(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 April 2005 (07.04.2005)

PCT

(10) International Publication Number
WO 2005/030230 A1

(51) International Patent Classification[7]: A61K 35/74, A61P 17/06

(21) International Application Number:
PCT/AU2004/001349

(22) International Filing Date:
30 September 2004 (30.09.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2003905332 30 September 2003 (30.09.2003) AU

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *of inventorship (Rule 4.17(iv)) for US only*

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/030230 A1

(54) **Title:** COMPOSITIONS AND METHODS FOR TREATMENT OR PREVENTION OF PSORIASIS AND RELATED DISORDERS

(57) **Abstract:** The present invention is concerned with probiotic bacteria and compositions comprising same for preventing and/or treating and/or managing the symptoms of psoriasis and related disorders.

"COMPOSITIONS AND METHODS FOR TREATMENT OR PREVENTION OF PSORIASIS AND RELATED DISORDERS"

TECHNICAL FIELD

The invention relates to probiotic bacteria and compositions comprising same for preventing and/or treating and/or managing the symptoms of psoriasis and related disorders.

BACKGROUND

Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

Psoriasis is a chronic, recurrent and non life-threatening condition characterized by scaling and inflammation that in many cases requires continuous treatment. The most common form of psoriasis is characterized by swollen red skin lesions with a silvery white scale (plaques). 80-90% of people with psoriasis have this type. On the surface, psoriasis appears to be a skin disease.

Psoriasis affects about 2% of the world's population (ranging from 0.5% in Japan up to 2.5% in Scandinavia). According to the NIH, psoriasis affects approximately 5 million people in the USA. The gene frequency of psoriasis has been found to vary widely among different ethnic groups. Between 150,000 and 260,000 new cases of psoriasis occur each year in the US. The growth of the prevalence of psoriasis is expected to be parallel to the general growth of the population.

According to the NIH, psoriasis is associated with 2.4 million visits to dermatologists per year in the US. Overall, annual outpatient costs are estimated at $1.6 to $3.2 billion. Most severely affected patients may be hospitalised for long periods. It is estimated that 56 million hours of work are lost each year by people who suffer from psoriasis, and between $1.6 billion and $3.2 billion is spent annually on treating psoriasis.

Psoriasis tends to occur in episodes. The time between episodes varies greatly among patients. Some people relapse within weeks or months, others go years between episodes.

Psoriasis is divided into three degrees of severity: mild, moderate and severe depending on the % of skin surface that is affected:

Severe: > = 10% - Medium: 2-10 - Mild: < = 2%

Unlike multiple sclerosis and rheumatoid arthritis, mild forms of psoriasis do not tend to progress into more severe cases but people who experience frequent relapses tend to develop more severe psoriasis.

In most cases, patients who consult doctors for treatment are those with moderate to severe psoriasis. Patients with mild psoriasis may not go regularly to a doctor, preferring to use OTC drugs.

70-80% of psoriasis patients receive topical treatments while 20-30% receive phototherapy, systemic treatments or both.

Current topical treatments include emollients, coal tar, Anthralin, corticosteroids and Vitamin A and D derivatives such as Daivonex, Dovonex or tazarotene. However, these topical treatments can have disadvantages, for example, the disadvantages of coal tar include odour and staining, irritation and photosensitivity.

Anthralin topical medication can be irritating to the skin, and it has the tendency to stain anything it touches.

Corticosteroids are generally effective at treating the inflammation that occurs with psoriasis but common side effects can include thinning of the skin, easy bruising and stretch marks.

The Vitamin D derivatives, Daivonex, or Dovonex have been recognised as effective and safe for long-term control of psoriasis, with few side effects but are often prescribed in combination with other therapies, e.g. steroids and UVB.

Vitamin A derivatives such as the retinoic acid receptor agonist or tazarotene can cause skin irritation.

Phototherapy involving UV light is often used in moderate-to-severe cases. It involves the use of either UVA or UVB light exposure to the affected skin. UVA therapy is usually done in conjunction with methoxalen (PUVA), a photosensitising drug.

