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(54) Title: INGESTIBLE MATERIAL FOR THE TREATMENT OF DISEASE IN THE HUMAN DIGESTIVE SYSTEM

(57) Abstract: An ingestible material adapted to reduce and/or prevent disease in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes disease in said human digestive system to a level below that required to cause the disease, is provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

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INGESTIBLE MATERIAL FOR THE TREATMENT OF DISEASES IN THE HUMAN DIGESTIVE SYSTEM

This invention relates to an ingestible material for the treatment of disease in the human digestive system, for use particularly, but not exclusively as a medical or cosmetic treatment for Rosacea.

Rosacea is a common facial dermatosis. Its primary symptom is an increase in the sensitivity of the facial vasculature. Sufferers can experience facial flushing around the cheeks, chin, nose, forehead, neck and occasionally the upper chest. It is common for the eyes to be affected and in the worst cases this can result in irreversible injury to the sufferer's vision.

The disease is generally progressive and can lead to a permanent erythema (redness) across affected areas and the development of telangiectasia (thread veins). Further, sufferers can experience papules and pustules, and in severe cases a condition known as rhinophyma may develop, where the tissue of the nose becomes inflamed and overgrown leading to disfigurement. Rosacea usually begins in individuals aged between 30 and 50 years with a lighter complexion, although anyone can suffer from it at any age.

The cause of Rosacea is currently unknown. The development of symptoms can often be traced to a period of acute, or repeated, irritation of the facial skin, for example through excessive exposure to sunlight or through the use of topical facial preparations, for example acne medications or cosmetic treatments. However, frequently the onset of symptoms is gradual and no clearly definable event marks the initiation of the disease. Once the onset of the disease has occurred and the facial vasculature has become hypersensitised, any number or combination of factors may provoke a worsening of symptoms, including sunlight, wind, cold, heat, physical exertion, humidity or the consumption of certain foods or medications. Rosacea has

been associated with disorders of the digestive system but this association has never been satisfactorily explained.

Current treatments for Rosacea are aimed at suppressing the symptoms rather than addressing the cause. Antibiotics have been proven to combat the symptoms, however their effectiveness can reduce with time. Antibiotics used include tetracyclines, macrolides (erythromycin and clarithromycin) and imidazoles (most notably metronidazole). Topical preparations containing metronidazole have also been used in the treatment of Rosacea. The mechanism by which antibiotics influence the pathogenesis of Rosacea has not been established.

The papulo-pustular element of Rosacea has been successfully treated with retinoids, however, these do not address the underlying vascular disorder, and can exacerbate the vascular symptoms.

Various light-based therapies are also available which destroy the underlying malfunctioning vasculature. Although results can vary greatly, some patients can experience an almost complete remission of their symptoms, however this can take many treatment sessions, and further treatments may be required to maintain the remission.

In the development of the present invention it has been found that Rosacea is caused by digestive system disorders. The plasma kallikrein-kinin system can be activated in response to inflammatory reactions in the digestive system. Such inflammatory reactions are varied and can be extremely mild in some cases and may not present local symptoms. They can occur in many regions of the digestive tract especially in the stomach, the small and the large intestine.

Various digestive disorders have already been connected to Rosacea, and typical examples include:

Helicobacter Pylon infection. Infection by this bacterium has been associated with Rosacea, and there have been a small number of striking examples where Rosacea has been cured by its eradication. However, it has also been demonstrated that eradication of H. Pylon in the majority of Rosacea sufferers only provides some symptomatic improvement at best, and is unlikely to cure the disease. It has also been demonstrated that most Rosacea sufferers are not infected with H. Pylori, which would indicate that H. Pylori cannot be the sole cause of Rosacea.

Crohn's Disease and ulcerative colitis. There have been numerous reports of sufferers of these diseases developing Rosacea, and of patients reporting a correlation between the activity of their digestive disease and the activity of their facial symptoms.

