.8 ±4.6 a	94.0 ±2.1 c	46.0 ±5.1 a	66.6 ±6.5 b	<0.0001	0.0090	0.0079	
Percentage of phosphorus absorption (%)	35.3 ±3.4 ab	72.6 ±1.6 c	34.6 ±3.7 a	46.8 ±3.5 b	<0.0001	0.0002	0.0005	
Amount of urinary phosphorus excretion(mg/3 day)	19.2 ±1.0 a	58.8 ±2.8 c	26.9 ±1.8 ab	32.3 ±2.4 b	<0.0001	0.0001	<0.0001	
Amount of phosphorus accumulation (mg/3 day)	26.5 ±5.0	35.2 ±3.4	19.1 ±5.0	34.3 ±5.9	0.0220	0.4041	0.5085	
Percentage of phosphorus accumulation (%)	20.5 ±3.8	27.3 ±2.8	14.3 ±3.7	23.8 ±4.0	0.0311	0.1950	0.7105	

Industrial Applicability

Long-term administration of a composition of the present invention, which is a combination of a fermented dairy product and an oligosaccharide, can for example suppress the excessive incorporation of phosphorus caused by the increase of pH due to reduction of gastric acid secretion, and return phosphorus absorption to a normal range. In other words, compositions of the present invention can improve abnormality of phosphorus metabolism. Compositions of the present invention can ameliorate diseases caused by excessive incorporation of phosphorus. Compositions of the present invention are constituted from ingredients that have been proven to be excellent in safety and taste property from a long history of use in foods, which causes a small burden on the body when administered, and thus can be administered for a long period of time.

CLAIMS

1. A composition for use in suppressing phosphorus absorption, which comprise a fermented dairy product and an oligosaccharide as active ingredients.
5
2. The composition of claim 1, wherein the oligosaccharide is an oligosaccharide that comprises galactose as a constituent sugar.
3. The composition of claim 2, wherein the oligosaccharide is galacto-oligosaccharide.
10
4. The composition of any one of claims 1 to 3, wherein the fermented dairy product is a fermented dairy product obtained using lactic acid bacteria that belong to the genus *Lactobacillus* and/or lactic acid bacteria that belong to the genus *Streptococcus*.
- 15 5. The composition of any one of claims 1 to 4, wherein the fermented dairy product is yogurt and/or unmatured cheese.
6. The composition of any one of claims 1 to 5, for use in oral administration to a subject with reduced gastric acid secretion and/or elevated gastric acid pH.
20
7. The composition of any one of claims 1 to 6, for use in daily oral administration over a period of at least four weeks or more.
8. The composition of any one of claims 1 to 7, for use as a food additive.
25
9. Use of a fermented dairy product and an oligosaccharide in the manufacturing of a composition for use in suppressing phosphorus absorption.