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(54) Title: COMPOSITION FOR COSMETIC OR PHARMACEUTICAL-DERMATOLOGICAL USE

(57) Abstract: Composition in the form of a cosmetic formulation or dermatological medicament, suitable for maintaining skin cells at, or helping to restore skin cells to, their basal physiological state, enabling them to effect a regeneration of the dermis and the epidermis, comprising: - curcumin - a phosphosaccharide and possibly - a metal or basic oxide, or a biologically acceptable salt thereof, or a labile coordination compound thereof able to form, with at least one of said compounds: complexes, derivatives or associations which enhance their activity, in combination with excipients and/or diluents normally employed for cosmetic or pharmaceutical use.



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COMPOSITION FOR COSMETIC OR PHARMACEUTICAL-DERMATOLOGICAL USE

Field of the invention

The present invention relates to compositions for cosmetic or pharmaceutical-dermatological use, suitable for maintaining skin cells at, or helping to restore skin cells to, their basal physiological state, enabling them to effect a regeneration of the skin.

State of the art

For humans, it is a reality that the skin's well-being involves both a pathological aspect and one of aesthetics and cosmetics. In this respect, there is now an established tendency in contemporary society to not only counter pathologies of the skin but also, for aesthetic reasons, to resist entirely natural processes such as formation of wrinkles.

These phenomena in any case have in common a general impoverishment of dermal and epidermal functional characteristics. Damage to the skin, though, is nearly always the result of various concomitant causes, some of which are due to external agents, such as ultraviolet radiation or environmental contaminants, while others are ascribable to factors within the body and are mostly linked to natural ageing processes, a weakening of the dermal-epidermal interface or the exacerbation of pathologies which manifest themselves at skin level.

Very often these factors act simultaneously on the skin and can lead to various degrees of cellular distress in the epidermis, which, in time, exhibits changes such as loss of elasticity (elastosis) and wrinkles.

From this the need arises to maintain skin cells at, or contribute to restoring skin cells to, their basal physiological state, enabling them to effect a regeneration of the skin.

There are countless known compositions whose aim is precisely to resist the appearance of the aforesaid ageing phenomena, though their level of effectiveness is not currently such that the aforementioned need is satisfied.

Summary of the invention

The Applicants have now found that the aforesaid results are obtained with the composition of the present invention comprising:

- curcumin
- a phosphosaccharide and possibly
- a metal or basic oxide, or a biologically acceptable salt thereof, or its labile coordination compound able to form, with at least one of said compounds: complexes, derivatives or associations which enhance their activity,

in combination with excipients and/or diluents normally employed for cosmetic or pharmaceutical-dermatological use.

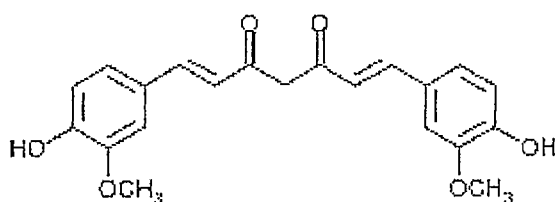
Indeed, said compositions are able to restore skin cells to their basal physiological state, enabling them to effect a regeneration of the dermis and epidermis as demonstrated by experiments undertaken at both the cellular and clinical levels.

The present invention therefore provides formulations for cosmetic use comprising the aforesaid compositions, in particular for preventing wrinkle formation and able to prevent elastosis.

The present invention also provides compositions in the form of a medicament for dermatological use, particularly for treating skin pathologies where it is essential to block the inflammatory process, by modulating the calcium and free radical channels caused by oxidative processes, in order to achieve skin regeneration.

Detailed description of the invention

Curcumin, characterized by the following formula:



is a natural extract of *Curcuma longa* or *Curcuma xanthorrhiza*, known for its generic antibacterial, antifungal and antiparasitic activity (Ars Pharmaceutica 2000, 41(3), 307-321).

The pharmacological characteristics (Planta medica, 1991, 57, 1) of both the pure product and all analogues (curcuminoids) derived from the extraction process (J. Cellular Biochem. 1996, 265, 72) as well as its safety of use in medicine, have been known for some time.

Curcumin and curcuminoids also behave as muscle relaxants (Life Science 2005, 76, 3089), inhibit the activation of nuclear factor NFkB where the paths causing and sustaining inflammation converge (J. Biol. Chem. 1995, 270, 24995), and are able to inactivate ROS (Reactive Oxygen Species) particularly superoxide ions (Ann. Chim. 2002, 92, 281).

Curcumin is preferably present in the composition of the invention at concentrations between 0.0005% and 10% on the total composition weight.

The phosphosaccharide used in the composition of the present invention is preferably chosen from the group consisting of mannose, glucose, galactose and fructose phosphates. Fructose 1-6 diphosphate (abbreviated to FDP hereinafter) is particularly preferred.

