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(71) Applicant: **VIVOX APS** [DK/DK]; Palle Juul-Jensens Boulevard 82, 8200 Aarhus N (DK).

(72) Inventor: **VILLADSEN, Jan Alexander**; Åkrogs Strandvej 29A, 8240 Risskov (DK).

(74) Agent: **PATRADE A/S**; Ceresbyen 75, 8000 Aarhus C (DK).

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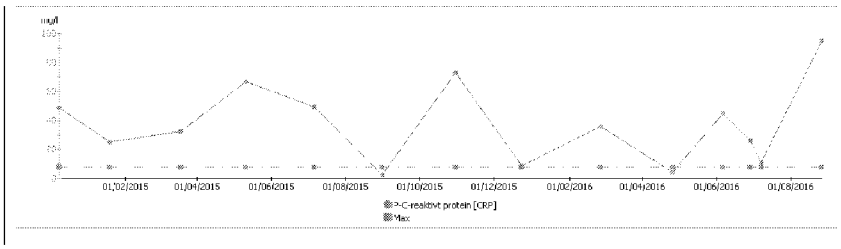

Fig. 1

(57) Abstract: A fermented composition comprising a dried fermented material comprising a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, e.g. Arabino-galactanes wherein the material is selected from one or more materials of vegetable origin, or of fungal origin, which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae. Further, a method for obtaining the fermented composition is described and compositions comprising the fermented composition for stabilizing, improving the composition of and/or normalizing the intestinal microflora, and/or in treatment, alleviation, prophylaxis of various symptoms and/or diseases.

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A fermented composition comprising a high content of one or more lactic acid bacterial strains and a method for making the composition and use thereof

Field of the Invention

The present invention relates to a fermented composition comprising a high content of one or more lactic acid bacterial strains and use thereof.

The present invention also relates to a method for preparing a fermented composition, which comprises a high content of one or more lactic acid bacterial strains.

In addition, the present invention relates to compositions for use as a medicament comprising a fermented composition having a high content of one or more lactic acid bacterial strains.

Background of the Invention

Since 400 BC microbes from human or animal stools combined with selected herbs has been used in treating gastrointestinal diseases such as diarrhoea. The use of feces (stool) to treat severe diarrhoea or food poisoning was first described by Ge Hong, a Chinese medicine doctor in the 4th century BC. In the 16th century, another Chinese physician, Li Shizhen, described using fresh or fermented fecal products, called "yellow soup", to treat severe diarrhoea, fever, pain and constipation. The accurate name for this procedure today is fecal microbiota transplants. In the Arab world up to and during W.W.II both German and British physicians reported the use of fresh camel stool extract by bedouin tribes for treating dysenteries. Besides this both in Europe, Middle East and Asia herbal medicine was one way to fight diseases and infections in humans and animal, and it have been known for more than 3,000 years that plants comprise many constituents having a positive nutritional, immune stimulating, and pharmacological effects. Despite this long-term knowledge and search for isolating the active ingredients from plants, and algae/macro algae/seaweed researchers seldom succeed because of the complexity and interplay between the individual components of the plants and seaweed.

For long the use of benign selected gastrointestinal bacteria, naturally occurring in the intestinal system has been used for fermentative purposes, in particular lacto bacteria species have been used for yoghourt and cheese. Other bacteria can be propionic bacteria which in combination with lacto bacteria are used for manufacturing Swiss cheese. Such live microorganisms are called probiotics. Probiotics are live microorganisms which are believed to provide health benefits, when administered to a human or an animal.

Prebiotics refer to chemicals that induce the growth or activity of microorganisms e.g., bacteria and fungi) contribute to the well-being of the host. For example, when an individual animal, including humans, eats prebiotics, the composition of microorganisms in the intestinal microflora of the gastrointestinal tract is altered.

A group of components having prebiotic effects of interest and showing a positive nutritional and pharmacological effect are beta glucans. Beta glucans can be found in grain, in particular oat and barley, other sources can be edible fungus/mushrooms, in particular mushrooms of the family Agaricus.

The by-products obtained from lactic acid fermentation of beta glucan containing components, herein under macro algae (sea-weed), are considered to have a protective effect against the development of some cancer forms, gastrointestinal cancers and some leukaemia and lymphomas. The by-products has also in pilot studies by the inventor demonstrated effect on human cronic inflammatory conditions in the intestine (inflammatory bowel disease) and joints (arthritis and artropaties).

There is an ongoing interest in the positive immune stimulatory, nutritional and pharmacological effects of the by-products obtained from various prebiotics, including glucans, in particular beta glucans.

Based on in vitro studies and animal experiments, beta-glucans have played a pivotal role in regulating the intestinal mucosal immune response due to interleukin signalling such as the interleukins: IL-1, IL6, IL10IL-17, IL21 and IL 23 probably due to the involvement of the innate immune system such as upregulating the Toll-like receptor TLR-2, TLR-4 and TLR-6. Mice deficient in the IL-1 receptor antagonist (IL1 Ra-/-)

spontaneously develop a T cell driven autoimmune arthritis, (Ref 1.) Blocking IL-17 with an antibody has been described to cause clinical IBD (Crohn's Disease) in patients treated with anti-IL- 17 such as e.g. Sekukinumab. (Ref 2.)

Object of the Invention

Thus it is an object of the present invention to provide a fermented composition, which is rich in prebiotics and probiotics.

It is also an object of the present invention to provide a method for making the fermented composition.

It is an object of the present invention to provide a fermented composition, which can improve stabilize and/or normalize the intestinal microflora in individuals, including humans or animals.

It is also an object of the present invention to improve the overall condition of the dietary tract and reduce symptoms and/or diseases arising from anormalities in the dietary tract or composition of intestinal microflora (dysbiosis)in individuals, including humans or animals.

In addition, it is an object of the present invention to use the fermented composition in treating, reducing or eliminating symptoms of various diseases or conditions as mentioned below.

Description of the Invention

These objects are solved by a fermented composition comprising a dried fermented material comprising a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, wherein the fermented material is selected from one or more materials of vegetable origin, of fungal origin which is combined with a dried or dried and fermented second material originating from one or more species of seaweed, micro algae and/or macro algae.

In this respect the inventor of the present invention surprisingly found that a fermented composition comprising a combination of probiotics and prebiotics promote the well-being of the individual and also provides unexpected and improved nutritional and/or pharmacological effects in animals and humans.

The fermented product is found to have a stabilising effect on the mucosal layer of the bowel/digestive tract of mammals, such as humans or animals. The stabilising effect on the mucosal layer in the bowel has a positive effect to the wellbeing of the individual and may reduce certain symptoms related to diseases or conditions, that reduce the wellbeing of the individual.

Moreover, the fermented product comprising a combination of prebiotics and probiotics according to the present invention is believed to reduce or alleviate symptoms related to certain inflammatory and/or non-inflammatory diseases as discussed further below.

Prebiotics are for example polysaccharides and/or oligosaccharides such as dietary fibers, in particular soluble dietary fibers. Examples of such prebiotics are beta-glucans, lamiarin and fucoidan. Other prebiotics are e.g. proteoglycans and/or glycoproteins.

β-Glucans or beta-glucans comprise a group of β-D-glucose polysaccharides naturally occurring in the cell walls of cereals, yeast, bacteria, and fungi, with significantly differing physicochemical properties dependent on source. Typically, β-glucans form a linear backbone with 1-3 β-glycosidic bonds. In addition, some β-glucans, e.g. laminarin, may form a backbone with 1-3 β-glycosidic bonds with at least some branches of 1-6 β-glycosidic bonds. β-glucans vary with respect to molecular mass, solubility, viscosity, branching structure, and gelation properties.

Laminarin (also known as laminaran), a polysaccharide of glucose is also a β-glucan with β(1-3)-glycosidic bonds in the backbone and branches of (1-6)-glycosidic bonds) found e.g. in brown algae.