Systemic medications such as Methotrexate, Cyclosporin or Oral retinoids such as Soriatane or acitretin are effective in the management of moderate to severe psoriasis but are associated with organ toxicity and birth defects requiring careful monitoring. As a result, systemic drugs are usually prescribed after safer topical and light therapy treatments have failed or have been poorly tolerated.

There are many treatments that can improve the condition of the skin and reduce the symptoms of psoriasis. However, current treatments have proven to be neither curative nor preventative and do not provide a consistent response. In addition, they are often associated with some mild to severe side-effects.

Currently, there are over 15 "bio-therapies" in various stages of development that target the immune system, e.g. fusion proteins, monoclonal antibodies, cytokines, and gene therapy. Their efficacy and their side effects are still to be determined. In addition, because of their expected high price, these new "biotherapies" are likely to be targeted at the most severe patients and patients not responding to treatment.

Most of these treatments aim at controlling the faulty immune response; it is admitted that these treatments do not cure but produce remission of some duration.

Clearly alternative and perhaps complementary methods of treatment are required.

It is the object of the present invention to overcome or ameliorate at least one of the disadvantages of the prior art, or to provide a useful alternative.

SUMMARY OF THE INVENTION

It has surprisingly been found that probiotic bacteria provide such a safe and effective alternative for the prevention and/or treatment of psoriasis and related disorders.

According to the present invention there is provided a method for preventing and/or treating and/or managing psoriasis, a related disorder and/or symptoms thereof, comprising the step of administering a probiotic bacterium, to a subject in need of such treatment.

Preferably, the bacterium is a Lactobacillus, a Bifidobacterium, a Lactococcus or an Enterococcus. More preferably, the bacterium is a lactic acid bacterium and even more preferably it is a Lactobacillus species. The preferred species is *Lactobacillus fermentum*. Even more preferably, the bacterium is *Lactobacillus fermentum* strain VRI 003 (accession number NM02/31074) or VRI 002 (accession number NM02/32959). Other preferred probiotic bacteria are *Lactobacillus casei* and *Bifidobacterium lactis*. It will be understood that any combination of two or more probiotic bacteria may also be used.

Even more preferably, the probiotic is part of a composition, such as for example a food preparation, food supplement or a pharmaceutical preparation (e.g. tablets, capsules, powders, liquid formulations, creams, lotions and the like).

In a preferred embodiment, the composition comprises live cells of the probiotic bacteria. However, it will be clear to the skilled addressee that the composition may also comprise dead cells of the probiotic bacteria.

The probiotic bacterium can be advantageously combined with other compounds such as prebiotics, non-digestible dietary components, dietary fibre or pharmaceutically active compounds. Preferably, the prebiotic comprises or consists of inulin, a resistant starch, an oligosaccharide, a gum or a beta-glucan. Even more preferably, the prebiotic is an unmodified high amylose maize starch or a beta-glucan.

The composition can be prepared as a tablet, capsule, powder, gel, paste, liquid formulation, dietary supplement, a food product, cream or a lotion and the like. Preferably, the composition is prepared in a tablet or capsule form.

The terms "subject" and "individual" are used interchangeably in this specification and in the context of the present invention include within their scope any mammal which can develop, or already has psoriasis or a related disorder. The preferred subjects for administration of the treatment of the present invention are humans, domestic pets and farm animals.

The required dosage amount will vary according to the severity of the condition to be treated, the cause of the condition, age of the subject and other standard clinical parameters which can be easily determined by routine procedures within the skill set of those skilled in the art.

The probiotic bacterium or the composition comprising said bacterium, may be administered by any known means but preferably it is administered orally or topically.

The probiotic bacterium, or the composition comprising said bacterium, may be administered in conjunction with one or more other pharmaceutically active agents. The probiotic bacterium, or the composition comprising said bacterium, may be administered simultaneously (co-administered) with the other treatments or it may be administered sequentially in any order.

It is preferred that the bacterium or a composition comprising it, be administered daily. It can be administered several times per day, or it may be administered infrequently or discontinuously (for example every second or third day), depending on the progress of treatment of the condition in question, its cause and severity. These parameters can also be easily determined by those skilled in the art.

