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(54) Benævnelse: **KOSMETISK SAMMENSÆTNING TIL FORYNGELSE AF HUDEN**

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DESCRIPTION

Technical sector of the invention

[0001] This invention relates to a cosmetic composition for rejuvenating the skin ("antiaging") containing retinaldehyde or, generally, a retinoic acid precursor as listed in claim 1. The invention also relates to a method for rejuvenating the skin, and to some uses of the compositions according to the invention.

Background of the invention

[0002] For several years now, retinoic acid, or acidic forms of vitamin A, has been used to treat a variety of skin affections, for example, aging, acne, wrinkles, psoriasis, age blemishes and discolouring. See for example, 1) Vahlquist, A. and col., J. Invest. zermatol., Vol. 94, Holland D. B. and Cunliffe, W. J. (1990), pag. 496-498; Ellis, C. N. and col., "Pharmacology of Retinols in Skin", Vasel, Karger, Vol. 3, (1989), pag. 249-252; Lowe, N. J. and col., "Pharmacology of Retinols in Skin", Vol. 3, (1989), pag. 240-248; 2) Fourie, Stephanus Petrus 'Dermatological preparation'. CHEMICAL ABSTRACTS, vol. 90, no. 12, 19 March 1979, Columbus, Ohio, US; abstract no. 92433; 3) Kligman, AM, "Guidelines for the use of topical tretinoin (Retin-A) for photoaged skin", J Am. Acad. Dermatol. 1989; 21:650-4; 4) Kligman and col., "Topical tretionoin for photoaged skin", J Am. Acad. Dermatol. 1986; 15:836-59.

[0003] The documents of patents US 3.856.934, 2. WO2009/037093, WO98/55075 WO 93/19743, US 5.998.395, GB-A 906.000, FR 2.785.185 and US 6.319.957 describe dermatological or cosmetic uses of retinoic acid forms. The latter two describe formulae that contain retinoic acid and US 6.319.957 describes a cosmetic formula that also includes an anti-inflammatory substance.

[0004] Document US 6.319.957 defines a composition comprising retinoic acid, a corticoid, and hydroquinone. As hydroquinone is a substance that is being contraindicated or even prohibited in some countries, hydroquinone must be replaced with a technical equivalent thereof, insofar as its anti-pigmenting function is concerned.

[0005] The above formulae are not without their drawbacks, consisting mainly in the fact that their therapeutic effect is very variable and unpredictable. According to these inventors, the variability is to a large degree due to the metabolic differences of the patients treated.

[0006] It is known that oxidative stress caused by the reactive oxygen species (ROS) that are produced in the skin, causes aggravated ageing and undesirable atypical pigmentation. Also, the reactive oxygen species induce specific cell signalling cascades that will have disastrous effects on the tissue structure measured by the development of an important inflammatory

response.

[0007] Therefore, to block the undesired effects of oxidative stress, it is important to block both the ROS that are produced and also the associated inflammatory response. All with the aim of stopping the tissue deterioration and improving the skin structure.

[0008] With this objective, patent document US 20110262373 describes a treatment that effectively blocks both processes by using retinoic acid combined with different anti-oxidants. This combination not only counteracts the ROS produced but also will block the inflammatory response. Patent US 20110262373 describes an antiaging medicine that is based on retinoic acid with medical effects, associated synergistically with at least an anti-inflammatory (indometacin), anti-oxidants and vitamins, with or without hyaluronic acid.

[0009] Patent US 20110262373 provides a formula of a medical substance, and not simply cosmetic, that provides a solution to the above-explained problem, and is equally effective irrespective of the particular characteristics of the subject patients Despite the synergy of the components, which allows lowering the toxicity to low levels, this medicine is not completely free of irritative effects, because in short it is a medical substance.

[0010] It has been considered that it would be interesting to be able to lower the toxicity or aggression to cosmetic and not medical levels, using a percusor of retinoic acid, like retinaldehyde or other percusors, used in cosmetic proportions, but this has not been put into practice, to date, since there are two obstacles:

- the potential step of retinaldehyde to retinoic acid, which can lead to the same drawbacks already highlighted, and
- that the therapeutic effect is very reduced with respect to US 20110262373.