Fucoidan is a sulfated polysaccharide (MW: average 20,000) and designates a group of certain fucose-containing sulfated polysaccharides that have a backbone built of (1-3)-linked α-l-fucopyranosyl or of alternating (1-3)- and (1-4)-linked α-l-fucopyranosyl residues, but also include sulfated galactofucans with backbones built of (1→6)-β-d-galacto- and/or (1→2)-β-d-mannopyranosyl units with fucose or fuco-oligosaccharide branching, and/or glucuronic acid, xylose or glucose substitutions. Fucoidan is found mainly in various species of brown algae, such as Ascophyllum nodosum and/or Saccharina latissimi, and brown seaweed such as mozuku, kombu, bladderwrack, wakame, and hijiki. Fucoidan is used as an ingredient in some dietary supplement products and is believed to have immuno-stimulating properties as is the case with β-glucans.

Macroalgaes are also known to contain components with the known activity as in the table below:

COMPONENT	ACTIVITY
Sulphated galactanes	Antioxidants
Polyols	Collagen syntesis stimulation
Phlorotannins	Adipogenesis
Fucoidan	Anticoagulant, antioxydant
Other (not identified yet)	Effect on fibroblast growthrate

Table 1

Other important prebiotics are e.g. proteoglycans and/or glycoproteins.

Particularly preferred are large proteoglycans called arabinogalactan-proteins (AGPs) that appears to be implicated in signalling events and developmental processes in various species of green and brown algae and land plants.

In the present application glycoproteins are defined as proteins with a sugar attached to them. Glycoproteins may adhere to cells and enable development of functional tissues in the intestine such as creating increased intestinal mucus production and may also have anticoagulant properties which is found in both brown and green algaes. It has been suggested by several groups that probably the active compound or com-

pounds of the algal species are related to high molecular weight polysaccharide, or a complex form with carbohydrate and protein (proteoglycan).

The fermented composition comprises in particular a combination of one or more of oat (avenum sativum), barley ((Hordeum vulgare L.)) and/or one or more species of fungi, which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae.

The oat, Avena Sativa, is an important source of beta glucans and is thus a preferred ingredient of the fermented composition according to the present invention. Most oats contain 3-6% β-glucan by weight. Oats can be selectively bred based on favourable β-glucan levels and/or one or more specific varieties of oat may be selected according to their content of β-glucan. Oat β-glucans are linear and linked at the 1,3 and 1,4 carbon sites.

In particular oat bran comprises high levels of beta glucans, such as from 5.5% to 23.0% and it is thus in particular preferred to include oat bran in the fermented composition according to the present invention.

Another source of beta glucans is barley (Hordeum vulgare L.). Barley contains gluten, which may make it an unsuitable grain for consumption by some people with gluten-related disorders, such as celiac disease, non-celiac gluten sensitivity and/or wheat allergy sufferers. Nevertheless, some wheat allergy patients can tolerate barley. Thus, barley may be another important but less preferred source of beta glucans and other dietary fibers to include in the fermented composition.

In principle any variety of oat and/or barley can be used in the fermented composition according to the present invention and/or a combination of one or more varieties of oat may be selected, based on their content of beta glucans. In addition, germinated oat and/or germinated barley, also called malted barley or malted oat, may be used to produce the fermented composition according to the present invention.

Preferably, the oat and/or barley used are a non-GMO species, i.e. the species are not genetically modified. In particular, the use of glyphosate resistant genetically modified strains of oat or barley should be avoided, because such genetically modified oats

/barley strains may contain glyphosate, which is believed to have a negative impact on the intestinal mucosa and/or microbiotica in the intestines, especially in respect of neurotransmitter, e.g. dopamine, synthetizing gut mictobiotica. In addition other important functions, such as synthesis of secondary bile salts may be reduced or halted if the food contains glyphosates.

The one or more species of fungus are in particular fungus selected from edible mushrooms, more particularly edible species of Agaricus, Reishi, Ganoderma Applanatum, Shiitake and/or Maitake, in particular species of agaricus such as Agaricus blazei Murill, A. Bisporus, A. Essettei, A. Bitorquis A. Subfloccosus, A. vaporarius and/or A. Cupressicola, because these species and varieties of fungus also contain high concentrations of beta glucans.

Certain species of seaweed, micro algae and/or macro algae are also rich in prebiotics, in particular β-glucans. The Laminaria family such as in particular the species Laminaria dentata, Laminaria saccharina, Laminaria digitata, Laminaria hyperborean, Laminaria Fuculencu, Laminaria Alata and/or Laminaria cichorioides contain significant amounts of β-glucans, in particular laminarin as mentioned above. Other sources of β-1,3/1,6-D-glucans, e.g. laminarin or similar β-glucans, and/or fuciodan may be Durvillaea antarctica (Chamisso), Alaria fistulosa, A. marginata, red algae, such as the Palmaria family, in particular Palmaria palmata, all species of brown algae, such as Ascophyllum nodosum and/or Saccharina latissimi, and/or Fucus evanescens.

As mentioned above, the fermented composition according to the present invention comprises one or more probiotic bacterial strain(s). Preferably, a number of different strain(s) of probiotic bacteria may be used according to the present invention.

Preferably, the probiotic bacteria are lactic acid-producing bacteria (lactic acid bacteria). Lactic acid bacteria are often linked with food fermentations because they produce lactic acid during the fermentation process, which results in acidification of the fermentation broth. In addition, the acidification inhibits the growth of other unwanted microorganisms, e.g. pathogenic microorganisms. Further, several lactic acid bacteria strains produce proteinaceous bacteriocins, toxins produced by bacteria to inhibit the

growth of similar or closely related bacterial strain(s). Thus, lactic acid bacteria provide an additional hurdle for growth of other unwanted microorganisms, e.g. microorganisms, which are pathogenic and/or cause spoilage.

The lactic acid bacteria are frequently used in production of food. In addition they contribute to the healthy microflora of maintaining the mucosal surfaces in humans and/or animals.

In addition, the production of lactic acid and other metabolic products by the lactic acid bacteria may contribute to the nutritional, organoleptic, textural, and/or pharmacological profile of the fermented composition.

Fermentation of the material comprising one or more materials of vegetable origin, of fungal origin and/or material originating from one or more species of seaweed, micro algae and/or macro algae using lactic acid bacteria causes degradation of the material, including the cell walls and thus renders the β-glucans and other prebiotics more readily available for digestion and or more readily available for the gut microflora present in the dietary tract if humans and animals.

Thus in order to provide a product comprising the β-glucans and other prebiotics more and also render these more readily available for the gut microflora, the material is not digested completely during fermentation, i.e. the fermentation process is stopped before degradation of the material is complete.

The one or more lactic acid bacterial strains are selected from the group consisting of the genus Lactobacillus, Enterococcus, Pediococcus or Lactococcus, or combinations thereof.

Alternatively or in combination with the above mentioned, the one or more of the lactic acid bacteria strains are selected from one or more species from the genus of, Leuconostoc, Streptococcus, Aerococcus, Carnobacterium, Oenococcus, Teragenococcus, Vagococcus, Bifidobacterium, Leucosporia and/or Weisella; these genera belong to the order Lactobacillales.

In particular, the lactic acid bacteria are selected from the group consisting of Lactobacillus plantarum; Lactobacillus rhamnosus, Pediococcus pentosaceus; Pendiococcus acidilactici; Enterococcus faecium, and/or combinations thereof.

More particularly the one or more lactic acid bacteria stain(s) is selected from the group consisting of one or more of Lactobacillus plantarum LSI (NCIMB 30083), Lactobacillus rhamnosus (NCIMB 30121, Enterococcus faecium (NCIMB 30122), Pediococcus pentosaceus HTS (LMG P-22549) and/or Pendiococcus acidilactici (NCIMB 30086).

Preferably, the one or more lactic acid bacterial strains are present in a total amount of 10^5-10^{12} CFU per gram because this provides the desired effects, because the fermented composition contains a high content of viable lactic acid bacteria and thus provides an effective daily dose of probiotics for humans and other animals in a daily dose of the fermented composition according to the present invention, which has a volume, which appears acceptable by most individuals, in particular humans.

A particularly preferred fermented composition comprises a high level of prebiotics by means of a combination of minimum 50% (by weight) of a fermented material, which includes one or more of species of oat and/or barley, in particular grains and/or bran of oat and/or barley, and more particularly oat bran, and/or species of edible species fungus/mushrooms, such as mentioned above, and up to 30 % (by weight) of a dried or dried and fermented second material originating from one or more species of seaweed, micro algae and/or macro algae.