In the context of the present invention the term " related disorders" as it pertains to psoriasis includes dry flaking skin that reoccurs in the same location on the skin at intervals and may be influenced or become more severe by exposure to stress, and similar scalp and skin conditions.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

DESCRIPTION OF THE PREFERRED EMBODIMENT

It has now been found that probiotic bacteria are highly effective in the prevention and/or treatment and/or management of psoriasis, related disorders and/or symptoms thereof. Probiotic bacteria include, for example, Lactobacillus, Bifidobacterium, Bacillus, Lactococcus and Enterococcus. The present invention demonstrates that a diverse range of probiotic bacteria can be used to achieve the desired effects and outcomes. Preferably, the probiotic bacterium is a lactic acid bacterium and also preferred is that the bacterium is a Lactobacillus species. Even more preferably, the bacterium is *Lactobacillus fermentum*, *Lactobacillus casei* and/or *Bifidobacterium lactis*. The preferred strains of *Lactobacillus fermentum* are strains VRI002 and VRI 003.

The present invention provides a method for the prevention and/or treatment and/or management of psoriasis, a related disorder and/or symptoms thereof, comprising the administration of a probiotic bacterium, or a composition comprising the bacterium, to a subject. The probiotic can be combined with other agents, for example, a prebiotic, a non-digestible dietary component, dietary fibre or a pharmaceutically active compound such as an immunomodulating agent.

The methods and compositions of the present invention have been developed for human and veterinary applications in the treatment and/or prevention of psoriasis and related disorders. The compositions may also be used to reduce or manage symptoms associated with psoriasis and related disorders.

Typically, the effective daily dosage is in the range of about 10^8-10^{12} bacteria and frequency of administration is once or twice daily. For long-term intake the amount may, for example, be below the above-mentioned range; and in other circumstances, it can be used at an amount above the range. The probiotic bacterium can be formulated by

known means, using conventional pharmaceutically acceptable carriers, excipients, solvents or adjuvants. Such procedures and ingredients are well known and are amply described in standard texts and manuals, for example "Remington: The Science and Practice of Pharmacy", 1995, Mack Publishing Co. Easton, PA 18042, USA, which is incorporated herein by reference.

The probiotic bacterium thereof may also be formulated into a food product by the usual well-known means.

Preferably, the composition comprising the probiotic comprises wet or dried bacteria.

The food or drink product of the invention contains at least one of the bacterium ort a material containing the same and a processed product thereof as the effective ingredient. A composition can be formulated to be suitable for oral administration in a variety of ways, for example in the form of a tablet, a capsule, a liquid, a dietary supplement, a paste, a gel, a food product and the like. The topical formulation can be prepared as a lotion or a cream. Other formulations will be readily apparent to one skilled in the art.

The bacterium can be used in food or drink products or can be used in combination with other food materials and food components appropriately prepared in conventional manner. Preferably, the composition is prepared as a dairy or diary-based food product with or without other components that are routinely used in the production of such diary products.

The compositions of the present invention may also include known antioxidants, buffering agents, and other agents such as colouring agents, flavourings, vitamins or minerals. Thickening agents may be added to the compositions such as corn starch, guar gum, xanthum gum and the like. Preferred additional components of a therapeutic composition of this invention can include prebiotics such as inulin, non-digestible dietary components, dietary fibre, pharmaceutically acceptable compounds and other nutrients. Dietary or supplementary enzymes such as lactase, amlyase, glucanase, catalase, and the like enzymes can also be included. Preferred prebiotics include unmodified high amylose maize starch or beta-glucan. Dietary supplements such as, but not limited to, amino acids can also be added with the probiotic.

The probiotic bacterium can combined with a physiologically compatible carrier. Carriers can be comprised of solid-based, dry materials for formulation into tablet,

capsule or powdered form; or the carrier can be comprised of liquid or gel-based materials for formulations into liquid or gel forms or cream based formulations. The specific type of carrier, as well as the final formulation depends, in part, upon the selected route(s) of administration.

Typical carriers for dry formulations include, but are not limited to, trehalose, malto-dextrin, rice flour, micro-crystalline cellulose (MCC) magnesium stearate, inositol, FOS, GOS, dextrose, sucrose, glucose and like carriers. Dry formulations (e.g., powders) may be added to supplement commercially available foods (e.g., solid foods, liquid formulas, diary products, or water). Similarly, the specific type of formulation depends upon the route of administration.