[0011] Patent EP 1.689.356 by Pierre Fabre Dermo-Cosmétique, describes compositions aimed at the topical application, comprising as active ingredient fragments of sodium hyaluronate (with a molecular weight between 50,000 and 750,000 Da) and retinal, but it is not clear that this provides a solution to the above-mentioned problems. Also, it is possible that it enhances them. But the hyaluronate is a salt and not an acid, although one can be obtained from the other. It does not describe whether hyaluronic acid is included in the combination. Also on the market cosmetic anti-wrinkle or antiaging creams are known by the same previous owner, which contain a mixture of retinaldehyde and hyaluronic acid.

[0012] However neither patent EP 1.689.356 or the cosmetic anti-wrinkle or antiaging creams indicated above have the effectiveness of the retinoic acid based medicine, q.v. that described in US 20110262373. The drawback of the medicines with respect to the cosmetic products is their higher potential of producing a toxic effect, normally due to the greater proportion of medical active ingredients.

[0013] The aim of this invention is a cosmetic antiaging product that has the effectiveness of a pharmaceutical product, but which is exempt of its irritative or toxic effects.

Explanation of the invention

[0014] For this, the inventors have created a new cream which essentially is characterized by variable proportions of between 0.01 % and 0.5% by weight with respect to the total weight of the composition of a retinoic acid precursor, as defined in the appended claims, and between 0.05 % and 5% by weight with respect to the total weight of the composition of melatonin.

[0015] Preferably, the retinoic acid precursor is retinaldehyde. Alternatively, it can be retinol or retinyl esters, e.g. retinyl retinoate, in a proportion between 0.01 and 0.5% by weight with respect to the total weight of the composition. In this description and claims all the % are % by weight with respect to the total weight of the composition.

[0016] Preferably, the proportion of retinaldehyde is between 0.05% and 0.1% by weight with respect to the total weight of the composition.

[0017] The melatonin is included preferably in a proportion between 0.05 and 5% by weight with respect to the total weight of the composition, and preferably between 0.5 and 1%.

[0018] In the preferred embodiment, the composition includes also at least one anti-inflammatory other than melatonin, an anti-oxidant other than melatonin and/or a vitamin. Preferably the anti-inflammatory other than melatonin is an anti-inflammatory from the group made up of liquorice extract, aloe vera, alpha-bisabolol, azulene, glycyrrhetic acid and rosmarinum oficinalis extract and, more preferably, it is from the group made up of aloe vera and liquorice extract.

[0019] In an advantageous cosmetic formula it is proposed to associate 3 activities possessed by three groups of substances which together with the retinaldehyde obtain an antiaging action of this substance higher than that obtained on its own or with other groups of substances with another activity.

[0020] The cosmetic formula is made up of retinaldehyde as the essential substance, always in association with melatonin, an anti-oxidant that enhances the action of retinaldehyde, and preferably from the following groups of substances which, given the synergistic effect of this activity, enhance the antiaging action of retinaldehyde:

1st Group: substance with antiaging action: retinaldehyde (aldehydic form of retinol used in cosmetics) + melatonin

2nd Group: substances with anti-inflammatory action authorized for use in cosmetics.

3rd Group: Substances with anti-oxidant action authorized for use is cosmetics.
It may happen that part of the retinaldehyde metabolises by oxidation to retinoic acid, due to the action of retinaldehyde dehydrogenase, with the actual retinaldehyde acting as anti-oxidant and that the retinoic acid acts also, as in patent US 20110262373, synergyzing with PPAR-γ which blocks the inflammatory response. However this oxidation and action are produced always inside the keratinocyte.

4th Group: vitamins authorized for use in cosmetics.

[0021] For example, the actual retinaldehyde is already the aldehydic form of vitamin A.

[0022] The preferred anti-oxidants are Green tea extract, resveratrol and elagic acid.

[0023] Also it has been envisaged to include in the formula an activator of PPAR-α, PPAR-β and/or PPAR-γ, other than retinaldehyde, such as for example aloe vera, Green tea, resveratrol, lipoic acid, pyncogenol, L-carnosine, taurine, isoflavones and/or Vitamin E.

[0024] The melatonin or N-acetyl-5-methoxytriptamine is a hormone present in superior animals and in some algae, in concentrations that vary according to the daytime/night-time cycle. Melatonin is produced in the pineal gland and synthesized from the neurotransmisor serotonine.

