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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) **Title**: ANTI-AGEING COMPOSITION COMPRISING RESVERATROL AND ANDROGRAPHOLIDE

(57) **Abstract**: The invention relates to an oral anti-ageing composition, in particular to an oral anti-ageing composition comprising resveratrol and an aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata. The inventors have observed a synergistic up-regulation of haemoxygenase-1 (HO-1) in primary human dermal fibroblast cells treated with a combination of aqueous extract of the whole herb of Andrographis paniculata and resveratrol. Thus in a first aspect of the invention, an oral anti-ageing composition is provided, the oral anti-ageing composition comprising resveratrol and an aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata, wherein the oral or topical anti-ageing composition comprises more than 0.4 % w/w andrographolide, wherein the oral anti-ageing composition comprises a daily dosage of 10 to 500, preferably 50 to 300 mg resveratrol in the form of one or more unit doses. Other aspects of the invention are also described.

ANTI-AGEING COMPOSITION COMPRISING RESVERATROL AND ANDROGRAPHOLIDE

The invention relates to an oral anti-ageing composition, in particular to an oral anti-ageing composition comprising resveratrol and an aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata.

Moi et al (Proc. Natl. Acad. Sci. U.S.A,. 91, 21, 9926–30 (October 1994)) discloses that nuclear factor erythroid-2 related factor 2 (also known as NFE2L2 or Nrf2) is a transcription factor (protein) that in humans is encoded by the NFE2L2 gene. According to Lee et al (J. of Biochem & Mol Biol. 37, 139-143 (2004)) and Hybertson et al (Mol Aspects Med. 32, 234-46 (2011)), Nrf2 has been shown to be involved in the defence against oxidative injury in various tissues. Under basal conditions, Nrf-2 is inactive and bound in the cytoplasm by cytosolic regulatory protein Kelch-like ECH-associated protein 1 (Keap1). According to Itoh et al (Genes Dev., 13, 1, 76–86 (January 1999)) the protein Cullin 3 degrades Nrf2 by ubiquitination. According to Kobayashi et al (Mol. Cell. Biol., 24, 16, 7130–9 (August 2004)) Keap1 helps Cullin 3 ubiquitinate Nrf2. When Nrf2 is ubiquitinated, it is transported to the proteasome where it is degraded and its components recycled such that under normal conditions, Nrf2 has a half-life of only 20 minutes.

Yamamoto et al (Mol. Cell (Biol., 28, 8, 2758–70 (April 2008)) and Sekhar et al (Toxicol. Appl. Pharmacol., 244, 1, 21–6 (June 2009)) disclose that oxidative stress or electrophilic stress disrupts critical cysteine residues in Keap1, disrupting the Keap1-Cullin 3 ubiquitination system. When Nrf2 is not ubiquitinated, it builds up in the cytoplasm and translocates into the nucleus. Itoh et al (Biochem. Biophys. Res. Commun., 236, 2, 313–22 (July 1997)) disclose that in the nucleus, Nrf2 combines (forms a heterodimer) with a small Maf protein (a transcription factor) and binds to small regions of DNA known as Antioxidant Response Elements (ARE's) in the upstream promoter region of many anti-oxidative genes, and initiates their transcription.

According to Lee et al and Hybertson et al, the antioxidant genes include "phase II" enzymes such as NAD(P)H: quinone oxidoreductase 1 (NQO-1) and haemoxygenase-1 (HO-1). Increased oxidative stress has been shown to have a detrimental effect on hair pigmentation (Lu et al, J Invest Dermatol, 129, 1790-804 (2009); Arck et al, FASEB J. 2, 1567-9 (2006)).

The main function of the hair follicle is to produce a hair fibre. The hair follicle develops from the embryonic epidermis as an epidermal finger which differentiates into the fibre, the outer root

sheath (ORS) and the inner root sheath (IRS). Mature follicles undergo follicular cycling through phases of organ growth and hair fibre production (anagen) for 3-7 years, cessation of fibre growth and organ involution (catagen) over about 2 weeks and a quiescent phase (telogen) which lasts about 3 months where the organ rests and the hair fibre remains anchored but no longer grows before the hair fibre falls (exogen) and is regenerated to start the cycle again (Dry, J Genet 16, 281-340 (1926), Chase, Physiol Rev 34, 1, 113-26 (1954) and Kligman, J Invest Dermatol 33, 307-16 (1959)). WO 2014/095289 (Unilever et al. discloses in Example 4 that sulforaphane significantly up-regulates NQO-1 and HO-1 gene expression in human hair follicles and is thus an Nrf2 agonist, and in Example 3 that sulforaphane significantly up-regulates human hair follicle growth.

