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(54) Title: TOPICAL COMPOSITION

(57) Abstract: This invention concerns the use of the brucine (2,3-dimethoxystrychnidin-10-one) or a dermatologically acceptable derivative thereof in the treatment of damaged mammalian skin.

TOPICAL COMPOSITION

This invention relates to a topical composition. In particular, it relates to a dermatological composition suitable for topical application to mammalian skin. Such composition is useful in the cosmetic or medical treatment of damaged mammalian skin, especially damage caused by sunburn, minor burns, ulcers or the like.

Brucine (2,3-dimethoxystrychnidin-10-one)is a highly toxic alkaloid resembling strychnine, which can be used as an addition agent for lubricants.

It has now unexpectedly been found that brucine or a dermatologically acceptable derivative thereof is useful in the regeneration of mammalian tissue.

According to the present invention there is provided the use of brucine or a dermatologically acceptable salt thereof, or a hydrate thereof, in the manufacture of a medicament for the treatment of damaged mammalian skin.

The invention also provides a dermatological composition suitable for topical application to mammalian skin, which comprises:

(a) approximately 0.05-0.3% by weight of brucine or a dermatologically acceptable salt thereof, or a hydrate thereof;

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(b) approximately 0.8-3% by weight of a hydroxy acid or a salt, ester or amide thereof;

(c) approximately 0.15-5% by weight of water; and

(d) the balance comprising a dermatologically acceptable oil or water or a combination thereof.

In the present invention, brucine is preferably used in the form of a salt, more preferably its sulphate salt. In a particularly preferred embodiment, brucine is used in the form of brucine sulphate heptahydrate. Brucine or a salt thereof or a hydrate thereof is preferably present in the composition in an amount of from approximately 0.1-0.2%, especially approximately 0.15%, by weight of the composition.

The hydroxy acid used in the composition of the present invention may be any suitable hydroxy acid, such as, for example, glycolic, lactic, malic, tartaric, citric, mandelic or salicylic acid or a mixture thereof. The hydroxy acid may be present in the form of the free acid and/or in the form of one of its associated salts, especially salts with an organic base or an alkali metal, or in the form of an ester or amide thereof. Sodium salicylate is particularly preferred. The hydroxy acid is preferably present in the composition in an amount of from approximately 1.0-2.5%, more preferably approximately 1.2-1.8%, and especially approximately 1.5%, by weight of the composition.

Component (c) of the composition comprises water in an amount of from approximately 0.15-5%, preferably from approximately 0.5-3%, more preferably from approximately 0.75-2.5%, and especially approximately 2%, by weight of the composition.

Component (d) of the composition comprises a dermatologically acceptable oil, or water, or a combination thereof. In a preferred embodiment, the composition is in the form of a water-in-oil emulsion. In a particularly preferred embodiment, component (d) consists of a dermatologically acceptable oil. Any suitable oil may be used, such as mineral oil or a vegetable oil, e.g. sunflower oil, or a mixture thereof. Pure mineral oil is preferred. In a particularly preferred embodiment, the mineral oil is free from preservative.

In a further preferred embodiment, component (d) of the composition consists of water.

The composition of the invention may also include a masking agent such as caffeine or the like, preferably in an amount of from approximately 0.03-0.08%, especially approximately 0.05%, by weight of the composition.

The composition of the invention may be formed by (a) heating the brucine or salt thereof or hydrate thereof in a suitable solvent, such as an alcohol, preferably

ethanol or isopropanol, until the brucine is dissolved; (b) adding the hydroxy acid and masking agent (if used) to the water or a portion thereof and heating to a temperature in the range of from 70°C to 85°C until they are dissolved; (c) heating the oil, if present, to a temperature in the range of from 70°C to 85°C; (d) mixing the brucine and hydroxy acid solutions and any of the water remaining, or, if oil is present, adding the brucine and hydroxy acid solutions and any of the water remaining, to the heated oil; and (e) heating the resulting product to a temperature in the range of from 80°C to 95°C so as to evaporate substantially all of the solvent. The resulting product may then be homogenised until fully blended.