Food allergies/intolerances. There have only been a small number of reports in medical literature describing a possible connection between classic allergic reactions to food and Rosacea. This may be because food allergies can be diverse and the association of Rosacea symptoms to a specific allergic reaction may be difficult to demonstrate. It may also be the case that Rosacea sufferers learn to avoid offending foods without medical intervention. However, the existence of food "triggers" in Rosacea patients has been well documented, but the mechanism by which the foods provoke a worsening of symptoms has not been established.

However it has now been found that the majority of Rosacea cases are caused by a reaction in response to the presence of luminal bacteria in the intestines. Luminal bacteria feed on partially digested food, frequently undigested carbohydrates. Bacteria are commonly resident in human intestines, especially within the colon. However, bacteria can proliferate, both within the colon and elsewhere, if there is sufficient quantity and type of fermentable material present in the intestines and enough time for the bacteria to consume it. The presence of these bacteria or an increase in the population of these bacteria can, in susceptible individuals and with the necessary conditions present within the digestive tract,

provoke a mild (or sometimes pronounced) inflammatory reaction in the walls of the intestines and lead to activation of the plasma kallikrein-kinin system leading to an increase in plasma concentrations of bradykinin.

This reaction may be caused by a particular persistent pathogen or by the endotoxins produced by a particular persistent pathogen, by a defect in the mucosal barrier which leads to increased exposure to the bacteria or their endotoxins, or by an overly aggressive immune response to the resident luminal bacteria or their endotoxins. The inflammation and/or activation of the plasma kallikrein-kinin system can be caused by any one or any combination of these circumstances, and the response is individual to the patient. Some individuals may be able to tolerate a quantity of bacteria or their endotoxins greater than others without suffering any detectable reaction.

However it is caused, this reaction is frequently chronic and sufferers may not experience directly detectable symptoms. (Current evidence suggests that many cases of Crohn's disease are caused by a particularly severe immune reaction to luminal bacteria in the intestines.)

When bradykinin binds to receptors on afferent neurons, it can stimulate and sensitise such neurons, provoking the release of a number of proinflammatory substances and in particular the neuropeptides substance P and calcitonin gene-related peptide. These substances, in turn, can act on target cells in the periphery such as mast cells, immune cells and vascular smooth muscle causing inflammation characterised by vasodilation, plasma extravasation, edema and hypersensitivity. Inflammatory symptoms resulting from the release of substances by afferent neurons is referred to as neurogenic inflammation. The vascular symptoms of Rosacea are a consequence of neurogenic inflammation.

It is possible to prevent the above described sequence by reducing luminal bacterial populations with antibiotics to prevent activation of the plasma kallikrein-

kinin system, thereby inhibiting bradykinin-induced hypersensitisation of afferent neurons. However, once the bacteria begin to develop resistance to the antibiotics this treatment becomes less effective.

The present invention is intended to overcome some of these problems by addressing the proliferation of luminal bacteria in the digestive tract.

Therefore, according to the present invention an ingestible material adapted to reduce and/or prevent disease in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes disease in said human digestive system to a level below that required to cause the disease, is provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

In a preferred construction the material is adapted to reduce and/or prevent inflammation in the human digestive system by reducing and/or maintaining the quantity of bacteria which causes the inflammation in said human digestive system to a level below that required to cause the inflammation.

Preferably the material is adapted to reduce and/or prevent exposure to luminal bacteria and/or bacterial endotoxins and/or the products of bacterial fermentation in the intestines which causes activation of the plasma kallikrein-kinin system, by reducing and/or maintaining the quantity of bacteria within the human digestive tract which reduces exposure to luminal bacteria and/or bacterial endotoxins and/or products of bacterial fermentation to a level below that required to cause activation of the plasma kallikrein-kinin system.

Preferably the ingestible material is adapted to reduce and/or maintain the quantity of luminal bacteria in the human digestive system, and in particular the small intestine, which activates the kallikrein-kinin system which leads to the

production of bradykinin and/or related kinins, which stimulates and/or sensitizes afferent neurons, which leads to the occurrence of Rosacea symptoms.

