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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 September 2014 (04.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/132213 A1

(51) International Patent Classification:
A61K 36/03 (2006.01) *A61K 31/56* (2006.01)
A61K 31/05 (2006.01) *A61P 17/00* (2006.01)
A61K 31/357 (2006.01) *A61K 9/00* (2006.01)

(21) International Application Number:
PCT/IB2014/059294

(22) International Filing Date:
27 February 2014 (27.02.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1303469.9 27 February 2013 (27.02.2013) GB

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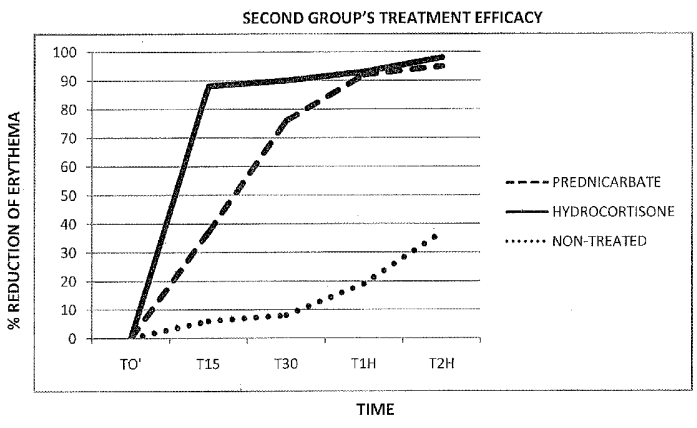
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP,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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

(54) **Title**: COMPOUNDS, PROCESSES FOR EXTRACTING THEM FROM KELP, COMPOSITIONS CONTAINING SAID COMPOUNDS AND USE OF SAID COMPOSITIONS

FIGURE 2



(57) **Abstract**: A composition is prepared by: preparing an aqueous solution of sodium citrate and citric acid; and combining fresh kelp with the aqueous solution. The ratio between the sodium citrate and citric acid in the aqueous solution is about 10:1, by mass. The composition includes at least one of: 4-(3,5- dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine-1,3,6,8-tetraol; 8-(2,4,6- trihydroxyphenoxy)-4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine -1,3,6- triol; 8-(2,4,6-trihydroxyphenoxy)-9-(3,5-dihydroxyphenoxy)dibenzo [1,4]dioxine-1,3,6-triol; and (8S,9S,10R, 13R,14S,17R)- 2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-17-(R,E)-5-isopropylhept-5 -en-2-yl)-10,13-demethyl-1H-cyclopenta[a]phenanthren-3-ol.

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COMPOUNDS, PROCESSES FOR EXTRACTING THEM FROM KELP, COMPOSITIONS CONTAINING SAID COMPOUNDS AND USE OF SAID COMPOSITIONS

Field of the invention

The present invention relates to a process of extracting compounds form kelp, particularly, but not limited to the kelp specie, *ecklonia maxima*. The compounds are useful in allopathic, complementary and alternative medicines, and are particularly useful in transdermal medicaments.

Background to the invention

Products from kelp, also known as brown seaweed, are useful, among other uses, as sources of alginate for the food industry, plant feeds and dietary supplements, e.g. to supplement dietary iodine and promote healthy thyroid function. Kelp products have also been used to treat conditions related to endocrinology and dermatology, such as goitre and eczema respectively.

The cell walls of kelp contain a polysaccharide known as alginic acid, which absorb water to become an insoluble, viscous gel that protects the kelp and its contents. Current processes to extract the carbohydrate substances such as alginic acid from kelp entails first converting the insoluble alginic acid to a soluble form. This is done by heating the harvested kelp in a solution of caustic acid. This reaction converts the insoluble alginic acid into a soluble form of sodium alginate, which partly dissolves the cell wall and releases the cell content. The soluble alginate by-product is processed into different grades of alginate and used for various purposes, including as a food or thickening agent, and in paint or rubber.

This process of extraction has numerous disadvantages. The step of soaking the kelp in hot water denatures the cell contents – especially when the cell walls are dissolved and the cell contents are released into the hot water, which disrupts the carbohydrate substances. Further, the caustic acid also contributes to denaturing the carbohydrate substances through its corrosive

action. Moreover, the caustic acid is also an environmental toxin. The process might release substantial quantities of the carbohydrate substances form the cells, but in doing so, much of the carbohydrates become denatured and ineffective and the full pharmacological potential of the carbohydrate substances found in kelp are therefore not harnessed.