The seaweed and/or algae in the second material is in particular selected from one or more of brown algae, such as Ascophyllum nodosum and/or Saccharina latissimi, red algae, green algae, such as kelps, Laminaria saccharina, Laminaria digitata, and/or Laminaria hyperborean.

In an embodiment of the present invention, the fermented composition may comprise minor amounts of one or more material originating from one or more Brassica species. The Brassica species may preferably be selected from one or more of rape species; the Brassica spp. may preferably be selected from one or more of rape species. Preferably,

the rape species is a rapeseed product, such as rapeseeds as such, rapeseed flour, or rapeseed cake, preferably rapeseeds or rapeseed flour. The material originating from brassica species may be present in an amount of up to 15% by weight, such as 1-10% by weight or more preferred 5-10% by weight.

In order to allow for easy uptake and to allow for formulation of the fermented composition into tablets etc. the fermented composition is pulverized, preferably after being dried, to provide a material having a final average particle size of up to 100µm-1mm, preferably up to 100-500µm or more particular up to 100-1,000µm. In principle the maximum size of the powder/granules can be up to 1,000µm depending on the size of the nozzle used for making the tablets/capsules or pellets.

In order to allow for easy and more accurate administration, the fermented composition is provided in a unit dosage form, said unit dosage form is present in a powder or paste, and optionally incorporated into capsules, tablets, caplets, lozenges, bags, a suspension, or the fermented composition is provided in a topical composition, such as an emollient, a cream or a suspension.

Suitable adjuvants for making the above mentioned formulations of the fermented composition are in particular commonly used pharmaceutically acceptable components, such as by the fermented composition is enclosed by capsules made from macroalgae extracts, gelatine, or vegetable cellulosic based capsules, or by forming tablets, caplets or lozenges by using a binder such as agarose, lactose, dibasic calcium phosphate, sucrose, maise or potato starch, microcrystalline cellulose, povidone, polyvinylpyrrolidone, modified cellulose, e.g. hydroxypropyl methylcellulose and/or hydroxyethylcellulose, or provided in a liquid formulation, in particular a cream, an emoillent or a suspension, which may comprise a mixture of glycerine and/or aloe vera gel and/or grated beeswax, and distilled water.

The present invention also relates to a method for preparing a fermented composition as discussed above. The method comprises the steps of:

(i) providing a material comprising a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, such as a combination of

- one or more species of vegetable origin, in particular species of oat and/or barley and/or one or more species of fungus, in particular fungus selected from edible mushrooms, ,

(ii) providing one or more lactic acid bacteria strain(s);

(iii) subjecting the material to fermentation by combining the material provided in step a) with the one or more lactic acid bacterial strain(s) provided in step b), and

(iv) continuing the fermentation until the fermented composition is provided having a pH value of less than 6, preferably a pH in the range of 3-5, or in particular a pH in the range of 3.5 to 4.5,

providing a second fraction of a dried or dried and fermented material of one or more species of seaweed, micro algae and/or macro algae, and

combining the first and second fractions to provide the fermented composition.

In order to improve the fermentation process and speed up the fermentation process material may be fractionized by grinding, cutting, chopping, slicing, and/or fractionizing providing a fractionized material prior to the fermentation step. The initial fractionation may provide the material in a reduced size to increase the surface of the material and thus speed up the fermentation step, because the material becomes more easily available to the lactic acid bacteria during fermentation.

Experiences have shown that material of one or more species of seaweed, micro algae and/or macro algae possess a high antioxidative effect. Thus if the composition contains a large fraction, such as more than 30 % by weight of the algae and/or seaweed, the antioxidative effect may cause the fermentation by the lactic acid bacteria strains(s) to stop, at least for a period. After a certain period of time, which may be after several days or even several weeks the fermentation process may then sometimes restart. This will result in prolonged production time, which results in unwanted increased production costs.

Thus, in order to avoid such stops during fermentation and/or increased production costs, the method preferably comprises providing a first fraction of a first fermented material of one or more of species of oat, one or more species of barley and/or species of edible fungus, in particular fungus selected from edible mushrooms, such as men-

tioned above providing a second fraction of a dried or dried and fermented material of one or more species of seaweed, micro algae and/or macro algae and combining the first and second fractions to provide a fermented composition as discussed above.

Fermentation may initiated by adding a starter culture comprising one or more lactic acid bacterial strain(s) as discussed above or alternatively by adding a fraction of a previously fermented batch containing lactic acid bacteria strain(s) as discussed above. Some materials, e.g. seaweed, naturally contain lactic acid bacteria strains on the surface of the material, and inoculation using a starter culture may thus be avoided when fermenting such material or a material containing a large fraction thereof.

After inoculation, and an initial temperature increasing period, the fermentation step or steps are performed at a steady state temperature in the range 15-45°C, such as 20-45°C, such as 25-45°C, such as 30-40°C or such as 40-45°C depending on the optimum temperature of the one or more lactic acid bacterial strains. In particular, it may be advantageous to carry out the fermentation in the upper end of the temperature range, such as 40-45°C, because this temperature range may inhibit or even prevent growth of other, potentially pathogenic, microorganisms during the fermentation step. Preferably, an initial temperature increase is provided by heat produced by the fermentation itself and thus without the use of energy from external energy sources in the initial phase. During steady state, the temperature may be controlled by conventional temperature regulation means, e.g. electrical heating, to be within the above-mentioned ranges. This saves energy and reduces the overall production costs.

It is essential that the fermentation process does not fully digest the material of vegetable, fungus or seaweed and/or algae origin, because this will eliminate or at least significantly reduce the content of prebiotics in the fermented composition. Even though the fermentation should be continued as quickly as possible, a certain time of fermentation is required to provide the desired degradation of the material as provided initially, in order to “open” the material (e.g. by at least a partial degradation of the cell walls in the material). This will allow an easy access to the prebiotics and other nutritional substances in the fermented material when the fermented material is digested in the dietary tract of an animal, including humans, and thus ensure the nutritional and/or pharmacological effects of the fermented composition. Therefore, the

fermentation step may be continued for up to 10 days, such as up to 9 days or less, e.g. 8 days or less, such as 7 days or less, e.g. 6 days or less, such as 5 days or less, e.g. 4 days or less, such as 3 days or less, e.g. 48 hours or less, or e.g. 24 hours or less.

The material may be further supplemented with rice, beans, peas, soy, brassica spp, such as one or more of rape species, e.g. a rapeseed product and/or vegetables, preferably starch containing vegetables such as potatoes, or a flour thereof, in an amount of up to 1-15% (by weight) of the composition, such as up to 5-10% (by weight) of the initial material which is subjected to lactic acid fermentation.

The moisture content of the plant material to be fermented may be another relevant parameter to control in order to control the fermentation process and the resulting fermented composition. Thus, the moisture content during the fermentation may be in the range of 20-60% (w/w), such as in the range of 25-55% (w/w), e.g. preferably in the range of 35-45% (w/w). Thus the fermentation occurs in practice in solid state as a paste, and thus similar to a silage process.

After finalising the fermentation, the fermented material is preferably subjected to drying to allow for easy packaging and to allow for incorporation into tablets etc. as discussed above. In addition the drying step conserves viable lactic acid bacteria in the material and thus prolongs the viability thereof.

The drying step is preferably a gentle drying without the addition of heat or low addition of heat in order not to cause a significant reduction in the content of viable lactic acid bacteria in the fermented composition. Suitable drying techniques are e.g. freeze drying; vacuum drying, flash drying, or air drying at temperatures below 45°C.

The fermented and optionally dried composition is preferably pulverized by grinding, cutting, chopping, slicing, and/or fractionizing, in particular to a final average particle size as mentioned above.

When pulverizing a material, the shear forces on the material, which occurs during pulverisation, e.g. grinding processes and the like as mentioned above, results in a temperature increase of the pulverized material. The temperature increase may result

in killing or inactivation of the viable lactic acid bacteria present in the fermented composition, which reduces the overall quality; in particular if an uncontrolled temperature increase occurs in the fermented composition.

Therefore, in order to minimize or even eliminate the reduction in the count of viable lactic acid bacteria in the fermented composition, the pulverization of the material, in particular of the dried material, is carried out at temperatures below 40°C, such as within the range of 15-35°C, or in particular 20-35°C. Preferably, the temperature of the final product is reduced by reducing the initial temperature of the material prior to pulverizing by subjecting the material to cooling, freezing and/or by pulverizing the material while cooling the pulverizing equipment, and/or by mixing the material with an inert cryogenic material, such as solid carbon dioxide, liquid nitrogen, or by pulverisation under a gaseous atmosphere having a controlled temperature range, e.g. as mentioned above and/or similar combinations thereof.