Suitable liquid or gel-based carriers include but are not limited to: water and physiological salt solutions; oils (e.g. vegetable); urea; alcohols and derivatives (e.g., methanol, ethanol, propanol, butanol); glycols (e.g. ethylene glycol, propylene glycol, and the like). Preferably, water-based carriers possess a neutral pH value (i.e., pH 7.0).

Preservatives may also be included within the carrier including methylparaben, propylparaben, benzyl alcohol and ethylene diamine tetraacetate salt. The composition of the carrier can be varied so long as it does not interfere significantly with the pharmacological activity of the active ingredients.

Preferred embodiments of the invention will now be described by way of example only.

EXAMPLES

Example 1: Origin and Identification of VRI 003

The *Lactobacillus fermentum* VRI 003 variant was isolated from a healthy human subject. In a series of laboratory experiments, the VRI 003 variant was found to adhere to the gastrointestinal epithelial tissue. It was also shown to have a demonstrable effect on human gastrointestinal pathogens, and was resistant to bile acids. The VRI 003 variant also survived in a low pH environment and was resistant to pepsin and to nutrient limited conditions.

The bacterial variant VRI 003 was cultured on Rogosa agar (Oxoid) Plates and incubated at 37°C in an anaerobic chamber for 24 hours. The strain was purified by successive transfers on MRS agar (Oxoid) plates incubated at 37°C in an anaerobic chamber for 24 hours and the final culture stored at -70°C in 20% glycerol by

subculturing in MRS broth at 37°C for 24 hours in anaerobic conditions prior to the addition of glycerol to the culture broth. The culture is also stored as a freeze dried preparation in glass vials.

Variant VRI 003 was a catalase negative, Gram positive rod which produced gas when grown anaerobically on brain heart infusion (BHI) (Oxoid) broth containing glucose. It was broadly identified therefore as a heterofermentative lactobacillus and confirmed to be *L. fermentum* strain according to the API carbohydrate kit (50 CHL kit; Biomerieux; supplier data base and database with a certainty of 99.9%. In particular, sugars 5, 10, 11, 12, 13, 25, 28, 29, 30, 31, 32 and 25 are utilized by strain VRI 003. the cell is a short rod, Gram positive and consistent with the description of the morphology of *Lactobacillus fermentum*.

Lactobacillus fermentum strain VRI 003 was deposited under the provision of the Budapest Treaty, at the Australian Government Analytical Laboratories, PO Box 385 Pymble 2073, NSW, Australia, on 27 August 2002 and the deposit was allocated the accession number NM02/31074.

Example 2: Origin and Identification of *Lactobacillus fermentum* VRI-002

Lactobacillus fermentum strain VRI-002 was isolated from a faecal sample from a healthy Swedish female 30-35 years old. The woman had a history of resistance to diarrhoea induced by food poisoning organisms and traveller's diarrhoea. The strain represented one of the dominant lactobacilli (about log 8 per gram wet wt faeces) when an homogenate of the fresh faecal sample was inoculated onto Rogosa agar and incubated anaerobically at 37°C. The strain was purified by successive transfers on MRS agar and the final culture stored at -70°C in 20% glycerol and subsequently freeze dried.

It was identified as a catalase negative, Gram-positive rod which produced gas when grown anaerobically on brain heart infusion broth (BHI) containing glucose. It was therefore heterofermentative and confirmed to be *Lactobacillus fermentum* according to the API carbohydrate kit and database with a certainty of 99.9%. The sequence of the 16s rRNA was consistent with the database for *Lactobacillus fermentum*. VRI-002 was deposited with Australian Government Analytical Laboratories, AGAL, of PO Box 385, Pymble NSW 2073, Australia, on 12 December 2002 and given the accession number NM02/32959. This strain can also be sourced from University of New South Wales, Microbiology Culture Collection, Sydney, New South Wales, Australia.

Example 3: Culture and Formulations

(i) Growth of the culture

Lactobacillus fermentum variant VRI 003 is grown in a fermentation vessel at 37□C. The vessel is then cooled and the fermentation broth concentrated, preferably by centrifugation. The collected culture is dried, preferably by freeze-drying and subsequently milled. The milled material is then blended with the major excipient to give the desired level of microbes per gram of dry material. The level to be used is dependent on the application (range up to log 11 per gram). The standardised material is then used in the formulation by mixing all ingredients in a blender (preferably a V-blender).