As mentioned above, kelp products have been indicated in dermatological conditions, but to date, kelp products lack efficacy in treating dermatological conditions, when compared to conventional drugs. In particular, current kelp products lack efficacy as topical anti-inflammatory preparations.

Conventional topical anti-inflammatory drugs used to treat dermatological conditions such as dermatitis, eczema and psoriasis, include glucocortisones such as hydrocortisone (e.g. Mylocort®) and the newer generation prednicarbate (e.g. Peitel®). These are distinguished from topical non-steroidal anti-inflammatory drugs such as diclofenac (e.g. Voltaren®) and salicylates (e.g. Reparil®) specifically indicated for muscular use. Despite the noted anti-inflammatory effects of these topical steroid drugs, they have unwanted side effects. Most notably, these treatments result in cutaneous atrophy, especially hydrocortisone. This effect is less evident when using prednicarbate, but is of concern to a patient who suffers from a chronic skin condition that requires long-term topical anti-inflammatory treatment. Other adverse reactions from topical steroid drugs include telangiectasia, distended striae, folliculitis and allergic reactions such as itching and skin irritation.

The present invention seeks to provide substances suitable for topical anti-inflammatory treatment with therapeutic efficacy that is comparable to conventional topical anti-inflammatory drugs, while ameliorating or avoiding their adverse side effects.

The invention further seeks to provide for the extraction of carbohydrate substances from kelp while limiting the risk that the carbohydrate substances may be denatured.

Summary of the invention

According to a first aspect of the present invention there is provided a process for preparing of a composition, said process comprising:

preparing an aqueous solution of sodium citrate and citric acid; and

combining fresh kelp with said aqueous solution.

The ratio between the sodium citrate and citric acid in the aqueous solution may be about 10:1, by mass and the ingredients in the aqueous solution may be present in the following quantities, expressed as percentages of the mass of the kelp:

Water:	30%;
Sodium citrate:	3,3%; and
Citric acid:	0.33%

The process may include combining the kelp with one or more preservative, e.g. preservatives selected from gluconolactone, sodium benzoate, and a combination of ethylhexylglycerin and phenoxyethanol (Microcare® PHG), and the process may include combining the kelp with the preservatives in the following quantities, expressed as percentages of the mass of the kelp:

Gluconolactone:	0.9%;
sodium benzoate:	0.3%; and
Microcare PHG:	0.75%;

The process may include dissolving the preservatives in warm water and combining the solution with the kelp before combining the kelp with the aqueous solution of sodium citrate and citric acid. The combined mass of water in the aqueous solution of sodium citrate and citric acid and in the solution of preservatives in water, may be about 30% of the mass of the kelp.

The combination of the kelp and the aqueous solution of sodium citrate and citric acid, may be exposed to a rapid decrease in pressure, e.g. by exposing the combination to high pressure, which is released rapidly. Preferably, the

combination may be exposed to a pressure of about 600bar, followed by a rapid reduction to about atmospheric pressure.

The kelp may be in the form of comminuted kelp stipes.

According to another aspect of the present invention there is provided a composition prepared by a process as described herein above.

According to a further aspect of the present invention there is provided a composition comprising at least one pharmaceutically acceptable excipient and at least one of:

a. 4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine-1,3,6,8-tetraol;
b. 8-(2,4,6-trihydroxyphenoxy)-4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine -1,3,6-triol;
c. 8-(2,4,6-trihydroxyphenoxy)-9-(3,5-dihydroxyphenoxy)dibenzo [1,4]dioxine-1,3,6-triol; and
d. (8S,9S,10R, 13R,14S,17R)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-17-(R,E)-5-isopropylhept-5-en-2-yl)-10,13-demethyl-1H-cyclopenta[a]phenanthren-3-ol.

The pharmaceutically acceptable excipients may include at least one preservative selected from gluconolactone, sodium benzoate, and a combination of ethylhexylglycerin and phenoxyethanol (Microcare® PHG).