In order to eliminate growth of unwanted strains of microorganisms during the fermentation step, the material is preferably pasteurized or sterilized prior to being fermented.

The temperature increase during the initial pasteurisation or sterilisation step also results in a partial (thermal) hydrolysis of the material of plant, fungus and/or algae/seaweed origin, which may promote the fermentation process, e.g. by releasing some of the nutrients present in that material and render these readily available for the lactic acid bacteria, at least during the start-up period of the fermentation process.

The fermented composition, which comprises a high level of prebiotics and probiotics, which is obtainable by the process as described above may thus be a food or feed product, a food or feed supplement or from part of a food/feed product or a food supplement.

In the present context, the terms "food" refers to edible material, which is intended for human consumption. The term “feed” refers to edible material, which is intended for animal consumption. In an embodiment of the present invention the term "animal(s)" preferably includes domesticated animals or animals which are bred on a commercial manner, e.g. for food supply. Thus the term “animal” may include pigs, piglets, cattle,

horses, dogs, cats and poultry such as chicken, turkey, hens, ducks, geese and/or fish, e.g. salmon or trout.

Thus the terms "food" and “feed” may be used interchangeably.

When used as an ingredient, additive or supplement in food/feed products, the food/feed product preferably comprises in the range 1-50% by weight of the dry feed/food ingredient, such as in the range 5-30%, such as 10-30% or such as 5-20%.

The inventors of the present invention surprisingly found that the composition according to the present invention has nutritional and/or pharmacological effects.

Another aspect of the present invention the fermented composition may be used in a natural medicine product (or a herbal medicine product); in a medicinal product and/or as an adjuvant product which is used in combination with one or more other drugs. The term adjuvant as used herein refers to a composition, which enhances or promotes the effects of another drug. Alternatively, the adjuvant may suppress unwanted side effects of another drug or a combination of other drugs.

Thus the present invention also relates to a composition for use as a medicament comprising a fermented composition having a high content of one or more lactic acid bacterial strains, and one or more materials of vegetable origin, of fungal origin and/or the material originates from one or more of seaweed, micro algae and/or macro algae having a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins. Alternatively said substance comprises a fermented composition as described above or as being obtainable by the method as described above.

Preferably, the composition according to the present invention may be used in the treatment of, or as adjuvant to a conventional medical treatment, or for alleviation, stabilisation or prophylaxis of clinical diseases in a mammal (such as a human or an animal), where the composition comprises a fermented composition according to the present invention.

Thus the present invention may relate to a composition for use in the treatment, adjuvant treatment, alleviation, stabilising or prophylaxis of constipation; fatigue, inflammation, diarrhoea; inflammatory bowel diseases or irritable bowel syndrome, such as pan cholitis, duodenitis, ileitis, jejunitis, cholitis, sigmoiditis, morbus Crohn's disease, and/or cholitis ulcerosa; overweight or obesity, including severe obesity, and/or avoiding regaining weight after a gastric bypass surgery procedure; diabetes, in particular type 2 diabetes; allergy (such as gluten allergy and/or lactose allergy/atopic dermatitis); rheumatism or arthritis; connective tissue disorders, such as psoreasisartritis, psoreasisartropatis, spondylartropatias or spondylarthritis, psoriasis,morbus bechterew, sclerodermia; pregnant women in risk of pre-eclampsia and/or in connection with pregnancy and/or women after giving birth; bacterial infections, such as infections caused by gram positive bacteria, in particular Staphylococcus strains and/or Clostridium strains, more specifically Staphylococcus aureus and/or Clostridium perfringens/difficile; ideopatic back pain, backpain caused by Modic 1 and/or Modic 2 changes; and/or skin diseases, such as psoriasis, anti NF alpha antibody induced paoreasis, rosacia, acne, and/or rinophyma; and/or as an adjuvant before, during and/or after antibiotic treatment or radiotherapy of the intestines in a mammal, including humans or animals, wherein said composition comprises a fermented composition, as described above, which comprises a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, where the latter originates from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from edible mushrooms, more particularly edible species of mushrooms as discussed above, which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae. Alternatively, said composition comprises a fermented composition as described above or as being obtainable by a method as described above.

Preferably, the composition is an adjuvant product for administration in combination with one or more other drugs.

Thus a composition may comprise one or more drugs and the adjuvant, where the adjuvant comprises a fermented composition as described above, or as being obtainable by a method as described above.

The fermented product according to the present invention is believed to normalize and/or activate the intestinal micro flora (i.e, the intestinal bacterias, virae, fungi) in humans and/or animals. The term "normalization" refers to restoring the intestinal microenvironment from a dysbiotic stage, e.g. in connection with, during or after the patient, the human/animal, experienced imbalance (dysbiosis) in the intestinal micro flora, e.g. in connection with a disease as mentioned above and/or in connection with suffering from side effects in connection with taking another drug. The term "activating" refers to an increased activity of the intestinal micro flora, which exceeds the activity expected by the amount of lactic acid bacteria administered.

Researchers have found that often the cause of a disease, a condition, or an injury in mammals, i.e. human or animal individuals, is usually a result of an instable, abnormal and/or an infected intestinal flora. This may prime the human or animal organism to react, e.g. in the form of a discomfort, a disease, a condition, or an injury. The inventors of the present invention surprisingly found that a fermented composition (or a substance) according to the present invention may be highly suitable for counteracting such discomfort, disease, condition, or injury or side effect(s) of another drug or a combination of other drugs.

A disease may be a result of an inflammatory condition, or a non-inflammatory condition.

Non-inflammatory conditions are sometimes causing diffuse symptoms and may therefore be difficult to identify and cure. An example is irritated bowel syndrome (IBS), which is a non-inflammatory disorder of the intestines.

In an embodiment of the present invention the fermented composition (or the substance) is used for the treatment, alleviation, stabilization or prophylaxis of irritated bowel syndrome.

Psoriasis is a multiple of long-lasting autoimmune diseases characterized by patches of abnormal skin (hyperkeratosis). These skin patches are typically red, itchy, and scaly. They may vary in severity from small and localized to complete body coverage. The main types of psoriasis are plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis. Furthermore, sequelae as a consequence of psoriasis are also encompassed by the definition of treatment, alleviation, stabilisation or prophylaxis of psoriasis. Sequelae that are associated with psoriasis are an increased risk of psoriatic arthritis, lymphomas, cardiovascular diseases, Crohn's disease, and depression.

In an embodiment of the present invention the fermented composition (or the substance) for the treatment, alleviation, stabilisation or prophylaxis of psoriasis may preferably comprise a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins originating from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from edible mushrooms as discussed above, which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae, or said substance comprises a fermented composition as described above, or as being obtainable by a method as described above.

In an embodiment of the present invention wherein the Psoriasis Area and Severity Index (PASI) of a mammal suffering from psoriasis is reduced by 10% or more when the fermented composition or the substance according to the present invention is administered to a mammal, such as 20% or more, e.g. 30% or more, such as 40% or more, e.g. 50% or more, such as 60% or more, e.g. 70% or more, such as 80% or more, e.g. 90% or more, such as 95% or more, e.g. 100%.

In particular, the fermented composition according to the present invention is suitable for administration to pregnant women, e.g., to treat, reduce or eliminate overweight and/or obesity, and/or avoiding regaining weight after a gastric bypass surgery procedure, diabetes, such as diabetes type 2 and/or pre-eclampsia in pregnant women. In addition, administration of the fermented composition according to the present inven-

tion to pregnant women may reduce or even eliminate the risk of getting diabetes and/or pre-eclampsia during pregnancy and/or in connection with giving birth.
Cesarean versus Vaginal Delivery: Long term infant outcomes and the Hygiene Hypothesis.
(Ref: Josef Neu, MDa,b,a,b and Jona Rushing, MDc,c Clin Perinatol. Clin Perinatol. 2011 Jun; 38(2): 321–331.)

The C-reactive protein (CRP) is a pentameric protein found in blood plasma of a mammal. The levels of C-reactive protein may rise in response to inflammation and is used as a marker of inflammation. Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments.

