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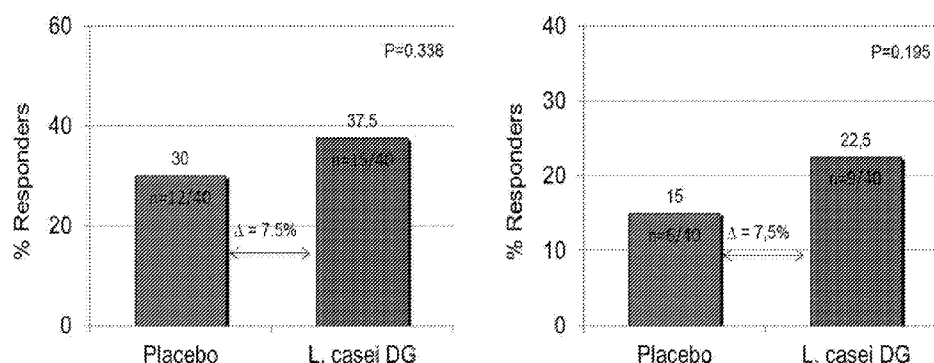
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(54) Title: NEW MEDICAL USE OF PROBIOTICS

Fig.1



(57) Abstract: The present invention relates to the use of a composition based on bacteria and/or yeasts and/or other microorganisms, taken singularly or in combination, for the treatment of the symptoms of and/or for treating Irritable Bowel Syndrome (IBS) or also similar pathologies affecting the gastrointestinal apparatus. In particular, the bacteria are selected from the following genera: *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Propionibacterium*, *Streptococcus*, *Lactococcus*, *Aerococcus* and *Enterococcus*.

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DESCRIPTION

NEW MEDICAL USE OF PROBIOTICS

Technical field

The present invention relates to the use of a composition based on bacteria, preferably of the genus *Lactobacillus* and/or *Bifidobacterium*, and/or yeasts and/or other microorganisms, taken singularly or in
5 combination, for treating the symptoms of and/or treating Irritable Bowel Syndrome (IBS) or also similar pathologies affecting the gastrointestinal apparatus.

State of the Art

Gastrointestinal disorders are a very widespread condition and represent a
10 major portion of the costs that states have to bear for public health as well having a strong negative impact on the quality of life of affected individuals.

In particular, Irritable Bowel Syndrome (IBS), or irritable colon syndrome, is one of the most common gastrointestinal disorders. It affects around 15-
15 20% of the population in the United States and Europe and the abdominal discomfort or pain often correlated with it is associated with changes in intestinal habits.

IBS has traditionally been considered a disorder of the psychological sphere associated with motor anomalies of the intestine and visceral
20 hyperalgesia. Despite the lack of clear anomalies at the digestive level, the recent application of quantitative morphological and molecular techniques has revealed alterations within the gastrointestinal mucosa or in the lumen at the tissue, cellular and molecular level in a large percentage of patients suffering from IBS.

25 In light of the foregoing, there is a strongly felt need for new and/or alternative therapeutic solutions which may alleviate the symptoms associated with this pathology and/or treat the pathology.

Summary of the invention

The Applicant has found that the administration, or use, of a composition based on bacteria and/or yeasts and/or other microorganisms, taken singularly or in combination, is a solution to the above-mentioned need. In particular, bacteria belonging to a genus selected from among:
5 *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Propionibacterium*, *Streptococcus*, *Lactococcus*, *Aerococcus* and *Enterococcus*, preferably bacteria belonging to the genus *Lactobacillus* and/or *Bifidobacterium*, have shown to be particularly effective.

In fact, it has been surprisingly demonstrated by the Applicant that the
10 administration, or use, preferably in oral form, of a composition based on bacteria belonging to the genus *Lactobacillus* and/or *Bifidobacterium*, in particular a probiotic composition comprising the bacterial species *Lactobacillus paracasei*, alleviates the symptoms associated with IBS, in particular by improving the abdominal pain and discomfort associated
15 therewith.

Furthermore, the use of a composition based on these bacteria brings about:

- an increase, in general at the level of the intestinal microbiota, in the bacterial population of the genus *Lactobacillus* and, at the same time, a
20 significant reduction in the bacterial population belonging to the genus *Ruminococcus*, a pathobiont normally associated with IBS;
- an increase in the intestinal concentration of short-chain fatty acids, in particular butyric and/or acetic acid; and
- a reduction in proinflammatory cytokines, in particular IL-6 and/or IL-15.

25 **Brief description of the drawings**

The present invention will be described in detail below, also with the aid of the following figures and with examples that are not intended to have any limiting character.