According to yet another aspect of the present invention there is provided a composition as described herein above, for use in a method of treatment of a mammalian subject by topical application of the composition on the subject's skin.

According to yet a further aspect of the present invention there is provided a method of treating a mammalian subject by topical application to the subject's skin, of a composition as described herein above.

The method of treatment may comprise soothing the subject's skin and/or treatment targeting a dermatological condition of the subject's skin, such as: inflammation, erythema, dermatitis, eczema, pruritus and psoriasis.

Detailed description of the invention

The present invention will now be illustrated, by way of non-limiting example.

Preparation process:

Fresh kelp of the specie Ecklonia maxima was harvested and processed to remove the fronds, float and holdfasts so that only the stipe remains. The stipes were comminuted by cutting them into smaller pieces and further processing them into a coarse paste.

The kelp was combined with various other substances/ingredients (in a process that is described below) and quantities and relative proportions of the substances are expressed in the table below. The kelp is the base ingredient and the proportions of all other ingredients are expressed in relation to the mass of the kelp.

Ingredients	Quantities	Proportions (w/w of kelp)
Kelp	100 kg	-
Filtered water	30 kg	30%
Sodium citrate	3.3 kg	3.3%
Citric Acid	0.330 kg	0.33%
Gluconolactone	0.900 kg	0.9%
Sodium benzoate	0.300 kg	0.3%
Microcare® PHG	0.750 kg	0.75%

Table 1: Typical quantities and proportions of the formulation

The formulation was used in a process to extract carbohydrate substances from the kelp, particularly to release the carbohydrate substances from the cell contents of the kelp in a systematic way.

As a first step of the process, the three preservative agents, gluconolactone, sodium benzoate and Microcare® PHG, were dissolved in slightly less than 50% of the water. The water used for the process was heated beyond ambient temperature, but well below temperatures known to denature polysaccharides, and thus the carbohydrate substances. Preferably, the gluconolactone and sodium benzoate were dissolved first in the warm water, where after the Microcare® PHG was added thereto and dissolved therein. For purposes of explanation, this aqueous solution of preservatives in water will be referred to herein as the "first mixture", although a person skilled in the art would appreciate that the process steps are not limited to the order in which they are described herein. The first mixture was allowed to cool down before it was used in a second step of the process.

In the second step, the first mixture was gradually added to (combined with) the kelp, while blending the kelp in a mixing tank. The gradual addition of the first mixture to the kelp was performed in a way to ensure complete blending of the ingredients. For purposes of explanation, this combination of the first mixture and the kelp will be referred to herein as the "second mixture".

In a third process step, the sodium citrate and citric acid were dissolved in the remainder of the warm water and for the purposes of explanation, this aqueous solution of sodium citrate and citric acid will be referred to herein as the "third mixture".

In a fourth process step, the third mixture was gradually added to (combined with) the second mixture, while blending the combination of in the mixing tank in a way to ensure complete blending of the mixtures. For the purpose of explanation, the resulting mixture will be referred to herein as the "reaction mixture".

Finally, the reaction mixture was left in the mixing tank, while operating the mixer over a period of time to allow the reaction mixture to blend, preferably between 30 minutes and 2 hours. Sufficient time was allowed for the insoluble alginic acid to be converted to soluble sodium alginate, which partly dissolved

the kelp cell walls, releasing the kelp cell contents (including the abovementioned carbohydrate substances).

The reaction mixture typically had a pH of between 5.1 and 5.3 and a viscosity of about 40,000 cP.

After the period of time allowed for the reaction mixture to blend, the reaction mixture was compressed to an elevated pressure of about 600bar, before being rapidly exposed to ambient pressure and the sudden pressure drop caused the kelp's cells to rupture and its cell content released from the cell structures into the reaction mixture. The reaction mixture became a fine homogenate composition with a viscosity of about 100,000 cP.

In commercial embodiments of the present invention, the homogenate composition can be combined with petrolatum or Shea Butter, if required.

