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(54) Title: PROBIOTIC BACTERIA FOR REDUCING THE OCCURENCE OF SYMPTOMS OF WINTER INFECTIONS

(57) Abstract: Use of probiotic bacteria selected from the group consisting of Lactobacillus, Bifidobacterium species and mixtures thereof for preparing a composition which can be administered orally to reduce • the occurrence of systemic symptoms of winter infections; • the occurrence of severe symptoms of winter infections; • the use of medication during winter infections; in humans.

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PROBIOTIC BACTERIA FOR REDUCING THE OCCURENCE OF SYMPTOMS OF WINTER INFECTIONS

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The present invention relates to the use of probiotic bacteria (probiotics), especially probiotic bacteria selected from the group consisting of *Lactobacillus*, *Bifidobacterium* species and mixtures thereof to reduce the impact of winter infections in healthy adults.

10

Many species of bacteria have evolved and adapted to live and grow in the human intestine. The intestinal habitat of an individual contains 300 to 500 different species of bacteria and about 10^{12} viable bacteria per gram of large intestine are found (Simon GL, Gorbach SL. *Gastroenterology* 86: 174 (1984); Borriello SP, Barclay FE. *J Med Microbiol* 21: 299 (1986)). The constant interaction between the host and its microbial guests can confer important health

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benefits on the human host.

The term "probiotic bacteria" (or just "probiotic") as used herein denotes a live or attenuated bacterium, which provides specific health benefits to the host when consumed as a food component or supplement and beneficially affects the host cell by improving its microbial balance.

20

Probiotics including *Lactobacillus* and *Bifidobacillus* have a long history of safe use in the dairy industry (Shortt C. *Trends in Food Science and Technology* 10: 411 (1999)). Fermented milk products and especially yoghurt represent the main source of probiotics in human diet. The consumer awareness of probiotics is the highest in Japan with Europe coming in second and the United States a distant third (Scheinbach S. *Biotechnol Adv* 16: 581 (1998)). In Japan full-scale bifidus and yogurt production has a long history of safe use; beginning in 1977 with home delivery of products containing *Bifidobacterium longum* and *S. thermophilus*. By 1984 the number of fermented products in Japan had reached 20 (Ichikawa. *Functional Foods, Designer Foods* (1993)).

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Through yoghurt, cheese and other fermented dairy products consumers have been exposed to lactic acid bacteria (LAB) without established risk for centuries and accordingly these bacteria are generally regarded as safe (GRAS) (FAO/WHO. *London, Ontario, Canada* (2002); Naidu AS, Bidlack WR, Clemens RA. *Crit Rev Food Sci Nutr* 39: 13 (1999)). Cases of infections due to

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5 lactobacilli and bifido bacteria are extremely rare (Saxelin M, et al. *Clin Infect Dis* 22: 564 (1996) ; Gasser F. *Bulletin de L'Institut Pasteur* 92: 45 (1994)) and estimated to represent 0.05 % to 0.4 % of cases of infective endocarditis and bacteraemia, however a recent study found no correlation between an increased incidence of bacteraemia and increased usage of probiotic lactobacilli (Salminen S, Arvilommi H. *Clin Infect Dis* 32: 1577 (2001)).

10 Several probiotic microorganisms are known to exert a positive effect on a broad range of functions related to stimulation of the host's immune system (Clancy R, Gleeson, M., Cox, A., Dorrington, M., D'Este, C., Callister, P., Pyne, D., Fricker, P., Pang, G., Henriksson, A. *In preparation* (2005)). Among the major genera of colonic bacteria, bifidobacteria and lactobacilli
15 are thought to have most beneficial effects on the human host (Orrhage K, Nord CE. *Drugs Exp Clin Res* 26: 95 (2000)). These microbes have been shown previously to protect against pathogens (Goldin BR, Gorbach SL. *Nutrition* 12: 216 (1996)), to boost the immune system, protect individuals from infection (van der Waaij D, Berghuis-de Vries, J.M., Lekkerkerk-van Wees, J.E.C. *J. Hyg* 69: 405 (1971)), to modify allergic responses (Vanderhoof JA, Young RJ.
20 *Ann Allergy Asthma Immunol* 93: S33 (2004); Kalliomaki MA, Isolauri E. *Immunol Allergy Clin North Am* 24: 739 (2004); Miraglia del Giudice M, De Luca MG. *J Clin Gastroenterol* 38: S84 (2004)) and to exert some cancer protective effects in vitro and in vivo (Singh J, et al. *Carcinogenesis* 18: 833 (1997); McIntosh GH, Royle PJ, Playne MJ. *Nutr Cancer* 35: 153 (1999); Wollowski I, Rechkemmer G, Pool-Zobel BL. *Am J Clin Nutr* 73: 451S (2001)).