It will be appreciated that the present invention can also be used to reduce and/or maintain the quantity of bacteria in the human digestive tract which causes disease and/or inflammation, which can be used to treat the symptoms of other diseases and disorders. These symptoms can result either from activation of the plasma kallikrein-kinin system leading to hypersensitisation of afferent neurons or these symptoms can result from other mechanisms of disease resulting from luminal bacteria in the intestines.

Such disorders may include abdominal bloating, acne or acneform eruptions (which includes acne vulgaris), Alzheimer's disease, affective disorders, alopecia, anaphylaxis, ankylosing spondylitis and other spondyloarthropathies, anxiety disorders, arthritis, asthma, attention deficit disorder (ADD & ADHD), attentional disorders, atypical face pain, autism (including all autistic spectrum disorders e.g. Asperger's syndrome, Pervasive Developmental Disorder, Rett's Syndrome etc.), autoimmune disorders (including hypothyroidism, scleroderma, lupus, polymyositis, vasculitis), blushing, body dysmorphic disorder, bruxism, cataplexy, chronic pain, chronic fatigue, chronic pelvic pain syndromes (which includes interstitial cystitis), colonic cancer, concentration impairment, Crohn's disease, dandruff, depression, dizziness, eating disorders (bulimia, anorexia, bingeing), emesis, fibromyalgia, Gulf War syndrome, hypersomnia, hypothyroidism, impulse-control disorders, insomnia, intermittent explosive disorder, irritable bowel syndrome, kleptomania, memory impairment, migraine/severe headache, mood disorders, morning fatigue, motion sickness, multiple chemical sensitivity, myofascial pain syndrome, narcolepsy, obesity, obsessive-compulsive disorder, pancreatitis, panic disorder, pathological gambling, personality disorders, post traumatic stress disorder, premenstrual dysphoric disorder, primary dysmenorrhea, psoriasis, psoriatic arthritis, psychosis, pyromania, Raynaud's disease, repetitive strain injury, restless leg disorder, rheumatism, rhinitis, rosacea, schizophrenia, sebaceous hyperplasia, seborrhea,

sensitive skin (as defined in U.S. Patent US6241993), sick building syndrome, sinusitis, social phobia, somatoform disorders, substance abuse and addiction (including alcoholism), temporo-mandibular disorders, tinnitus, tonsillitis, Tourette's disorder, trichotillomania, ulcerative colitis, a reduced level of restorative sleep, various other neuropsychiatric disorders and various other cognitive dysfunctions and any other diseases belonging to the affective spectrum disorder.

The ingestible material may be adapted to reduce and/or maintain the quantity of luminal bacteria in the human digestive system which prevents or reduces activation of the plasma kallikrein-kinin system and the production of bradykinin.

It has been found that if this ingestible material is consumed with warm water approximately 30 minutes to one hour after food is consumed, the transit time of food through the digestive tract is significantly reduced. In a preferred embodiment, the ingestible material results in a transit time of food of between 24 and 35 hours. If the transit time of food through the digestive tract is reduced to this length of time the luminal bacterial populations are decreased and their capacity to cause disease and/or inflammation in the human digestive tract is reduced or abolished, and the above described sequence leading to the occurrence of Rosacea symptoms is inhibited.

In a preferred construction the ingestible material stimulates peristaltic contractions in the walls of the intestines due to the size and texture of its particles. Further, the size and texture of the particles may be further adapted to cause no injury to the intestinal walls.

The material can be non-soluble in water, and be provided with the property of retaining water or other liquids. When mixed with water or another liquid, the material can be provided with the optimum viscosity to assist its passage through the digestive tract. The material may possess or may be used in conjunction with other

materials or liquids that possess lubricative properties which further assist its passage through the digestive tract by reducing its impedance due to friction.

It has been found that coarse wheat bran is provided with many of the physical properties described above. Therefore the indigestible material may be coarse wheat bran, or be provided with similar physical properties to those of coarse wheat bran.