(ii) Formulations

(a) Formulation A: High amylose maize based (symbiotic formulation)

Lactobacillus fermentum VRI 003	100mg
Hi-maize 958 (or 1043)	170 mg
Stearic acid	up to 4.5mg
Silica dioxide	up to 4.5mg

(b) Formulation B: Microcrystalline cellulose (MCC based)

Lactobacillus fermentum VRI 003	100mg
Avicell Ph 112 (or relevant equivalent)	170mg
Stearic acid	up to 4.5mg
Silica dioxide	up to 4.5mg

(c) Formulation C: Either the High amylase maize base or the MCC based as described in A and B, with colloidal silica (up to 4.5mg) instead of silica dioxide or with silica dioxide as well (up to 4.5mg).

One of the desired characteristics for VRI 003 is that it remains viable and has the capacity to grow within the human gastrointestinal tract after dosage. As outlined above this characteristic was one of the selection criteria for a desirable strain. However, this is not necessarily essential for the desired beneficial effects.

An additional consideration in this regard is that even though the strain has the capacity to survive the various conditions within the tract, the strain must retain viability and desired strain characteristics when grown on a large scale and dispensed in a product form. The following is an analysis of the viability and strain characteristics of VRI 003

after large scale culture and freeze-drying, as well as after encapsulation in gelatin capsules.

(iii) Viability of freeze-dried VRI 003

The viability of VRI 003 after large-scale production and freeze-drying was determined by analysing the colony forming units per gram (CFU/g) of dried material. The dried powder was examined both before and after encapsulation in the gelatin capsules. The number of viable cells was determined for ten individual 1g samples of the powder. The contents of ten capsules were also individually analysed.

VRI 003 maintained high levels of viability through production and encapsulation. The dried powder typically contained a minimum of 10^{10} cfu/g and the contents of the capsules contained typically 100 mg.

When the capsules were stored in foil/foil packaging, a 1.5 log, or less, loss of viability was noted with storage at 30□C and 25□C for 6 months.

Culture conditions and formulation of *Lactobacillus fermentum* VRI 002 strain were conducted according to Examples 1 and 3 above.

The other probiotic bacteria used in the Examples herein were cultured and formulated in a similar fashion, following well established culturing procedures and instructions provided with the bacterial samples.

Example 4: Reduction in symptoms of psoriasis with oral dosage of Lactobacillus fermentum VRI 003

Case Study 1

A 37 year old male had been suffering from medically-diagnosed psoriasis for the past 20 years. The following courses of treatment have been tried: tar-based treatment, PUVA light treatment, Chinese medicines and acupuncture and zinc-based treatments. The skin appeared red and scaly dry and the affected areas were well-distributed all over the body. Prior to commencing the study, the subject was not using any other medication but only applied moisturiser on the affected areas.

Treatment with *L. fermentum* VRI 003 commenced with 3 capsules in the morning with food and 3 capsules in the evening with food for 4 weeks of a daily basis. Each capsule contained 4.2 x 10^{10} cfu. Following completion on the course of probiotics, symptoms associated with psoriasis improved: associated allergy reduced and the skin was less red and less dry, discomfort associated with psoriasis had decreased

considerably, itchiness had reduced and the areas affected significantly reduced to a minimum. The subject reported a significant improvement on his quality of life.

Case Study 2

A 28 year old female has been suffering from medically-diagnosed psoriasis. This condition had persisted for 16 years and had been severe. Symptoms included red, dry and sore skin. Thick, scaly patches were spread all over the legs, stomach, back, arms and scalp. Previously, steroid creams have been tried.

Treatment with *L. fermentum* VRI 003 commenced with 3 capsules in the morning with food and 3 capsules in the evening with food for 4 weeks on a daily basis. Each capsule contains 4.2×10^{10} cfu. No other medication was being used prior to taking *L. fermentum* VRI 003. Improvement in the following areas has been reported: inflammation, texture (less scaling), appearance (less red), and itchiness. An overall improvement on the subject's quality of life was also reported.

