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— *of inventorship (Rule 4.17(iv))*

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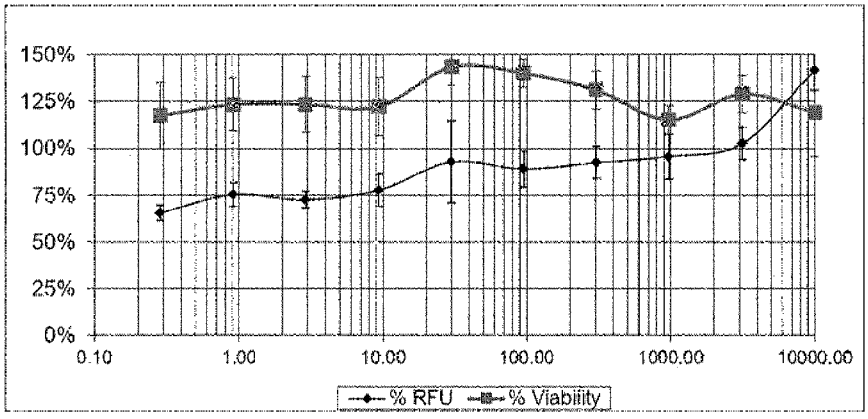
(54) **Title**: PROBIOTIC/ANTIOXIDANT BLEND

FIGURE 1



(57) **Abstract**: The present disclosure is directed to a probiotic/antioxidant composition containing at least one isolated probiotic bacteria and at least one isolated antioxidant bacteria in a probiotic/antioxidant combination which acts synergistically as an antioxidant in an amount sufficient to inhibit one or more of the pathways that contribute to skin inflammation.

Probiotic/Antioxidant Composition

FIELD OF THE INVENTION

[0001] The invention is in the field of compositions that can benefit from use of a proboiotic/antioxidant composition with improved antioxidant capabilities.

BACKGROUND OF THE INVENTION

[0002] Probiotic microorganisms are believed to provide many advantages when used in topical compositions or in food compositions. Probiotic microorganisms are known to have beneficial properties such as sooth inflammation, balance skin microflora, inhibit growth of harmful bacteria, and so on.

[0003] The potential for antioxidants and probiotics to inhibit oxidation is directly dose dependent, with higher amounts of antioxidants and probiotics exerting a greater inhibitory effect.

[0004] The use of a low concentration of a probiotic/antioxidant composition containing at least one probiotic and at least one antioxidant in a probiotic/antioxidant combination which acts synergistically as an antioxidant in an amount sufficient to inhibit one or more of the pathways that contribute to skin inflammation would reduce costs in food and cosmetic preservation and enhance antioxidant performance.

SUMMARY OF THE INVENTION

[0005] An embodiment of this invention is composition comprising a probiotic and an antioxidant in a probiotic/antioxidant wt/wt ratio of about 0.1/2.5 to about 1.0/95 and wherein said probiotic/antioxidant composition act synergistically as an inhibitor at a concentration of < about 10 µg/mL and is lost at concentrations of > about 10 µg/mL.

[0006] In an embodiment the probiotic is lactobacillus.

[0007] In an embodiment the antioxidant is Thermus thermophillus.

[0008] In an embodiment the composition contains at least one additive chosen from an antioxidant, a filler, a preserving agent, a fragrance, a neutralizing agents, a thickener, a cosmetic active agent, an emollient, and mixtures thereof.

[0009] In and embodiment the composition added to a cosmetic taking the form of a mascara, an eyeliner, a product for the eyebrows, a product for the lips, a face powder, an

eye shadow, a foundation, a make-up product for the body, a concealer product, a nail varnish, a skincare product, and a hair care product.

[0010] In an embodiment the composition is added to a food.

[0011] The composition of claim 1, wherein the composition further comprises an at least one pigment, dye, or stain.

[0012] In an embodiment the probiotic/antioxidant wt/wt ratio is 0.5/2.85.

[0013] In an embodiment the probiotic/antioxidant wt/wt ratio is 1/95.

[0014] In an embodiment the composition is 70% alpha-glucan oligosaccharide, about 19% polyminia sonchifolia root juice, about 10% maltodextrix, about 1% lactobacillus, about 95% thermus thermophillus ferment, about 5% glycerin, a methylsilanol hydroxyproline aspartate, and a Triticum monococcum [wheat] seed extract.