In particular:

- 30 - Figure 1 shows how the intake of *L. casei* DG[®] improves abdominal pain and the IBS degree-of-relief.

- Figure 2 shows how the intake of L. casei DG[®] induces a significant increase in the genus *Lactobacillus* and a significant reduction in the genus *Ruminococcus*.

- Figure 3 shows how the intake of L. casei DG[®] induces a significant increase in short-chain fatty acids (butyric and acetic acids).

- Figure 4 shows how the intake of L. casei DG[®] induces a significant reduction in the proinflammatory cytokines IL-6 and IL-15.

Detailed description of preferred embodiments of the invention

A first aspect of the present invention relates to a composition based on bacteria and/or yeasts and/or other microorganisms, taken singularly or in combination, for use in the treatment of the symptoms of and/or for treating Irritable Bowel Syndrome (IBS) or also similar pathologies affecting the gastrointestinal apparatus.

Preferably, the composition – also defined probiotic composition or probiotic – comprises the bacteria belonging to the genus *Lactobacillus* and/or *Bifidobacterium*.

The symptoms against which the above-described composition has demonstrated benefits are preferably represented by abdominal pain and discomfort associated with IBS.

Preferably, the treatment of the symptoms of and/or for the treatment of Irritable Bowel Syndrome (IBS) or also similar pathologies affecting the gastrointestinal apparatus is associated with an increase, in general at the level of the intestinal microbiota, in the bacterial population of the genus *Lactobacillus* and/or, preferably at the same time, a significant reduction in the bacterial population belonging to the genus *Ruminococcus*, i.e. a pathobiont normally associated with IBS.

Therefore, the effectiveness in the treatment of IBS and the symptoms thereof is correlated with the increase, in general at the level of the intestinal microbiota, in the bacterial population of the genus *Lactobacillus* and/or, preferably at the same time, a significant reduction in the bacterial population belonging to the genus *Ruminococcus*.

According to a further preferred aspect of the invention, the treatment of the symptoms of and/or for treating Irritable Bowel Syndrome (IBS) or also similar pathologies affecting the gastrointestinal apparatus is associated with an increase in the intestinal concentration of short-chain fatty acids, in particular butyric and/or acetic acid and/or with a reduction in proinflammatory cytokines, in particular IL-6 and/or IL-15.

In this context, the definition of “probiotic” is the one formulated by a group of experts jointly convened in 2001 by the FAO and the WHO: “*Live microorganisms which when administered in adequate amounts confer a health benefit on the host*”. In particular, in Italy, the Ministry of Health has defined probiotics as “*microorganisms which demonstrate to be able, once ingested in sufficient amounts, to exert functions that are beneficial for the body*”, substantially echoing the definition of the two above-mentioned organisations.

Preferably, the bacteria of the genus *Lactobacillus* belong to at least one of the following species: *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus amylolyticus*, *Lactobacillus amylovorus*, *Lactobacillus alimentarius*, *Lactobacillus aviaries*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus casei*, *Lactobacillus cellobiosus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus johnsonii*, *Lactobacillus kefiranoferiens*, *Lactobacillus kefir*, *Lactobacillus mucosae*, *Lactobacillus panis*, *Lactobacillus collinoides*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus reuteri*, *Lactobacillus sakei*, *Lactobacillus salivarius* and *Lactobacillus sanfranciscensis*.

Preferably, the bacteria of the genus *Bifidobacterium* belong to at least one of the following species: *B. animalis*, *B. bifidum*, *B. breve*, *B. infantis*, *B. longum*, *B. adolescentis*, *B. catenulatum*, *B. angulatum*, *B. asteroides*,

B. boum, *B. choerinum*, *B. coryneforme*, *B. cuniculi*, *B. denticolens*, *B. dentium*, *B. gallicum*, *B. gallinarum*, *B. indicum*, *B. inopinatum*, *B. lactis*, *B. magnum*, *B. merycicum*, *B. minimum*, *B. pseudocatenulatum*, *B. pseudolongum*, *B. pullorum*, *B. ruminantium*, *B. saeculare*, *B. subtile*, *B.*
5 *thermacidophilum*, *B. thermophilum* and *B. tsurumiense*.

The yeasts are preferably of the genus *Saccharomyces*, more preferably of the species *Saccharomyces cerevisiae* and/or *Saccharomyces boulardii*.

In general, the microorganisms comprised in the composition of the
10 present invention are single microorganisms or combinations of any microbial species included in the QPS list of the EFSA.

The microorganisms of the composition of the present invention are preferably alive and the composition is therefore also definable as a probiotic.