Hence, one way to determine the extent or the severity of spondylarthritis, such as psoriasis, and in particular psoriatic arthritis, may be by measuring the level of C-reactive protein (CRP) in a mammal.

It is common that a maximum level (statistically evaluated) of CRP is accepted by the skilled person, whereby a mammal is still considered normal and healthy. In Denmark the health authorities has set a value of 8 (statistically evaluated) as the borderline for distinguishing between a healthy and a non-healthy person – based on the CRP value. In the present context the maximum level of CRP accepted for a normal/healthy mammal may be a CRP value below 8. Thus, a mammal having a CRP level below 8 are considered normal and healthy and mammals having a CRP value of 8 or above are considered abnormal/sick.

In the event said mammal is subjected to an inflammation the CRP level increases to a value of above 8 as described above. In an embodiment of the present invention the CRP level in a mammal is lowered to a CRP level below 8 after administering one or more daily doses of the fermented composition according to the present invention, in the mammal. In particular, the CRP Level in a mammal is lowered to a CRP level below 8 in 5 months or less, such as in 4 months or less, e.g. in 3 months or less, such as in 2 months or less, e.g. in 1 months or less, such as in 25 days or less, e.g. in 22 days or less, such as in 20 days or less, e.g. in 18 days or less, such as in 17 days or less,

e.g. in 16 days or less, such as in 15 days or less, e.g. in 14 days or less, such as in 12 days or less, e.g. in 10 days or less.

In a further embodiment of the present invention the CRP level in a mammal is lowered to a CRP level which is at most 75% of the CRP level before administering the fermented composition according to the present invention, determined as an average value over a period of 10 days, such as at most 60%, e.g. at most 50%, such as at most 40%, e.g. at most 30%, such as at most 20%, e.g. at most 10%.

Tests have revealed that the CRP level is lowered in a mammal to a level below 8 after administering a daily dose of the fermented composition in a period of minimum 14 days. After interrupting the administration of the fermented composition for 14 days the CRP level again rose to a level above 8. The CRP level then again dropped to a level of below 8 when resuming the administration of a daily dose of the fermented product according to the present invention.

Allergy, include a number of allergic diseases or conditions caused by hypersensitivity of the immune system to something in the environment. In some cases the allergic reaction causes little but highly annoying problems in a mammal and in other situations the allergic reaction may be severe and immediate action is needed. The allergic diseases may include hay fever, food allergies, atopic dermatitis, allergic asthma, allergic arthritis, atopic eczema, and anaphylaxis. Symptoms may include red eyes, an itchy rash, runny nose, shortness or trouble of breath, increased hart beating, suffocation, or swelling.

In an embodiment of the present invention the fermented composition (or the substance) for the treatment, alleviation, stabilisation or prophylaxis of allergy may preferably comprise a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins the latter originating from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from edible mushrooms, more particularly edible species of fungus/mushrooms, such as discussed above, which is combined with a dried or dried and fermented material originating from one or more species of

seaweed, micro algae and/or macro algae, or said substance comprises a fermented composition as described above, or as being obtainable by a method as described above.

In particular, the fermented composition (or the substance) is suitable for the treatment, alleviation, stabilisation or prophylaxis of gluten allergy and/or lactose allergy.

Preferably, a mammal suffering from allergy, such as gluten allergy and/or lactose allergy, may, when taken the composition according to the present invention experience no allergic reaction or at least reduced symptoms arising from the allergy in question. Thus, when taking the composition according to the invention, the mammal may be able to eat normally afterwards, i.e. without eliminating gluten and/or lactose from the diet.

Constipation refers to bowel movements that are infrequent or where the content of the intestines is hard to pass, which may result in feces which is hard and/or failure to pass stools or gas. Constipation is a common cause of painful defecation. Severe constipation includes obstipation and fecal impaction, which can progress to bowel obstruction and become life-threatening. Constipation is common. In the general population rates of constipation varies from 2 to 30%. Old people living in care homes the rate of constipation is 50% to 75%. Furthermore, sequelae as a consequence of constipation are also encompassed by the definition of treatment, alleviation, stabilisation or prophylaxis of constipation. Sequelae that are associated with constipation are spinal cord lesions, Parkinsons, colon cancer, anal fissures, proctitis, pelvic floor dysfunction, anismus, descending perineum syndrome, and Hirschsprung's disease.

In an embodiment of the present invention the fermented composition (or the substance) for the treatment, alleviation, stabilisation or prophylaxis of constipation may preferably comprise a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins originating from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from edible mushrooms, such as discussed above, which is combined with a dried or dried and fermented material originating from one

or more species of seaweed, micro algae and/or macro algae, or said substance comprises a fermented composition as described above, or as being obtainable by a method as described above.

In an embodiment of the present invention the fermented composition (or the substance) is administered to a mammal in combination with one or more drugs in order to avoid the constipating side effect many medications have.

Preferably, constipation in a mammal may be treated or alleviated within 15 hours from intake of the fermented composition according to the present invention, such as within 10 hours, e.g. within 8 hours, such as within 6 hours, e.g. within 4 hours, such as within 3 hours, e.g. within 2 hours, such as within 1 hour.

Fatigue is a subjective feeling of tiredness which is distinct from weakness, and has a gradual onset. Patients suffering from inflammatory diseases often also suffer from fatigue. Unlike weakness, fatigue can be alleviated by periods of rest. Fatigue can have physical or mental causes. Recent studies points at that functional fatigue such as Myalgic encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS), also known chronic fatigue and immune dysfunction syndrome (CFIDS) may have its cause by the altered intestinal microbiota of the patient since some of the intestinal microbes actually can secrete neurotransmitters such as dopamine. Physical fatigue is the transient inability of a muscle to maintain optimal physical performance, and mental fatigue is a transient decrease in maximal cognitive performance resulting from prolonged periods of cognitive activity. Furthermore, sequelae as a consequence of fatigue are also encompassed by the definition of treatment, alleviation, stabilization or prophylaxis of fatigue. Sequelae that are associated with fatigue, in particular prolonged fatigue, are e.g. chronic fatigue, which may be a symptom of many diseases and conditions known to the skilled person.

In an embodiment of the present invention the mammal experience a decreased fatigue, and/or increased energy, physical and/or mentally, by administering one dose daily of the fermented composition (or the substance) according to the present invention for 30 days or less, such as 25 days or less, e.g. 20 days or less, such as 15 days or

less, e.g. 10 days or less, such as 5 days or less, e.g. 3 days or less, such as 2 days or less, e.g. 1 days or less.

In an embodiment of the present invention the fermented composition (or the substance) for the treatment, alleviation, stabilization or prophylaxis of fatigue may preferably comprise a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins originating from one or more fermented materials of one or more of species of oat, species of barley and/or species of fungus, in particular fungus selected from mushrooms, more particularly edible species of mushrooms, such as discussed above, and which is combined with dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae.

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the dietary tract, in particular, the colon and small intestine. Diarrhoea, duodenitis, ileitis, jejunitis, cholitis, sigmoiditis, morbus Crohn's disease, and/or cholitis ulcerosa are the principal symptoms and types of inflammatory bowel disease. Not only does inflammatory diseases such as Crohn's disease, affect the small intestine and large intestine, it can also affect the mouth, esophagus, stomach and the anus whereas ulcerative colitis primarily affects the colon and the rectum. Furthermore, sequelae as a consequence of inflammatory bowel disease are also encompassed by the definition of treatment, alleviation, stabilization or prophylaxis of inflammatory bowel disease. Sequelae that are associated with inflammatory bowel disease are arthritis, in particular Psoreatic Arthritis and spondyloartropaties and Morbus Bechterew (4:Van prate et al. Ann Rheum Diseases 2013 72: 414-7; 5:Mielants H et al J Rheumatol 1995; 22 2273-8) pyoderma gangrenosum, primary sclerosing cholangitis, and non-thyroidal illness syndrome (NTIS).