DETAILED DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 depicts testing of probiotic and antioxidant blend composition. Viability is the measure of toxicity of the cells in culture. RFU is the measure of the dose dependent antioxidant effect of the probiotic/antioxidant composition (% RFU).

[0016] Figure 2 depicts testing of the antioxidant blend composition. Viability is the measure of toxicity of the cells in culture. RFU is the measure of the dose dependent antioxidant effect of the probiotic/antioxidant composition (% RFU).

[0017] Figure 3 is the proposed testing of the probiotic blend composition. Viability is the measure of toxicity of the cells in culture. RFU is the measure of the dose dependent antioxidant effect of the probiotic/antioxidant composition (% RFU).

DETAILED DESCRIPTION

[0018] The terms used in this specification generally have their ordinary meanings in the art, within the context of the invention, and in the specific context where each term is used. Certain terms are discussed below, or elsewhere in the specification, to provide additional guidance to the practitioner in describing the compounds, compositions, and methods of the invention and how to make and use them. Moreover, it will be appreciated that the

same thing can be said in more than one way. Consequently, alternative language and synonyms may be used for any one or more of the terms discussed herein, nor is any special significance to be placed upon whether or not a term is elaborated or discussed herein. The use of examples anywhere in this specification, including examples of any terms discussed herein, is illustrative only, and in no way limits the scope and meaning of the invention or of any exemplified term. Likewise, the invention is not limited to the examples presented.

[0019] The present disclosure is directed to a composition comprising a probiotic and an antioxidant in a probiotic/antioxidant wt/wt ratio of about 0.1/2.5 to about 1.0/95 and wherein said probiotic/antioxidant composition act synergistically as an inhibitor at a concentration of < about 10 µg/mL and is lost at concentrations of > about 10 µg/mL.

[0020] It is well established in the dermatological literature that various pathways are responsible for inflammatory human skin, degradation of food product, and aging. These pathways are triggered by any number of perturbations (UV light, chemical irritants, mechanical trauma). The processes are often oxidative in nature, and scientific literature has demonstrated that topical and/or systemic antioxidants are effective at inhibiting these oxidative steps.

[0021] A sampling of pathways responsible for inflammation, aging, and degradation follow.

[0022] "Adhesion Pathway" is the pathway by which cells adhere to blood vessels and other skin tissues when injury or immune challenge has occurred.

[0023] "Chemotaxis Pathway" means the pathway where chemical signals cause inflammatory cells to migrate toward a site, such as skin or tissue, where immune challenge has occurred. If such inflammatory cells are prevented from migrating to the site of immune challenge the resulting damage that such cells provide to skin or tissues can be mitigated.

[0024] "Collagenase Pathway" means the pathway by which the enzyme collagenase breaks down the peptide bonds in collagen and destroys extracellular structures such as those found in bacteria or infiltrating lymphocytes at the sites of inflammation. The collagenases released will cause tissue damage by breaking down collagen fibrils in the extra cellular matrix.

[0025] "COX Pathway" means the pathway by which the cyclooxygenase (COX) enzyme (including but not limited to cyclooxygenase-2 or COX-2) converts arachidonic acid and/or

other fatty acids to prostaglandin or prostanoids which ultimately contributes to inflammation or pain in immune challenged tissue such as skin.

[0026] "PDE Pathway" means that pathway by which PDE (phosphodiesterase) including phosphodiesterase-4 (PDE4) cleaves the phosphodiester bond that may be found in proteins and other molecules present in bacteria, viruses, and other molecules that contribute to skin inflammation. PDE4, in particular, is a member of a family of enzymes that catalyze the degradation of cAMP to the corresponding 5'-nucleotide monophosphate. PDE4 is abundant and is the major regulator of cAMP metabolism in almost every pro-inflammatory and immune cell. PDE4 inhibitors exert their anti-inflammatory effects by inhibiting the breakdown of cAMP (leading to an increased concentration of cAMP in immune cells) which will ultimately lead to a decrease in the production and release of pro-inflammatory cytokines such as Interleukin 1-.beta. (IL-1.beta.) and Tumor Necrosis Factor .alpha. (TNF.alpha.).