Hair ageing is a major age-related consumer issue (hair loss, thinning hair, loss of shine, increased number of grey hairs, etc). Biological routes for hair growth or preventing hair greying provide effective opportunities to target consumer hair issues. Currently, Minoxidil ™ and Finasteride ™ are the only clinically proven, mildly effective products available for hair growth and both are classified as medicines and therefore not suitable for cosmetic use. The identification of cosmetic ingredients which are able to boost hair growth, maintain anagen and/or prevent catagen may prove to be effective anti-ageing treatments to prevent or attenuate some of the symptoms associated with hair ageing.

According to Woolery-Lloyd et al (Seminars in Cutaneous Medicine and Surgery, Elsevier (2011)), hyperpigmentation is a common dermatological condition that is seen in all skin types but is most prominent in skin of colour. In skin of colour, any inflammation or injury to skin can almost immediately be accompanied by alterations in pigmentation. Talalay et al. (PNAS, 104, 44, 17500 (30 October 2007)) discloses that application of sulforaphane to the skin of mice and healthy human subjects elevates NAD(P)H: quinone oxidoreductase 1 (NQO-1) protecting against ultraviolet radiation induced inflammation and edema in mice and reducing susceptibility to erythema in humans.

Kundu et al. (Biochemical Pharmacology, 72, 1506 (2006)) reports that resveratrol inhibited 12-O-tetradecanoyl-phorbol-13-acetate (TPA) induced oxidative stress, expression and activity of pro-inflammatory enzyme cyclooxygenase-2 (COX-2).

Summary of the invention

The inventors have observed a synergistic up-regulation of haemoxygenase-1 (HO-1) in primary human dermal fibroblast cells treated with a combination of aqueous extract of the whole herb of Andrographis paniculata and resveratrol.

Thus in a first aspect of the invention, an oral anti-ageing composition is provided, the oral anti-ageing composition comprising resveratrol and an aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata, wherein the oral or topical anti-ageing composition comprises more than 0.4 % w/w andrographolide, wherein the oral anti-ageing composition comprises a daily dosage of 10 to 500, preferably 50 to 300 mg resveratrol in the form of one or more unit doses.

In a second aspect of the invention, the oral anti-ageing composition of the first aspect of the invention is provided for use as a medicament.

In a third aspect of the invention, the oral anti-ageing composition of the first aspect is provided for use in evening skin tone, or treating or preventing hyperpigmentation.

In a fourth aspect of the invention, the oral or topical anti-ageing composition of the first aspect of the invention is provided for use in treating hair ageing.

For the purposes of this invention, “treating hair ageing” means promoting hair fibre growth or reducing hair fibre loss.

Detailed description of the invention

In a preferred embodiment of the invention, the oral anti-ageing composition of the invention comprises a daily dosage of 10 to 500, preferably 50 to 250 mg aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata in the form of one or more unit doses.

Preferably the aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata comprises at least 5, preferably at least 10, most preferably at least 20 % w/w andrographolide. However, preferably the oral anti-ageing composition comprises no more than 20, more preferably 10, most preferably 5 % w/w andrographolide.

The oral anti-ageing composition of the invention may be in the form of a solid, a slurry, a solution, a suspension, a gel or an emulsion. When solid, the oral anti-ageing composition of the invention may be in the form of a supplement of one or more unit dosages such as capsules, cachets, lozenges, pills, tablets, caplets, each comprising a predetermined amount of the essential ingredients of the invention.