The stated phosphosaccharides, and in particular FDP, are metabolites of glycolysis able to provide easily available energy for cell biochemistry. FDP also possesses prostaglandin E2 (PGE2) and cyclooxygenase inhibitory activity, and is able to preserve the antioxidative capacity of keratinocytes irradiated with ultraviolet B radiation (British J. Pharmacol. 2002, 137, 497). Furthermore, in the presence of sodium and magnesium ions, FDP is accredited with protecting neurones from ischemic attack (Yao Xue Bao. 2003, 38, 325) and cells from various noxae, and facilitating metabolic recovery in ischemic tissue even in conditions of hypoxia (Am. J. Physiol. 1994, 267, H 2325). In this respect, FDP is used mainly for ischemic myocarditis where it interacts with the plasma membrane and stimulates enrichment of the energy-rich intracellular phosphate pool, including 2-3 diphosphogluconate (Esafosfina – information from Biomedica Foscama).

Curcumin and phosphosaccharides chosen from the group specified above have surprisingly shown a good synergistic effect when used in combination, enabling skin cells to recover as much as possible their basal level of efficiency.

Preferably phosphosaccharide is used in concentrations between 0.001% and 25% by weight on the total composition weight.

In accordance with a preferred embodiment, the compositions of the present invention contain the salts or biologically acceptable oxides of a metal able to form, with at least one of the aforesaid essential compounds, coordination

compounds or associations which enhance their activity.

The metals contained in the salts or oxides possibly present are chosen from calcium, magnesium, copper, bismuth, zinc, aluminium, manganese, antimony, tin, gold, silver, chromium, cobalt, vanadium or titanium.

Preferably the compositions of the present invention contain oxides or salts of the aforesaid metals able to completely or partially complex curcumin.

If the aforesaid salts or oxides are present in quantities such that the relative metals completely complex curcumin, the compositions of the present invention contain only complexed curcumin.

Instead, if the aforesaid salts or oxides are present in quantities such as to partially complex curcumin, the compositions of the present invention comprise an association of curcumin and complexed curcumin.

This latter type of composition gave the best results in terms of skin cell regeneration following oxidative stress.

Preferred are zinc salts and in particular zinc acetate and zinc oxide.

Formation of the zinc-curcumin complex can be achieved by dissolving the zinc salt in a hydroalcoholic solution to which curcumin is added in a 1:1 molar ratio.

The zinc ion coordinates to the keto-enolic group of curcumin. The same result is obtained by directly adding curcumin to the composition of the invention which contains zinc salts or zinc oxide, as demonstrated by the bathochrome effect, seen in the colour of the compositions after addition of said compound.

Coordination of curcumin with the metal increases its lipophilicity, therefore raising its capacity to act at the cellular level.

In accordance with a further aspect of the present invention, further so-called functional compounds can be present in the composition, useful for sustaining and directing cellular activity when the recovery of basal-physiological conditions indicates full cellular activity has been restored.

In this case, the composition of the present invention will be enriched with one or more compounds chosen from the group consisting of fruit acids, (α -hydroxy acids), glucosaminoglycans, urea, urea in protein mixtures, flavones, flavonoids, terpenes, diterpenes, vaseline, saturated and unsaturated fatty acids, lipids, phospholipids, coumarin and derivatives, proteins, protides, amino acids, vitamins,

in particular D and H group, ceramides, sphingosines, boswellic acids and derivatives, in particular those characterized by acetyl and formyl groups, starch and its derivatives, as well as monosaccharides.

The composition of the present invention can also advantageously contain one or more compounds, in pharmaceutically compatible doses, chosen from the group consisting of pyrrhione and its complex salts (in particular salts of the aforelisted metals), fumaric acid derivatives, Mahonia extracts, anthraquinone derivatives, retinoic acid derivatives, vitamin D derivatives and lactoferrins. In this case the composition will prove to be an excellent coadjuvant in the therapeutic treatment of psoriasis and other skin diseases, avoiding or in any case limiting the use of steroidal substances.

Some examples of formulations in accordance with the invention are given below, as well as clinical trials and in vitro cell trials which demonstrate the effectiveness of the compositions of the present invention. In the examples, 100 grams of a prepared product produced in accordance with the present invention comprise a lipophilic-based excipient in which the stated components are dispersed.

EXAMPLE 1

- Curcumin 0.002 g
- FDP 4.0 g
- Zinc acetate 0.01 g

EXAMPLE 2

- Curcumin 0.002 g
- FDP 4.0 g

EXAMPLE 3

- Curcumin 0.002 g
- FDP 4.0 g
- Zinc acetate 0.005 g

EXAMPLE 4

- Curcumin 0.002 g
- FDP 4.0 g
- Zinc oxide 0.01 g

TEST 1

The prepared product of example 1 was used in a test conducted on a sample of twenty female volunteer patients aged between 20 and 25 years with unblemished skin, after obtaining their informed consent regarding the test method.

