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(54) Titre : COMPOSITION DE DEPIGMENTATION DESTINEE A LA PEAU ET COMPRENANT DE L'ADAPALENE, AU MOINS UN AGENT DE DEPIGMENTATION ET AU MOINS UN AGENT ANTI-INFLAMMATOIRE

(54) Title: DEPIGMENTING COMPOSITION FOR THE SKIN, COMPRISING ADAPALENE, AT LEAST ONE DEPIGMENTING AGENT AND AT LEAST ONE ANTI-INFLAMMATORY AGENT

(57) Abrégé/Abstract:
The invention relates to a depigmenting composition for the skin, comprising, in a physiologically acceptable medium, adapalene, at least one depigmenting agent and at least one anti- inflammatory agent, and to its pharmaceutical or cosmetic use.

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(57) Abstract: The invention relates to a depigmenting composition for the skin, comprising, in a physiologically acceptable medium, adapalene, at least one depigmenting agent and at least one anti- inflammatory agent, and to its pharmaceutical or cosmetic use.

DEPIGMENTING COMPOSITION FOR THE SKIN, COMPRISING ADAPALENE, AT LEAST ONE DEPIGMENTING AGENT AND AT LEAST ONE ANTI-INFLAMMATORY AGENT

The invention relates to a depigmenting composition for the skin, comprising, in a physiologically acceptable medium, adapalene (6-[3-(1-adamantyl)-4-methoxyphenyl]-2-naphthanoic acid), at least one depigmenting agent and at least one anti-inflammatory agent, and to its pharmaceutical or cosmetic use.

A.M. Kligman describes, in US Patent 3,856,934, a depigmenting composition comprising hydroquinone, retinoic acid and a corticosteroid. This type of combination allows good depigmentation of the skin but causes substantial adverse effects such as irritation and itching.

Retinoic acid (tretinoin) is known to have, on its own, a skin depigmenting activity (Guevara I.A. and Pandya A.G. Int. J. Dermatol. 40, 210-215 (2001)). In addition, tests carried out on the tail of a mouse not irradiated with UVB radiation for six weeks show that tretinoin, used at 0.01% or 0.03%, induces depigmentation of the tail which begins from the first week of treatment and progresses to reach a clear depigmentation at 6 weeks. In mice which are irradiated with UVB radiation and treated, the dose of 0.03% is capable of inhibiting the induction of pigmentation by UVB radiation, whereas the lower dose has no effect. Tretinoin is therefore a depigmenting agent on its own. On the other hand, under the same experimental conditions, adapalene has no depigmenting activity, as is shown in Example 5 hereinafter. Due to its lack of depigmenting activity in particular, nothing therefore encouraged those skilled in the art to combine it with a depigmenting agent in a depigmenting composition possibly containing an anti-inflammatory agent.

However, the Applicant has discovered, surprisingly, that the combination of adapalene, a depigmenting agent and an anti-inflammatory agent makes it possible to obtain a much more rapid depigmenting response than that obtained with the depigmenting agent alone.

The Applicant has also discovered, surprisingly, that good tolerance of the skin is obtained with the combination of adapalene, a depigmenting agent and an anti-inflammatory agent, at the same time keeping a considerable depigmenting activity.

The invention therefore relates to a depigmenting composition for the skin, comprising, in a physiologically acceptable medium, adapalene, at least one depigmenting agent distinct from adapalene, and at least one anti-inflammatory agent distinct from adapalene. The composition according to the invention therefore comprises at least three different active ingredients.

The term "physiologically acceptable medium" is intended to mean a medium which is compatible with the skin, the mucous membranes and/or the integuments.

The term "depigmenting agent" is intended to mean any active agent having skin-depigmenting activity. This activity makes it possible to decrease the pigmentation of the skin that already exists and also to prevent any additional pigmentation above the natural pigmentation.

By way of non-limiting example of a depigmenting agent, mention may be made of phenolic derivatives, such as hydroquinone, hydroquinone monoethyl ether, hydroquinone monobenzyl ether or 4-hydroxyanisole, kojic acid and its derivatives, azelaic acid and its derivatives, linoleic acid, resorcinol and its derivatives, ellagic acid, hydroxy acids such as glycolic

acid, ascorbic acid, zinc peroxide, and mercury chloride.