15 Alternatively, the microorganisms of the composition are dead or in the form of a lysate or extract or fractions, and the composition is therefore also definable as a paraprobiotic.

In an alternative form, the composition further comprises the metabolic bioproducts generated by microorganisms defined as postbiotics and/or
20 any other product of bacterial derivation.

Thus, the composition of the present invention is also a probiotic or a paraprobiotic or a postbiotic, known or presumed.

The bacteria within the composition can be taken singularly or in various combinations.

25 Preferably, the bacteria comprised in the composition are capable of surviving gastrointestinal transit and thus of reaching the colon alive and colonising it.

Preferably, the *Lactobacillus casei* is the strain DG[®] (*Lactobacillus paracasei* CNCM I-1572). The bacterial strain *L. casei* DG[®] was deposited
30 by SOFAR S.p.A. with the National Collection of Microorganism Cultures

of the Pasteur Institute in Paris on 05/05/1995, with the deposit number CNCM I-1572.

The bacteria within the composition are administered in a quantity ranging from 1 billion to 100 billion, preferably between 10 and 75 billion, more preferably between 15 and 50 billion, more preferably between 20 and 30 billion of viable bacterial cells per intake.

Preferably, intake takes place at least 1-2 times a day.

Administration can occur by any route. Preferably, the composition is taken orally, more preferably in the form of pills, capsules, tablets, granular powder, hard-shelled capsules, orally dissolving granules, sachets, lozenges or drinkable vials.

Alternatively, the composition of the invention is formulated as a liquid, for example as a syrup or beverage, or else it is added to food, for example to a yogurt, cheese or fruit juice.

Alternatively, the composition of the invention is formulated in a form capable of exerting a topical action, for example via enema.

The oral formulation of the composition of the present invention further comprises excipients generally accepted for the production of probiotic and/or pharmaceutical products.

Preferably, the composition comprises anti-caking agents, preferably silicon dioxide, magnesium stearate.

Preferably, the composition comprises coating agents, preferably gelatine, colouring agents.

In a further embodiment of the invention, the composition of the invention comprises vitamins, trace elements, preferably zinc or selenium, enzymes and/or prebiotic substances, preferably fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), inulin, guar gum, both animal and vegetable proteins, antioxidants, plant extracts or combinations thereof.

EXAMPLE

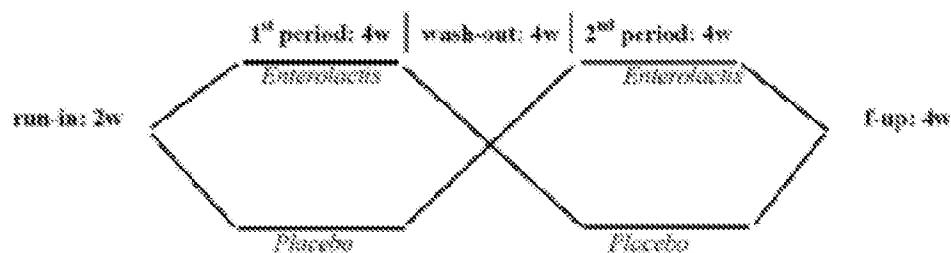
In this context it was experimentally demonstrated, by means of a multi-centre randomized, double-blind placebo-controlled crossover clinical

study, that the administration of the claimed composition to patients suffering from IBS:

- improves abdominal pain and the IBS degree-of-relief (Fig.1);
- induces a significant increase in the genus *Lactobacillus* and a significant reduction in the genus *Ruminococcus* (Fig. 2);
- induces a significant increase in short-chain fatty acids, in particular butyric and acetic acid (a drastic reduction in the concentrations thereof is typical of various pathological situations) (Fig.3); and
- significantly reduces the proinflammatory cytokines IL-6 and IL-15 (Fig.4).

The study was carried out in accordance with a crossover design, coupled with a new-generation high-throughput DNA sequencing technology (schematised in the Table I below), which represents the best possible way to assess the changes in human intestinal flora, due to the great complexity and marked interindividual variability of the bacterial composition in the faecal microbial ecosystem.

Table I



In particular, the study comprised 5 stages:

- Run-in period (2 weeks): the subjects did not take treatment A (Enterolactis® Plus), or treatment B (placebo),
- Treatment period 1 (4 weeks): the subjects took treatment A or treatment B.

- Wash-out period (4 weeks): in which the subjects did not take treatment A or treatment B
- Treatment period 2 (4 weeks): the subjects took treatment B or treatment A.
- 5 • Follow-up (4 weeks): the subjects did not take treatment A or treatment B

Treatments A and B can be the composition of the present invention, in the specific example Enterolactis[®] plus, or else the placebo. At the start of the treatment it was not known what the subject took and only at the end of the treatment, i.e. when the blind was broken, the sequence of intake was known.