[0027] "Elastase Pathway" means the pathway by which the enzyme elastase degrades proteins including elastin that are found in bacteria and other molecules. When the Elastase Pathway is triggered the cascade of reactions contributes to inflammation or pain in immune challenged tissue such as skin. Elastase, a peptidase released from infiltrating neutrophils at the site of inflammation, will break down elastin, an elastic fiber that, together with collagen, helps determine the mechanical properties of skin and other tissues. Inhibition of elastase will minimize the damage that may be caused by infiltrating neutrophils which in turn will help preserve the integrity of the extra cellular matrix.

[0028] "Histamine Pathway" means the pathway where the amino acid histidine is decarboxylated to form histamine in response to immune challenge or other injury to tissue or skin. Histamine is a biogenic amine that is synthesized and stored in mast cells which reside primarily in the skin. Histamine plays a major role in the initiation of the inflammatory cascade. Upon stimulation, mast cells (and basophils) will release their stored histamine which will bind to H1 receptors on a variety of cells (including smooth muscle cells and endothelial cells in blood vessels) exerting its biologic effects. These effects include vasodilation, separation of endothelial cells (causing abnormal vascular permeability), pain and itching. Inhibition of histamine release provides amelioration from many of the adverse effects of inflammation.

[0029] "Histamine Receptor Pathway" means that pathway by which cellular receptors for histamine are activated to bind to histamine, which in turn contributes to the inflammatory condition of tissues or skin.

[0030] "LO Pathway" means the pathway by which the enzyme lipooxygenase, preferably 5-lipooxygenase, catalyzes the conversion of arachidonic acid to 5-hydroperoxyeicosatetraenoic acid and then to leukotriene A4, which ultimately contributes to inflammation or pain in immune challenged tissue such as skin.

[0031] "PLA-2 Pathway" means the pathway by which the phospholipase A2 (PLA-2) enzyme hydrolyzes phospholipids to form fatty acid lysophospholipid products such as arachidonic acid, which ultimately converts to leukotrienes and prostaglandins, which contribute to the inflammatory response in immune challenged tissue such as skin.

[0032] "VEGF Pathway" means the pathway by which VEGF (vascular endothelial growth factor) causes angiogensis (the formation of blood vessels) in immune challenged skin. In addition to inducing angiogenesis, VEGF also is responsible for increasing vascular leakage which will lead to increased edema in damaged tissue or skin.

[0033] "Immune challenged" means tissues or skin subjected to environmental, bacterial or viral assaults and where any one or more of the Pathways that contribute to inflammation have been triggered.

[0034] "Inflammation" means, when used to describe skin, that the skin has been subjected to moderate to severe environmental or chemical assault and is moderately to severely immune challenged. Examples of inflammation include sunburn, windburn, acne, insect bites, cuts, burns, rosacea, and the like. Inflammation typically produces one or more of redness, pain, and heat in the skin. An anti-inflammatory reduces the inflammation response.

[0035] "Inhibitor" or "inhibit" means, when used with a particular Pathway, an ingredient or combination of ingredients that inhibits the Pathway in whole or in part. For example, Histamine Pathway Inhibitor means an ingredient or combination of ingredients that inhibits the Histamine Pathway in whole or in part.

[0036] "Irritant", when used to describe skin, means that the skin has been aggravated by environmental assaults or toxins, or application of products containing one or more ingredients to which the skin is sensitized or otherwise incompatible. Irritation may result in

redness, itchiness, dryness, blemishes, enlarged pores, and so on. Irritated skin may also exhibit one or more of redness, pain, and heat.

[0037] "Pathway", when used with respect to inflammation, means a cascade of reactions that occurs when skin or tissue is exposed to immune challenge, and which ultimately contributes to skin inflammation.

[0038] Percentages mentioned herein shall mean percentage by weight unless otherwise indicated and are represented as wt/wt.

[0039] As used herein, *"about"* or *"approximately"* shall generally mean within 20 percent, preferably within 10 percent, and more preferably within 5 percent of a given value or range. Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients and/or reaction conditions are to be understood as being modified in all instances by the term "about".

[0040] "Film former" or "film forming agent" or "film forming resin" as used herein means a polymer which, after dissolution in at least one solvent (such as, for example, water and organic solvents), leaves a film on the substrate to which it is applied, for example, once the at least one solvent evaporates, absorbs and/or dissipates on the substrate.

[0041] "Keratinous substrates", as used herein, include but are not limited to, skin, hair, lashes and nails.

[0042] As used herein, the term ratio is used to express the relationship in quantity or amount of probiotic and antioxidant.