It is accepted that coarse wheat bran reduces the transit time of food through the digestive tract, although the exact reasons for this are still uncertain. Studies have shown that bran-shaped flakes constructed from a plastic material are as effective at reducing transit time as coarse wheat bran. (see: Roughage Revisited, The Effect in Intestinal Function of Inert Plastic Particles of Different Sizes and Shape, Stephen J. Lewis, MD and Kenneth W. Heaton, FRCP, in: Digestive Diseases and Sciences Vol 44, No 4 (April 1999) pp 744-748). This suggests it is the morphology of the wheat bran particles which stimulate the enteric nervous system via multimodal receptors in the mucosa, which stimulates peristaltic movement. Part of the object of the invention is to stimulate peristaltic movement, so any material which achieves this function would be suitable.

In one embodiment the material is adapted to cause no allergic or irritative reaction to the walls of the digestive tract. In a further embodiment the material is adapted to reduce any allergic or irritative reaction in the walls of the digestive tract.

The material may also be unfermentable by bacteria, or may be adapted to reduce any bacterially fermentable properties, as this will further prevent occurrences of luminal bacteria. The material may also be selectively fermentable by bacteria, having fermentable properties that favour those bacterial species that are considered to be less capable of causing disease and/or inflammation. This may modify the luminal environment of the digestive tract because the competition

between species may result in a hostile environment for those bacteria considered to be responsible for causing the disease and/or inflammation.

In a preferred construction the material may have, or may be adapted to have when ingested, a reduced pH level which reduces the pH level in the intestines and/or the stomach, which further inhibits the growth and/or proliferation of luminal bacteria.

In a further embodiment, the ingestible material may possess, or may be used in combination with another material which possesses antibacterial properties. With this arrangement the treatment material will be capable of modifying the environment within the digestive tract to make it more hostile to the growth and/or survival of bacteria.

In one embodiment the ingestible material is coarse wheat bran with gluten and possibly other protein reduced/removed. This can be done in any known way, for example the coarse wheat bran may be hydrolysed to achieve this end.

In one alternative embodiment the ingestible material can comprise finely shredded 100% pure cotton paper, which is greater than 185gm per square metre. The cotton can preferably be boiled in water for 20 minutes, drained and then mixed with a carrier food, for example porridge or rice pudding.

The invention also includes a method of reducing and/or preventing disease and/or inflammation in a human digestive system, comprising the consumption of an ingestible material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

The invention further includes a method as defined above, which is combined with a general diet consisting of reduced carbohydrates and in particular carbohydrates that are not monosaccharide.

In a second aspect of the present invention an ingestible material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours is used for the manufacture of a medicament for reducing and/or preventing disease and/or inflammation in the human digestive system.

Preferably the ingestible material is used for the manufacture of a medicament for the treatment of disease and/or inflammation in the human digestive system which causes activation of the kallikrein-kinin system which leads to the production of bradykinin which sensitises afferent neurons, which leads to one or more Rosacea symptoms.

In a third aspect of the present invention an ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation comprises a carrier substance and a material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

Preferably the carrier liquid is water and the ingestible material comprises water and coarse wheat bran, or a material provided with the physical properties of coarse wheat bran.

The invention can be performed in various ways, but three embodiments will now be described by way of example.

An ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system which leads to activation of the plasma kallikrein-kinin system by reducing and/or maintaining the quantity of bacteria which cause the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation comprises coarse wheat bran mixed with warm water.

In experiments it has been found that the consumption of 30-40g of coarse wheat bran mixed with warm water 3 or 4 times daily approximately 30 minutes to one hour after food has been consumed produced a remission of Rosacea symptoms within approximately 3-4 weeks. Further, no injury or irritation was caused to the walls of the intestines.

However, in some cases the gluten in the wheat bran caused an allergic or intolerant reaction in the intestines, in particular the upper small intestine, after a number of weeks of the treatment. This led to inflammation in the digestive tract and activation of the kallikrein-kinin system, leading to the subsequent chain reaction as described above leading to a worsening of Rosacea symptoms.

Therefore, in a second embodiment of the present invention, an ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system which causes activation of the kallikrein-kinin system by reducing and/or maintaining the quantity of bacteria which causes the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation, comprises hydrolysed coarse wheat bran mixed with warm water.