Forty subjects suffering from IBS randomly received the composition of the present invention comprising *L. casei* DG[®] (Enterolactis[®] plus), 2 times a day for 4 weeks, or the equivalent product without bacteria (placebo).

15 The subjects of the study had the characteristics shown in Table II.

Table II

Characteristics	Placebo/ <i>L. casei</i> DG (n = 20)	<i>L. casei</i> DG/ placebo (n=20)
Age, years ($\pm$ SD)	44.55 ($\pm$ 12.98)	37.35 ($\pm$ 11.25)
Female gender, n (%)	15 (75%)	11 (55%)
Ethnic origin		
- Caucasian, n (%)	20 (100%)	20 (100%)
- Other, n (%)	0 (%)	0 (0%)
IBS subtype (4)		
- IBS-D, n (%)	6 (30%)	8 (40%)
- IBS-C, n (%)	7 (35%)	5 (25%)
- IBS-M, n (%)	1 (5%)	2 (10%)
- IBS-U, n (%)	6 (30%)	5 (25%)
Abdominal pain score* ($\pm$ SD)	2.70 ($\pm$ 1.24)	3.28 ($\pm$ 1.95)

Data are reported as number of patients (%) or mean $\pm$ SD. *Mean value at run-in period.

The compositions administered were the following:

Composition of the invention:

- L. casei DG[®] (*Lactobacillus paracasei* CNCM I-1572), at least 24 billion live cells

- 5 - anti-caking agents: SiO₂ and magnesium stearate
- coating: food-grade gelatine and colouring agent E171

Composition of placebo:

- anti-caking agents: SiO₂ and magnesium stearate
- coating: food-grade gelatine and colouring agent E171

- 10 The two compositions are aesthetically indistinguishable.

The total duration of the study was 18 weeks.

The parameters for assessing the effectiveness of the treatment are the following:

- 15 ✓ Abdominal pain/discomfort in the past 24 hours (the responders were defined as patients with a $\geq 30\%$ reduction in the mean weekly abdominal pain and/or discomfort score, compared to the mean value of the run-in period, for at least 2 of the 4 weeks of the treatment period) using a daily 11-point numerical scale from “0” (none) to “10” (very severe)
- 20 ✓ IBS degree-of-relief in the past 7 days compared to the period preceding the beginning of the study (the responders were defined as patients with a score of 1 = “completely relieved” or 2 = “considerably relieved” for at least 2 of the 4 weeks of the treatment period), using a balanced 7-point ordinal scale, where 1 =
- 25 “completely relieved”, 4 = “unchanged” and 7 = “as bad as I can imagine”
- 30 ✓ Composition of the intestinal microbiota (analysed by means of an Ion Torrent PGM, with nucleotide sequencing of portions of the gene encoding for the bacterial ribosomal RNA 16S subunit), of the short-chain fatty acids (SCFAs) (analysed by high-performance liquid chromatography, coupled with tandem mass spectrometry)

and IgA and cytokines in stools (analysed by means of specific ELISA tests)

- ✓ Daily stool frequency and consistency assessed using the Bristol scale
- 5 ✓ Overall satisfaction with the treatment assessed using the VAS scale
- ✓ Hospital Anxiety and Depression Scale (HADS): seven points each for anxiety and depression, with a 4-point (0-3) Likert scale for each point, which provides a minimum score of 0 and a maximum score of 21 for each subscale
- 10 ✓ Quality of life assessment using the validated Short-Form 12 Items Health Survey (SF-12), on a scale from 0 to 100
- ✓ Intake of emergency drugs

The intake of L. casei DG[®] led to the following results:

- 15 • As regards the abdominal pain and/or discomfort score, the percentage of responders was 37.5% (n = 15) in the L. casei DG[®] group vs 30.0% (n = 12) in the placebo group.
- Similarly, as regards the IBS degree-of-relief, the percentage of responders was 22.5% (n = 9) in the L. casei DG[®] group vs 15.0% (n = 6) in the placebo group.
- 20 • The stool concentrations of butyrate and acetate increased from the start to the end of the treatment with L. casei DG[®], whereas they decreased during the placebo treatment.
- The mean levels of IgA and IL-6 in stools decreased from the start to the end of the treatment with L. casei DG[®], whereas they increased during the placebo treatment.
- 25 • The mean value of IL-15 decreased during the treatment with L. casei DG[®], whereas it increased with the placebo.