25 It has now surprisingly been found that probiotic bacteria (probiotics), especially probiotic bacteria selected from the group consisting of *Lactobacillus*, *Bifidobacterium* species and mixtures thereof can be used to reduce the impact of winter infections in healthy adults.

30 Common virus infections such as the common cold or influenza cause a considerable economic burden due to loss in productivity and high medical costs.

Accordingly, object of the present invention is the use of probiotic bacteria selected from the group consisting of *Lactobacillus*, *Bifidobacterium* species and mixtures thereof for preparing a
35 composition which can be administered orally to reduce

- the occurrence of systemic symptoms of winter infections;
 - the occurrence of severe symptoms of winter infections;
 - the use of medication during winter infections;
- in humans.

5 The term "winter infections" as used herein especially denotes common cold, influenzal infection and/or flu, especially to common cold, influenzal infection and/or flu occurring from November to March in the northern hemisphere and from May to September in the southern hemisphere.

10 The term "systemic symptoms of winter infections" as used herein denotes symptoms such as headache, muscle ache, fatigue and/or temperature and is used in contrast to typical local symptoms such as sore or scratchy throat, hoarseness, nasal congestion, runny nose, cough, sneezing and/or ear ache.

15 The term "severe symptoms of winter infections" as used herein denotes symptoms that disturb and irritate the human during a winter infection most of the time and are ranked with a "3" in a ranking system ranging from 0 to 3, whereas

0 = symptom has not been present in previous 24 hours;

1 = mild symptom, i.e. can be felt but it has not been disturbing or irritating;

2 = moderate symptom, has sometimes been disturbing or irritating;

20 3 = severe symptom, has been disturbing or irritating most of the time.

The term "medication" as used herein denotes analgesics (painkillers to relieve (minor) aches and pains), antipyretics (drugs to reduce fever), and/or anti-inflammatory drugs.

25 It was not to be foreseen by the person skilled in the art that the use according to the present invention would reduce the duration of common winter infections and at the same time the severity of symptoms of winter infections.

30 According to a preferred embodiment of the present invention, the probiotic bacteria are preferably selected from one or both of the following groups:

Lactobacillae:

Lactobacillus acidophilus, *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Lactobacillus paracasei*, *Lactobacillus helveticus*, *Lactobacillus fermentum* and mixtures thereof

Bifidobacteriae:

35 *Bifidobacterium infantis*, *Bifidobacterium longum*, *Bifidobacterium lactis*, *Bifidobacterium animalis* and mixture thereof.

The use of *Lactobacillus acidophilus* is especially preferred.

5 Even more preferred, the probiotic bacteria are selected from the group consisting of
Lactobacillus acidophilus CBS 116411 (LAFTI® L10), *Lactobacillus casei* CBS 116412 (LAFTI®
L26) – both deposited at the *Centraal Bureau voor Schimmel Cultures* at 15 October 2004 –
and *Bifidobacterium lactis* B94 CBS 118529 (LAFTI® B94), deposited at the *Centraal Bureau*
10 *voor Schimmel Cultures* at 14 September 2005. The mentioned LAFTI® products are obtainable
at DSM Food Specialties.

LAFTI® B94 and LAFTI® L26 originate from human intestinal origin, whereas LAFTI® L10 is of
dairy origin. The use of LAFTI® L10 is especially preferred.

15 According to a preferred embodiment of the invention, the probiotic comprises a biologically
pure culture of said deposited strain. According to a more preferred embodiment, the probiotic
comprises a biologically pure culture of said deposited strain in combination with any other
valuable probiotic strain.