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE 1

Ingredients	**% by weight**
Brucine sulphate heptahydrate	0.15
Sodium salicylate	1.5
Distilled water	2.0
Caffeine	0.05
Mineral oil (preservative-free)	qv100

A water-in-oil emulsion was prepared by adding the sodium salicylate and caffeine to the water and heating

to approximately 80°C for 1-2 minutes until clear. The brucine sulphate heptahydrate was dissolved in approximately 20.0 ml of ethanol by heating to a temperature of approximately 80°C. The mineral oil was heated to approximately 80°C and the sodium salicylate/caffeine and brucine solutions were added thereto. The resulting product was heated to approximately 90°C for approximately 5 - 10 minutes to evaporate the ethanol. The product was then homogenised until fully blended.

EXAMPLE 2

Ingredients	**% by weight**
Brucine sulphate heptahydrate	0.15
Sodium salicylate	1.5
Caffeine	0.05
Distilled Water	qv100

An aqueous formulation was prepared by adding the sodium salicylate and caffeine to the water and heating to approximately 80°C for 1-2 minutes until clear. The brucine sulphate heptahydrate was dissolved in approximately 20.0 ml of ethanol by heating to a temperature of approximately 80°C. The sodium salicylate/caffeine and brucine solutions were mixed together and heated to approximately 90°C for approximately 5 - 10 minutes to evaporate the ethanol.

The compositions prepared in Examples 1 and 2 were found to be effective in reducing trauma and regenerating damaged skin resulting from sunburn, minor burns and ulcers.

The results of a clinical study carried out using the emulsion of Example 1 are shown in Table I.

TABLE I

PATIENT NUMBER/ GENDER	AGE	OCCUPATION	TYPE OF BURN	SEVERITY OF BURN (1-5)*	TIME FROM INJURY TO TREATMENT	APPLICATION	RESULTS AND OBSERVATIONS
1. Female	55	Secretary	Hot Water	3	1 hour	Every 5 to 10 minutes for 3 hours	Pain gone in 10 minutes. Redness gone in 20 minutes. Completely healed by 3rd hour with no scarring. No further application needed
2. Female	41	Receptionist	Curling Iron	2	30 Minutes	Every 5 to 10 minutes for 4 hours	Pain gone by second application. Redness gone by 1st hour. No scarring.
3. Female	39	Lab Tech	Acid Burn	5	5 Minutes	Every 10 minutes for 1 day	Pain gone by 2nd hour. Most redness gone by 3rd hour. Product applied throughout 1st day. Redness greatly reduced on day 2. No pain on 2nd day. No scarring noticed
4. Male	25	Construction Worker	Sunburn	2	2 hours	Every 10 minutes for 1 day. Two applications next morning.	Pain gone by 1st Hour. Redness redacted to 75% by next morning. No scarring. No visible injury on 3rd day.
5. Male	41	Firefighter	Fire	3	4 hours	Every 10 minutes for 1 day. Once an hour the next day.	Pain gone by 4th application. Redness reduced by 50% next morning. Redness completely gone by end of second day. No pain on second day. No scarring noticed after one week.

Table I (cont'd)

PATIENT NUMBER/ GENDER	AGE	OCCUPATION	TYPE OF BURN	SEVERITY OF BURN (1-5) *	TIME FROM INJURY TO TREATMENT	APPLICATION	RESULTS AND OBSERVATIONS
6. Female	43	Billing Agent	Hot engine	3	2 hours	Every 10 to 15 minutes for 1 day	Most pain gone by 1st hour. All pain gone by end of day. Redness gone by 4th hour. No sign of scarring noticed after 2nd day
7. Male	14	Student	Friction burn from rope	2	3 hours	Every 10 minutes for 1½ days.	Pain gone by 1st hour. Redness cut in half by 4th application. No scarring noticed one week later.
8. Female	27	Office Worker	Severe sunburn	5	3½ days	Every 15 to 30 minutes for 2 days	Pain reduced by 50% after 4th hour. Pain completely gone by end 1st day. Normal activities resumed on second day. Redness reduced by 50-% by end of 1st day. Age spots appeared due to severity of burn. Able to return work on next day. Completely healed by 4th day.