Furthermore, diarrhea may arise in patients subjected to a gastric bypass operation. Gastric bypass operation refers to a surgical procedure in which the size of the stomach is reduced by being divided into a small upper pouch and a much larger lower "remnant" pouch and then the small intestine is rearranged to connect to both. The operation may normally be prescribed to treat morbid obesity (defined as a body mass index greater than 40), and/or avoiding regaining weight after a gastric bypass surgery

procedure, type 2 diabetes, hypertension, sleep apnoea, and other comorbid conditions. The intestinal mucosal microbiome has been proven to be site specific; this means that the removal of a part of the intestine, causes lack of the site specific normal microflora. Therefore, a patient who has been subjected to gastric bypass has to be on a life-long diet with food additives.

When the gastric bypass patient eats a sugary food, the sugar passes rapidly into the intestine, where it gives rise to a physiological reaction called dumping syndrome. The body will flood the intestines in an attempt to dilute the sugars resulting in diarrhea. Hence, patients subjected to gastric bypass operations often suffer from diarrhea.

In an embodiment of the present invention treatment of diarrhea (either arising from Inflammatory bowel disease (IBD), e.g. Crohn's disease, gastric bypass operations, or from infection by bacteria, such as E. coli, virus or parasites) in a mammal may be obtained by administering one dose daily of the fermented composition (or the substance) according to the present invention within 5 days or less, such as 4 days or less, e.g. 3 days or less, such as 2 days or less, e.g. 1 days or less, such as 20 hours or less, e.g. 15 hours or less, such as 10 hours or less, e.g. 5 hours or less, such as within 2 hours or less.

In the present contest the term “treatment of diarrhoea in a mammal” relates to the subjective opinion of the mammal of the improved health and/or the objective inspection of the stool obtained from the mammal, e.g. using the Bristol Stool Chart.

In an embodiment of the present invention alleviation of diarrhoea in a mammal may be obtained by administering one dose daily of the fermented composition (or the substance) according to the present invention within 5 days or less, such as 4 days or less, e.g. 3 days or less, such as 2 days or less, e.g. 1 days or less, such as 20 hours or less, e.g. 15 hours or less, such as 10 hours or less, e.g. 5 hours or less, such as within 2 or less.

In the present contest the term “alleviation of diarrhoea in a mammal” relates to the subjective opinion of the mammal of the improved health and/or the objective inspection of the stool obtained from the mammal, e.g. using the Bristol Stool Chart.

In an embodiment of the present invention the fermented composition (or the substance) for the treatment, alleviation, stabilisation or prophylaxis of inflammatory bowel disease may preferably comprise a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins originating from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from edible mushrooms, more particularly edible mushrooms of species, such as discussed above which is combined with dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae.

The fermented composition (or substance) according to the present invention has surprisingly shown to be effective against bacterial infection.

In an embodiment of the present invention the fermented composition (or the substance) may be used for the treatment, alleviation, stabilization or prophylaxis of bacterial infection and may preferably comprise a combination of oat, barley and/or edible fungi, such as discussed above and seaweed/algae.

In the present context, the term “bacterial infection” relates to infections caused by either gram positive bacteria or gram negative bacteria. Preferably, the bacterial infection referred to in the present invention may be caused by gram positive bacteria, in particular Staphylococcus, preferably Staphylococcus aureus, and/or Clostridium, preferably Clostridium perfringens.

As mentioned, one such bacterial infection may be a staphylococcus infection, in particular a Staphylococcus aureus infection, which may results in e.g. furunculosis, or even worse in chronic furunculosis.

Furunculosis is most common in animals, such as dogs or cats, but it may also occur in humans. Animals and humans suffering from furunculosis may develop furuncle, which is a deep folliculitis (an infection and inflammation of one or more hair follicles).

Furuncles are bumpy, red, pus-filled lumps around a hair follicle that are tender, warm, and very painful. They range from pea-sized to golf ball-sized. A yellow or white point at the center of the lump can be seen when the boil is ready to drain or discharge pus. In a severe infection, an individual may experience fever, swollen lymph nodes, and fatigue.

Furuncles may appear on the buttocks or near the anus, the back, the neck, the stomach, the chest, the arms, legs or feet, or even in the ear canal.

Staphylococcus aureus may spread to different parts of the body via the bloodstream (bacteremia), causing bacterial infections (or sequelaes) like wound infections, abscesses, osteomyelitis, endocarditis, or pneumonia that may severely harm or even kill the infected animal or human.

Staphylococcus aureus strains may also produce enzymes and exotoxins that likely cause or increase the severity of certain diseases. Such diseases are also considered sequelae as a consequence of bacterial infection and are also encompassed by the definition of treatment, alleviation, stabilisation or prophylaxis of bacterial infection, and include food poisoning, septic shock, toxic shock syndrome, and scalded skin syndrome. Almost any organ system can be infected by Staphylococcus aureus.

Another bacterial infection may be a Clostridium infection, which may results in e.g. food poisoning, sepsis or myonecrosis, such as gas gangrene. The Clostridium infection may in particular be caused by Clostridium perfringens.

Myonecrosis, e.g. gas gangrene, is a condition of necrotic damage, specific to muscle tissue. It is often seen in infections with Clostridium perfringens that cause myonecrosis by producing alpha toxins. This alpha toxin is a lethal toxin and also known as phospholipase C (lecithinase). It increases vascular permeability and produces necrotizing activity. The toxins secreted are very powerful and destroy nearby tissue and generating gas at the same time.

Bacterial infections in mammals, e.g. infections arising from the above mentioned pathogenic microorganisms may be treated, alleviated, stabilized by administering a fermented composition (or the substance) according to the present invention to the infected mammal. The fermented composition (or the substance) according to the present invention may preferably comprise a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, the latter originating from one or more fermented materials of one or more species of oat, species of barley and/or species of fungus, in particular fungus selected from mushrooms, more particularly edible species of mushrooms, such as already discussed above, which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae, or said substance comprises a fermented composition as described above, or as being obtainable by a method as described above.

In an embodiment of the present invention the fermented composition (or the substance) is administered to a mammal (an animal or a human) in combination with one or more drugs in order to avoid the bacterial infection; the bacterial infection side effects; or the side effects many medications may have.

For example, a patient which is treated with antibiotics, e.g. penicillines, erytromycines, macrolides (azithromycin or roxithromycin), gentamycins and/or fungicides to fight an infection from pathogenic microorganisms, may experience diarrhea, because the intestinal microflora is also affected by the antibiotics administered to the patient. Thus in order to normalize the intestinal microflora, the patient may be given the fermeted composition according to the present invention. The combination of prebiotics, in particular ß-glucans, and probiotics stimulates the regeneration of a healthy intestinal microflora, and thus reduces, eliminates symptoms, e.g. diarrhea, which arise from treatment with antibiotics; or the period in which the patient suffers from such symptoms is reduced significantly in relation to a situation where administration is not followed by the administration of the fermented composition as mentioned above.

Preferably, bacterial infections in a mammal, such as bacterial infections caused by *Staphylococcus aureus* and/or by *Clostridium difficile/perfringens*, may be avoided by

a prophylactic treatment with the fermented composition according to the present invention. For prophylactic treatment, it is preferred that the individual, human or animal, takes a daily dose of the fermented composition regularly, in particular a dose daily, over a period, such as at least one week.

In an embodiment of the present invention one dose or a single dose relates to 50 gram fermented product according to the present invention or less, such as 40 g or less, e.g. 30 gram or less, such as 25 gram or less, e.g. 20 gram or less, e.g. 15 gram or less, such as 10 gram or less or 5 gram. The dose is preferably a unit daily dose, which is taken in one dose. Alternatively, a daily dose may be divided into two or more smaller doses, e.g. by dividing a daily dose of 15 gram into 3 doses of 5 g each, which are taken at 3 different times at the day.

In another embodiment of the present invention the substance and/or the fermented composition may be used as an adjuvant product accompanied by one or more other drugs.

For example, when using certain antibodies, such as sekukinumab, usteokinumab, for blocking the action of certain interleukines, in particular IL17, IL19 and/or IL21, it may result in an increased permeability of the colon and/or small intestines in mammals suffering from a (latent) inflammatory bowel disease. Anti-interleukines are frequently used in the treatment of certain inflammatory arthritis diseases, such as psoreasisrtritis, Spondylartritis, and/or Morbus Bechterew (4,5). Previous research has shown that it is necessary to provide constant stimulation of intestinal mucosa in order to maintain the impermeability if the intestines because the treatment with anti-interleukines may result in that patients with a latent inflammatory bowel disease (IBD), such as latent ileitis or latent Morbus Chron, develops a fulminant IBD when treated with anti-interleukines. Other drugs which may influence the intestine mucosa are NSAID´s Non Steroid Antiinflammatory Drugs, such as Cox-I or Cox-II inhibitors such as Ibuprofene, Diclofenac, Naprosyne, Arcoxia, and others.