20 Depending on the type of application and/or administration, a composition according to the
present invention comprises:
from 10^7 cfu to 10^{11} cfu probiotic bacteria, preferred from 10^8 cfu to 10^{11} cfu probiotic bacteria,
more preferred from 10^8 cfu to 10^{10} cfu probiotic bacteria, most preferred from 10^8 cfu to 10^9 cfu
probiotic bacteria (cfu = colony forming units).

25 Preferably the composition according to the present invention may be a food composition or a
dietary supplement, e.g. in form of a tablet, granule, capsule, paste, food additive, feed additive.
Preferred examples of a food composition are chocolate (bars), cereals and cereal bars
containing said chocolate and fermented dairy products (e. g. buttermilk, soured milk, yogurt
30 (drinks), curd, quark desserts and so on) containing said probiotic bacteria.

According to the present invention the human is preferably a healthy adult, i.e. a human that is
more than 16 years old and does not suffer from any known immune deficiency.

35 According to an especially preferred embodiment of the invention, the composition comprises a
probiotic in combination with a prebiotic.

The term "prebiotic" as used herein denotes a component, which has a favorable influence on
the growth of probiotics. Preferably the prebiotic is selected from the group consisting of
40 pentosans (or arabinoxylans), b-glucans, pectins, and pectic polysaccharides, mannans,

5 arabinans, galactans, fructo-oligosaccharides, resistant starch and mixture thereof. Prebiotic
have been fully described in US 6,241,983. Most preferred fructo-oligosaccharides are selected
from the group consisting of inulin, banana fiber, and soy fructo-oligosaccharides or soy
oligosaccharides. Most preferred mannans are selected from the group consisting of guar gum,
locust bean gum, konjac and ad xanthan gum. Resistant starch as used in the context of this
10 invention includes those forms defined as RS1, RS2, RS3, and RS4 in Brown et al (Brown, Mc
Knaught and Moloney (1995) Food Australia 47:272-275). Resistant starch and modified
resistant starch have been both extensively described in US 6,348,452.

The invention is illustrated by the following example, which should not be construed as limiting
15 the scope of the invention.

5 Examples:Demographic data:

Number of subjects screened: 303

Number of subjects recruited: 300

10 Number of subjects completing the study: 294 (Active: 148 Control: 146)

Number of subjects included into calculation: 285 (Active: 142 Control: 143)

Number of subjects suffering from cold/flu: 224 (79%)

15 In order to ensure equal risk of disease – the susceptibility to respiratory infections declines with age – the age range of the screened subjects was restricted to 18 to 25 years. Furthermore only students were recruited to avoid socioeconomic factors such as the density, housing, and distribution of the study population as well as family structure and exposure to children.

Treatments administered:

20 The following treatments were given according to the study protocol:

LAFTI® L10 was taken at a daily dose of 5×10^9 CFU in one application. It was normally taken in the morning with breakfast (one capsule with 5×10^9 CFU LAFTI® L10). This treatment was administered for 10 consecutive weeks.

The same protocol was followed for a placebo.

25

Primary objective:

To assess the reduction in duration of winter infections

Secondary objective:

30 Determination of severity of symptoms

Incidence of winter-infections

Number of sick-days leave

Results:

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1. Intake of medication:

Active : 283 days

Control: 367 days

Overall mean: 325.0 days

40

5 Overall mean 325.0 days

This leads to the Chi-square value: $2 \times 42.0^2 / 325.0 = 10.86$

p-value < 0.01

Result:

Subjects of the active group take 23% less medication as compared to the control group. This

10 reduction is statistically significant ($p < 0.01$)

Mainly painkillers (paracetamol, etc) have been taken.

Conclusion:

L10 reduces the use of medication by 23% ($p < 0.01$)

15

Sum of local and systemic symptom occurrences:

Occurrences of all symptoms with score 3:

Active: 583 days with a score 3

Control: 663 days with a score 3

20 This leads to the Chi-square value: $2 \times 40^2 / 623 = 5.174$

p-value = 0.02

Occurrences of all symptoms with score 2:

Active: 1610 days with a score 2

Control: 1651 days with a score 2

25 This leads to the Chi-square value: $2 \times 20.5^2 / 1630.5 = 0.52$

p-value = 0.47

Occurrences of all symptoms with score 1:

Active: 2961 days with a score 1

Control: 2934 days with a score 1

30 This leads to the Chi-square value: $2 \times 13.5^2 / 2947.5 = 0.12$

p-value = 0.73

Results:

The total occurrence with symptoms rated as 1 or 2 differs not significantly between the two groups ($p > 0.05$).