In particular, the depigmenting composition for the skin may comprise, as depigmenting agent, a phenolic derivative, in particular hydroquinone.

The invention also relates to a depigmenting composition for the skin, comprising, in a physiologically acceptable medium, adapalene, at least one depigmenting agent distinct from adapalene and at least one anti-inflammatory agent distinct from adapalene.

To give an order of magnitude, the composition according to the invention advantageously comprises between 0.0001% and 20% by weight of adapalene relative to the total weight of the composition, and between 0.0001% and 20% by weight of depigmenting agent relative to the total weight of the composition, and preferably, respectively, between 0.001% and 10% by weight of adapalene relative to the total weight of the composition, and between 0.025% and 5% by weight of depigmenting agent relative to the total weight of the composition.

The composition comprises at least one steroidal or non-steroidal anti-inflammatory agent in preferential concentrations ranging from 0.001% to 20.00% by weight relative to the total weight of the composition.

Among steroidal anti-inflammatory agents, mention may be made, by way of non-limiting example, of clobetasone butyrate, clobetasol propionate, clobetasol dipropionate, hydrocortisone, cortisone, prednisolone, miconazole, prednisone, triamcinolone acetonide, methylprednisolone, fluometholone, fluocinolone acetonide, desonide, betamethasone, dexamethasone, or mixtures thereof.

Among non-steroidal anti-inflammatory agents, mention may be made, by way of non-limiting example, of indole derivatives, arylcarboxylic derivatives such as ibuprofen, oxicams, pyrazole compounds, salicylic acid and selective COX-2 inhibitors.

In particular, the depigmenting composition for the skin may comprise fluocinolone acetonide as anti-inflammatory agent.

The composition may also comprise any additive normally used in the cosmetics or pharmaceutical field, such as sequestering agents, antioxidants, sunscreens, preserving agents, fillers, electrolytes, humectants, dyes, common inorganic or organic bases or acids, fragrances, essential oils, cosmetic active agents, moisturizers, vitamins, essential fatty acids, sphingolipids, self-tanning compounds, and skin calmative and protective agents such as allantoin. Of course, those skilled in the art will take care to select this or these optional additional compound(s), and/or the amount thereof, such that the advantageous properties of the composition according to the invention are not, or are not substantially, adversely affected.

These additives may be present in the composition in a proportion of from 0.001% to 20% by weight relative to the total weight of the composition.

As examples of sequestering agents, mention may be made of: ethylenediaminetetraacetic acid (EDTA), and also derivatives or salts thereof, dihydroxyethylglycine, citric acid and tartaric acid.

As examples of preserving agents, mention may be made of benzalkonium chloride, phenoxyethanol, benzyl alcohol, diazolidinylurea and parabens.

As examples of humectants, mention may be made of:

glycerol and sorbitol.

A subject of the present invention is also the composition according to the invention as described above, as a medicament.

The invention also relates to the use of the composition according to the invention as described above, in the pharmaceutical and cosmetics field.

The compositions of the invention are particularly suitable for the treatment and prevention of hyperpigmentary disorders such as melasma, chloasma, lentigines, senile lentigo, freckles, post-inflammatory hyperpigmentations due to an abrasion, a burn, a scar, a dermatosis, a contact allergy; naevi, hyperpigmentations with genetic determinism, hyperpigmentations of metabolic or drug-related origin, melanomas or any other hyperpigmentary lesions.

The compositions according to the invention also find application in the cosmetics field, in particular in protection against the harmful effects of the sun, for preventing and/or for combating photo-induced or chronological ageing of the skin and of the integuments.

The examples of formulations below make it possible to illustrate the compositions according to the invention, without, however, limiting the scope thereof. Examples illustrating the depigmenting activity of the various compositions according to the invention are also described.

In the compositions hereinafter, the proportions of the various constituents are expressed as a percentage by weight relative to the total weight of the composition.

