DESCRIPTION

Title of Invention:

Anti-Allergic Agent, Agent for Improving Allergic Diarrhea and Pharmaceutical Composition

Technical Field

[0001]

The present invention relates to an anti-allergic agent, an agent for improving allergic diarrhea and a pharmaceutical composition containing the same.

Background Art

[0002]

In the society of modern times, the number of patients suffering from allergic diseases is increasing, and allergic diseases are also called modern diseases. Causes of allergic diseases include environmental causes such as dust or ticks and causes derived from foods, and once a patient catches an allergic disease, the patient is forced to remove the causes of the allergy in the life. Methods for relieving allergic diseases include drug therapies by administration of drugs (NPL 1), but drug therapies are not necessarily effective means because of the side effects.

[0003]

In many of the parts where allergic diseases are caused, accumulation and activation of mast cells are significant. Mast cells express high-affinity receptors for IgE, and when IgE which is specific to a particular allergen is produced, mast cells are accumulated. Then, crosslinking and degranulation of mast cells through allergen/IgE occur, and inflammatory mediators are released [Fig. 1(a) to Fig. 1(c)].

Citation List

Non Patent Literature

[0004]

NPL 1: *Wakariyasui Kusuri No Chishiki – Shitte Anshin, Kusuri No Mochiikata-*, edited by Ei Ninomiya, Shinnippon-Hoki Publishing Co., Ltd., issued on March 22, 1995, 379-395 pages

Summary of Invention

Technical Problem

[0005]

An object of the invention is to provide an anti-allergic agent which improves an allergic disease and which does not have side effects.

Solution to Problem

[0006]

On extensive investigation, the present inventors have found that palmitic acid bound to glyceride at the β-position (hereinafter referred to as β-palmitic acid) has an anti-allergic effect, in particular an improvement effect on allergic diarrhea, and the inventors have thus completed the invention.

[0007]

That is, the invention is as follows.

(1) An anti-allergic agent comprising β-palmitic acid as an active ingredient.

(2) An agent for improving allergic diarrhea comprising β-palmitic acid as an active ingredient.

(3) A pharmaceutical composition comprising the anti-allergic agent according to the item (1) above or the agent for improving allergic diarrhea according to the item (2) above.

(4) An additive for preventing or treating an allergy comprising β-palmitic acid as an active ingredient.

(5) An oral composition for preventing or treating an allergy, where the additive according to the item (4) above has been added.

Advantageous Effects of Invention

[0008]

β-Palmitic acid is contained in specific edible oils and fats such as lard derived from pigs and inhibits the production of allergen-specific IgE in an allergic disease. Also, β-palmitic acid decreases the number of mast cells in the large intestine and can inhibit the degranulation of mast cells.

[0009]

Accordingly, when the anti-allergic agent or the agent for improving allergic

diarrhea of the invention which contains β-palmitic acid as an active ingredient is added, a pharmaceutical composition having an anti-allergic effect or an improvement effect on allergic diarrhea and an oral composition for preventing or treating an allergy, which are safe and which have few side effects can be derived.

[0010]

In this regard, although the effects of β-palmitic acid except for an anti-allergic effect, such as reinforcement of bones of babies or improvement of gut flora, have been known, the inventors are the first to find the anti-allergic function itself.

Brief Description of Drawings

[0011]

[Fig. 1] Fig. 1(a) to Fig. 1(c) are figures for explaining the mechanism of accumulation and activation of mast cells in a part of an allergic disease.

[Fig. 2] Fig. 2 shows the results of observation of the incidence rates of allergic diarrhea after the administration of soybean oil, vegetable oils and fats, or vegetable oils and fats with an increased β-palmitic acid ratio (test oils and fats).

[Fig. 3] Fig. 3(a) to Fig. 3(c) show the results of analysis of the influence on the parameters of allergic diarrhea (the amount of allergen-specific IgE production, the number of mast cells in the large intestine and the number of degranulated mast cells) using soybean oil (Soy4), vegetable oils and fats (Soy0.4+Cont3.6) or vegetable oils and fats with an increased β-palmitic acid ratio (Soy0.4+Beta3.6)

Description of Embodiments

[0012]

The β-palmitic acid which is the active ingredient of the invention means all the compounds which are identical in view of the chemical formula. Also, the β-palmitic acid may be a pure product or a mixture with another substance. For example, a raw material in which the presence of β-palmitic acid has been confirmed by measuring β-palmitic acid by a known measurement method may be used directly.