The process of hydrolysis is known, and involves boiling the subject material in acid for several hours. The result is that most of the protein including the gluten content in wheat bran is destroyed, rendering it far less allergenic.

In a third embodiment of the present invention an ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system which causes activation of the kallikrein-kinin system by reducing and/or maintaining the quantity of bacteria which causes the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation, comprises finely shredded 100% pure cotton paper, which is greater than 185gm per square metre.

The cotton is boiled in water for 20 minutes, drained and then mixed with a carrier food, for example porridge or rice pudding. Once prepared the cotton is essentially pure fibrous flakes of cellulose, which are hypoallergenic.

Therefore, an ingestible material is provided which when consumed after food leads to a reduction of the transit time of the food through the digestive tract, and a reduction in the chance of luminal bacteria initiating an inflammatory reaction in the digestive tract and activation of the plasma kallikrein-kinin system, which subsequently reduces the symptoms of Rosacea.

The invention also includes a method of treating disease and/or inflammation in the human digestive system which causes activation of the kallikrein-kinin system, comprising the consumption of an ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation.

The method comprises the following steps:

- 1) Mixing approximately 30-40g of coarse wheat bran with warm water.
- 2) Consuming the mixture approximately 30 minutes to one hour after the consumption of a meal of food.
- 3) Repeating steps 1) and 2) three to four times a day after each meal of food.

The method of treating disease and/or inflammation as described above also includes using coarse wheat bran with reduced levels of, or no, protein and gluten present in it.

It will be appreciated that the present invention can also be used in the treatment and/or prevention of diseases or conditions which are caused by disease and/or inflammation in the intestines induced by intestinal luminal bacteria and/or their endotoxins and/or the products of their fermentation.

Such disorders may include abdominal bloating, acne or acneform eruptions (which includes acne vulgaris), Alzheimer's disease, affective disorders, alopecia, anaphylaxis, ankylosing spondylitis and other spondyloarthropathies, anxiety disorders, arthritis, asthma, attention deficit disorder (ADD & ADHD), attentional disorders, atypical face pain, autism (including all autistic spectrum disorders e.g. Asperger's syndrome, Pervasive Developmental Disorder, Rett's Syndrome etc.), autoimmune disorders (including hypothyroidism, scleroderma, lupus, polymyositis, vasculitis), blushing, body dysmorphic disorder, bruxism, cataplexy, chronic pain, chronic fatigue, chronic pelvic pain syndromes (which includes interstitial cystitis), colonic cancer, concentration impairment, Crohn's disease, dandruff, depression, dizziness, eating disorders (bulimia, anorexia, binging), emesis, fibromyalgia, Gulf War syndrome, hypersomnia, hypothyroidism, impulse-control disorders, insomnia, intermittent explosive disorder, irritable bowel syndrome, kleptomania, memory impairment, migraine/severe headache, mood disorders, morning fatigue, motion sickness, multiple chemical sensitivity, myofascial pain syndrome, narcolepsy,

obesity, obsessive-compulsive disorder, pancreatitis, panic disorder, pathological gambling, personality disorders, post traumatic stress disorder, premenstrual dysphoric disorder, primary dysmenorrhea, psoriasis, psoriatic arthritis, psychosis, pyromania, Raynaud's disease, repetitive strain injury, restless leg disorder, rheumatism, rhinitis, rosacea, schizophrenia, sebaceous hyperplasia, seborrhea, sensitive skin (as defined in U.S. Patent US6241993), sick building syndrome, sinusitis, social phobia, somatoform disorders, substance abuse and addiction (including alcoholism), temporo-mandibular disorders, tinnitus, tonsillitis, Tourette's disorder, trichotillomania, ulcerative colitis, a reduced level of restorative sleep, various other neuropsychiatric disorders and various other cognitive dysfunctions and any other diseases belonging to the affective spectrum disorder.

As the present invention is intended to prevent and/or reduce any disease in the human digestive system, it can therefore also be used pro-actively to promote or maintain the general good health of the digestive system and/or the prevention of any of the fore-mentioned diseases that can be caused by the presence of luminal bacteria in the digestive tract.