Example 1:

Adapalene	0.10
Hydroquinone	4.00
Fluocinolone acetonide	0.01
Magnesium aluminium silicate	3.00
Butyl hydroxytoluene	0.04
Methyl paraben	0.18
Propyl paraben	0.02
Cetyl alcohol	4.00
Stearic acid	3.00
Stearyl alcohol	4.00
Glyceryl stearate/PEG-100 stearate	3.50
Methyl gluceth-10	5.00
Glycerol	4.00
Citric acid	0.05
Sodium metabisulfite	0.20
Purified water	qs 100

This composition should be applied once a day until complete depigmentation is obtained, for the treatment of chloasma.

Example 2:

Adapalene	0.10
4-Hydroxyanisole	3.00
Fluocinolone acetonide	0.01
Magnesium aluminium silicate	3.00
Butyl hydroxytoluene	0.04
Methyl paraben	0.18
Propyl paraben	0.02
Cetyl alcohol	4.00
Stearic acid	3.00
Stearyl alcohol	4.00
Glyceryl stearate/PEG-100 stearate	3.50
Methyl gluceth-10	5.00

Glycerol	4.00
Citric acid	0.05
Sodium metabisulfite	0.20
Purified water	qs 100

This composition should be applied twice a day until complete depigmentation is obtained, for the treatment of lentigines.

Example 3:

Adapalene	0.1
Hydroquinone	2
Desonide	0.05
Carbomer	0.1
Methyl paraben	0.18
Propyl paraben	0.02
Cetyl alcohol	1
Stearic acid	0.8
Caprylic-capric triglyceride	1.5
Cyclomethicone	1
Mineral oil	2
Propylene glycol	5
Glycerol	2
Triethanolamine	5
Citric acid (qs pH 5.5-6.0)	/
Purified water	qs 100

This composition should be applied once a day until complete depigmentation is obtained, for the treatment of melasma.

Example 4:

Adapalene	0.1
4-Hydroxyanisole	2
Salicylic acid	1

Steareth-2	3
Steareth-21	2
Caprylic-capric triglyceride	4
Isohexadecane	5
Cetearyl alcohol	1
Stearic acid	1.5
Sodium sulphite	0.2
Propylene glycol	8
Glycerol	2
Phenoxyethanol	1
Citric acid (qs pH 5.5-6.0)	/
Purified water	qs 100

This composition should be applied twice a day until complete depigmentation is obtained, for the treatment of lentigines.

Example 5 - Measurement of the depigmenting activity of the combination of adapalene and a depigmenting agent

The evaluation of the depigmenting and/or anti-pigmenting activity of 3% hydroquinone and of 0.1% adapalene, alone or in combination for 8 weeks, is carried out on the tail of an SKH:HR2 mouse irradiated with ultraviolet B radiation, or not irradiated. The tail of the SKH:HR2 mouse is naturally pigmented and this pigmentation increases under the effect of repeated UVB irradiation. The depigmenting activity is measured on the natural pigmentation after application of the test product to the tail of non-irradiated animals. The anti-pigmenting activity is measured by the inhibition of the induction of the UV-induced pigmentation: the test product is applied to the tail of UVB-irradiated animals.

The treatment is carried out 5 days a week for 8 weeks. 20 μl of test product diluted in acetone are applied to

the tail with a gap between applications: the hydroquinone is applied in the morning and the adapalene 4 h later. On the days of irradiation, the treatment is applied after irradiation.

The animals are irradiated 3 times a week for 8 weeks (Monday, Wednesday, Friday) at the dose of 90 mJ/cm^2 of UVB.

The pigmentation is evaluated once a week before irradiation, by means of a score on a scale of 0 to 4. The scores are divided up as follows:

Depigmentation scale: scores -1 to -4.
0: natural pigmentation
-1: slight depigmentation
-2: moderate depigmentation
-3: marked depigmentation
-4: complete depigmentation

Pigmentation scale: scores 1 to 4
1: slight pigmentation
2: moderate pigmentation
3: marked pigmentation
4: strong pigmentation

The results are given in Figures 1 and 2.