[0013]

A typical example of raw materials (mixtures) which are rich in β-palmitic acid is lard, and lard can also be used. However, lard has a peculiar “animal smell”, and to solve this problem, it is also known that a raw material rich in β-palmitic acid is obtained by

modifying chemically or modifying enzymatically vegetable oil or fat rich in palmitic acid (JP-T-8-509620 (the term "JP-T" as used herein means a published Japanese translation of a PCT patent application), JP-T-8-509621 and JP-A-6-70786). Also, for example, Betapol (Loders Croklaan) is a commercial product, and the product may be directly purchased and appropriately mixed with another raw material.

[0014]

When β-palmitic acid is contained in the mixture with another substance, the β-palmitic acid content of the fatty acid composition is preferably 10% or more, more preferably 20 to 90%, further preferably 30 to 80%, particularly preferably 40 to 70%, most preferably 50 to 60%. By controlling the β-palmitic acid content of the fatty acid composition at 10% or more, a sufficient anti-allergic effect is obtained.

[0015]

The intake method of β-palmitic acid is not particularly limited as long as β-palmitic acid is absorbed in the body in the end by the method, such as oral intake, gavage or enteral intake, but oral intake is preferable.

[0016]

The recommended intake of β-palmitic acid per day is preferably 0.1 g to 100 g, more preferably 0.2 g to 80 g, further preferably 0.4 g to 60 g, further preferably 0.6 g to 50 g, further preferably 0.8 g to 40 g, further preferably 1.2 g to 30 g, particularly preferably 1.6 g to 20 g, most preferably 2 g to 10 g.

[0017]

As demonstrated in the Examples, a further anti-allergic effect is expected when β-palmitic acid is taken continuously, and the recommended frequency of intake of β-palmitic acid is preferably twice or more, more preferably three times or more, further preferably four times or more, further preferably five times or more, particularly preferably six times or more, most preferably seven times or more. The recommended frequency of intake may be per package.

[0018]

β-Palmitic acid and the raw material containing β-palmitic acid can be widely used as a raw material without side effects for an anti-allergic agent, an agent for improving allergic diarrhea, pharmaceutical compositions containing the agents, an oral composition for preventing or treating an allergy or the like.

[0019]

With respect to the anti-allergic agent or the agent for improving allergic diarrhea of the invention, β-palmitic acid or a combination of β-palmitic acid and a pharmaceutically acceptable pharmaceutical carrier can be administered to mammals including humans orally or through gavage.

[0020]

With respect to the anti-allergic agent or the agent for improving allergic diarrhea of the invention, the unit dosage form of the pharmaceutical preparation thereof is not particularly limited, and a dosage form which is generally used for a general drug can be appropriately selected depending on the purpose of the treatment. Here, specifically, tablets, pills, powder, a liquid solution, a suspension, an emulsion, granules, subtle granules, capsules, a syrup, an elixir, suppositories, an injection, an ointment, a patch, eye drops, nasal drops or the like can be selected and used. A preparation can be administered according to a general method using the dosage forms.

[0021]

When a pharmaceutical preparation is produced (formulation) using the anti-allergic agent or the agent for improving allergic diarrhea of the invention, the pharmaceutical carrier is not particularly limited, and a pharmaceutical carrier which is generally used for a general drug can be appropriately selected depending on the purpose of the preparation. Here, specifically, additives such as excipients, binders, disintegrants, lubricants, stabilizers, fluidity promoters, corrigents, flavors, colors, aroma, diluents, surfactants and solutions for injections can be selected and used. A preparation can be produced according to a general method using the pharmaceutical carriers.

[0022]

Examples of binders include starch, dextrins, gum arabic powder, gelatin, hydroxypropyl starch, methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl cellulose, crystalline cellulose, ethyl cellulose, polyvinylpyrrolidone, macrogols and the like.

[0023]

Examples of disintegrants include starch, hydroxypropyl starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, low-substituted hydroxypropyl cellulose and the like.

[0024]

Examples of surfactants include sodium lauryl sulfate, soy lecithin, sucrose fatty acid esters, polysorbate 80 and the like.

[0025]

Examples of lubricants include talc, wax, hydrogenated vegetable oil, sucrose fatty acid esters, magnesium stearate, calcium stearate, aluminum stearate, polyethylene glycol and the like.

[0026]

Examples of fluidity promoters include light silicic anhydride, dried aluminum hydroxide gel, synthetic aluminum silicate, magnesium silicate and the like.