Case Study 3: Dandruff

A 50 year old male who had suffered for over 30 years with dandruff which was managed using regular use of a dandruff shampoo, took 10^{11} cfu freeze dried powdered *L fermentum* VRI 003 with breakfast each day in a glass of milk for one week and has been symptom free for the last 14 months.

Case Study 4: Scalp Psoriasis

A 45-55 year old male had suffered scalp psoriasis for many years and took 3 capsules with food in the morning and the evening (each capsule contained 4.2×10^{10} cfu) for 4 weeks. Itchiness had eased considerably and the condition is clearing. Extended treatment and/or a higher dose could be recommended for greater improvement in a shorter time.

Further case studies - Reduction in symptoms of psoriasis with oral dosage of Lactobacillus fermentum VRI 003

Case Study 5:

Three subjects were given a dose of 1×10^{11} per day for four weeks of Lactobacillus fermentum VRI 003. At the end of the study the following outcomes were noted:

Volunteer A experienced reduced size of the patches as well as less flaking of skin. There was also a slight decrease in the redness/inflammation of the psoriasis patches. For Volunteer B, some of the patches, especially in the upper limbs improved but affected areas of the lower body showed no improvement during the course of the

study, and in fact some patches became itchier and increased in size. With Volunteer C, less flaking and less thickening of the flakes observed by the end of the second week. Clear patches started appearing.

Case Study 6:

One subject with dry flaking skin on the face and one hand initially tested minimum of 4-6 x 10^9 per day for 2 weeks of *L. fermentum* VRI 003 and noted a slight worsening, however on decreasing the dose to 2 x 10^9 per day for 2 weeks, the dryness of the skin decreased and flaking was no longer evident.

It was concluded that the *L. fermentum* VRI 003 has the capacity to reduce the severity of the psoriasis over a range of doses.

Example 5: Reduction of symptoms of psoriasis with oral dosage of *L. fermentum* VRI 002

Case Study No. 1

A 24-year old female presented with mild psoriasis in the form of dry, coarse, red and itchy plaques. Treatment over several years included UVB, UVA, cyclosporin and acupuncture. The subject was not taking any medication prior to taking probiotics.

Treatment with *L. fermentum* VRI 002 commenced with 3 capsules in the morning and 3 capsules at night with food (each capsule contained approximately 2.45 x10^{10} CFU). Following 3 weeks of treatment, the subject reported improvement of the following symptoms associated with psoriasis: flaking had thinned, plaques appeared less red, skin was less dry and scaly and the size of the patches had likewise decreased. Beneficial effects on the gastrointestinal tract were also reported.

Case Study No. 2

A 37-year old male had been suffering from medically-diagnosed psoriasis for the past 20 years. The following courses of treatment has been tried: tar-based treatment, PUVA light treatment, Chinese medicines and acupuncture and zinc-based treatments. The skin appeared red and scaly dry and well-distributed all over the body. Prior to taking probiotics, the subject was not using any other medication but only applied moisturiser on the affected areas.

Treatment with *L. fermentum* VRI 002 commenced with 3 capsules in the morning with food and 3 capsules in the evening with food (each capsule contained approximately 2.45 x10^{10} CFU). After 2 and a half weeks of taking *L. fermentum* VRI

002, the skin had dramatically improved: patches decreased in size and thickness, redness was decreased and the subject's energy levels started to rise. These improvements persisted even after 2 weeks of not taking *L. fermentum* VRI 002. The subject reported improvement of his skin condition without any side effects unlike previous psoriasis treatment.

Case Study No.3

A 33-year old male presented with medically-diagnosed psoriasis for the past 16 years. Symptoms include round, white, scaly patches itching severely. Dryness also causes bleeding occasionally. Previous treatment with steroid-based creams and UV therapy were tried. Treatment at presentation include Exorex cream.

Treatment with *L. fermentum* VRI 002 commenced with 3 capsules in the morning with food and 3 capsules in the evening with food (each capsule contained approximately 2.45 $x10^{10}$ CFU). After two weeks of daily taking *L. fermentum* VRI 002, the flaking pattern has slowed down, patches appeared pink instead of red, inflammation has decreased, dryness and scaling has been considerably decreased and itching had been minimised. Overall, the subject reported an increase in quality of life after taking *L. fermentum* VRI 002.