The prepared product was spread onto one arm while a placebo prepared product, formed solely of a lipophilic-based excipient, was applied to the opposite arm. The entire experiment was conducted "double blind", the codes relating to the placebo and prepared product being opened only at the end of the study.

Clinical assessments were undertaken at the start and at the end of the trial. The parameters relating to the assessment, which was conducted by non-invasive biophysical measurements, were: dryness, irritation and scaling of the skin. In particular, skin hydration was assessed by measuring the electrical capacitance of the skin using the corneometer CM 820 PC (Courage and Khazaka Electronic GmbH, Cologne, Germany), while the biomechanical properties of the skin were measured with the aid of an apparatus (Dermaflex, Cortex Technology, Denmark) which records deformations of the skin following application of pressure thereto, measuring its distensibility and elasticity. Skin elasticity and distensibility are correlated with the efficacy of the elastic and collagen fibre network.

The test results are given in table 1, as means of the values measured for each assessment parameter, together with the respective standard deviation and standard error values.

Each mean value was calculated on five measurements taken at the start and at the end of the treatment period (20 days). The units are arbitrary. The prepared product of the invention is indicated in the table as "active cream".

Table 1

		Mean	Std. deviation	Std. error
Elasticity	Placebo	42.214	9.126	2.033
	Active cream	61.571	12.143	3.040
Hydration	Placebo	72.613	7.342	2.301
	Active cream	85.134	5.483	1.927
Distensibility	Placebo	1.430	0.213	0.042
	Active cream	1.241	0.223	0.035

Clinical assessment of the patients did not indicate any irritation phenomena and all subjects confirmed the effectiveness and acceptability of the preparation.

The study has therefore shown very significant increases in the hydration and elasticity values of skin ($p < 0.02$) after only 20 days' treatment. The results are of considerable interest because they concur in showing an improved structuring of the fundamental components of the dermis, with increased skin tone. Also to be noted is the substantial increase in skin hydration despite the young age of the tested patients. These results concur with the histological assessment of primary fibroblasts cultures treated with curcumin + zinc-curcumin + FDP.

TEST 2

Measurement of oxidative stress

Tests on the capacity of the indicated preparations to prevent oxidative damage, induced in dermal tissue cells, were conducted on human fibroblasts which were isolated then cultivated in a suitable culture medium. Oxidative stress was induced by adding a mixture of 40 mM xanthine and 2 mM hypoxanthine to the culture medium, a mixture with known ability to induce formation of Reactive Oxygen Species (ROS), agents which cause cell damage up to necrosis. The preparations under examination could be added, or not, to the broth at the same time as the xanthine/hypoxanthine mixture. The contact time between the xanthine/hypoxanthine mixture and the preparations was 2 hours, at the end of which the cells were transplanted into a fresh culture medium, i.e. containing

neither the stress-inducing mixture nor the substance, then allowed to quiesce for periods of 3 or 24 hours. At the end of the stated period, gene expression of the prostaglandin G/H synthase and cyclooxygenase₂ (COX₂) enzyme was detected which is indicative of the inflammatory state induced in cells by oxidative stress. The content of COX₂ mRNA in cells was then quantified by reverse transcriptase; said content was chiefly increased in cells that had borne oxidative stress the most and lowest in control cells not exposed to oxidative stress. The effectiveness of the different preparations in protecting cultured human fibroblasts from oxidative stress was shown by their ability to maintain COX₂ content as low as and as close to the value found in cells not exposed to stress.

Synergy between curcumin, zinc and FDP in protection from oxidative stress.

Expression of COX₂ (normalized fluorescence units vs housekeeping gene 18s rRNA) 24 hours after oxidative stress, in "insulted" cells in the presence of curcumin, curcumin complexed with Zn and FDP used separately, and in the presence of the ternary system.

	COX ₂
Non-insulted, untreated cells	2.12
Insulted, untreated cells	12.00
curcumin 3 μ M	5.00
curcumin 6 μ M	4.90
Zn-curcumin complex 3 μ M	4.56
FDP 5 mM	7.14
curcumin 3 μ M + FDP 5 mM	4.00
curcumin 3 μ M + Zn-curcumin complex 3 μ M	4.00
curcumin 3 μ M + Zn-curcumin complex 3 μ M + FDP 5 μ M	3.00

TEST 3

COX₂ expression after oxidative insult

The previous test was repeated with different compositions and the results measured at 3 hours and 24 hours.