Claims

1. An ingestible material adapted to reduce and/or prevent disease in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes disease in said human digestive system to a level below that required to cause the disease, is provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.
2. An ingestible material as claimed in Claim 1 in which the ingestible material is adapted to reduce and/or prevent inflammation in the human digestive system by reducing and/or maintaining the quantity of bacteria which causes the inflammation in said human digestive system to a level below that required to cause the inflammation.
3. An ingestible material as claimed in Claim 1 or Claim 2 in which the ingestible material is adapted to reduce and/or maintain the quantity of luminal bacteria in the intestines to a level below that required to cause activation of the kallikrein-kinin system leading to the production of bradykinin and/or related kinins, which stimulate and/or sensitize afferent neurons, leading to the occurrence of Rosacea symptoms.
4. An ingestible material as claimed in any of Claims 1-3 in which the size and texture of the particles of the ingestible material stimulates peristaltic contractions in the walls of the intestines.
5. An ingestible material as claimed in Claim 4 in which the size and texture of the particles of the ingestible material are adapted to cause no injury to the intestinal walls.

6. An ingestible material as claimed in Claim 5 in which the ingestible material is non-soluble in water, and is adapted to retain water.
7. An ingestible material as claimed in Claim 6 in which the ingestible material is provided with substantially the optimum viscosity to pass through the digestive tract when it is combined with water.
8. An ingestible material as claimed in any of Claims 4-7 in which the ingestible material is adapted to cause no allergic or irritative reaction to the walls of the digestive tract.
9. An ingestible material as claimed in Claim 8 in which the ingestible material is substantially unfermentable by bacteria.
10. An ingestible material as claimed in Claim 8 in which the ingestible material is selectively fermentable by bacterial species that are less capable of causing disease and/or inflammation in the human digestive tract than luminal bacteria
11. An ingestible material as claimed in Claim 9 or 10 in which the ingestible material is adapted to have a pH level when ingested which reduces the pH level in the intestines and/or the stomach, such that the growth and/or proliferation of luminal bacteria is reduced and/or maintained.
12. An ingestible material as claimed in any of Claims 9-11 in which the ingestible material is provided with antibacterial properties.
13. An ingestible material as claimed in any of the preceding Claims in which the ingestible material comprises coarse wheat bran.
14. An ingestible material as claimed in Claim 13 in which the ingestible material comprises hydrolysed coarse wheat bran.

15. An ingestible material as claimed in any of Claims 1-12 in which the ingestible material comprises finely shredded 100% pure cotton paper, which is greater than 185gm per square metre, which has been boiled in water for 20 minutes, drained and then mixed with a carrier food.

16. An ingestible material substantially as described herein.

17. A method of reducing and/or preventing disease and/or inflammation in a human digestive system, comprising the consumption of an ingestible material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

18. A method as claimed in Claim 17 in which the ingestible material comprises an ingestible material according to any of Claims 2-12.

19. A method as claimed in Claim 17 or 18, including the following steps:

- 1) Mixing approximately 30-40g of coarse wheat bran with warm water.
- 2) Consuming the mixture approximately 30 minutes to one hour after the consumption of a meal of food.
- 3) Repeating steps 1) and 2) three to four times a day after each meal of food.

20. The method as claimed in Claim 17 or 18, including the following steps:

- 1) Mixing approximately 20g of finely shredded 100% pure cotton paper, which is greater than 185gm per square metre, which has been boiled in water for 20 minutes and drained, with a carrier food.
- 2) Consuming the mixture approximately 30 minutes to one hour after the consumption of a meal of food.
- 3) Repeating steps 1) and 2) three to four times a day after each meal of food.

21. An ingestible material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours is used for the manufacture of a medicament for reducing and/or preventing disease and/or inflammation in the human digestive system.

22. An ingestible material as claimed in Claim 21 in which the ingestible material comprises an ingestible material according to any of Claims 2-16.

23. An ingestible material adapted to reduce and/or prevent disease and/or inflammation in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes the disease and/or inflammation in said human digestive system to a level below that required to cause the disease and/or inflammation comprises a carrier substance and a material provided with a composition and/or physical properties adapted to stimulate peristaltic contractions in the intestines, and which is provided with a texture and viscosity adapted to pass through the digestive tract in less than 35 hours.