[0027]

The β-palmitic acid content of the preparation of the invention is not particularly limited and can be appropriately selected depending on the effects and the efficacy of the invention and the like. Here, for example, the recommended β-palmitic acid content of a general preparation per day is preferably 0.1 g to 100 g, more preferably 0.2 g to 80 g, further preferably 0.4 g to 60 g, further preferably 0.6 g to 50 g, further preferably 0.8 g to 40 g, further preferably 1.2 g to 30 g, particularly preferably 1.6 g to 20 g, most preferably 2 g to 10 g.

[0028]

The pharmaceutical composition is for example a pharmaceutical drug or a quasi-drug and is not particularly limited as long as the effects and the efficacy of the invention are expected.

[0029]

Examples of the oral composition for preventing or treating an allergy include supplements and oral compositions for preventing or treating an allergy for an infant such as infant modified milk powder, peptide milk, follow-up milk, growing up milk, modified milk powder for a low-birthweight infant, lactose free milk powder, low-sodium special milk powder and powder to be added to breast milk. The oral composition for preventing or treating an allergy is not particularly limited as long as the effects and the efficacy of the invention are expected.

[0030]

In particular, when β-palmitic acid is applied to an oral composition for preventing or treating an allergy for an infant such as infant modified milk powder, allergic diarrhea in an infant can be inhibited, and effective growth of the infant is also expected.

[0031]

Also, when β-palmitic acid is applied to an oral composition for preventing or

treating an allergy for an infant such as infant modified milk powder, addition of a component other than β-palmitic acid is not particularly limited.

[0032]

For example, when infant modified milk powder containing β-palmitic acid to which an adequate amount of docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), arachidonic acid (ARA) or cholesterol, which promotes development and growth of an infant, is added and which has a similar composition to that of breast milk is produced and provided, allergic diarrhea in an infant can be inhibited, and further effective development and growth of the infant are also expected.

[0033]

Moreover, when infant modified milk powder containing β-palmitic acid from which β-lactoglobulin, which is a strong allergenic substance, has been removed or reduced, infant modified milk powder containing β-palmitic acid to which an adequate amount of a nucleoside or a nucleotide having immunomodulation function is added or infant modified milk powder containing β-palmitic acid which does not contain soy lecithin as an emulsifier is produced and provided, allergic diarrhea in an infant can be inhibited, and effective avoidance of allergies with different causes in the infant is expected.

[0034]

Furthermore, when infant modified milk powder containing β-palmitic acid in which lactadherin having the function of preventing infection is enriched or infant modified milk powder containing β-palmitic acid to which an adequate amount of at least one or more of fructooligosaccharides, nucleosides, nucleotides, taurine and zinc, which enhance the immunity, is added is produced and provided, allergic diarrhea in an infant can be inhibited, and effective enhancement of the immunity of the infant is also expected.

[0035]

In addition, when infant modified milk powder containing β-palmitic acid in which β-lactoglobulin, which is not digested or absorbed easily, is selectively degraded or infant modified milk powder containing β-palmitic acid in which digestible α-lactalbumin is enriched is produced and provided, allergic diarrhea in an infant can be inhibited, and effective improvement of the digestibility in the digestive tract of the infant is also expected.

[0036]

Furthermore, when infant modified milk powder containing β-palmitic acid to which an adequate amount of a fructooligosaccharide, a nucleoside or a nucleotide, which

promotes the formation of adequate gut flora, is added or infant modified milk powder containing β-palmitic acid to which an adequate amount of lactose, which promotes the formation of adequate gut flora, is added is produced and provided, allergic diarrhea in an infant can be inhibited, and effective improvement of bowel movement of the infant is also expected.

[0037]

In the present specification, the term infant includes a baby and a little child, more specifically includes a baby, a little child and a newborn baby, and further specifically includes a baby, a little child, a newborn baby, an immature infant, a premature baby and a low-birthweight infant. In the invention, the species of the infant include human unless otherwise specified.

[0038]

A baby means a child in the infancy, and the infancy means the period when the child drinks milk such as breast milk as the main source of nutrient. In the case of human, the infancy is generally when the child is under one year of age. A little child generally means a child in the preschool time. A newborn baby means a child in the neonatal period. The neonatal period means the period soon after the birth, and in the case of human, the neonatal period is generally the first four weeks after the birth.

[0039]

The form or the formulation of a supplement containing β-palmitic acid is not particularly limited as long as the form allows β-palmitic acid to be taken. Examples thereof include powder, liquid, paste, tablets and solid.

[0040]

A substance other than β-palmitic acid can be incorporated (added) optionally depending on the individual design. However, by adding a material for a supplement with known functionality or the like, a plurality of effects and efficacy in addition to the effects and the efficacy of the invention are expected. As the material for a supplement, known materials such as minerals, vitamins, proteins, carbohydrates (for example, dietary fiber and the like), lipids, microorganisms or metabolites thereof can be used individually. Also, a combination of some of the known materials can be used, and the combination of all the known materials can be also used.

[0041]

For example, a supplement containing β-palmitic acid to which an adequate amount

of a functional material having intestinal regulation function (such as oligosaccharides, dietary fiber, lactic acid bacteria, bifidobacteria and Propionibacterium-fermented compositions) is added can inhibit or treat an allergy and is also expected to effectively relieve or inhibit constipation or diarrhea. Also, for example, a supplement containing β-palmitic acid to which an adequate amount of calcium or vitamin D is added can inhibit or treat an allergy and is also expected to effectively prevent or treat osteoporosis.

[0042]

The supplement here is not limited to supplements in a narrow sense which are sold by pharmacies, drugstores and the like, and the supplement is not particularly limited as long as the supplement is supplied to the body for the purpose of nutritional supplement, nutritional regulation, maintenance of homeostasis or the like.

[0043]

The β-palmitic acid which is the active ingredient of the invention can also be used as an additive for preventing or treating an allergy. For example, β-palmitic acid may be used as an additive for a pharmaceutical composition, a food or a drink which is taken as diet and which is expected to have few side effects, a composition for preventing or treating an allergy or the like, and β-palmitic acid can be taken orally or through gavage.

[0044]

The β-palmitic acid which is the active ingredient of the invention exerts the excellent effects and the excellent efficacy not only in humans but also in mammals. Accordingly, the invention also relates to feed and a feed additive containing β-palmitic acid as an active ingredient and especially relates to milk powder and a milk powder additive for raising a mammal.

Examples

[0045]

The invention is explained in further detail below by showing the test results of the Examples and the Comparative Examples according to the invention. In this regard, however, the invention is not limited to these Examples.

[0046]

Feed 1, feed 2 and feed 3 were produced by adding, to the purified diet described below, 4% by mass of soybean oil, lipid having a composition obtained by replacing 90% by mass of the soybean oil with the “vegetable oils and fats” shown in Table 1 and lipid having

a composition obtained by replacing 90% by mass of the soybean oil with the "vegetable oils and fats with an increased β-palmitic acid ratio by enzymatic transesterification (test oils and fats)" shown in Table 1, respectively. The feed 1, the feed 2 and the feed 3 were given to six-week old mice continuously for two months (the group of mice to which the feed 1 was given is called the soybean oil group, the group of mice to which the feed 2 was given is called the vegetable oils and fats group, and the group of mice to which the feed 3 was given is called the test oils and fats group).

[0047]

The purified diet was prepared in accordance with AIN-93M (for maintenance), which is the standard feed for nutritional research using mice or rats which was presented by the American Institute of Nutrition (AIN) in 1993. Specifically, the purified diet contained 46.5692% by mass of corn starch, 14.0% by mass of milk casein, 15.5% by mass of pregelatinized corn starch, 10% by mass of granulated sugar, 4.0% by mass of purified soybean oil, 5.0% by mass of cellulose powder, 3.5% by mass of a mineral mix (AIN-93-MX), 1.0% by mass of a vitamin mix (AIN-93VX), 0.18% by mass of L-cystine, 0.25% by mass of choline bitartrate and 0.0008% by mass of tertiary butylhydroquinone.

[0048]

In the compositions of Table 1, the major fatty acid contents of the triglycerides were calculated by the areas % according to the standard methods for the analysis of fats, oils and related materials, provisional 17-2007 (capillary gas chromatography). Also, with respect to the β-palmitic acid contents, the fraction of the 2-position of monoglyceride was collected using *Candida antarctica* lipase B, immobilized enzyme, Novozyme 435 (manufactured by Novozymes), and the monoglyceride having palmitic acid at the 2-position was analyzed by gas-liquid chromatography (GLC). Furthermore, the ratios of palmitic acid bonded at the β-position to the total palmitic acid content were calculated by [fatty acid content of monoglyceride having palmitic acid at the 2-position/(palmitic acid triglyceride content × 3)] × 100 [%].