	3 hours	24 hours
Non-insulted, untreated cells	2.00	2.12
Insulted, untreated cells	10.00	12.00

curcumin 3 μ M	5.76	5.00
curcumin 6 μ M	5.45	4.90
curcumin 9 μ M	5.10	4.78

Zn-curcumin complex 3 μ M	4.97	4.56
Zn-curcumin complex 6 μ M	4.89	4.11
Zn-curcumin complex 9 μ M	4.77	4.00

FDP 5 mM	7.87	7.14
FDP 10 mM	6.90	6.45

boswellic acid 100 μ M	7.80	8.00
boswellic acid 300 μ M	8.10	8.90
curcumin 3 μ M + FDP 5 mM	3.50	4.00
curcumin 3 μ M + Zn-curcumin complex 3 μ M	3.20	2.78
curcumin 9 μ M + Zn-curcumin complex 9 μ M	3.30	2.90

curcumin 3 μ M + Zn-curcumin complex 3 μ M - FDP 3.30	3.00
5 μ m	
curcumin 9 μ M + Zn-curcumin complex 9 μ M + FDP 3.01	2.89
5 μ m	

From these results the synergistic effect exhibited by FDP and Zn salts on curcumin activity at the cellular level is clear, in the sense that viability of said cells is maintained and reactivated.

CLAIMS

1. Composition suitable for maintaining skin cells at, or helping to restore skin cells to, their basal physiological state, enabling them to effect a regeneration of the dermis and the epidermis, comprising:

- curcumin
- a phosphosaccharide and possibly
- an oxide, or a biologically acceptable salt of a metal able to form, with at least one of said compounds, complexes, derivatives or associations able to enhance their activity,

in combination with excipients and/or diluents normally used for cosmetic or pharmaceutical-dermatological use.

2. Composition as claimed in claim 1 containing curcumin at concentrations between 0.0005% and 10% on the total weight of the composition.

3. Composition as claimed in any one of claims 1-2 wherein the phosphosaccharide is chosen from the group consisting of mannose, glucose, galactose and fructose phosphates.

4. Composition as claimed in claim 3 wherein the phosphosaccharide is fructose 1-6 diphosphate.

5. Composition as claimed in any one of claims 1-4 containing the phosphosaccharide at concentrations between 0.001% and 25% by weight on the total weight of the composition.

6. Composition as claimed in any one of claims 1-5 comprising oxides or salts of a metal able to form, with at least one of the aforesaid compounds, complexes, derivatives or associations able to enhance their activity.

7. Composition as claimed in claim 6 wherein said metal is chosen from the group consisting of calcium, magnesium, copper, bismuth, zinc, aluminium, manganese, antimony, tin, gold, silver, chromium, cobalt, vanadium and titanium.

8. Composition as claimed in claim 7 containing metals able to complex curcumin.

9. Composition as claimed in claim 8 wherein the metals are present in quantities such that they completely complex curcumin.

10. Composition as claimed in claim 9 containing complexed curcumin.

11. Composition as claimed in claim 8 wherein the metals are present in quantities

such as to partially complex curcumin.

12. Composition as claimed in claim 8 containing a mixture of curcumin and complexed curcumin.

13. Composition as claimed in any one of claims 8-12 wherein the metal is zinc.

14. Composition as claimed in claim 13 wherein the zinc is in the form of zinc acetate or zinc oxide.

15. Composition as claimed in either of claims 13 or 14 wherein complexed curcumin is formed by dissolving the zinc salt in a hydroalcoholic solution and adding curcumin in a 1:2 molar ratio.

16. Composition as claimed in either of claims 14 or 15 wherein complexing occurs by adding curcumin to the composition containing zinc oxide.

17. Composition as claimed in any one of claims 1-16 containing at least one compound chosen from the class consisting of fruit acids (α -hydroxy acids), glucosaminoglycans, urea, urea in protein mixtures, flavones, flavonoids, terpenes, diterpenes, vaseline, saturated and unsaturated fatty acids, lipids, phospholipids, coumarin and derivatives, proteins, protides, amino acids, vitamins, in particular D and H group, ceramides, sphingosines, boswellic acids and derivatives, starch and its derivatives, and monosaccharides.

18. Composition as claimed in claim 17 wherein the boswellic acid derivatives are the acetyl and formyl.

19. Composition as claimed in any one of claims 1-8 containing at least one compound chosen from the class consisting of pyrithione and its complex salts, fumaric acid derivatives, Mahonia extracts, anthraquinone derivatives, retinoic acid derivatives, vitamin D derivatives and lactoferrins.

20. Medicament consisting of the composition claimed in any one of claims 1-19 usable in skin diseases where it is essential to block the inflammatory process by modulating calcium and free radical channels caused by oxidative processes, in order to achieve skin regeneration.

21. Medicament consisting of the composition claimed in claim 19 as a coadjuvant in the therapeutic treatment of psoriasis.

22. Formulation for cosmetic use consisting of the composition claimed in any one of claims 1-18, in particular for the prevention of wrinkle formation and suitable for

prevention of elastosis.