Analyses:

Analyses of the homogenate yielded various substances, which included, amongst others, fucoidans, xylomannans, saponins and flavonoids. These substances have known health benefits including anti-inflammatory and anti-viral properties. However, the carbohydrate substances in the homogenate that have particular relevance for the purposes of the present invention include various phlorotannis and phytosterols, including:

a. a phlorotannin: 1,3,5-trihydroxybenzene (phloroglucinol);
b. a phlorotannin: 4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine-1,3,6,8-tetraol;
c. a phlorotannin: 8-(2,4,6-trihydroxyphenoxy)-4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine -1,3,6-triol;
d. a phlorotannin: 8-(2,4,6-trihydroxyphenoxy)-9-(3,5-dihydroxyphenoxy)dibenzo [1,4]dioxine-1,3,6-triol; and
e. a phytosterol: (8S,9S,10R, 13R,14S,17R)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-17-(R,E)-5-isopropylhept-5-en-2-yl)-10,13-demethyl-1H-cyclopenta[a]phenanthren-3-ol.

The new preparation process described herein allows for the extraction of carbohydrate substances from the kelp cells without any significant denaturation (if any) of the cell contents, with the result that compounds that may have been denatured by prior art extraction methods can now be released intact.

Clinical trials:

A cohort, clinical trial was conducted to assess the topical anti-inflammatory efficacy of the homogenate yielded by the final step of the process described above.

The trial was conducted in two groups, with three discrete product subgroups per group. The first group consisted of:

- a subgroup treated with the homogenate of the present invention, prepared as described above;
- a subgroup treated with a placebo cosmetic product, comprising solely of constituent excipients of the present invention; and
- a non-treated (control) subgroup.

The second group consisted of:

- a subgroup treated with hydrocortisone product in the form of Mylocort® cream;
- a subgroup treated with prednicarbate product in the form of Peitel® pomade; and
- a non-treated (control) subgroup.

The cohort consisted of 10 healthy human subjects, consisting of both males and females. The cohort parameters excluded subjects with existing dermatopathies, those currently on pharmacological treatment, and those who reported atopy in the anamnesis. The participants further undertook not to alter their usual daily routine whilst under treatment.

To assess the therapeutic efficacy of the homogenate, three distinct skin areas were identified on the forearm of each subject. Each of the three skin

areas was respectively treated with one of the three products in each group. Erythema, the superficial reddening of the skin caused by dilation of the blood capillaries – and common to many dermatological conditions, was used as a clinical marker to compare the efficacy of the associated treatments. For purposes of explanation, the term “redness” is used herein to refer to erythema, and any variation in the colour as an indication of the treatment efficacy. The erythema was quantified by Mexameter® MX 18.

The colour of the non-treated skin area was measured before the trial commenced, to assign a basal value of erythema. This is indicated as T0. Redness was induced on the treated skin areas with urea though the application of an occlusive patch for 24 hours. The treated skin areas were respectively treated with the homogenate-product and the cosmetic-product as part of group 1; and with the hydrocortisone-product and the prednicarbate-product as part of group 2. The redness was measure at times T0' (immediately after removing the occlusive patch and topical application of the substances), T15 (15 minutes after application of the substances), T30 (30 minutes after application of the substances), T1H (one hour after application of the substances), and T2H (two hours after application of the substances).

Group 1

Treatment	**T15**	**T30**	**T1H**	**T2H**
Homogenate	36,29%	76,07%	93,05%	97,41%
Cosmetic	4,22%	8,19%	23,94%	45,09%
Non treated (control)	5,29%	6,12%	18,76%	37,88%

Table 2: Average reduction of erythema, expressed as percentage, as clinical marker for efficacy of substances in the first group of the clinical trial

Table 2 shows the efficacy of the group 1 treatments to reduce erythema, relative to the redness of the skin area before the trial commenced (T0). The results show a 97% reduction in erythema, when the subject’s skin was treated with the homogenate of the present invention and this falls only 3%

short of completely restoring the colour of the skin area prior to irritation. The homogenate treatment shows a significant reduction of erythema over time, with an average reduction of 93% in 1 hour after treatment and an average reduction of 97% after 2 hours. This is contrasted by the comparably poor results of both the cosmetic treatment and non-treated area, which only showed an average reduction of 45% and 38% of erythema respectively over a time of 2 hours.

The experimental results of Table 2 are also shown in Figure 1 and the large area under the curve for the homogenate-product suggests its significant therapeutic effect relative to a placebo treatment.