Case Study No.4

A 28-year old female had been suffering from medically-diagnosed psoriasis. This condition had persisted for 16 years and in the last 10 years, severity had greatly increased such that psoriasis covers most of the body. Symptoms included red, dry and sore skin. Thick, scaly patches spread all over the legs, stomach, back, arms and scalp. Previously, steroid creams had been tried.

Treatment with *L. fermentum* VRI 002 commenced with 3 capsules in the morning with food and 3 capsules in the evening with food for 4 weeks on a daily basis (each capsule contained approximately 2.45 $x10^{10}$ CFU). Symptoms markedly improved: patches were not as thick, size of the plaques had decreased, texture and itchiness of the affected areas have both dramatically improved.

Case study No. 5 - Mild facial psoriasis

A 40-50 year old male with dandruff and regular mild outbreaks of psoriasis on the face for years regularly takes one capsule per day with occasional doses of two capsules per day and about 80% regular compliance of taking the *L fermentum* each day) with each capsule containing a minimum of 2 billion *L fermentum* VRI 002. The psoriasis

disappears and so too has the dandruff. He can now use available shampoos instead of requiring special shampoos. The facial psoriasis breaks out when regular consumption of the *L fermentum* is missed.

Example 6: Effect of Different Strains of Probiotics in Improving the Symptoms of Psoriais

In this study, the effects of different strains of probiotic lactic acid bacteria (LAB) on the symptoms of psoriasis were assessed. The strains used were *L. casei* VRI 004 and *Bifidobacterium lactis* VRI 201. These strains are sourced from the University of New South Wales, Microbiology Culture Collection, Sydney, New South Wales, Australia.

These strains were given daily for four weeks at a dose of:

Probiotic Strain	Dose	Count (colony forming units (cfu)/capsule at time of manufacture)	Total Daily Dose (max cfu/day)
L. casei VRI 004	1 capsule in the morning + 1 capsule in the evening	2.1×10^{11}	4.2×10^{11}
B. lactis VRI 201	3 capsules in the morning + 3 capsules in the evening	6.9×10^{10}	4.14×10^{11}

The degree of severity of psoriasis was measured using a self-reported questionnaire. The following symptoms; texture of skin, size of the patches, degree of inflammation, itchiness and the effect on the quality of life were scored weekly. A score of 1 equated to improvement of the condition while a score of 10 indicated worsening of the symptoms. An absence of noticeable change on the affected area or quality of life gave a score of 0.

When *L. casei* was orally administered, psoriasis patches started to clear up and inflammation subsided considerably. Consequently, the skin began to flake off and formation of normal skin cells was observed.

Supplementation of *B. lactis* markedly reduced inflammation from affected areas. The reduction in inflammation correlated directly with the degree of itchiness experienced by the volunteer. As the redness of the affected area diminished the

tendency to scratch the psoriasis patches lessened. Quality of life also improved after administration of *B. lactis*.

Although the invention has been described with reference to specific examples, it will be appreciated by those skilled in the art that the invention may be embodied in many other forms, in keeping with the inventive concept and the spirit of the invention described herein.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for preventing and/or treating and/or managing psoriasis, a related disorder and/or symptoms thereof, comprising the step of administering a probiotic bacterium, to a subject in need of such treatment.

2. A method according to claim 1, wherein the bacterium is a Lactobacillus, a Bifidobacterium, a Lactococcus, an Enterococcus or a combination thereof.

3. A method according to claim 1 or claim 2, wherein the bacterium is a lactic acid bacterium or a combination of more than one species or variants of lactic acid bacteria.

4. A method according to any one of claims 1 to 3, wherein the bacterium is a *Lactobacillus fermentum.*

5. A method according to claim 4, wherein the bacterium is *Lactobacillus fermentum* strain VRI 003 (accession number NM02/31074) or strain VRI 002 (accession number NM02/32959).