This increase in permeability of the colon and/or small intestines can be reduced or even avoided by local stimulation of the colon and/or small intestines using prebiotics and probiotics as described above. Thus, it appears that changes in permeability of the

intestines can be reversible and thus may be reduced to improve the overall condition and/or wellbeing of the patient.

Thus, the present invention also relates to a combinational product comprising:

(a) a fermented composition according to the present invention, or a substance according to the present invention; and

(b) one or more drugs.

Without being bound by any theory, the fermented composition and/or the substance may comprise a dual function within the combined product according to the present invention. The dual function may in a first aspect lie in treating, stabilising and/or alleviating and/or in a second aspect lie in the prophylaxis of diseases, conditions and/or injuries in a mammal.

It should be noted that embodiments and features described in the context of one of the aspects of the present invention also apply to the other aspects of the invention.

In the present application, the term "treatment" refers to the use of an agent, such as the substance or the fermented composition according to the present invention, in an attempt to cure or mitigate a disease, a condition, or an injury in a mammal.

In the present application, the term "alleviation" used in the present invention refers to the action of an agent, such as the substance or the fermented composition according to the present invention, to reduce or eliminate symptoms in a mammal of a disease, a condition or an injury.

In the context of the present invention the term "prophylaxis" refers to the use of an agent, such as the substance or the fermented composition according to the present invention, in an attempt to prevent a disease, a condition or an injury in a mammal and/or for the protective treatment of a mammal.

In the context of the present invention the term "stabilising" refers to the use of an agent, such as the substance or the fermented composition according to the present

invention, to stabilise the intestinal flora in a mammal for the improvement of the well being (e.g. prevent, treat or alleviate a disease, a condition or an injury in a mammal).

Many diseases, conditions and/or injuries in a mammal may be the result of an instable, abnormal and/or an infected intestinal flora. Thus, the term "stabilising" used in the present invention refers to the use of an agent, such as the substance or the fermented composition according to the present invention, to stabilise, normalise and fight infected intestinal flora in a mammal.

The invention will now be described in further details in the following non-limiting examples.

Description of the Drawing

The present invention will be described in more detail below with reference to fig. 1 which shows the variation in CRP in a test person over a period as described in example 2.

Detailed Description of the Invention

Example 1: Preparation of a fermented composition according to the present invention.

Ingredient	Amount in % (by weight)
Oat bran	65
Seaweed Laminaria Digitata	25
Agaricus Blazei Murill	10

Table 2: composition of Fermented material.

A Composition as shown in Table 1 is poured into a fermentation tank and the moisture content was adjusted to about 40% humidity. The mixture was inoculated with a combination lactic acid-producing bacteria: Pediococcus pentosaceus, Pediococcus acidilactici and Lactobacillus plantarum (delivered by Chr. Hansen). The ingredients were mixed at room temperature and the temperature was slowly increased from the heat generated from the fermentation to a steady state temperature of about 42°C.

After 20 hours of fermentation the fermentation broth had a pH of 4.3.

The resulting fermented composition was subjected to spin flash drying in order to protect the lactic acid bacteria and keep a high number of viable cells.

Example 2:

In an in vitro test β-glucans induced a 17-20% increase in activated CD19+ B lymphocytes (a pre -B-cell) on when compared to controls made on tests using cells from the same donor. Incubation and exposure of the cells to β-glucans were made in a stable constant atmosphere at physiological conditions in a ViVoX TC Biosystem, invented by ViVoX ApS.

The test was carried out on white blood cells (Buffycoat) harvested from healthy blood donors.

Example 3:

A person suffering from chronic oligo arthritis antigen HLA B27-associated was tested and showed a CRP level of above 20, as seen on the test dates preceeding 01/06/2015 in fig. 1. The test person was prescribed a daily dose of 5 g of the fermented product according to example 1.

The CRP level was lowered to a level below 8 after administering the daily dose of the fermented composition in a period of more than 14 days after 01/08/2015. After interrupting the administration of the fermented composition for another 14 days, the CRP level again rose to a level above 8 as shown on fig. 1. The CRP level then again dropped to a level of below 8 when resuming the administration of the daily dose.

During the observation period, F-calprotectin was lowered from 50 to 30, i.e. 40% lower, in the period taking the fermented product compared to periods where the product was not taken.

F-Calprotectin (Faeces Calprotectin) comprises as much as 60% of the soluble protein content of neutrophil cytosol and is secreted by an unknown mechanism during inflammation. Faecal calprotectin was here used to detect intestinal inflammation, and serves as a marker for inflammatory bowel diseases.

Example 4:

6 persons which all had a BMI between 25 and 30 were all prescribed a daily dose of 25 g of the fermented product according to example 1 during a period of 6 months. No other treatment was carried out. The test persons were instructed in continuing their usual diet during the test period. One test person had to be excluded due to non compliance.

After 6 months, the test persons all showed a weight loss of between 3 to 11 kg., see table 3.

Person	Start weight	Weight after 6 months	Gender
1	67	60	Female
2	81	72	Male
3	106	96	Male
4	65	63	Female
5	64	61	Female
6	91	85	Female

Table 3

Example 5:

A female test person, (Person no. 6 in table 2) who had undergone a gastric bypass four years earlier, before initiating the test was prescribed a daily dose of 5 g of the fermented product according to example 1 during a period of 6 months.

The test person was instructed in continuing her usual diet during the test period. After the end of the test period there was not observed any significant increase in weight.

Example 6:

10 patients with mild to medium inflammatory bowel disease (IBD) were asked to take 5 gram in connection with main meals, i.e. 15 grams per day in a period of 3 months. Using the simple Clinical Colitis Activity Index (SCCAI) the scores toward remission in the patients was improved 56%, by lowering the SCCAI from an average of 8 to an average of 4). A reduction of SCCAI > 1.5 is considered clinically significant. (Ref 4).

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CLAIMS

1. A fermented composition comprising a dried fermented material comprising a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins wherein the material is selected from one or more materials of vegetable origin, or of fungal origin, which is combined with a dried or dried and fermented second material originating from one or more species of seaweed, micro algae and/or macro algae.

2. A fermented composition according to claim 1, wherein the material comprises a combination of

- a first fermented material which includes one or more of species of oat, species of barley and/or one or more species of edible fungi, and
- which is combined with dried or dried and fermented second material originating from one or more species of seaweed, micro algae and/or macro algae.

3. A fermented composition according to claim 1 or 2, wherein the one or more lactic acid bacterial strains are selected from the group consisting of the genus Enterococcus, Lactobacillus, Pediococcus or Lactococcus, and/or combinations thereof,
in particular selected from the group consisting of Pediococcus pentosaceus; Pendiococcus acidilactici; Lactobacillus plantarum; Lactobacillus rhamnosus; Enterococcus faecium, and/or combinations thereof
or more particularly the one or more lactic acid bacteria stain(s) is selected from the group consisting of one or more of Lactobacillus plantarum LSI (NCIMB 30083), Lactobacillus rhamnosus (NCIMB 30121, Enterococcus faecium (NCIMB 30122), Pediococcus pentosaceus HTS (LMG P-22549) and/or Pendiococcus acidilactici (NCIMB 30086).

4. A fermented composition according to any of the preceding claims, wherein the one or more lactic acid bacterial strains are present in a total amount of 10^5-10^{12} CFU per gram.

5. A fermented composition according to any of the preceding claims, wherein the fermented composition comprises a combination of

- minimum 50% (by weight) of a fermented composition comprising one or more species of oat and/or barly, in particular grains and/or bran of oat and/or barley, and/or one or morespecies of edible fungus species

and

- up to 30 % (by weight) of dried or dried and fermented second material of one or more species of seaweed, micro algae and/or macro algae, wherein the seaweed and/or algae is in particular selected from one or more of brown algae, such as Ascophyllum nodosum and/or Saccharina latissimi, red algae, green algae, such as kelps, Laminaria saccharina, Laminaria digitata, and/or Laminaria hyperborean.