Group 2

Treatment	**T15**	**T30**	**T1H**	**T2H**
Peitel® pomade	36,49%	75,54%	92,37%	95,38%
Mylocort® cream	87,52%	89,96%	92,70%	97,45%
Non treated (control)	6,68%	8,40%	19,23%	37,64%

Table 3: Average reduction of erythema, expressed as percentage, as clinical marker for efficacy of substances in the second group of the clinical trial

Table 3 and Figure 2 show the efficacy of the group 2 treatments to reduce erythema, relative to the redness of the skin area before the trial commenced (T0). The hydrocortisone treatment (Mylocort® cream) resulted in a significant reduction of erythema, and achieved an average reduction of 93% after 1 hour and an average reduction of 98% after 2 hours of treatment. The prednicarbate treatment (Peitel®; pomade) achieved an average reduction of 92% of erythema after 1 hour and an average reduction of 95% after 2 hours of treatment. The non-treated area only showed an average reduction 37% of erythema over a time of 2 hours.

Figure 3 compares the efficacy of the associated treatments. The hydrocortisone treatment brings about the greatest reduction in erythema in the shortest period of time, with an average reduction of 88% in 15 minutes.

The prednicarbate and the homogenate treatments follow a remarkably similar efficacy profile, with the only marked difference being that the homogenate-product achieves a greater average reduction of erythema (97%) after 2 hours than the prednicarbate-product (95%). Over a period of 2 hours, the associated treatments can be regarded as equivalent treatments.

A person skilled in the art will know that the cutaneous atrophy produced by topical steroid drugs is well documented. The effects of topical steroid drugs, especially glucocorticoids such as hydrocortisone and prednicarbate, on components of the inflammatory response include a change in the cellular activity of macrophages and monocytes, endothelial cells, basophils, fibroblasts and lymphocytes. Most notably, the down regulation of interleukin-1, a cytokine in macrophages and monocytes, and the inhibition of the mitotic activity of fibroblasts, result in cutaneous atrophy. Despite the marked anti-inflammatory action of the topical steroid drugs, its adverse side effects severely impact patients with a chronic need for topical relief of inflammation.

Kelp's anti-inflammatory action is at least partly due to its effects on the production of nitric oxide by cells involved in the inflammatory response. These effects do not interfere with either interleukin-1 or fibroblasts, therefore avoiding factors connected to natural skin growth and consequently cutaneous atrophy.

The homogenate-product therefore offers anti-inflammatory treatment with therapeutic efficacy that is comparable to that of topical steroid drugs over time, without the common adverse effects of associated treatments.

Claims

1. A process for preparing of a composition, said process comprising:
preparing an aqueous solution of sodium citrate and citric acid; and
combining fresh kelp with said aqueous solution.

2. A process according to claim 1, wherein the ratio between said sodium citrate and citric acid in the aqueous solution is about 10:1, by mass.

3. A process according to claim 2, wherein the ingredients in said aqueous solution are present in the following quantities, expressed as percentages of the mass of the kelp:

Water:	30%;
Sodium citrate:	3,3%; and
Citric acid:	0.33%

4. A process according to any one of the preceding claims, which includes combining the kelp with at least one preservative.

5. A process according to claim 4, wherein said at least one preservative is selected from: gluconolactone, sodium benzoate, ethylhexylglycerin and phenoxyethanol.

6. A process according to claim 4 or claim 5, which includes combining the kelp with the following preservatives in the following quantities, expressed as percentages of the mass of the kelp:

Gluconolactone:	0.9%;
Sodium benzoate:	0.3%; and
ethylhexylglycerin and phenoxyethanol:	0.75%.

7. A process according to any one of claims 4 to 6, which includes dissolving the preservatives in water and combining the solution with the kelp before combining the kelp with the aqueous solution of sodium citrate and citric acid .

8. A process according to claim 7, wherein the combined mass of water in the aqueous solution of sodium citrate and citric acid and in the solution of preservatives in water, is about 30% of the mass of the kelp.

9. A process according to any one of the preceding claims, in which the combination of the kelp and the aqueous solution of sodium citrate and citric acid, is exposed to a rapid decrease in pressure.