- Severity of burn indicates a standard used by those involved in this clinical study to identify the severity of a burn, 1 being least painful and 5 being most painful.

- The amount of formulation applied was sufficient to cover the area being treated.

- Patient No. 8 had previously been to three other doctors and had not found success with any treatment until she had used the product of Example 1. She had not been to work for three days.

- Patients in this clinical study were all able to return to work or school with no problems after using the product of Example 1.

The invention is not limited to the embodiments and examples described herein which may be modified or varied without departing from the scope of the invention.

CLAIMS:

1. The use of brucine (2,3-dimethoxystrychnidin-10-one) or a dermatologically acceptable salt thereof, or a hydrate thereof, in the manufacture of a medicament for the treatment of damaged mammalian skin.

2. Use according to claim 1 wherein brucine is in the form of brucine sulphate heptahydrate.

3. A dermatological composition suitable for topical application to mammalian skin, which comprises:

(a) approximately 0.05-0.3% by weight of brucine or a dermatologically acceptable salt thereof, or a hydrate thereof;

(b) approximately 0.8-3% by weight of a hydroxy acid or a salt, ester or amide thereof;

(c) approximately 0.15-5% by weight of water; and

(d) the balance comprising a dermatologically acceptable oil or water or a combination thereof.

4. A composition according to claim 3, wherein brucine is in the form of brucine sulphate heptahydrate.

5. A composition according to claim 3 or 4, wherein brucine or a salt thereof or a hydrate thereof is

present in an amount of from approximately 0.1-0.2%, especially approximately 0.15% by weight of the composition.

6. A composition according to one or more of claims 3 to 5, wherein the hydroxy acid is selected from glycolic, lactic, malic, tartaric, citric, mandelic or salicylic acid, or a salt thereof, or a mixture thereof, preferably sodium salicylate.

7. A composition according to one or more of claims 3 to 6, wherein the hydroxy acid or salt, ester or amide thereof is present in an amount of from approximately 1.0-2.5%, preferably approximately 1.2-1.8%, and especially approximately 1.5%, by weight of the composition.

8. A composition according to one or more of claims 3 to 7, wherein component (c) of the composition comprises water in an amount of from approximately 0.5-3%, preferably from approximately 0.75-2.5%, and especially approximately 2%, by weight of the composition.

9. A composition according to one or more of claims 3 to 8, wherein component (d) consists of water.

10. A composition according to one or more of claims 3 to 8, which is in the form of a water-in-oil emulsion, wherein preferably, component (d) consists of a dermatologically acceptable oil.

11. A composition according to one or more of claims 3 to 8 or 10, wherein the dermatologically acceptable oil is mineral oil or a vegetable oil, or a mixture thereof.

12. A composition according to claim 11, wherein the oil is mineral oil, preferably mineral oil which is free from preservative.

13. A composition according to one or more of the preceding claims, further comprising a masking agent, preferably caffeine, the masking agent preferably being present in an amount of from approximately 0.03-0.08%, especially approximately 0.05%, by weight of the composition.

14. A composition according to one or more of claims 3 to 13 for use in the treatment of damaged mammalian skin.

15. A method of preparing a composition according to one or more of claims 3 to 13, comprising the following steps:

(a) heating the brucine or salt thereof or hydrate thereof in a solvent, preferably ethanol, until the brucine is dissolved;

(b) adding the hydroxy acid and masking agent, if present, to the water or a portion thereof and heating to a temperature in the range of from 70°C to 85°C until they are dissolved;

(c) heating the oil, if present, to a temperature in the range of from 70°C to 85°C;

(d) mixing the brucine and hydroxy acid solutions and any of the water remaining, or, if oil is present, adding the brucine and hydroxy acid solutions and any of the water remaining, to the heated oil; and

(e) heating the resulting product to a temperature in the range of from 80°C to 95°C so as to evaporate substantially all of the solvent.