[0025] The melatonin in the skin has the function of eliminating the free radicals; it increases the enzymes responsible for metabolising the free radicals and is also capable of oxidising itself to eliminate them without producing a redox cycle, and thus it has been called a suicide anti-oxidant.

[0026] The inventors have found that melatonin in the indicated proportions enhances the effect of retinaldehyde in blocking the harmful effects of oxidative stress.

[0027] As an advantage, this association of components enhances the action of retinaldehyde, and the composition is not irritant.

Brief description of the drawings

[0028] Other advantages and characteristics of the invention will be appreciated from the following description, wherein, in a non-limiting manner, some preferable embodiments of the invention are described, with reference to the accompanying drawings, wherein:

Fig. 1, evolution of the pores in the skin on the face in a group of people treated with a composition according to the invention.

Fig. 2, evolution of the elasticity of the cheek skin in the group in Fig. 1.

Fig. 3, evolution of the elasticity of the forehead skin in the group in Fig. 1.

Fig. 4, evolution of the bacterial activity in the skin on the face in the group in Fig. 1.

Fig. 5, evolution of the fine wrinkles on the skin on the face in the group in Fig. 1.

Fig. 6, evolution of the hyperpigmentations in the skin on the face in the group in Fig. 1.

Description of some embodiments of the invention

[0029] The inventors formulated and tested a first basic cosmetic composition for rejuvenating the skin ("antiaging") that contained as active ingredients (percentages by weight):

- Retinaldehyde 0.075%
- Melatonin 0.75%

together with suitable excipients.

[0030] The results were similar to those obtained with medical compositions (non cosmetic) based on retinoic acid.

[0031] A second basic cosmetic composition was formulated and tested, identical to the first, but adding 1% of resveratrol as anti-oxidant:

- Retinaldehyde 0.075%
- Melatonin 0.75%
- Resveratrol 1.00%

[0032] The results improved, mainly regarding the pigmentation, apparently enhancing the blocking of the undesirable effects of oxidative stress, since less tissue deterioration was noticed and the dermal structure improved.

[0033] A third basic cosmetic composition was formulated and tested, identical to the second, but adding 2% of Green tea as an additional anti-oxidant:

- Retinaldehyde 0.075%
- Melatonin 0.75%
- Resveratrol 1.00%
- Green tea 2.00%

[0034] The results improved with respect to the previous basic formulae.

[0035] Finally, a fourth basic cosmetic composition was formulated and tested, identical to the first, but adding 5% of aloe vera as an anti-inflammatory:

- Retinaldehyde 0.075%
- Melatonin 0.75%
- Resveratrol 1.00%
- Green tea 2.00%
- Aloe vera 5.00%

[0036] Adding aloe vera makes the anti-inflammatory results improve, they are obtained more quickly and toxicity is less.

[0037] Probably a factor favouring the synergy is that both the Green tea, and the resveratrol act by improving the activation of the PPAR-γ, and also by favouring that of the actual retinaldehyde.

[0038] Clearly a synergistic action is observed between the components indicated as they are added to the basic composition of retinaldehyde and melatonin. The results are being analysed statistically to quantitatively assess the forms individually and the incremental action of each basic formula with respect to the previous one. In every case, the irritation induced is much less than that induced by similar compositions but with retinoic acid.

[0039] See the following Table I, summarising the above.

Table I

		Basic cosmetic composition No.			
	Function	1	2	3	4
Retinaldehyde	Ingredient	0,08%	0,075%	0,08%	0,075%
Melatonin	Ingredient	0.75%	0.75%	0.75%	0.75%
Resveratrol	Anti-oxidant	-	1.00%	1.00%	1.00%
Green tea	Anti-oxidant	-	-	2.00%	2.00%
Aloe vera	Anti-inflammatory	-	-	-	5.00%

[0040] These four basic cosmetic compositions and their possible variants (with additional components) are suitable for use in a method for rejuvenating the skin through the topical application of them.

[0041] According to the MASI (MAS1, 2, 3, 4, 5 or 6) skin pigmentation index, six corresponding families of components have been formulated.