The scientific literature clearly indicates (as the studies are published in pre-eminent scientific journals, such as Gastroenterology, JCI and Nature) that high levels of IL-15 are

30

associated with celiac disease, chronic inflammatory intestinal diseases, allergic disorders depending on intestinal antigens and also with severe diseases like lymphoma.

- Finally, *L. casei* DG[®] induces a significant increase in the genus *Lactobacillus* and a statistically significant decrease in the genus *Ruminococcus*, which is a pathobiont normally associated with IBS. In healthy subjects, this genus is present in low quantities, whereas in subjects with IBS it is normally present in high quantities. The probiotic treatment reduces the number of cells of such bacteria.

This genus can be seen as a sort of biological biomarker for IBS.

The results obtained at the end of the 18-week study period for each individual patient are summarised below:

- *L. casei* DG[®] improves abdominal pain and the IBS degree-of-relief, even though the differences versus the placebo are not statistically significant;

- *L. casei* DG[®] induces a significant increase in the genus *Lactobacillus* and a significant reduction in the genus *Ruminococcus*;

- *L. casei* DG[®] induces a significant increase in short-chain fatty acids (butyric and acetic acid), which are linked to a series of beneficial activities on the intestinal mucosa; a drastic reduction in the concentrations thereof is typical of various pathological situations; and

- *L. casei* DG[®] induces a significant reduction in the proinflammatory cytokines IL-6 and IL-15.

CLAIMS

1. Composition comprising bacteria and/or yeasts and/or other microorganisms, taken singularly or in combination, for use in the treatment of symptoms, preferably abdominal pain and discomfort associated with IBS and/or for treating Irritable Bowel Syndrome (IBS) or also similar pathologies of the gastrointestinal apparatus wherein said bacteria belong to the genus *Lactobacillus* and/or *Bifidobacterium*.
2. The composition according to claim 1, wherein the bacteria of the genus *Lactobacillus* belong to at least one of the following species: *Lactobacillus paracasei*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus amylolyticus*, *Lactobacillus amylovorus*, *Lactobacillus alimentarius*, *Lactobacillus aviaries*, *Lactobacillus brevis*, *Lactobacillus buchneri*, *Lactobacillus casei*, *Lactobacillus cellobiosus*, *Lactobacillus coryniformis*, *Lactobacillus crispatus*, *Lactobacillus curvatus*, *Lactobacillus delbrueckii*, *Lactobacillus farciminis*, *Lactobacillus fermentum*, *Lactobacillus gallinarum*, *Lactobacillus gasseri*, *Lactobacillus helveticus*, *Lactobacillus hilgardii*, *Lactobacillus johnsonii*, *Lactobacillus kefiranofaciens*, *Lactobacillus kefir*, *Lactobacillus mucosae*, *Lactobacillus panis*, *Lactobacillus collinoides*, *Lactobacillus paraplantarum*, *Lactobacillus pentosus*, *Lactobacillus plantarum*, *Lactobacillus pontis*, *Lactobacillus reuteri*, *Lactobacillus sakei*, *Lactobacillus salivarius* and *Lactobacillus sanfranciscensis*.
3. The composition according to claim 1 or 2, wherein the *Lactobacillus paracasei* is the L. casei DG[®] strain, deposited with the deposit number CNCMI 1572.
4. The composition according to any one of claims 1-3, wherein said bacteria of the genus *Bifidobacterium* belong to at least one of the following species: *B. animalis*, *B. bifidum*, *B. breve*, *B. infantis*, *B. longum*, *B. adolescentis*, *B. catenulatum*, *B. angulatum*, *B. asteroides*, *B. boum*, *B. choerinum*, *B. coryneforme*, *B. cuniculi*, *B. denticolens*, *B. dentium*, *B. gallicum*, *B. gallinarum*, *B. indicum*, *B. inopinatum*, *B. lactis*, *B. magnum*,

B. merycicum, *B. minimum*, *B. pseudocatenulatum*, *B. pseudolongum*, *B. pullorum*, *B. ruminantium*, *B. saeculare*, *B. subtile*, *B. thermacidophilum*, *B. thermophilum* and *B. tsurumiense*.

5 5. The composition according to any one of claims 1-4, wherein said yeast belongs to the genus *Saccharomyces*, preferably the species *Saccharomyces cerevisiae* and/or *Saccharomyces boulardii*.

6. The composition according to any one of claims 1-5 wherein said bacteria are alive or dead, as lysate or extract or fractions.

10 7. The composition according to any one of claims 1-6 further comprising metabolic products produced by said microorganisms defined as post-biotic and/or any other bacteria-derived product.