[0043] As used herein, the expression "at least one" means one or more and thus includes individual components as well as mixtures/combinations.

[0044] The term "probiotic" means bacteria belonging to the order Lactobacillales, including but not limited to those from the genus Lactobacillus, Leuconostoc, Pediococcus, Lactococcus, Enterococcus, Oenococcus, Sporolactobacillus, Teragenococcus, and so on; or a yeast belonging to the order Saccharomyces.

[0045] The term "antioxidant" means bacteria belonging to the order Thermophillus, including but not limited to Thermus Thermophillus, Geobacillus Thermophilus, Talaromyces Thermophilus, L. Bulgaricus S. Thermophilus, Lactococcus Thermophilus, Sphaerobacter Thermophilus.

[0046] The term "cosmetic" includes a composition in the form of aqueous gels or dispersions, emulsions, or anhydrous compositions and will generally be suitable for applying color to skin, hair, or lashes. Suitable aqueous gels contain from about 0.1 to 99% water from about 1-99.9% of other cosmetic ingredients. Emulsions may be in the oil in water or water in oil form, or silicon and water, or water and silicon and generally comprise from about 0.1 to 99% water and from about 0.1 to 99% oil. Anhydrous compositions generally contain less than about 1% water, in addition to 0.1 to 90% oils, and optionally other ingredients.

[0047] The compositions of the invention may contain particulate materials in the form of pigments, inert particulates, or mixtures thereof. If present, suggested ranges are from about 0.01-75%, preferably about 0.5-70%, more preferably about 0.1-65% by weight of the total composition. In the case where the composition may comprise mixtures of pigments and powders, suitable ranges include about 0.01-75% pigment and 0.1-75% powder, such weights by weight of the total composition.

[0048] In one embodiment, the composition may also comprise at least one coloring agent chosen from pigments, natural colorant, and dyes or a combination of pigments, natural colorants, and dyes. As used herein, pigments refer to colored solid particles at 25° C. that are not soluble in the liquid fatty phase. Pigments may include nacreous pigments (i.e., nacres), and pearling agents.

[0049] Pigments, dyes, and coloring agents also include encapsulation of the pigments, dyes, and coloring agents with a material such as a polymer, a pigment, a wax, a sugar derivative, or a combination of the proceeding material. Encapsulation of pigments, dyes, and coloring agents are disclosed in patent application US 20110229536 which processes and definitions are hereby incorporated by reference.

[0050] In one aspect, the composition may include fillers including, but not limited to, talc, kaolin, silica, barium sulfate, aluminum hydroxide, calcium silicate, silica, silicone powders, and acrylic acid copolymers.

[0051] In addition, the compositions may include one or more of the following components: sunscreen agent, SPF booster, secondary emulsifier, emollient, moisturizer, humectant, film former/waterproofing agent, bio-active (functional) ingredient, fragrance, a metal chelating agent such as edetic acid, an antibacterial agent, an antiseptic agent such as methyl-p-hydroxybenzoate, a stabilizer, such as phenacetin, etidronic acid, or oxyquinoline sulfate, an organic solvent, such as ethanol, benzyl alcohol, or benzyloxy ethanol, a water-

soluble polymer such as hydroxyethyl cellulose, and a humectant or any combinations thereof. The liquid mixture of the first and second parts contains preferably a medium composed mainly of water. Further, a persulfate such as ammonium persulfate may be added in the liquid mixture as the third part in order to improve the bleaching activity.

[0052] It is, of course, understood that the composition may further include optional ingredients generally known by one skilled the art to be suitable for use in cosmetic compositions. Lists of carriers and optional ingredients, which are well known in the art, are disclosed, for example, in "Cosmetics: Science and Technology," edited by M. S. Balsam and E. Sagarin, 2nd Edition, 1972, Wiley Pub. Co.; "The Chemistry and Manufacture of Cosmetics" by M. G. DeNavasse; and "Harry's Cosmeticology," J. B. Wilkinson et al., 7th Edition, 1982, Chem. Pub. Co.; the disclosures of each of the above being incorporated herein by reference.