[0042] The MAS Index (acronym of the expression in English *"Melasma Area and Severity Index*"), is an index used in dermatology and cosmetics to diagnose the severity and the area affected by melasma (or "cloasma"). Melasma is facial hyperpigmentation acquired reoccurringly that is due to the hyperfunction of the melanocytes. The associated factors are internal (UV radiation, infra-red rays, mechanical trauma or friction, psoralens of cosmetics, perfumes, lotions and creams, etc.) and endogenous such as sex, age, colour of skin (phototype III to V), genetic predisposition (cross-breeding), hormonal factors like pregnancy, oral anti-contraceptives, suprarenal and thyroid suffering, etc.). In turn, from each of these six families a specific topical cream has been prepared, that is reflected in the examples.

Examples

[0043] Some preferred compositions are described below, as well as some specific embodiments, that are specific cases of the four basic cosmetic compositions explained above. Each of them is particularly suitable for use in a method for rejuvenating the skin through the topical application of them, preferably in the specific cases of the MASI index indicated in each table.

MASI 1 (MASI < 10%)	Composition	Example 1
Retinaldehyde	0.05-0.1%	0,075%
Melatonin	0.5 - 1%	0.75%
Glycyrrhetic acid	0.5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%
Kojic acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%

MASI 2 (10 ≤ MASI < 30)	Composition	Example 2
Retinaldehyde	0.05-0.1%	0,08%
Melatonin	0.5 - 1%	0.75%
Gycyrrhetic acid	0.5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%
Kojic acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%

MASI 2 (10 ≤ MASI < 30)	Composition	Example 2
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%
Resveratrol	0.5 - 1.5%	1%
MASI 3 (30 ≤ MASI < 50)	Composition	Example 3
Retinaldehyde	0.05-0,1%	0,08%
Melatonin	0.5 - 1%	0.75%
Glycyrrhetic acid	0,5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%
Kojic Acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%
Resveratrol	0.5 - 1.5%	1%
Green tea	1 - 3%	2%
MASI 4 (50 ≤ MASI < 70)	Composition	Example 4
Retinaldehyde	0.05-0,1%	0,08%
Melatonin	0.5 - 1%	0.75%
Glycyrrhetic acid	0.5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%
Kojic acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%
Resveratrol	0.5 - 1.5%	1%
Green tea	1 - 3%	2%
Hyaluronic acid	0.5 - 1%	0.75%
MASI 5 (70 ≤ MASI < 90)	Composition	Example 5
Retinaldehyde	0.05-0.1%	0,075%
Melatonin	0,5 - 1%	0.75%
Glycyrrhetic acid	0,5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%

MASI 5 (70 ≤ MASI < 90)	Composition	Example 5
Kojic acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%
Resveratrol	0.5 - 1.5%	1%
Green tea	1 - 3%	2%
Hyaluronic acid	0.5 - 1%	0.75%
Glutamine	0.5 - 1.5%	1%
Grenadine extract	2 - 4%	3%

MASI 6 (MASI ≥ 90)	Composition	Example 6
Retinaldehyde	0.05-0.1%	0,075%
Melatonin	0.5 - 1%	0.75%
Glycyrrhetic acid	0.5 - 1%	0.75%
Aloe vera	4 - 6%	5%
Snail slime	5 - 10%	7.5%
Kojic acid	1 - 2%	1.5%
Stabilised vitamin C	1.5 - 2.5%	2%
Vitamin E	0.3 - 0.5%	0.4%
Niacinamide	1.5 - 2.5%	2%
Resveratrol	0.5 - 1.5%	1%
Green tea	1 - 3%	2%
Hyaluronic acid	0.5 - 1%	0.75%
Glutamine	0.5 - 1.5%	1%
Grenadine extract	2 - 4%	3%
N-Acetylglucosamine	1 - 3%	2%

[0044] Retinaldehyde is a precursor of retinoic acid, but only produces the oxidative step of aldehyde to acid through the intervention of a cytoplasmatic enzyme. Therefore, to the formula of this invention, which contains the precursor, preferably anti-oxidants will be added not to prevent the step into an acid but to prevent its degradation. The anti-oxidant can be the same as for patent US 20110262373. The step to acid will then be in the skin cells and the formula does not contain anything that accelerates or delays this step.