6. A method according to any one of claims 1 to 3, wherein the bacterium is a *Lactobacillus casei.*

7. A method according to claim 6, wherein the bacterium is a *Lactobacillus casei* strain VRI 004.

8. A method according to any one of claims 1 to 3, wherein the bacterium is a *Bifidobacterium lactis.*

9. A method according to claim 8, wherein the bacterium is *Bifidobacterium lactis* strain VRI 201.

10. A method according to any one of claims 1 to 9, wherein the probiotic bacterium is a component of a composition.

11. A method according to claim 10, wherein the composition is a food preparation, a food supplement or a pharmaceutical composition.

12. A method according to any one of claims 1 to 9, wherein live cells of the probiotic bacterium are administered.

13 A method according to any one of claims 10 to 12, wherein the composition comprises live cells of the probiotic bacterium.

14. A method according to any one of claims 1 to 9, wherein dead cells of the probiotic bacterium are administered.

15 A method according to any one of claims 10 to 12, wherein the composition comprises dead cells of the probiotic bacterium.

16. A method according to any one of claims 1 to 15, further comprising administration of, or a combination with, one or more of a prebiotic, a non-digestible dietary component, a dietary fibre and a pharmaceutically active compound.

17. A method according to claim 16, wherein said prebiotic is inulin, a resistant starch, an oligosaccharide, a gum or a beta-glucan.

18. A method according to claim 17, wherein said resistant starch is an unmodified high amylose maize starch.

19. A method according to any one of claims 1 to 18, wherein said probiotic bacterium or composition comprising said probiotic, is administered in the form of a tablet, a capsule a gel, a liquid formulation, a powder, a paste, a dietary supplement, a cream, lotion or a food product and the like formulation.

20. A method according to claim 19, wherein said probiotic bacterium or composition comprising said probiotic, is administered in the form of a tablet or capsule.

21. A method according to claim 19, wherein said probiotic bacterium or composition comprising said probiotic, is administered in the form a dietary supplement or a food product.

22. A method according to any one of claims 1 to 21, wherein said probiotic bacterium or the composition comprising said probiotic, is administered in conjunction with one or more other pharmaceutically active agents.

23. A method according to claim 22, wherein administration is simultaneous or sequential in any order.

24. A method according to any one of claims 1 to 23, wherein administration is daily.

25. A method according to any one of claims 1 to 24, wherein a daily dosage is about 10^8 - 10^{12} probiotic bacteria.

26. A method according to any one of claims 1 to 25, wherein administration is twice daily.

27. A method according to any one of claims 1 to 26, wherein said subject is human.

28. Use of a probiotic bacterium for the manufacture of a medicament for preventing and/or treating and/or management of psoriasis, a related disorder and/or symptoms thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001349

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: A61K 35/74, A61P 17/06

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)

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)
DWPI, MEDLINE; keywords: psoriasis, psoriatic, probiotic, lactobacillus, fermentum, VRI, lactis, bifidobacterium, lactococcus, enterococcus, casei

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2003/068250 A1 (DERMAVRI PTY LTD), 21 August 2003. Whole document.	1-28
X	WO 2003/010297 A1 (ALIMENTARY HEALTH LIMITED), 6 February 2003. Abstract, page 2 lines 15-17, page 5 lines 18-31 and claim 43.	1-28
X	WO 2003/010298 A1 (ALIMENTARY HEALTH LIMITED), 6 February 2003. Abstract, page 2 lines 15-17, page 6 lines 4-17 and claim 29.	1-28
X	WO 2003/010299 A1 (ALIMENTARY HEALTH LIMITED), 6 February 2003. Abstract, page 2 lines 14-18, page 5 line 26-page 6 line 8 and claims 38, 41.	1-28

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 October 2004	1 NOV 2004
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2004/001349

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2004/022727 A1 (VRI BIOMEDICAL LTD), 18 March 2004. Abstract, Examples 7-8 (page 37), 11 (page 39) and claims 2, 24-25.	1-28

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2004/001349

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	03068250						
WO	03010297	CA	2454803	EP	1409644	IE	20020626
		US	2003092163				
WO	03010298	CA	2454804	EP	1409645	IE	20020620
		US	2003091549				
WO	03010299	BR	0211438	CA	2454805	EP	1409643
		IE	20020624	US	2003113306		
WO	04022727						

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX