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[Summary of the Invention]

[0013]

As described above, a variety of research and investigative work has been carried out, but none thereof can be said to be a safe and simple adjuvant, and the practicality is not necessarily sufficient.

[0014]

The invention described in Patent Document 1 requires steps of long-term culturing, filtration, etc., the production method is complicated, and the effect on antibody titer is unknown. Furthermore, the invention described in Patent Document 2 carries out vaccination at the same time as nasal or oral administration of a culture of a microorganism of the aureobasidium genus itself, and it does not enable easy ingestion of an adjuvant. Moreover, in the invention described in Patent Document 3, *Lactobacillus rhamnosus* GG is used, and the growth rate of *Lactobacillus rhamnosus* GG is increased using β-glucan; it is stated that *Lactobacillus rhamnosus* GG is useful as a vaccine adjuvant, but the adjuvant effect is not studied, and a probiotic that can be used as a starter bacterium for fermented milk is not provided. Furthermore, cases of sepsis and liver abscess have been reported with *Lactobacillus rhamnosus* GG (Non-Patent Document 4 and Non-Patent Document 5).

[0015]

Moreover, Non-Patent Document 1 relates to a yoghurt drink containing *Lactobacillus casei* DN-114 001, for which an adjuvant effect for an influenza vaccine has been shown, but the fermentation thereof requires separate *Lactobacillus delbrueckii* ssp. *bulgaricus* and *Streptococcus thermophilus*. Furthermore, in Non-Patent Documents 2 and 3, it is unclear whether or not *Lactobacillus fermentum* CECT5716, B. *animalis* ssp. *lactis* (BB-12 (R)), and L. *paracasei* ssp. *paracasei* (L. casei 431 (R)), for each

of which an adjuvant effect for an influenza vaccine has been shown, can be used as a starter for fermented milk.

[0016]

Moreover, the invention described in Patent Document 4 relates to an acidic polysaccharide produced by *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and fermented milk produced using as a starter bacterium *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1; the effect studied here is the activation of NK cells, and the effect on antibody titer is unknown.

[0017]

As described above, various adjuvants have been proposed, but there is still no adjuvant that has a continuing effect in enhancing the antibody titer increase due to vaccination, and that is safe, can be easily produced, and can be ingested freely regardless of the age group.

[0018]

Therefore, it is desirable that the present invention provide an antibody titer-increasing agent, for example an adjuvant, that can continue the effect due to vaccination, and that is safe and economical and can be ingested freely regardless of the age group, and a method for producing same.

[0019]

In a first aspect, the present invention relates to the following.

[1]

An antibody titer-increasing agent comprising *Lactobacillus*

delbrueckii ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof.

[2]

The antibody titer-increasing agent according to [1], wherein it is an adjuvant.

[3]

The antibody titer-increasing agent according to [2], wherein it is an adjuvant for a vaccine.

[4]

The antibody titer-increasing agent according to [3], wherein it is an adjuvant for a vaccine for an infectious disease.

[5]

The antibody titer-increasing agent according to [4], wherein the infectious disease is influenza.

[0020]

[6]

The antibody titer-increasing agent according to any one of [1] to [5], wherein the culture is a composition obtained by culturing *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and *Streptococcus thermophilus*.

[7]

The antibody titer-increasing agent according to any one of [1] to [6], wherein it comprises 9×10^7 to 10^{12} cfu lactic acid bacteria, including *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1, per package.

[8]

The antibody titer-increasing agent according to any one of

[1] to [7], wherein it comprises 10 to 1000 g or 10 to 1000 mL per package.

[9]

A product formed by packaging the antibody titer-increasing agent according to any one of [1] to [8].

[0021]

[10]

A method (excluding a medical intervention) for increasing an antibody titer, the method comprising a subject ingesting or being made to ingest the antibody titer-increasing agent according to any one of [1] to [8].

[11]

The method according to [10], wherein ingestion of 10 to 1000 g or 10 to 1000 mL of the antibody titer-increasing agent per day is continued for at least three weeks.

[12]

The method according to [11], wherein ingestion of the antibody titer-increasing agent is continued from at least one week before the date of vaccination.

[0022]

In a second aspect, the present invention also relates to the following.

[I]

An adjuvant for a vaccine comprising *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof when used before, concurrently with or after vaccination to

increase an antibody titer in blood after vaccination.

[II]

The adjuvant according to [I], wherein it is for use in an influenza vaccine.

[III]

The adjuvant according to [II], wherein ingestion of the adjuvant commences from at least one week before a date of a vaccination.

[IV]

The adjuvant according to [II] or [III], wherein the adjuvant is for a vaccine for an infectious disease.

[V]

The adjuvant according to [IV], wherein the infectious disease is influenza.

[VI]

The adjuvant according to any one of [I] to [V], wherein the culture is a culture obtained using *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and *Streptococcus thermophilus*.

[VII]

The adjuvant according to any one of [I] to [VI], wherein it is provided in a package comprising 9×10^7 cfu of lactic acid bacteria, including *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1, per package.

[VIII]

The adjuvant according to any one of [I] to [VII], wherein the adjuvant is provided in a package comprising 10 to 1000 g or

10 to 1000 mL of the adjuvant.

[IX]

A product formed by packaging the adjuvant according to any one of [I] to [VIII].