[0045] Retinaldehyde blocks the undesired effects of aging by the reactive oxygen species and synergies with the PPAR-γ that blocks the inflammatory response. The PPAR-γ is activated by the aloe vera, which also behaves as moisturiser or skin regenerator-revitaliser.

[0046] Melatonin acts as an eliminator of the free radicals and as an anti-oxidant.

[0047] As for the different active ingredients that are added, the depigmentation and anti-oxidant strength increases by combining anti-oxidants (resveratrol+Green tea), with the aloe vera (anti-inflammatory) and the hyaluronic acid (molecule that penetrates the skin acts as "filler" moisturising the deeper layers).

[0048] In all the antiaging compositions formulated according to this invention, the irritation induced is much lower than that induced by similar compositions but with retinoic acid, and the therapeutic effects are very similar.

[0049] It is important to highlight that within the scope of protection of the invention, it is important to understand that retinaldehyde can be replaced by its technical equivalents. The inventors understand that the function of retinaldehyde is like the retinoic acid precursor, and therefore its technical equivalents are other precursors like for example retinol, retinyl retinoate or retinyl esters.

[0050] The precursors of retinoic acid provide a very similar therapeutic effect but without its irritative effects, and, in different degrees, increase stability and reduce photosensitivity.

[0051] The compositions of the examples can be completed with variable amounts of other substances, to adapt the formulae to the different degrees of the skin's humidity, and water.

Application example:

[0052] A group of 18 people has used a cosmetic composition according to the invention. Their age was between 30 and 80 years old (30-40 years old: 6 people; 40-50 years old: 4 people; 50-60 years old: 3 people; >60 years old: 5 people) (16 women and 2 men).

[0053] The composition was applied to 2 areas of the face: [a] on the forehead, specifically on the cross between the horizontal middle line of the forehead and the vertical middle line between eyebrow arches and the start of the scalp, and [b] on the cheeks, specifically on the cross between the horizontal line of the end of the nasal wing to the ear and the vertical line passing through the middle line of the eye.

[0054] The application time was between 2-6 months, on average 3 months.

[0055] Formulae with some differences were applied to these people. In general, the formulae used are within the following intervals:

Retinaldehyde	0.05%-0.1%
Indometacine	2%-3%

Hydroquinone	2%-5%
Sodium bisulphite	0.05%
Kojic acid	2-5%
Arbutine	2-4%
Acetate tocopherol (vit.E)	2-5%
Vitamin C	2-5%
Melatonine	0.1%

[0056] It can be considered that the composition applied in these assays is:

Retinaldehyde	0.1%
Indometacine	3%
Hydroquinone	5%
Kojic acid	3%
Arbutine	4%
Acetate tocopherol	3%
Vitamin C	3%
Melatonine	0.1%

[0057] Various parameters have been analysed before and after the treatment. The results are shown in Figs. 1 to 6. A reduction in the pores is observed, and in the bacterial activity, in the fine wrinkles, and in the hyperpigmentations, and an increase in the skin's elasticity both on the cheek and on the forehead.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US3856934A **[0003]**
- WO2009037093A **[0003]**
- WO9855075A **[0003]**

- WO9319743A [0003]
- US5998395A [0003]
- GB906000A [0003]
- FR2785185 [0003]
- US6319957B [0003] [0003] [0004]
- US20110262373A [0008] [0008] [0009] [0010] [0012] [0020] [0044]
- EP1689356A [0011] [0012]

Non-patent literature cited in the description

- **VAHLQUIST, A.**J. Invest. zermatol.19900000vol. 94, 496-498 [0002]
- **ELLIS, C. N.**Pharmacology of Retinols in SkinKarger19890000vol. 3, 249-252 [0002]
- **LOWE, N. J.**Pharmacology of Retinols in Skin, 1989, vol. 3, 240-248 [0002]
- **FOURIESTEPHANUS PETRUS**Dermatological preparationCHEMICAL ABSTRACTS, 1979, vol. 90, 12 [0002]
- **KLIGMAN, AM**Guidelines for the use of topical tretinoin (Retin-A) for photoaged skinJ Am. Acad. Dermatol., 1989, vol. 21, 650-4 [0002]
- **KLIGMANT**opical tretionoin for photoaged skinJ Am. Acad. Dermatol., 1986, vol. 15, 836-59 [0002]

Patentkrav

1. Kosmetisk sammensætning til foryngelse af huden, **kendetegnet ved, at** det omfatter:

- mellem 0,01 og 0,5 vægtprocent i forhold til sammensætningens samlede vægt af en prækursor for retinolsyre fra gruppen bestående af retinaldehyd, retinol, retinylretinoat og retinylestere, og

- mellem 0,05 og 5 vægtprocent i forhold til sammensætningens samlede vægt af melatonin.