[0049]

Two months after the initiation of the intake of the feeds, the entire bodies of the mice raised with the feeds 1 to 3 were sensitized with 1 mg of ovalbumin (OVA) using Freund's complete adjuvant. From one week after the sensitization of the entire bodies, 50 mg of OVA was orally administered at the frequency of three times a week. Allergic diarrhea was induced in this manner, and the symptoms were observed using the onset of

diarrhea observed from 30 minutes to 60 minutes after the oral administration as an indicator. The results are shown in Fig. 2.

[0050]

[Table 1]

Sample Name	Test Oils and Fats	Vegetable Oils and Fats
Major fatty acid content (%)		
C12-0	0.0	0.3
C14-0	0.5	0.8
C16-0	42.1	39.7
cisC16-1	0.0	0.1
C18-0	2.8	4.4
transC18-1	0.4	0.1
cisC18-1	46.3	46.8
transC18-2	0.4	0.2
cisC18-2	6.8	6.3
transC18-3, transC20-1	0.0	0.0
cisC18-3	0.0	0.1
C20-0	0.2	0.4
cisC20-1	0.2	0.1
C22-0	0.0	0.1
Total	99.8	99.4
Total trans acid amount	0.8	0.3
Total saturated fatty acids	45.7	45.7
Monovalent unsaturated fatty acids	46.9	47.1
Polyvalent unsaturated fatty acids	7.2	6.6
% of total C16-0 Sn-2 position	56.7%	6.1%

[0051]

As shown in Fig. 2, after the fourth oral administration and the administration thereafter, a decrease in the incidence rate of allergic diarrhea was observed in the test oils and fats group as compared with the other two groups. The results show that β-palmitic acid has an anti-allergic effect and is effective for improving allergic diarrhea.

[0052]

Next, in order to examine the relation between β-palmitic acid and the parameters of the onset of an allergic disease, the amounts of allergen-specific IgE production, the numbers of mast cells in the large intestine and the numbers of degranulated mast cells were analyzed by the following procedures using the soybean oil, the vegetable oils and fats or the vegetable oils and fats with an increased β-palmitic acid ratio.

[0053]

Two months after the initiation of the intake of the feeds, the entire bodies of the mice raised with the feeds 1 to 3 were sensitized with 1 mg of ovalbumin (OVA) using Freund's complete adjuvant. From one week after the sensitization of the entire bodies, 50 mg of OVA was orally administered at the frequency of three times a week. On the day following the seventh oral administration of OVA, serum was collected, and the amount of OVA-specific IgE [Fig. 3(a)] and the number of degranulated mast cells (mMCP-1) [Fig. 3(c)] were measured by DS mouse IgE ELISA (OVA) (DS Pharma Biomedical Co.,Ltd.) and MouseMCPT-1 (mMCP-1) ELISA Ready-SET-Go! (Affymetrix), respectively. At the same time, the mononuclear cells were collected from the lamina propria of the large intestine, and the number of mast cells was counted [Fig. 3(b)].

[0054]

As shown in Fig. 3(a) to Fig. 3(c), there was a correlation with the incidence rate of allergic diarrhea in Fig. 2, and decreases in the parameters were observed in the test oils and fats group as compared with the other two groups. The results show that β-palmitic acid inhibits the allergen-specific IgE production in an allergic disease, decreases the number of mast cells in the large intestine and inhibits the degranulation of mast cells.

Industrial Applicability

[0055]

Using the anti-allergic agent or the agent for improving allergic diarrhea of the invention, prevention or treatment of an allergic disease is expected to be achieved without side effects. In particular, it is effective to apply the anti-allergic agent of the invention to an oral composition for preventing or treating an allergy for a baby because allergic diarrhea in a baby can be prevented and the infant can be developed and grown effectively.

[0056]

The invention has been explained in detail using specific embodiments, but it is obvious to one skilled in the art that various changes and modifications can be made without departing from the intention and the scope of the invention. The present application is based on a Japanese patent application filed on May 22, 2014 (patent application No. 2014-106059), and the entire contents thereof are incorporated herein by reference.

CLAIMS

[Claim 1]

An anti-allergic agent comprising β-palmitic acid as an active ingredient.

[Claim 2]

An agent for improving allergic diarrhea comprising β-palmitic acid as an active ingredient.

[Claim 3]

A pharmaceutical composition comprising the anti-allergic agent according to claim 1 or the agent for improving allergic diarrhea according to claim 2.

[Claim 4]

An additive for preventing or treating an allergy comprising β-palmitic acid as an active ingredient.

[Claim 5]

An oral composition for preventing or treating an allergy, where the additive according to claim 4 has been added.