[X]

A method (excluding medical intervention) for enhancing a vaccine effect, the method comprising a subject ingesting or being made to ingest the adjuvant according to any one of [I] to [VIII].

[XI]

The method according to [X], wherein ingestion of 10 to 1000 g or 10 to 1000 mL of the adjuvant per day is continued for at least 3 weeks.

[0023]

[XII]

A method (excluding medical intervention) for increasing antibody titer in blood after vaccination, the method comprising a subject ingesting or being made to ingest the adjuvant according to any one of [I] to [VIII], before, concurrently with or after vaccination.

[XIII]

The method according to [XII], wherein the culture is a culture obtained using *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and *Streptococcus thermophilus*.

[XIV]

The method according to [XII] or [XIII], wherein the antibody titer is an influenza antibody titer.

[XV]

The method according to any one of [XII] to [XIV], wherein ingestion of 10 to 1000 g or 10 to 1000 mL of the adjuvant per day is continued for at least 3 weeks.

[XVI]

The method according to [XV], wherein ingestion of the adjuvant commences from at least one week before a date of a vaccination.

[XVII]

A use of *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof to increase an antibody titer in blood after vaccination.

[XVIII]

The use according to [XVII], wherein the culture is a composition obtained by culturing *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and *Streptococcus thermophilus.*

[XIX]

The use according to [XVII] or [XVIII] in a food or drink.

[XX]

A food or drink product comprising *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof when used for increasing an antibody titer in blood after vaccination.

[XXI]

The product of [XX] in the form of a fermented milk product or yoghurt product.

[XXII]

A method of increasing an antibody titer in a subject after vaccination, the method comprising orally administering an adjuvant according to any one of [I] to [VIII] to a subject before, concurrently with or after vaccination, such that the adjuvant is ingested by the subject.

[XXIII]

The method according to [XXII], wherein administration of 10 to 1000 g or 10 to 1000 mL of the adjuvant per day is continued for at least three weeks.

[XXIV]

The method according to [XXIII], wherein administration of the adjuvant commences from at least one week before a date of a vaccination.

[Effects of the Invention]

[0024]

The present invention enables *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof to be used in the medical prevention or treatment of a disease and to be also used

antigen-specific immunoresponse and can be expected to be a safe and simple antibody titer-increasing agent, for example an adjuvant.

Throughout the specification and the claims that follow, unless the context requires otherwise, the words “comprise” and “include” and variations such as “comprising” and “including” will be understood to imply the inclusion of a stated integer or group of integers, but not the exclusion of any other integer or group of integers.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement of any form of suggestion that such prior art forms part of the common general knowledge.

It will be appreciated by those skilled in the art that the invention is not restricted in its use to the particular application described. Neither is the present invention restricted in its preferred embodiment with regard to the particular elements and/or features described or depicted herein. It will be appreciated that the invention is not limited to the embodiment or embodiments disclosed, but is capable of numerous rearrangements, modifications and substitutions without departing from the scope of the invention.

CLAIMS

1. An adjuvant for a vaccine comprising *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof when used before, concurrently with or after vaccination to increase an antibody titer in blood after vaccination.

2. The adjuvant according to Claim 1, wherein ingestion of the adjuvant commences from at least one week before a date of a vaccination.

3. The adjuvant according to Claim 1 or 2, wherein the adjuvant is for a vaccine for an infectious disease.

4. The adjuvant according to Claim 3, wherein the infectious disease is influenza.

5. The adjuvant according to any one of Claims 1 to 4, wherein the culture is a composition obtained by culturing *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and *Streptococcus thermophilus*.

6. The adjuvant according to any one of Claims 1 to 5, wherein the adjuvant is provided in a package comprising 9×10^7 to 10^{12} cfu lactic acid bacteria, including *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1.

7. The adjuvant according to any one of Claims 1 to 6, wherein the adjuvant is provided in a package comprising 10 to 1000 g or 10 to 1000 mL of the adjuvant.

8. A product formed by packaging the adjuvant according to any one of Claims 1 to 7.

9. A method (excluding a medical intervention) for increasing an antibody titer in blood after vaccination, the method comprising a subject ingesting or being made to ingest the adjuvant according to any one of Claims 1 to 7, before, concurrently with or after vaccination.

10. The method according to Claim 9, wherein ingestion of 10 to 1000 g or 10 to 1000 mL of the adjuvant per day is continued for at least three weeks.

11. The method according to Claim 10, wherein ingestion of the adjuvant commences from at least one week before a date of a vaccination.

12. A use of *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof to increase an antibody titer in blood after vaccination.

13. The use according to Claim 12, wherein the culture is a composition obtained by culturing *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and and *Streptococcus thermophilus*.

14. The use according to Claim 12 or 13 in a food or drink.

15. A food or drink product comprising *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and/or a culture thereof when used for increasing an antibody titer in blood after vaccination.

16. The product of claim 15 in the form of a fermented milk product or yoghurt product.

17. A method of increasing an antibody titer in a subject after vaccination, the method comprising orally administering an adjuvant according to any one of Claims 1 to 7 to a subject before, concurrently with or after vaccination, such that the adjuvant is ingested by the subject.

18. The method according to Claim 17, wherein administration of 10 to 1000 g or 10 to 1000 mL of the adjuvant per day is continued for at least three weeks.

19. The method according to Claim 18, wherein administration of the adjuvant commences from at least one week before a date of a vaccination.