More specifically, the oral anti-ageing composition of the invention may be selected from the group of foodstuffs consisting of a beverage (for example a fruit or tea (for example Camellia sinensis) based beverage, a supplement, a soup (in dry, paste or liquid form), margarine, a ready-to-eat meal, a dressing, a mayonnaise, mustard, a tomato-based condiment, a sauce, a seasoning (for example as unit doses in the form of a powder, a compressed powder in the form of, for example, a cube, a liquid or suspension, or a gel), a yoghurt and a frozen confection. By "frozen confection" is meant a sweet-tasting fabricated foodstuff intended for consumption in the frozen state (i.e. under conditions wherein the temperature of the foodstuff is less than 0°C, and preferably under conditions wherein the foodstuff comprises significant amounts of ice). Frozen confections include ice cream, sorbet, sherbet, frozen yoghurt, water ice, milk ice and the like. Preferably the frozen confection has a total solids content (i.e. the sum of the weights of all the ingredients other than water, expressed as a percentage of the total weight) of at least 20 %, more preferably at least 25 %. Frozen confections may be aerated or unaerated. Preferably the frozen confection is aerated. The frozen confection may be manufactured by any suitable process, typically by preparing a mix of ingredients; then pasteurising and optionally homogenising the mix; and then freezing and optionally aerating the mix to produce the frozen confection.

Example: HO-1 protein antibody assay using primary human dermal fibroblast cells treated with lycopene, lutein, extract of Andrographis paniculata and combinations thereof

Culture of primary human dermal fibroblast cells

Primary human dermal fibroblast cells were obtained from Cell Research Corporation and cultured and passaged in Dulbecco's Modified Eagle Serum (DMEM) (Gibco) supplemented with 10 % foetal bovine serum (FBS). Cells were routinely plated out in 6-well tissue culture dishes, at a seeding density of ~5000 cells/cm2 in 2 ml complete medium/well for 24 hours, and incubated at 37 ^{0}C in 5 % CO2.

Addition of test solutions

Test solutions were prepared in ethanol or DMSO and added directly to the cells and treated for 24 hours. The test solutions were prepared with selected concentrations of test material as set forth in Table 2. The cells were then pelleted.

Preparation of cell lysate

All cell pellets were lysed on ice for 30 minutes in 1 ml cell lysis buffer per 2.5 x 106 cells. The lysis buffer contained 1 % NP-40, 0.1 % sodium deoxycholate, 0.1 % SDS, 6 mM sodium chloride and 0.05 M Tris at pH 7.6. Protease inhibitor cocktail (1000X; Sigma P8340) was added prior to use at a level of 10 µl per ml of lysis buffer. The clarified cell lysate was frozen at -80 ^{0}C until needed.

Total protein assay (Pierce)

The total protein concentration of each cell lysate was measured using the Pierce BCA protein assay kit. A set of eight standard solutions ranging from 0 to 1200 µg/ml protein was prepared from the supplied 2 mg/ml BSA stock solution. 10 µl of standard or cell lysate was added to duplicate wells of a flat-bottomed, 96-well microtitre plate. The reagent solution was prepared according to the kit instructions from 50 parts reagent A and 1 part reagent B. 200 µl of the final reagent was added to each well of the microtitre plate. The plate was mixed, covered and incubated at 37 ^{0}C for 30 minutes and absorbance read at 562 nm. A protein standard curve was constructed and used to determine the protein concentration of each cell lysate.

HO-1 ELISA (Assay Designs)

Protein samples were diluted in sample diluent, and 100 µl transferred to the pre-coated anti-human HO-1 immunoassay plate (Assay Designs (ERK-800)). A 7-point recombinant HO-1 standard curve, ranging from 25 to 0.39 ng/ml, was also prepared in sample diluent. The immunoassay plate was incubated at room temperature for 30 minutes, washed six times with Wash Buffer, and incubated for a further 60 minutes at room temperature with 100 µl/well of anti-human HO-1 antibody solution. The plate was washed as above and incubated for 30 minutes at room temperature with 100 µl/well of horseradish peroxidase conjugate solution. Again the plate was washed as above and 100 µl/well of tetramethylbenzidine substrate added to each well and left to stand for 15 minutes at room temperature in the dark. Following the addition of 100 µl/well

of stop solution, the absorbance was read at 450 nm and the unknown biopsy levels of HO-1 extrapolated from the standard curve.

Results

The results are summarised in Table 1. The vehicle for the aqueous extract of the whole herb of Andrographis paniculata was distilled water, and the vehicle for dimethyl sulphoxide (DMSO) and the combination was a 50/50 by volume mixture of distilled water and DMSO. The results show that 5 µM resveratrol did not up-regulate HO-1 protein levels in primary human dermal fibroblast cells compared to vehicle. 10 µg/ml of an aqueous extract of the whole herb of Andrographis paniculata obtained from Natural Remedies Private Limited (Bangalore, India) also did not up-regulate HO-1 protein levels in primary human dermal fibroblast cells compared to vehicle. In contrast both 50 and 100 µg/ml of an aqueous extract of the whole herb of Andrographis paniculata did significantly up-regulate HO-1 protein levels compared to vehicle. Furthermore combinations of 5 µM resveratrol with each of 10, 50 and 100 µg/ml of an aqueous extract of the whole herb of Andrographis paniculata was observed to synergistically up-regulate HO-1 protein levels compared to the levels seen with either ingredient singly.