8. The composition according to any one of claims 1-7, wherein the bacteria are in a quantity ranging from 1 billion to 100 billion, preferably 10-75 billion, more preferably 15-50 billion, more preferably 20-30 billion of
15 alive bacteria for each intake.

9 The composition according to any one of claims 1-8, wherein said composition is formulated for oral use, preferably as pills, capsules, tablets, granular powders, opercula, soluble granules, bags, pills or drinkable vials, or is formulated as liquid, preferably as syrup or beverage,
20 or is added to food, preferably yogurt, cheese or fruit juice; or is formulated in a form having a topical effect, preferably in the form of enema.

10. The composition according to any one of claims 1-9 wherein the intake is at least 1-2 times per day.

Fig.1

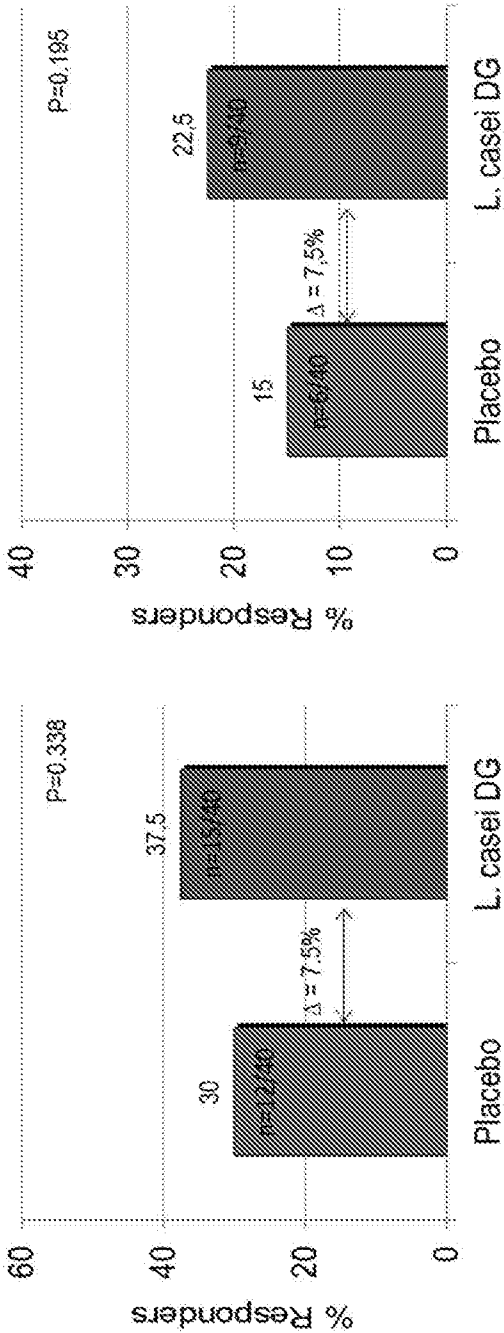


Fig.2

repeated measures Friedman test		p.value	MEDIAN RELATIVE ABUNDANCE			
Family			before		after	
			Enterol.	placebo	placebo	placebo
			Enterol.	placebo	placebo	placebo
p_Firmicutes.c_Bacilli.o_Lactobacillales.f_Lactobacillaceae		0.023	0.007%	0.344%	0.011%	0.017%
			before E	after E	before P	after P
p_Firmicutes.c_Clostridia.o_Clostridiales.f_Ruminococcaceae.g_Ruminococcus		0.043	4.435%	3.944%	5.245%	5.616%
p_Firmicutes.c_Clostridia.o_Clostridiales.f_Ruminococcaceae.g_Oscillospira		0.042	0.370%	0.427%	0.375%	0.408%
p_Firmicutes.c_Bacilli.o_Lactobacillales.f_Lactobacillaceae.g_Lactobacillus		0.011	0.007%	0.342%	0.010%	0.017%
p_Actinobacteria.o_Actinobacteriia.c_Actinomycetales.f_Actinomycetaceae.g_Actinomycetes		0.042	0.044%	0.047%	0.042%	0.049%