Figure 1 represents the kinetics of the mouse tail skin pigmentation scores as a function of treatment time with or without ultraviolet B irradiation (up to 8 weeks of treatment) with (♦) UVB + acetone, (▶) UVB + adapalene, (◀) UVB + hydroquinone, (●) UVB + hydroquinone + adapalene, (□) skin not irradiated + acetone, (Δ) skin not irradiated + adapalene, (o) skin not irradiated + hydroquinone, (∇) skin not irradiated + hydroquinone + adapalene.

Figure 2 represents the scores for pigmentation on the

tail at the end of the study (D57) with (□) acetone, (▨) hydroquinone, (■)adapalene, (▤) adapalene + hydroquinone with or without ultraviolet B irradiation.

Depigmenting activity: Hydroquinone alone at 3% induces a depigmentation which is clinically visible from the 6th week of treatment (D43) and statistically significant at the end of the study. Adapalene alone does not modify the natural pigmentation. When adapalene is combined with hydroquinone, it potentiates its depigmenting activity.

Anti-pigmenting activity: In the animals irradiated and treated concomitantly, hydroquinone shows an anti-pigmenting effect at the 6th and at the 7th week (D50), which becomes less marked at the end of the study. On the other hand, the adapalene + hydroquinone combination inhibits the pigmentation induced by UVB irradiation as soon as it appears and until the end of the study, where the difference is statistically significant (**, $p < 0.01$).

Conclusion

After 8 weeks of topical treatment on the tail of an SKH:HR2 mouse, it is noted that the hydroquinone + adapalene combination exhibits a strong anti-pigmenting activity and significantly inhibits the pigmentation induced by UVB irradiation as soon as it appears and until the end of the study. The hydroquinone + adapalene combination exhibits a significant benefit as a depigmenting agent, with respect to hydroquinone alone.

Example 6 - Measurement of the tolerance with respect to the combination of adapalene, an anti-pigmenting agent and an anti-inflammatory agent

The evaluation of the tolerance with respect to the adapalene + hydroquinone + fluocinolone acetonide combination ("adapalene trio") formulated in a cream, in comparison with that obtained with the combination retinoic acid (tretinoin) + hydroquinone + fluocinolone acetonide ("control trio") in the same vehicle for 4 weeks, is carried out on the tail of an SKH:HR2 mouse which is UVB-irradiated or not irradiated. The same measurements are also realized on the vehicle alone and without active agents. The tolerance after application of the test product is measured with ultraviolet B (UBV)-irradiation and without ultraviolet B-irradiation.

The treatment is carried out 5 days a week for 4 weeks. 20 μl of formulated test product are applied to the tail. On the days of irradiation, the treatment is applied after irradiation.

The animals are irradiated 3 times a week for 4 weeks (Monday, Wednesday, Friday) at the dose of 90 mJ/cm^2 of UVB.

The inflammation (erythema and squamae) is evaluated once a week before irradiation by means of a score on a scale of 0 to 4. The scores are divided up as follows:

0: normal skin without inflammation
1: slight inflammation
2: moderate inflammation
3: marked inflammation
4: severe inflammation.

The results are given in Figure 3.

Figure 3 presents the overall clinical score for inflammation on the tail at the end of the 4 weeks of study after application either of the vehicle (■), or of the adapalene trio (▥), or of the control trio (▧).

Conclusion

The signs of inflammation are clearly less marked with the adapalene trio than with the control trio.

The comparative study of adapalene trio versus control trio for 4 weeks on the tail in mice shows that the adapalene trio exhibits much better tolerance than the control trio.

Claims

1. Depigmenting composition for the skin, comprising adapalene, at least one depigmenting agent distinct from adapalene and at least one anti-inflammatory agent distinct from adapalene, in a physiologically acceptable vehicle.

2. Composition according to Claim 1, characterized in that the depigmenting agent is a phenolic derivative.

3. Composition according to either one of Claims 1 and 2, characterized in that the depigmenting agent is hydroquinone.

4. Composition according to any one of Claims 1 to 3, characterized in that the anti-inflammatory agent is fluocinolone acetonide.