Table 1: HO-1 protein (pg/µg protein) and normalised HO-1 protein (pg/µg protein), i.e., without the effect of vehicle control, levels of primary human dermal fibroblast cells treated with resveratrol, an aqueous extract of the whole herb of Andrographis paniculata, and mixtures thereof (hatched values indicate a synergy) (n = 3).

Experiment	Resveratrol (µM)	An aqueous extract of the whole herb of Andrographis paniculata (µg/ml)	HO-1 protein (pg/µg protein)	Normalised HO-1 protein (pg/µg protein)	Sum of normalised HO-1 protein (pg/µg protein)
H_2O			33.9 ± 8.5	-	-
H_2O/DMSO			41,8 ± 5.4	-	-
1.1	5		37.5 ± 8.1	-4.3	-
1.2		10	40.1 ± 5.7	6.2	-
1.3		50	73.3 ± 1.1	39.4	-
1.4		100	111.2 ± 14.2	77.3	-
1.5	5	10	53.5 ± 2.3	11.7	1.9
1.6	5	50	79.0 ± 27.2	37.2	35.1

1.7	5	100	180.3 ± 9.2	138.5	73.0

Conclusion

Combinations of resveratrol and an aqueous extract of the whole herb of Andrographis paniculata synergistically up-regulate HO-1 protein levels in primary human dermal fibroblast cells, and hence synergistically up-regulate Nrf2 protein levels.

Claims

1. An oral anti-ageing composition comprising resveratrol and an aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata, wherein the oral or topical anti-ageing composition comprises more than 0.4 % w/w andrographolide, wherein the oral anti-ageing composition comprises a daily dosage of 10 to 500, preferably 50 to 300 mg resveratrol in the form of one or more unit doses.

2. An oral anti-ageing composition according to claim 1 comprising a daily dosage of 10 to 500, preferably 50 to 250 mg aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata in the form of one or more unit doses.

3. An oral anti-ageing composition according to claim 1 or claim 2, wherein the aqueous or hydroalcoholic extract of the leaf and whole herb of Andrographis paniculata comprises at least 5, preferably at least 10, most preferably at least 20 % w/w andrographolide.

4. An oral anti-ageing composition according to any one of claims 1 to 3, wherein the oral anti-ageing composition comprises no more than 20, more preferably 10, most preferably 5 % w/w andrographolide.

5. An oral anti-ageing composition according to any one of claim 1 to 4 for use as a medicament.

6. An oral anti-ageing composition according to any one of claims 1 to 4 for use in evening skin tone, or treating or preventing hyperpigmentation.

7. An oral or topical anti-ageing composition according to any one of claims 1 to 4 for use in treating hair ageing.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K36/889 A61Q19/08 A61K31/05 A61P17/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61Q

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2005/048008 A1 (GUPTA SHYAM K [US]) 3 March 2005 (2005-03-03)	1-7
Y	the whole document example 7	1-7

X	WO 2014/095289 A2 (UNILEVER PLC [GB]; UNILEVER NV [NL]; CONOPCO INC DBA UNILEVER [US]) 26 June 2014 (2014-06-26) cited in the application	1-7
Y	the whole document claims 2,6,8 pages 27-28	1-7

A	CA 2 727 997 A1 (HIMALAYA GLOBAL HOLDINGS LTD [AE]) 14 July 2012 (2012-07-14) the whole document	1

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

[X] See patent family annex.

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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
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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/162457 A1 (MINEGISHI YOSHIHIKO [JP] ET AL) 25 June 2009 (2009-06-25) the whole document	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2015/069551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005048008 A1	03-03-2005	NONE	
WO 2014095289 A2	26-06-2014	NONE	
CA 2727997 A1	14-07-2012	NONE	
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		EP 1993522 A2	26-11-2008
		EP 2322158 A2	18-05-2011
		US 2009162457 A1	25-06-2009
		WO 2007049796 A2	03-05-2007