2. Kosmetisk sammensætning ifølge krav 1, **kendetegnet ved, at** det omfatter mellem 0,05 og 0,1 vægtprocent i forhold til sammensætningens samlede vægt af retinaldehyd.

3. Kosmetisk sammensætning ifølge krav 1 eller 2, **kendetegnet ved, at** det endvidere omfatter mindst ét antiinflammatorisk middel ud over melatonin, fortrinsvis fra gruppen bestående af lakridsekstrakt, alpha-bisabolol, azulen, glycyrrhetinsyre, aloe vera-ekstrakt og rosmarinum oficinalis-ekstrakt.

4. Kosmetisk sammensætning ifølge krav 1 til 3, **kendetegnet ved, at** det endvidere omfatter mindst én antioxidant ud over melatonin, fortrinsvis fra gruppen bestående af grøn te-ekstrakt, resveratrol og ellaginsyre.

5. Kosmetisk sammensætning ifølge krav 1 til 4, **kendetegnet ved, at** det omfatter mindst ét vitamin, fortrinsvis fra gruppen bestående af E-vitamin og C-vitamin.

6. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 5, **kendetegnet ved, at** det omfatter en aktivator af PPAR-α, PPAR-β og PPAR-γ ud over retinaldehyd, fortrinsvis fra gruppen bestående af: aloe vera, grøn te, resveratrol,

lipoinsyre, pycnogenol, L-carnosin, taurin, isoflavoner og E-vitamin.

7. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 6, **kendetegnet ved, at** det omfatter et hudrevitaliserende fugtgivende element, fortrinsvis aloe vera.

8. Kosmetisk sammensætning ifølge et af de foregående krav, **kendetegnet ved, at** det også omfatter hyaluronsyre og/eller niacinamid.

9. Kosmetisk sammensætning ifølge et af de foregående krav, **kendetegnet ved, at** det også omfatter et eller flere depigmenteringselementer, fortrinsvis fra gruppen bestående af kojisyre, fytinsyre og arbutin.

10. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,075 %
Melatonin	0,75 %

11. Kosmetikpræparat ifølge krav 10, **kendetegnet ved, at** det endvidere omfatter

Resveratrol	1,00 %
og/eller	
Grøn te	2,00 %
og/eller	
Aloe vera	5,00 %

12. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %

13. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %
Resveratrol	0,5-1,5 %

14. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %
Resveratrol	0,5-1,5 %
Grøn te	1-3 %

15. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %
Resveratrol	0,5-1,5 %
Grøn te	1-3 %
Hyaluronsyre	0,5-1 %

16. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

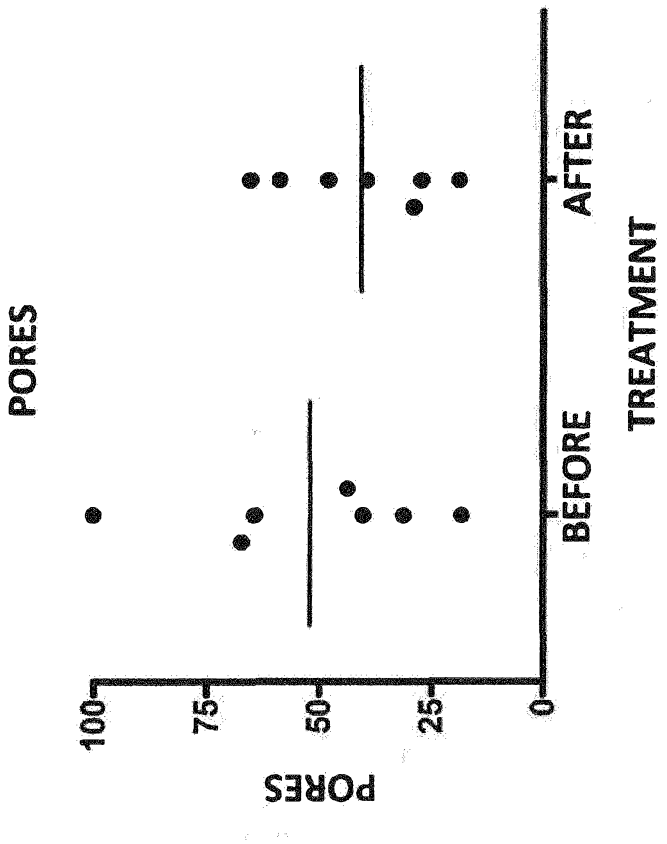
Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %
Resveratrol	0,5-1,5 %
Grøn te	1-3 %
Hyaluronsyre	0,5-1 %
Glutamin	0,5-1,5 %
Grenadineekstrakt	2-4 %