10. A process according to claim 9, wherein said combination is exposed to high pressure, which is released rapidly.

11. A process as claimed in claim 9 or claim 10, in which the combination is exposed to a pressure of about 600bar, followed by a rapid reduction to about atmospheric pressure.

12. A process according to any one of the preceding claims, in which the kelp comprises comminuted kelp stipes.

13. A composition prepared by a process according to any one of the preceding claims.

14. A composition comprising at least one pharmaceutically acceptable excipient and at least one of:
    a. 4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine-1,3,6,8-tetraol;
    b. 8-(2,4,6-trihydroxyphenoxy)-4-(3,5-dihydroxyphenoxy)dibenzo [b,e][1,4]dioxine -1,3,6-triol;
    c. 8-(2,4,6-trihydroxyphenoxy)-9-(3,5-dihydroxyphenoxy)dibenzo [1,4]dioxine-1,3,6-triol; and
    d. (8S,9S,10R, 13R,14S,17R)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-17-(R,E)-5-isopropylhept-5-en-2-yl)-10,13-demethyl-1H-cyclopenta[a]phenanthren-3-ol.

15. A composition according to claim 14, in which the pharmaceutically acceptable excipients include at least one preservative selected from: gluconolactone, sodium benzoate, ethylhexylglycerin and phenoxyethanol.

16. A composition according to any one of claims 13 to 15 for use in a method of treatment of a mammalian subject by topical application of said composition on the subject's skin.

17. A composition for use in a method of treatment according to claim 16, wherein said method of treatment comprises soothing said subject's skin.

18. A composition for use in a method of treatment according to claim 16 or claim 17, wherein said method of treatment targets a dermatological condition of said subject's skin.

19. A composition for use in a method of treatment according to claim 18, wherein said dermatological condition includes at least one of: inflammation, erythema, dermatitis, eczema, pruritus and psoriasis.

20. A method of treating a mammalian subject by topical application to said subject's skin, of a composition according to any one of claims 13 to 15.

21. A method according to claim 20, which comprises soothing said subject's skin.

22. A method according to claim 20 or claim 21, which targets a dermatological condition of said subject's skin.

23. A method according to claim 22, wherein said dermatological condition includes at least one of: inflammation, erythema, dermatitis, eczema, pruritus and psoriasis.

24. A process for preparing a composition according to any one of claims 1 to 12, substantially as herein described with reference to the examples.

25. A composition according to any one of claims 13 to 16, substantially as herein described with reference to the examples.

26. A composition for us in a method of treatment according to any one of claims 17 to 19, substantially as herein described with reference to the examples.

27. A method of treatment according to any one of claims 20 to 23, substantially as herein described with reference to the examples.