6. A fermented composition according to any of the preceding claims, wherein the fermented composition is pulverized, preferably after being dried and, to provide a material having an average particle size of up to 100µm-1mm, preferably up to 100-500µm or more particular up to 100-300µm.

7. A fermented composition according to claim 6, wherein the fermented composition is provided in a unit dosage form, said unit dosage form is present in a powder or paste, and optionally incorporated into capsules, tablets, caplets, lozenges, bags, a suspension, or the fermented composition is provided in a topical composition, such as an emollient or a cream.

8. A fermented composition according to any of the preceding claims, wherein the fermented composition is enclosed by capsules made from macroalgae extracts, gelatine, or vegetable cellulosic based capsules, or by forming tablets, caplets, pellets or lozenges by using a binder such as agarose, lactose, dibasic calcium phosphate, sucrose, maise or potato starch, microcrystalline cellulose, povidone, polyvinylpyrrolidone, modified cellulose, e.g. hydroxypropyl methylcellulose and/or hydroxyethylcellulose, or provided in a liquid formulation, in particular a cream, an emoillent or a suspension, which may comprise a mixture of glycerine and/or or aloe vera gel and/or grated beeswax, and distilled water.

9. A method for preparing a fermented composition according to anyone of claims 1-8, the method comprises the steps of:

(i) providing a first material comprising a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or glycoproteins, such as a combination of

- one or more of species of vegetable origin, in particular oat and/or barley, and/or one or more species of fungus, in particular fungus selected from mushrooms, more particularly edible species of fungus,

(ii) providing one or more lactic acid bacteria strain(s);

(iii) subjecting the material to fermentation by combining the material provided in step a) with the one or more lactic acid bacterial strain(s) provided in step b), and

(iv) continuing the fermentation until the fermented composition is provided having a pH value of 3-5,

- providing a second fraction of a dried or dried and fermented material of one or more species of seaweed, micro algae and/or macro algae, and
- combining the first and second fractions to provide the fermented composition.

10. A method according to claim 9 wherein the fermentation is performed at a temperature in the range 15-45°C, such as 20-45°C, such as 25-45°C, such as 30-40°C or such as 40-45°C.

11. A method according to claim 9 or 10, wherein fermented material is subjected to drying.

12. A method according to any of claims 9-11, wherein the fermented and optionally dried composition is pulverized by grinding, cutting, chopping, slicing, and/or fractionizing.

13. A method according to any of the preceding claims 9-12, wherein the pulverization of the material, in particular the dried material, is carried out at temperatures below 40°C, such as within the range of 15-35°C, or in particular 20-35°C, preferably by reducing the initial temperature of the material prior to pulverizing by subjecting the material to cooling or freezing and/or by pulverizing the material while cooling the pulverizing equipment, and/or by mixing the material with an inert cryogenic material, such as solid carbon dioxide, liquid nitrogen and/or similar inert combinations thereof.

14. A method according to any of the preceding claims 9-13 wherein the material is sterilized prior to being fermented.

15. Use of the fermented composition according to anyone of claims 1- 8 or being preparable by a method according to any of claims 9-14 in a food product or food supplement, in a natural medicine product; in a medicinal product and/or as an adjuvant product which is intended for use in combination with one or more other drugs.

16. A composition for use as a medicament comprising a fermented composition having a high content of one or more lactic acid bacterial strains, and one or more materials of vegetable origin, of fungal origin and/or the material originates from one or more of seaweed, micro algae and/or macro algae having a high content of beta-glucans, polysaccharides, oligosaccharides, proteoglycans and/or said substance comprises a fermented composition according to any of claims 1-8, or as being preparable by a method according to claims 9-14.

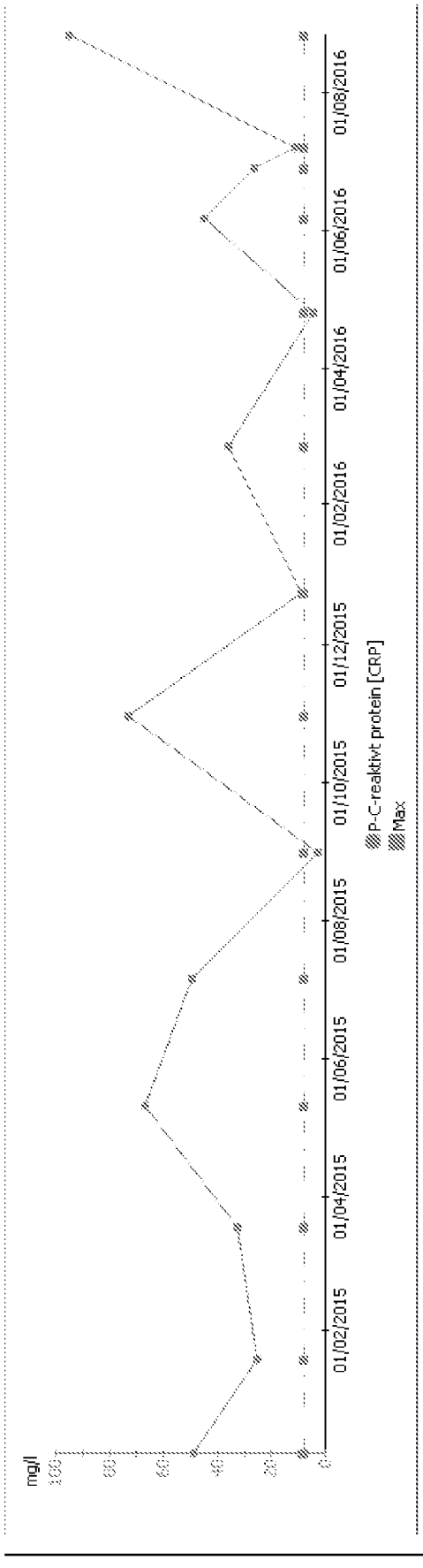
17. A composition for use in the treatment, adjuvant treatment, alleviation, stabilising or prophylaxis of constipation; fatigue, inflammation, diarrhoea; irritable bowel syndrome or inflammatory bowel diseases, such as duodenitis, ileitis, jejunitis, cholitis, sigmoiditis, morbus crohn's disease, and/or cholitis ulcerosa; overweight or obesity, including severe obesity, and/or avoiding regaining weight after a gastric bypass surgery procedure; diabetes, in particular type 2 diabetes; allergy (such as gluten allergy and/or lactose allergy); rheumatism or arthritis; connective tissue disorders, such as psoreasisartritis, psoreasisartropatis, spondylartropatias or spondylarthritis, or morbus bechterew; sclerodermia, pregnant women in risk of pre-eclampsia and/or in connection with pregnancy and women after giving birth; bacterial infections, such as infections caused by gram positive bacteria, in particular Staphylococcus strains and/or Clostridium strains, more specifically Staphylococcus aureus and/or Clostridium difficile/perfringens; Ideopatic back pain, Backpain caused by Modic 1 and 2 changes, in ; and/or skin diseases, such as psoriasis, anti-TNF alpha antibody induced Psoreasis, rosacia, acne, and/or rinophyma and as a adjuvenant before, under and/or after antibiotic treatment or radiotherapy of the intestines, in a mammal, including humans or animals, wherein said substance comprises

-a fermented composition having a high content of one or more lactic acid bacterial strains and a high content of beta-glucans, polysaccharides, oligo-saccharides, proteoglycans and/or glycoproteins which originates from one or more fermented materials of vegetable origin and/or of fungal origin which is combined with a dried or dried and fermented material originating from one or more species of seaweed, micro algae and/or macro algae,

or said substance comprises a fermented composition according to any of claims 1-8, or as being preparable by a method according to claims 9-14.

18. A composition according to claim 16 or 17, wherein the composition an adjuvant product for administration in combination with one or more other drugs.

19. A composition according to any of claims 16-18 comprising one or more drugs and an adjuvant, wherein the adjuvant comprises a fermented composition according to any of claims 1-8, or as being preparable by a method according to claims 9-14.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P-C-reaktivt protein [CRP]
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Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/DK2017/050414

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/899 A61K36/8998 A61K45/06 A61K35/66 A61K35/747
A61K36/02 A23L7/104 A23L33/135 A61P31/04 A61P37/00
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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 A23L 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, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 February 2018	16/02/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Escolar Blasco, P

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