N.B.: only taxa with a median relative abundance > 0.01 %

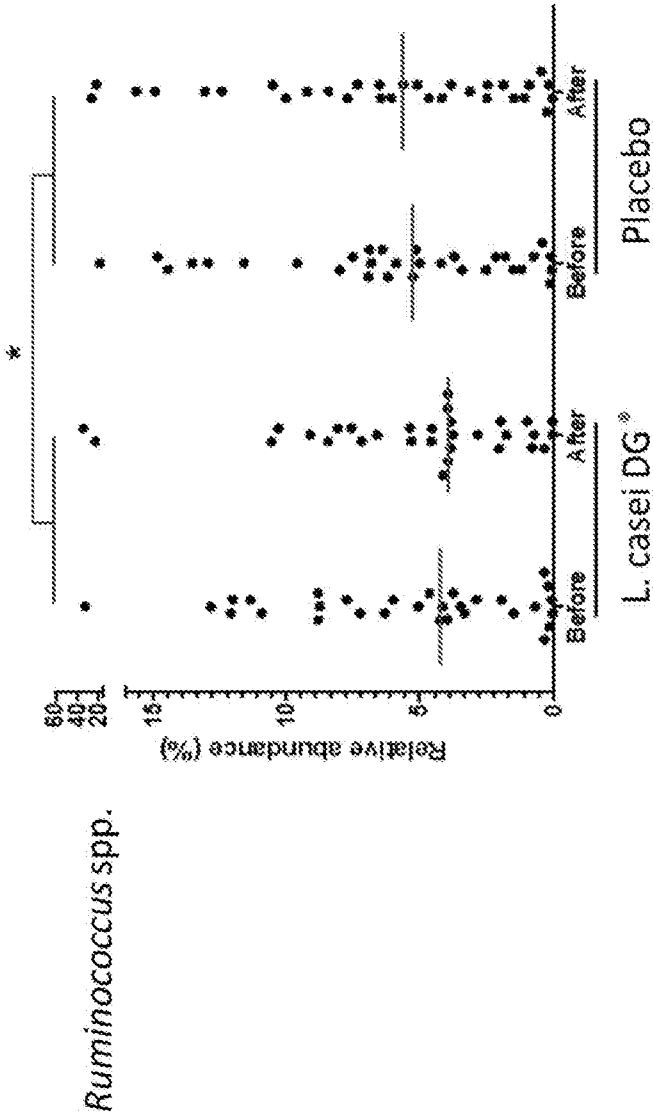
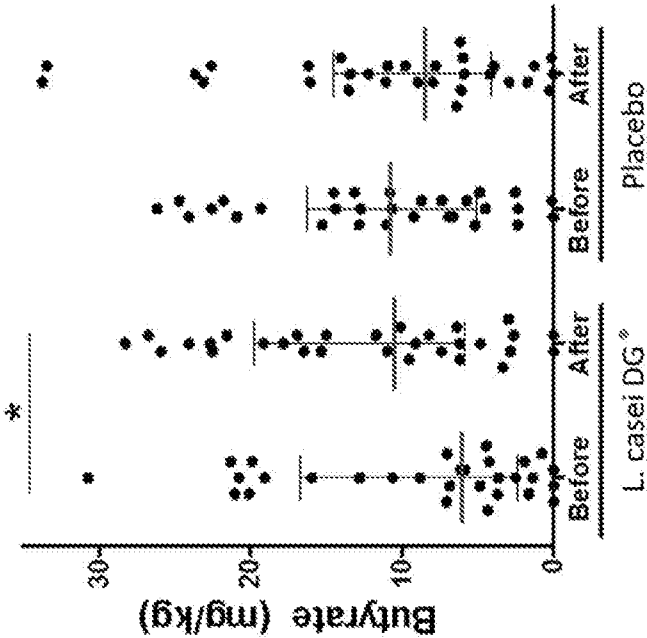