FIGURE 1

FIRST GROUP'S TREATMENT EFFICACY

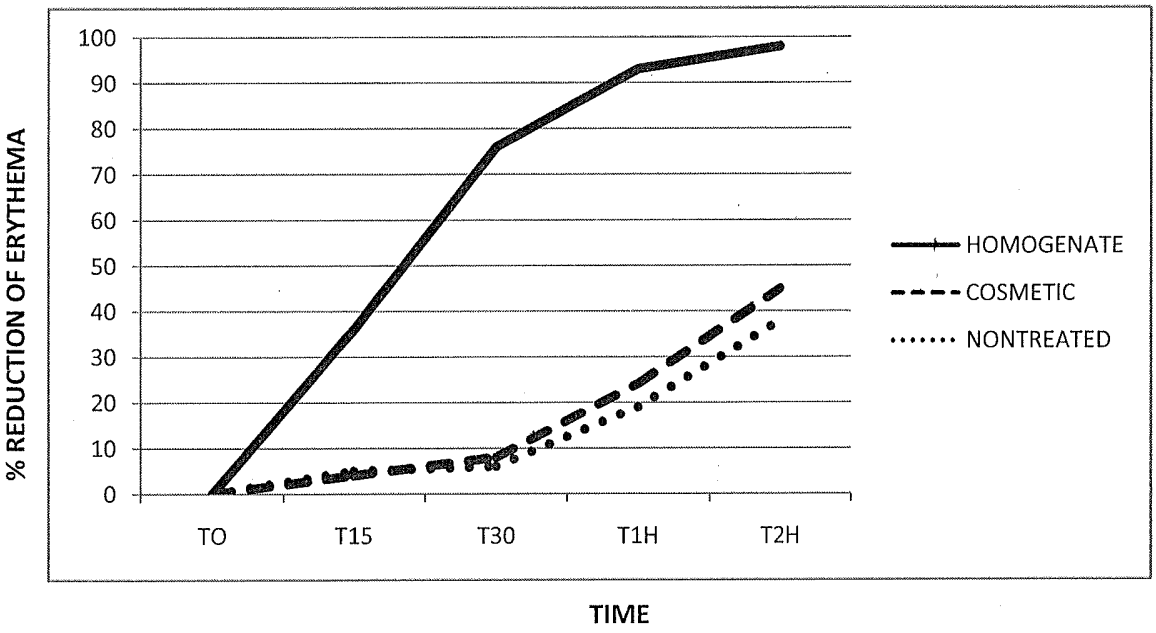


FIGURE 2

SECOND GROUP'S TREATMENT EFFICACY

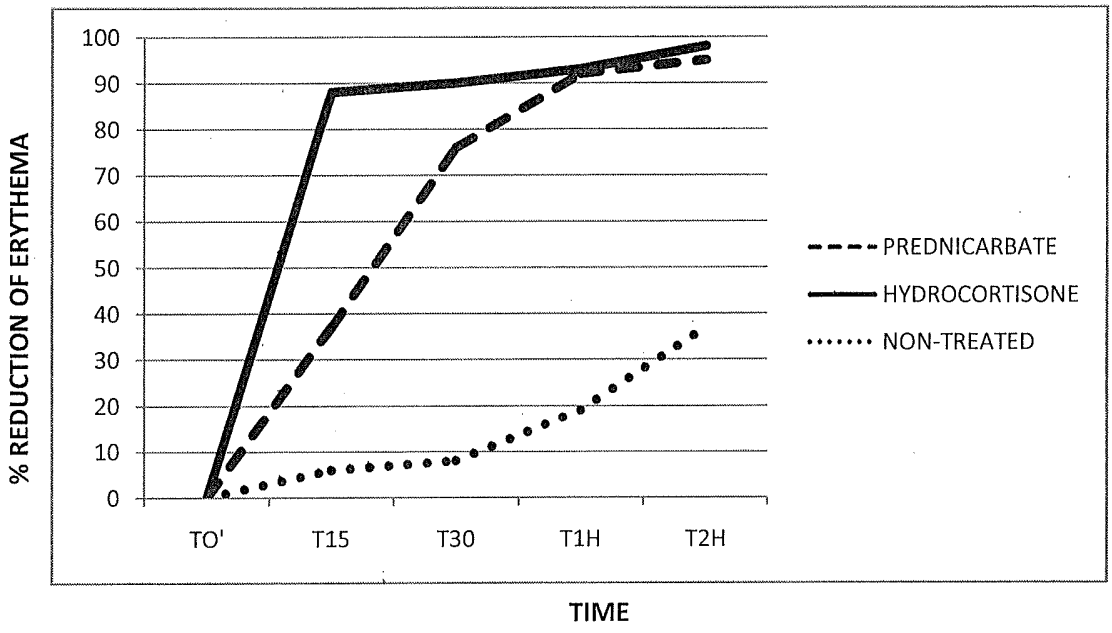
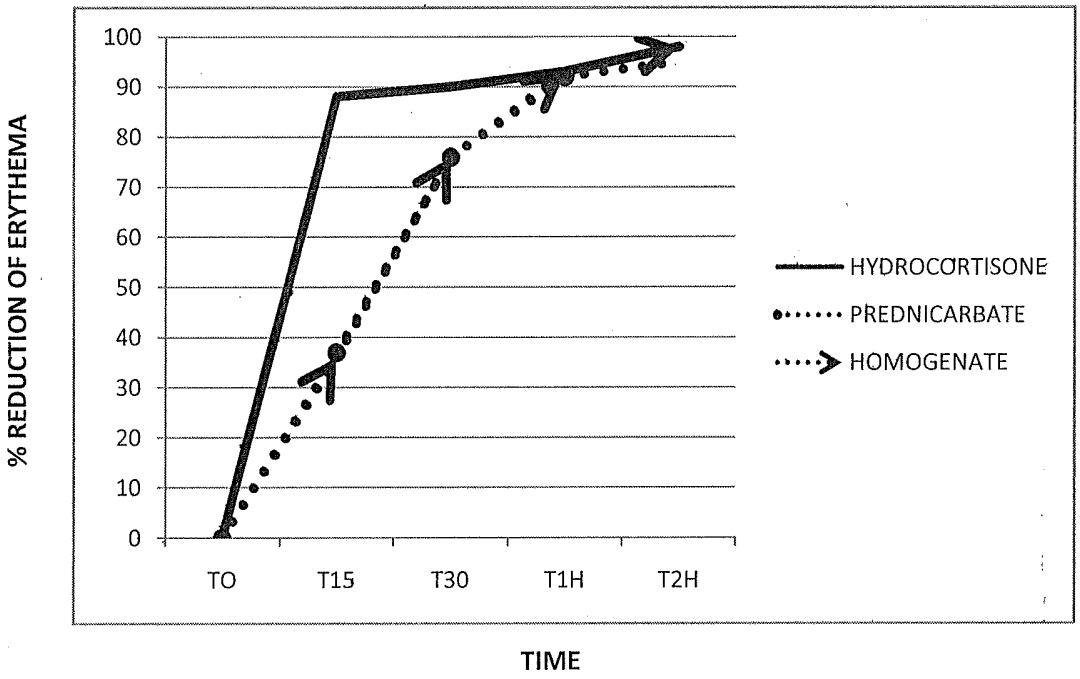