EXAMPLE

[0053] Antioxidant/Probiotic composition

Ratio tested	INCI Name of all components
10	Probiotic Blend: 70% Alpha-glucan oligosaccharide 19% Polyminia sonchifolia root juice 10% Maltodextrix 1% Lactobacillus
60	Antioxidant Blend: 95% Thermus thermophillus ferment 5% Glycerin
20	Methylsilanol hydroxyproline aspartate
10	Triticum monococcum [wheat] seed extract

[0054] Inflamation was measured by the magnitude of cytokine release after exposure to a single dose of irritant. The anti-inflammatory potential of the skin model is measured by the tissue viability. The tissue viability is determined by measuring the relative conversion of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) in the skin model treated with the antioxidant/probiotic composition, probiotic alone, antioxidant alone, and a negative/solvent control (sterile, deionized water) and a positive control (hydrocortisone cream).

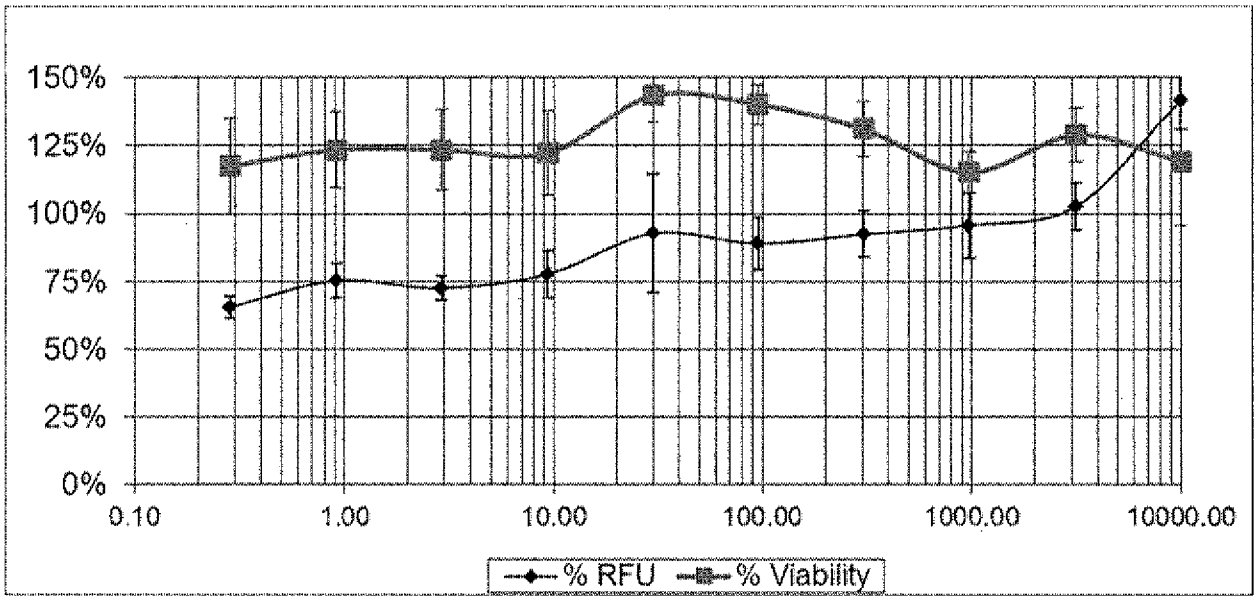
[0055] The skin model is the EpiDerm ™ skin model (MatTek Corporation, Ashland, MA). The skin model was exposed to antioxidant/probiotic composition, probiotic alone, antioxidant alone, and a negative/solvent control, applied topically to the skin model, for six

hours in the presence and absence of phorbol-12-myristate 13-acetate (PMA). The toxicity of the test article was determined by the NAD(P)H-dependent microsomal enzyme reduction of MTT.

WHAT IS CLAIMED IS:

1. A composition comprising a probiotic and an antioxidant in a probiotic/antioxidant wt/wt ratio of about 0.1/2.5 to about 1.0/95 and wherein said probiotic/antioxidant composition act synergistically as an inhibitor at a concentration of < about 10 µg/mL and is lost at concentrations of > about 10 µg/mL.
2. The composition of claim 1, wherein the probiotic is lactobacillus.
3. The composition of claim 1, wherein the antioxidant is Thermus thermophillus.
4. The composition of claim 1, further comprising at least one additive chosen from an antioxidant, a filler, a preserving agent, a fragrance, a neutralizing agents, a thickener, a cosmetic active agent, an emollient, and mixtures thereof.
5. The composition of claim 1, wherein the composition added to a cosmetic.
6. The composition of claim 1, wherein the composition is added to a food.
7. The composition of claim 5, wherein the cosmetic is in a form chosen from a mascara, an eyeliner, a product for the eyebrows, a product for the lips, a face powder, an eye shadow, a foundation, a make-up product for the body, a concealer product, a nail varnish, a skincare product, and a hair care product.
8. The composition of claim 1, wherein the composition further comprises an at least one pigment, dye, or stain.
9. The composition of claim 1, wherein the probiotic/antioxidant wt/wt ratio is 0.5/2.85.
10. The composition of claim 1, wherein the probiotic/antioxidant wt/wt ratio is 1/95.
11. A composition of claim 1 comprising about 70% alpha-glucan oligosaccharide, about 19% polyminia sonchifolia root juice, about 10% maltodextrix, about 1% lactobacillus, about 95% thermus thermophillus ferment, about 5% glycerin, a methylsilanol hydroxyproline aspartate, and a Triticum monococcum [wheat] seed extract.

FIGURE 1


150%
125%
100%
75%
50%
25%
0%
0.10
1.00
10.00
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1000.00
10000.00
% RFU
% Viability

FIGURE 2

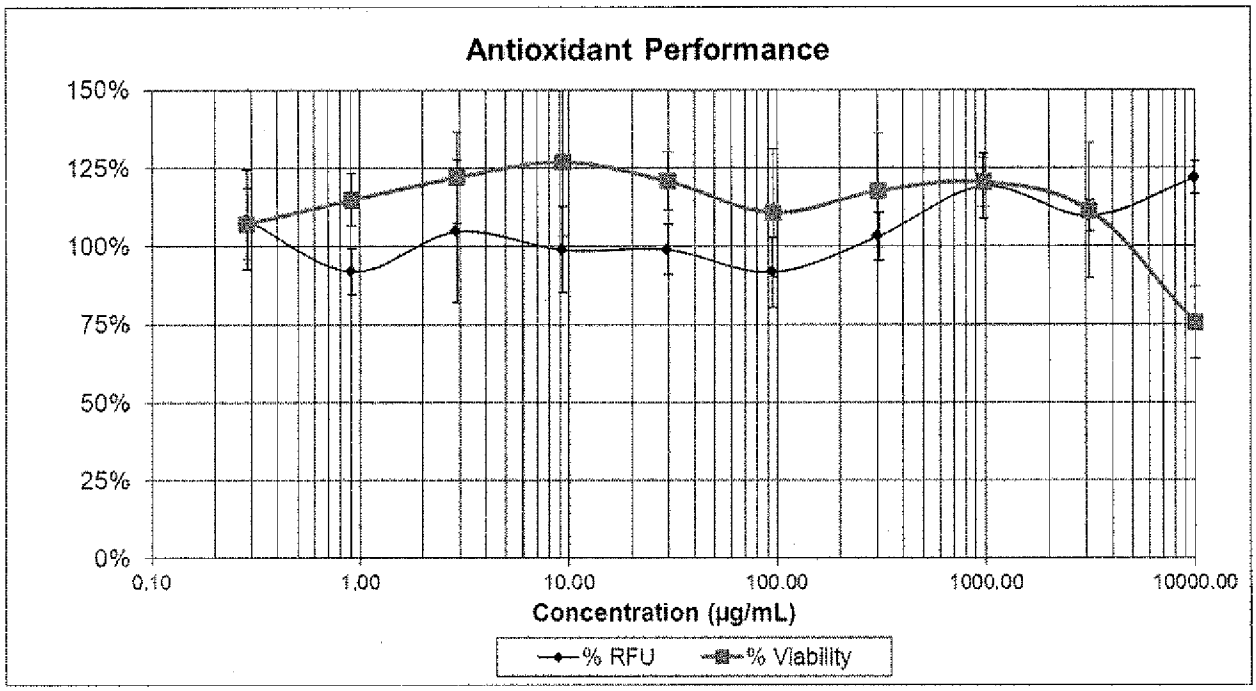
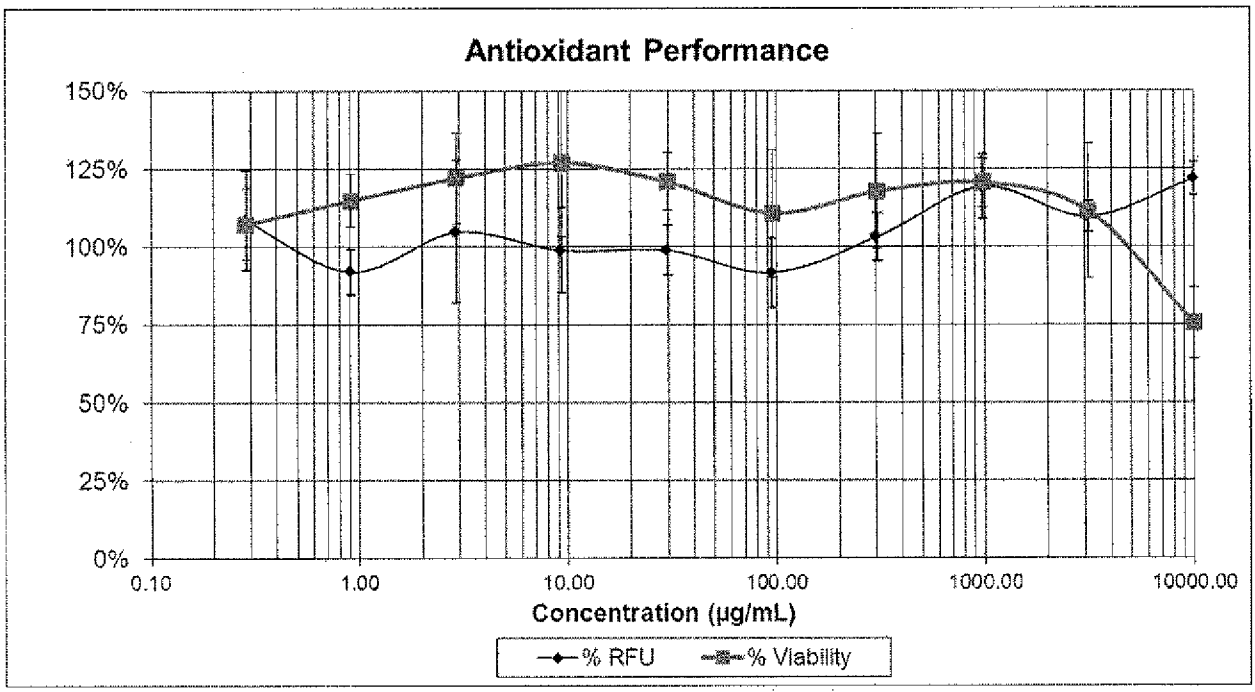