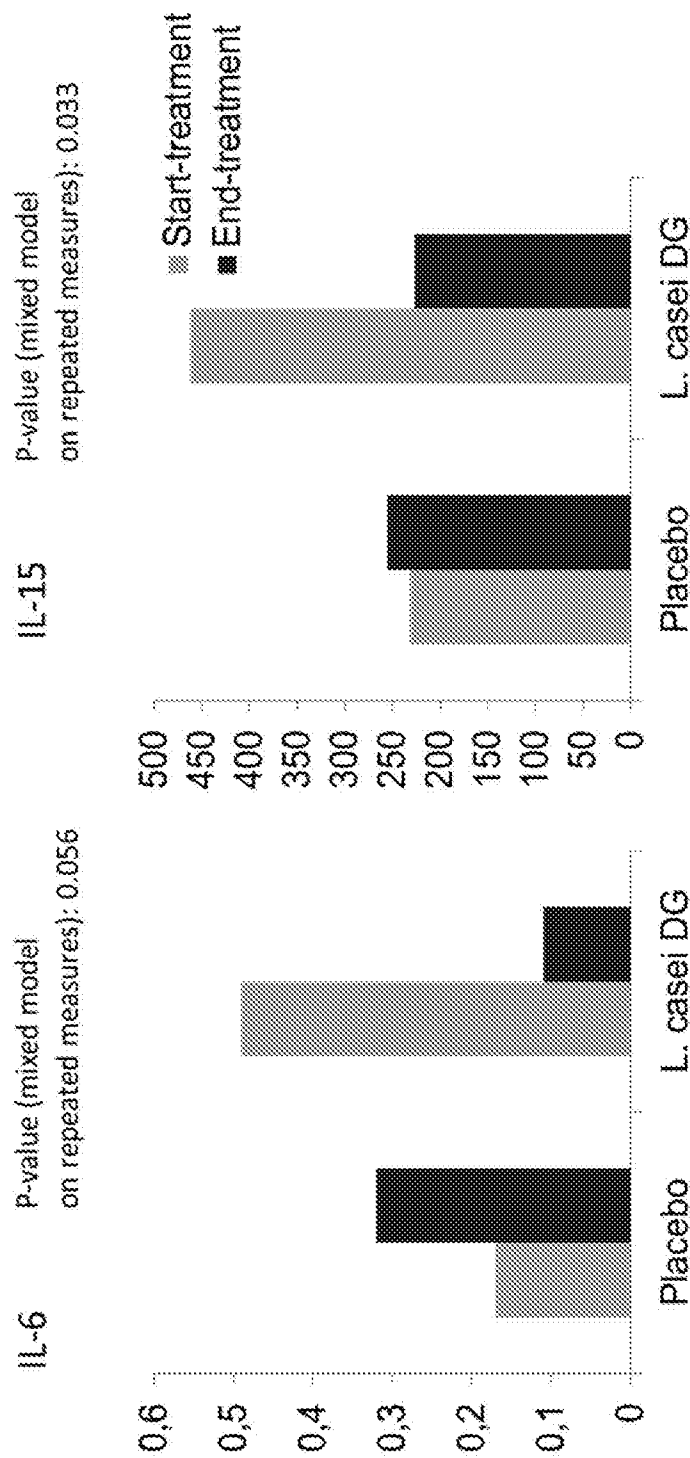
Fig.3

P-value (mixed model
on repeated measures): 0.043



Wilcoxon test		MEDIAN ABUNDANCE (mg/kg)	
L. casei DG [®] treatment		before	after
Acetate	0.521*	36.63	43.06
Propionate	0.289	15.15	16.73
Butyrate	0.047*	5.99	10.73
Isobutyrate	0.133	1.11	1.22
Isovalerate	0.428	1.14	0.95
Valerate	0.060	1.82	2.14
Placebo treatment		before	after
Acetate	0.388	47.83	33.08
Propionate	0.622	16.37	17.13
Butyrate	0.746	10.52	6.47
Isobutyrate	0.387	1.55	1.64
Isovalerate	0.360	1.04	1.28
Valerate	0.572	2.45	1.90

Fig.4



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053389

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K35/745 A61K35/747 A61K36/064 A61P1/00
ADD.

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 A61P

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 practicable, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Anonymous: "Effect of Lactobacillus Casei DG (Enterolactis Plus) in Patient With Irritable Bowel Syndrome: a Pilot Study", ClinicalTrials.gov, 11 February 2015 (2015-02-11), XP055338992, Retrieved from the Internet: URL:https://clinicaltrials.gov/ct2/show/NC T02371499 [retrieved on 2017-01-25]	1-10
Y	page 1 - page 3 ----- -/--	1-10



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Camilleri, Alain

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/053389

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	abstract page 1124, left-hand column, paragraph 1 - page 1131, right-hand column, paragraph 1 -----	1-10
X	ROBIN SPILLER ET AL: "Randomized double blind placebo-controlled trial of Saccharomyces cerevisiae CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation", UNITED EUROPEAN GASTROENTEROLOGY JOURNAL UEG WEEK 2015 ORAL PRESENTATIONS, vol. 4, no. 3, 21 August 2015 (2015-08-21) , pages 353-362, XP055339155, ISSN: 2050-6406, DOI: 10.1177/2050640615602571	1-10
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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2010/008278 A1 (NUTRICIA NV [NL]; KNOL JAN [NL]; BEN AMOR KAOUTHER [NL]; WIND RICHELE) 21 January 2010 (2010-01-21)	1-10
Y	abstract page 3, lines 4-16 page 5, line 16 - page 6, line 35 page 10, lines 5-23 examples claims -----	1-10

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Information on patent family members

International application No

PCT/IB2017/053389

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