FIGURE 3
COMPARABLE EFFICACIES OF ASSOCATED TREATMENTS



INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/059294

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/03 A61K31/05 A61K31/357 A61K31/56 A61P17/00 A61K9/00
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 A61P

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, 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	DATABASE WPI Week 201374 Thomson Scientific, London, GB; AN 2013-U43125 XP002723482, & CN 102 715 495 A (TIANJIN CHUNSHENG ISLAMIC FOODS CO LTD) 10 October 2012 (2012-10-10) abstract ----- DATABASE WPI Week 200445 Thomson Scientific, London, GB; AN 2004-472328 XP002723483, & JP 2004 180653 A (SEAFOOD SUTERA KK) 2 July 2004 (2004-07-02) abstract ----- -/--	1-15, 24-27 1-15, 24-27

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

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
23 April 2014	08/05/2014

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/059294

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOEL VINAY THOMAS ET AL: "Potential pharmacological applications of polyphenolic derivatives from marine brown algae", ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY, ELSEVIER, AMSTERDAM, NL, vol. 32, no. 3, 2 September 2011 (2011-09-02), pages 325-335, XP028318554, ISSN: 1382-6689, DOI: 10.1016/J.ETAP.2011.09.004 [retrieved on 2011-09-17] the whole document ----	16-23
X	WIJESINGHE W A J P ET AL: "Exploiting biological activities of brown seaweed Ecklonia cava for potential industrial applications: a review", INTERNATIONAL JOURNAL OF FOOD SCIENCES AND NUTRITION, UK, vol. 63, no. 2, 1 March 2012 (2012-03-01), pages 225-235, XP009177655, ISSN: 1465-3478 the whole document ----	16-23
X	JOE MIN-JEONG ET AL: "The inhibitory effects of eckol and dieckol from Ecklonia stolonifera on the expression of matrix metalloproteinase-1 in human dermal fibroblasts", BIOLOGICAL & PHARMACEUTICAL BULLETIN, vol. 29, no. 8, August 2006 (2006-08), pages 1735-1739, XP002723484, ISSN: 0918-6158 figure 3; table 1 ----	16-23
X	NOEL THOMAS ET AL: "Beneficial Effects of Marine Algal Compounds in Cosmeceuticals", MARINE DRUGS, vol. 11, no. 1, 14 January 2013 (2013-01-14), pages 146-164, XP055114664, DOI: 10.3390/md11010146 abstract; figures 5,6 ----	16-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2014/059294

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 102715495 A	10-10-2012	NONE	
JP 2004180653 A	02-07-2004	NONE	