24. An ingestible material as claimed in Claim 23 in which the ingestible material comprises an ingestible material according to any of Claims 2-12.

25. An ingestible material as claimed in Claim 23 or 24 in which the carrier substance is water and the material comprises water and coarse wheat bran.

26. An ingestible material as claimed in Claim 23 or 24 in which the carrier substance is a carrier food and the material comprises finely shredded 100% pure cotton paper, which is greater than 185gm per square metre, which has been boiled in water for 20 minutes and drained.

INTERNATIONAL SEARCH REPORT

Internat: Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78 A61P1/00

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)
IPC 7 A61K

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

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

WPI Data, EPO-Internal, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FOLINO MARISA ET AL: "Dietary fibers differ in their effects on large bowel epithelial proliferation and fecal fermentation-dependent events in rats." JOURNAL OF NUTRITION, vol. 125, no. 6, 1995, pages 1521-1528, XP009018240 ISSN: 0022-3166 the whole document	13,19, 22,25
X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 14, 22 December 1999 (1999-12-22) & JP 11 246422 A (YAKULT HONSHA CO LTD), 14 September 1999 (1999-09-14) abstract --- -/--	13,19,22

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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

Date of the actual completion of the international search

2 October 2003

Date of mailing of the international search report

22/10/2003

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Authorized officer

Thalmair, M

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/03127

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 017, no. 247 (C-1059), 18 May 1993 (1993-05-18) & JP 05 000067 A (TOUWA KASEI KOUGIYOU KK), 8 January 1993 (1993-01-08) abstract ---	13, 19, 22
X	EP 0 586 933 A (NIPPON BEET SUGAR MFG) 16 March 1994 (1994-03-16) experiment 1 ---	13, 14, 22
X	US 4 526 800 A (HOWARD ALAN N) 2 July 1985 (1985-07-02) the whole document ---	13, 22
Y	PATENT ABSTRACTS OF JAPAN vol. 017, no. 567 (C-1120), 14 October 1993 (1993-10-14) & JP 05 163157 A (SAKAI CHEM IND CO LTD), 29 June 1993 (1993-06-29) abstract ---	15, 22, 26
Y	TAKEDA H ET AL: "EFFECT OF PARTICLE SIZE OF DIETARY FIBER ON ITS SETTLING VOLUME IN WATER AND PROTECTIVE ACTIVITY AGAINST AMARANTH FOOD RED NO. 2 TOXICITY IN RATS" NIPPON NOGEIKAGAKU KAISHI, vol. 65, no. 2, 1991, pages 171-176, XP009018295 ISSN: 0002-1407 abstract ---	15, 20, 22, 26
Y	MORITA T ET AL: "Dietary fiber and fat-derivatives prevent mineral oil toxicity in rats by the same mechanism" JOURNAL OF NUTRITION 1993 UNITED STATES, vol. 123, no. 9, 1993, pages 1575-1585, XP009018294 ISSN: 0022-3166 the whole document -----	15, 20, 22, 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/03127

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 19, 20 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: ~~1-12~~ 1-12 (whole), 16-18 (whole), 21 (whole), 22 (part):
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-12 (whole), 16-18 (whole), 21 (whole), 22 (part)

Present claims 1-12, 16-18, 21 as a whole and 22 (part) relate to a material/method defined by reference to a desirable characteristic or property, namely

- ingestible,
- adapted to reduce and/or prevent disease in a human digestive system by reducing and/or maintaining the quantity of bacteria which causes disease in said human digestive system to a level below that required to cause the disease,
- physical properties adapted to stimulate peristaltic contractions in the intestines,
- a texture and viscosity adapted to pass through the digestive tract in less than 35 hours. etc.

The claims cover all materials/methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such materials/methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the materials/methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to materials/methods in which the ingestible material comprises coarse wheat bran or comprises finely shredded 100% pure cotton paper.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/GB 03/03127

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