35 The total occurrence with a symptom rated as 3 is significantly higher in the control group (663 days) as compared to the active group (583 days) ($p = 0.02$).

Conclusion:

L10 reduces occurrences of severe symptoms by 11% ($p = 0.02$)

40

5 Systemic symptom occurrences:

Number of days without a symptom occurrence

Active: 2926 days without a symptom

Control: 2762 days without a symptom

10 Number of symptom occurrences:

Active: 1179 occurrences

Control: 1323 occurrences

This leads to the 2x2 contingency table:

	Observed		Sum (with+without)	Expected	
	With symptom	Without symptom		With symptom	Without symptom
Active	1179	2926	4105	1254.1	2850.9
Control	1323	2762	4085	1247.9	2837.1
Sum (A+C)	2502	5688	8190	2502.0	5688.0

15

This leads to the Chi-square value: $75.1^{2*}(1/1254.1+1/1247.9+1/2850.9+1/2837.1) = 12.97$
p-value < 0.01

Result:

20 For the local symptoms there is no statistically significant difference between the two groups.
With the systemic symptoms, the symptom occurrence is significantly higher (11%) in the placebo group ($p < 0.01$)

Conclusion:

25 L10 reduces occurrences of systemic symptoms by 11% ($p < 0.01$)

5 Claims:

1. Use of probiotic bacteria selected from the group consisting of *Lactobacillus*,
10 *Bifidobacterium* species and mixtures thereof for preparing a composition which can be
administered orally to reduce the occurrence of systemic symptoms of winter infections in
humans.
2. Use according to claim 1, characterized in that the systemic symptoms are headache,
muscle ache, fatigue and/or temperature.
- 15 3. Use of probiotic bacteria selected from the group consisting of *Lactobacillus*,
Bifidobacterium species and mixtures thereof for preparing a composition which can be
administered orally to reduce the occurrence of severe symptoms of winter infections in
humans.
- 20 4. Use of probiotic bacteria selected from the group consisting of *Lactobacillus*,
Bifidobacterium species and mixtures thereof for preparing a composition which can be
administered orally to reduce the use of medication during winter infections in humans.
- 25 5. Use according to claim 4, characterized in that the medication consists of analgesics
(painkillers to relieve (minor) aches and pains), antipyretics (drugs to reduce fever), and/or
anti-inflammatory drugs.
- 30 6. Use according to claim 5, characterized in that the probiotic bacteria is selected from the
group consisting of *Lactobacillus acidophilus* CBS 116411, *Lactobacillus casei* CBS
116412, and *Bifidobacterium lactis* B94 CBS 118529.
7. Use according to any of the preceding claims characterized in that said composition is in
the form of a food or a food supplement.
- 35 8. Use according to any of the claim 7, characterized in that said composition is in the form of
a fermented dairy product.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/005661

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K35/74 A23C9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A23C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE VRESE M ET AL: "Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: A double blind, randomized, controlled trial" CLINICAL NUTRITION, CHURCHILL LIVINGSTONE, LONDON, GB, vol. 24, no. 4, 1 August 2005 (2005-08-01), pages 481-491, XP004996029 ISSN: 0261-5614 abstract part "Symptoms"table 4 page 488, right-hand column, last paragraph - page 489, left-hand column, paragraph 1 ----- -/--	1-3

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *Z* document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	TURCHET P ET AL: "Effect of fermented milk containing the probiotic Lactobacillus casei DN-114001 on winter infections in free-living elderly subjects: a randomised, controlled pilot study." THE JOURNAL OF NUTRITION, HEALTH & AGING 2003, vol. 7, no. 2, 2003, pages 75-77, XP009105928 ISSN: 1279-7707 abstract page 76, right-hand column, paragraphs 1,2	1-3,7,8
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Information on patent family members

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