17. Kosmetisk sammensætning ifølge et hvilket som helst af kravene 1 til 9, **kendetegnet ved, at** det omfatter:

Retinaldehyd	0,05-0,1 %
Melatonin	0,5-1 %
Glycyrrhetinsyre	0,5-1 %
Aloe vera	4-6 %
Snegleslim	5-10 %
Kojisyre	1-2 %
Stabiliseret C-vitamin	1,5-2,5 %
E-vitamin	0,3-0,5 %
Niacinamid	1,5-2,5 %

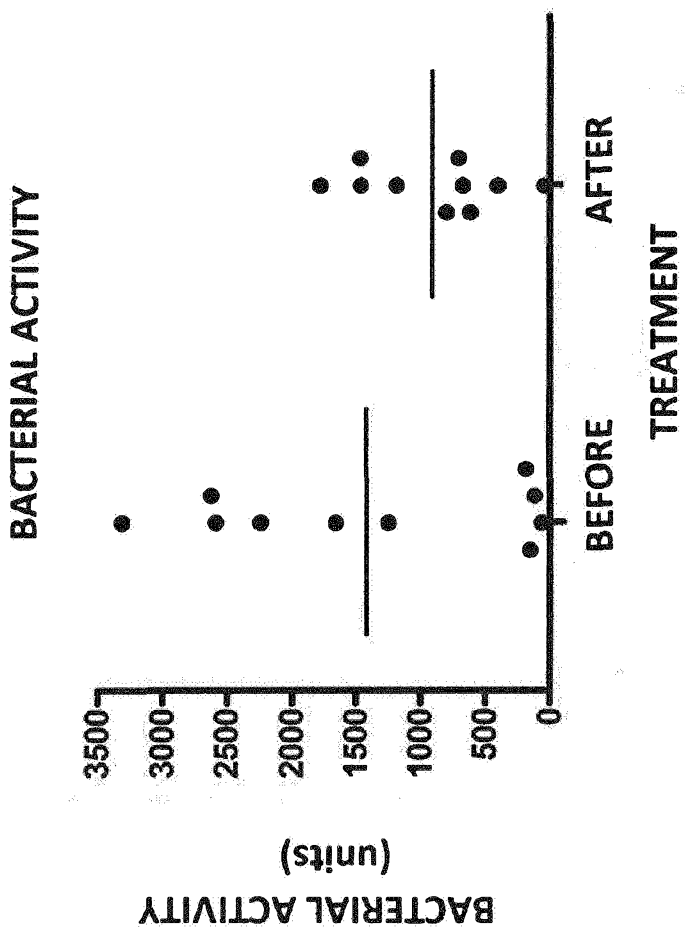
Resveratrol	0,5-1,5 %
Grøn te	1-3 %
Hyaluronsyre	0,5-1 %
Glutamin	0,5-1,5 %
Grenadineekstrakt	2-4 %
Acetylglucosamin	1-3 %