5. Composition according to any one of Claims 1 to 4, as a medicament.

6. Use of a composition according to any one of Claims 1 to 4, in the manufacture of a pharmaceutical preparation for use in the prevention or treatment of hyperpigmentary disorders such as melasma, chloasma, lentigines, freckles, post-inflammatory hyperpigmentations due to an abrasion, a burn, a scar, a dermatosis, a contact allergy, naevi, hyperpigmentations with a genetic determinism, hyperpigmentations of metabolic or drug-related origin, melanomas or any other hyperpigmentary lesions.

7. Use according to Claim 6, in the manufacture of a pharmaceutical preparation for use in the prevention or treatment of melasma.

8. Cosmetic use of a composition according to any one of Claims 1 to 4, for protection against harmful

effects of the sun, for preventing and/or for combating photo-induced or chronological ageing of the skin and of the integuments.

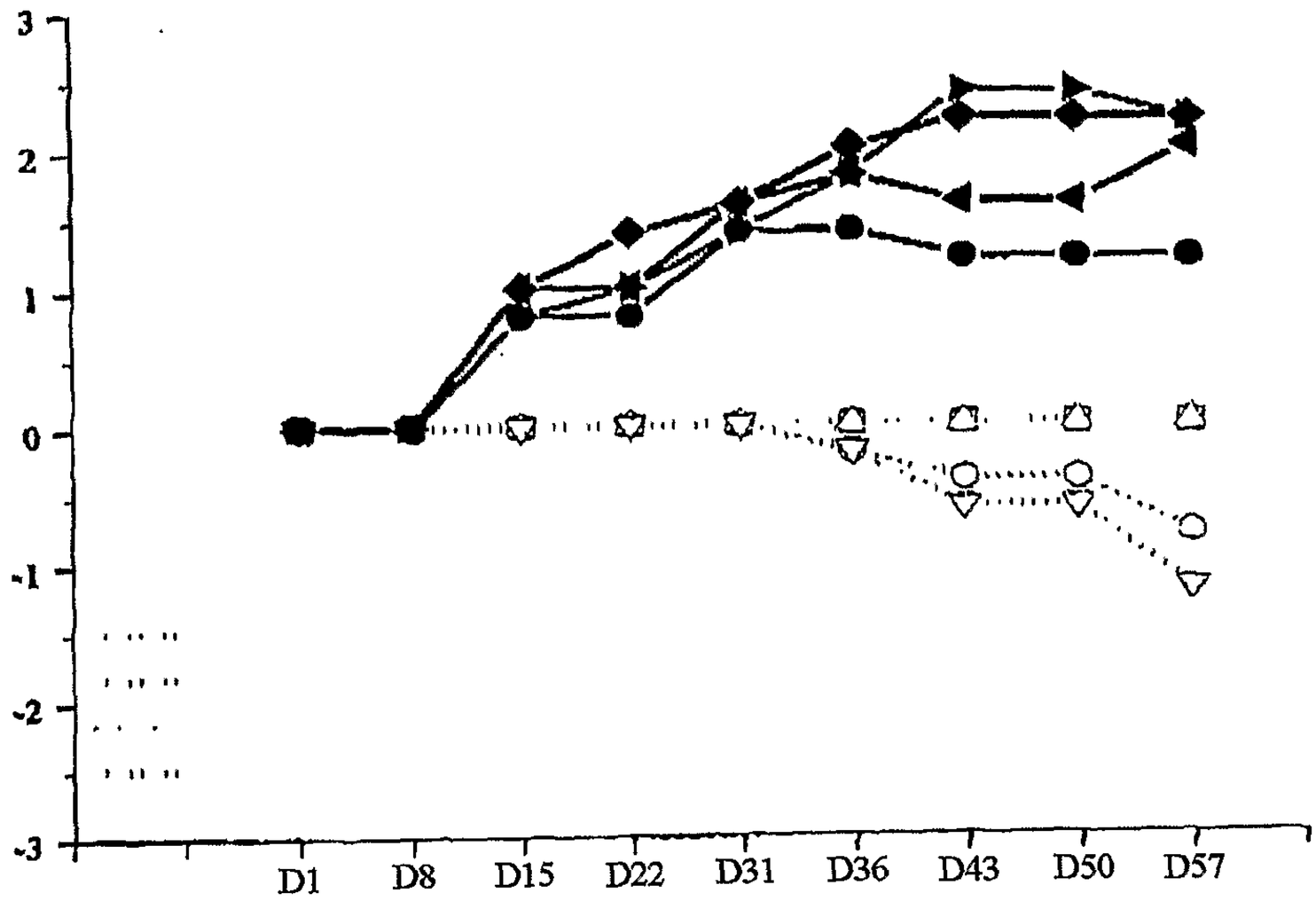

Figure 1

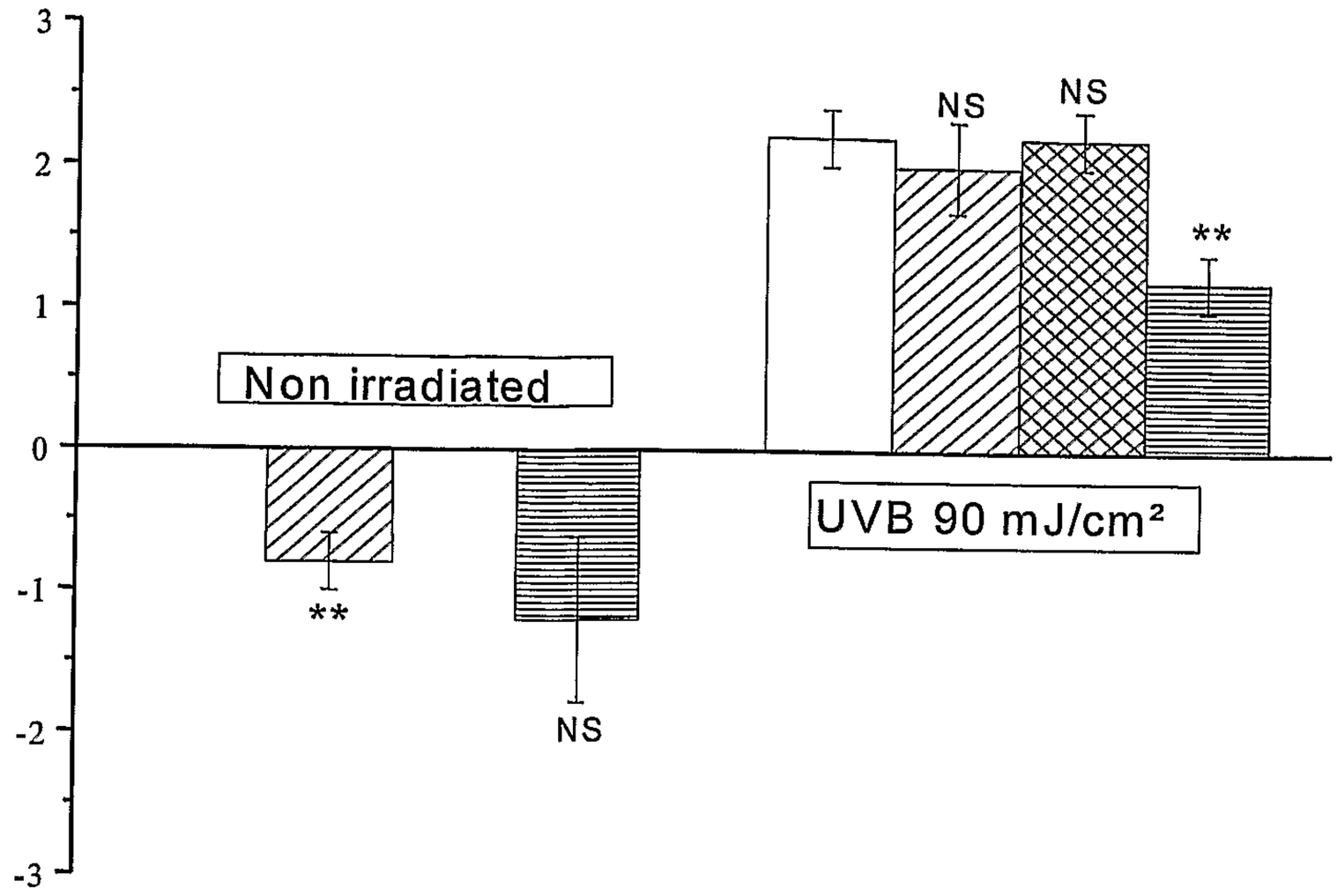

Figure 2

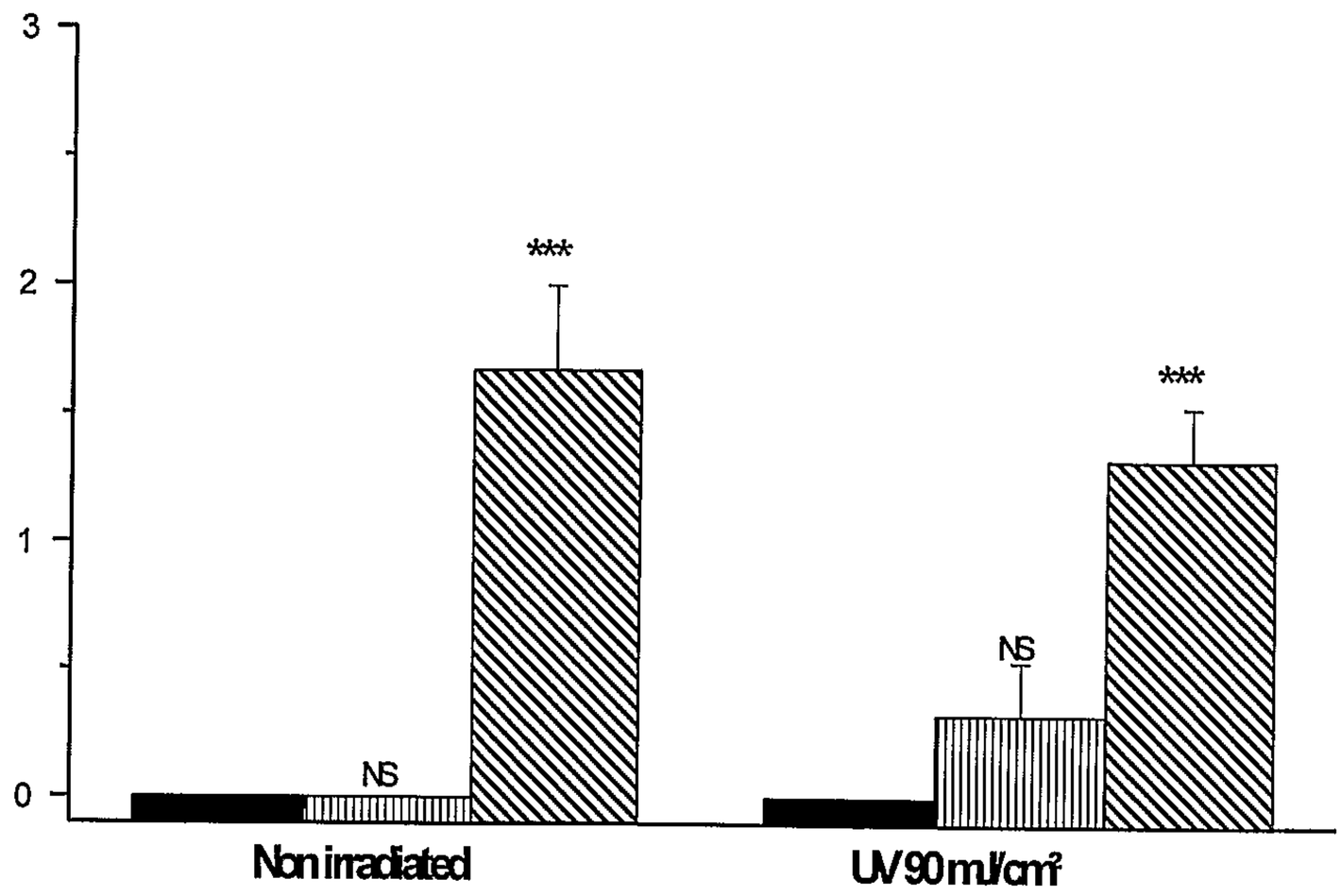

Figure 3