Antioxidant Performance
150%
125%
100%
75%
50%
25%
0%
0,10
1,00
10,00
100,00
1000,00
10000,00
Concentration (µg/mL)
% RFU
% Viability

FIGURE 3


Antioxidant Performance
150%
125%
100%
75%
50%
25%
0%
0.10
1.00
10.00
100.00
1000.00
10000.00
Concentration (µg/mL)
% RFU
% Viability

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/029347

A. CLASSIFICATION OF SUBJECT MATTER

A01N 63/00(2006.01)i, A61K 35/66(2006.01)i, A61K 35/74(2006.01)i, A61P 29/00(2006.01)i

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)

A01N 63/00; A61K 8/02; A61K 8/49; A61K 38/43; A61K 8/99; A61Q 19/08; A61K 8/66; A61K 9/127

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords: lactobacillus, thermus thermophillus

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011-0223219 A1 (DAO KHANH NGOC et al.) 15 September 2011 See abstract; paragraphs [0026]-[0047],[0138]-[0140]; whole claims.	1-11
A	US 2011-0280850 A1 (STARR ELIZABETH I. et al.) 17 November 2011 See abstract; paragraphs [0001]-[0032],[0074]-[0075]; claims 1,4,6,11,15.	1-11
A	US 2009-0285868 A1 (RICHARD HERVE et al.) 19 November 2009 See abstract; paragraphs [0151],[0256]-[0309],[0321]-[0327]; claim 11.	1-11
A	US 2010-0080845 A1 (MAES DANIEL H. et al.) 01 April 2010 See abstract; paragraphs [0043]-[0046],[0082]; Formula 2.	1-11

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

☒ See patent family annex.

* Special categories of cited documents:

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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
28 NOVEMBER 2012 (28.11.2012)	**28 NOVEMBER 2012 (28.11.2012)**

Name and mailing address of the ISA/KR

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YOO, JUN SEOK

Telephone No. 82-42-481-5627

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2012/029347

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