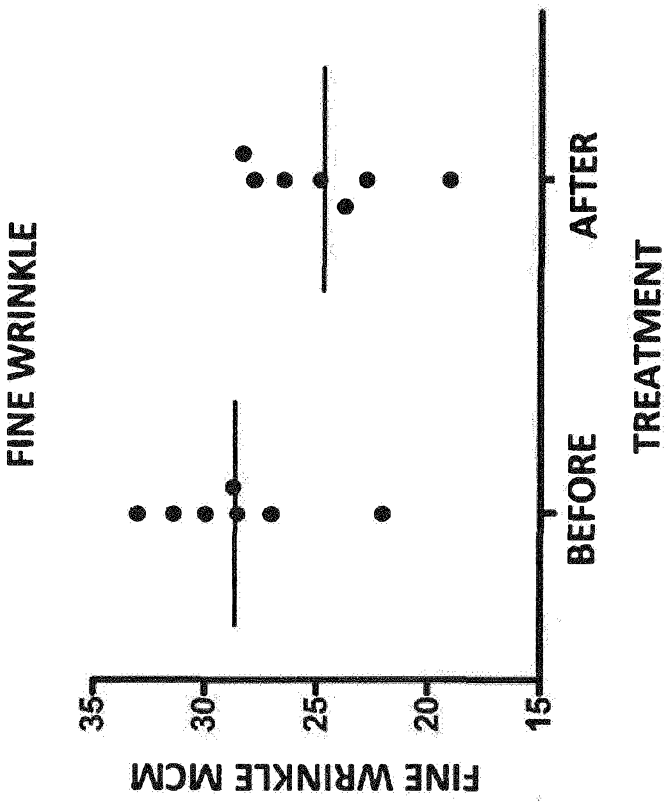
DRAWINGS

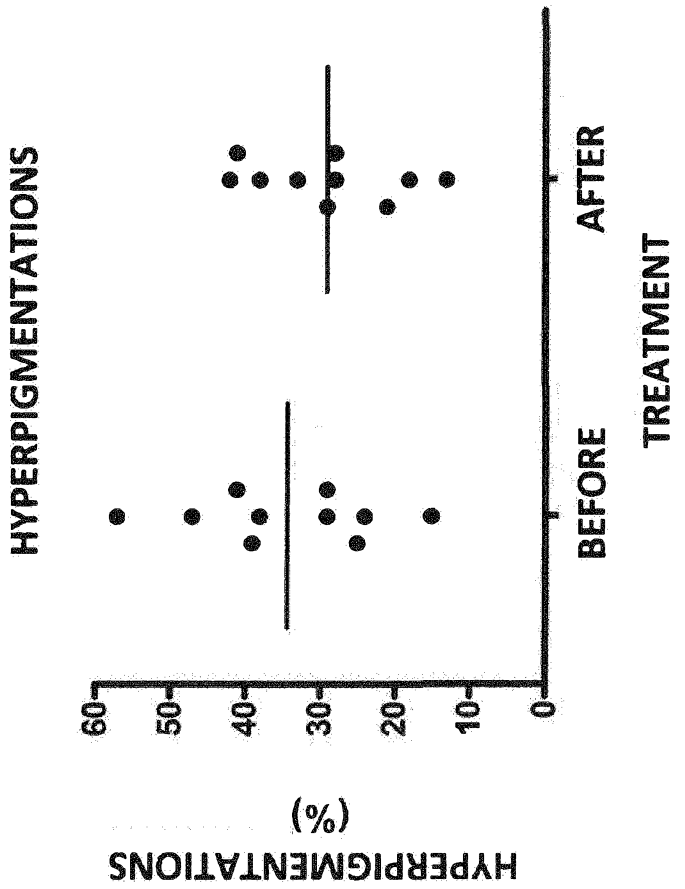


CHEEK ELASTICITY
ELASTICITY
(% recovery after
deformation)
95
90
85
80
75
70
65
60
55
50
45
40
BEFORE
AFTER
TREATMENT

FOREHEAD ELASTICITY
ELASTICITY
(% recovery after deformation)
100
90
80
70
60
50
40
BEFORE
AFTER
TREATMENT


BACTERIAL ACTIVITY
3500
3000
2500
2000
1500
1000
500
0
BEFORE
AFTER
TREATMENT
BACTERIAL ACTIVITY
(units)


FINE WRINKLE
FINE WRINKLE MCM
35
30
25
20
15
BEFORE
AFTER
TREATMENT


HYPERPIGMENTATIONS
HYPERPIGMENTATIONS (%)
60
50
40
30
20
10
0
BEFORE
AFTER
TREATMENT