COMPOSITIONS AND METHODS FOR TREATING EXCESS PIGMENTATION

FIELD OF THE INVENTION

[0001] The present disclosure generally relates to the field of biochemistry. It is referred herein to compositions and methods, in particular compositions and methods that reduce skin pigmentation or promote lightening of the skin, and uses thereof.

BACKGROUND OF THE INVENTION

[0002] Melasma is an acquired pigmentary disorder characterized by hyperpigmented macules and/or patches affecting sun-exposed skin. It most commonly affects females with darker skin types. Triggering factors include sun exposure, genetic influences and female sex hormones. Melasma, although not life threatening, poses a significant emotional and psychosocial burden on patients, and this has been reported in numerous studies. Multiple therapeutic approaches for melasma are available but the majority do not effectively reduce pigmentation over a prolonged period. To date, the approach to treating melasma includes the use of tyrosinase inhibitors, corticosteroids, retinoids, natural topical compounds, for example niacinamide, camouflage, and procedural therapies, such as chemical peels, micro-needling, LASER and light treatments.

[0003] The most effective treatments for melasma currently use topical creams containing hydroquinone alone or in combination with other active compounds, such as tretinoin and fluocinolone. However, few patients experience full removal of pigment and there is a high incidence of side effects such as skin irritation, erythema, irritant and allergic contact dermatitis. As such, there is a significant need for better formulation and agents for the treatment of melasma.

SUMMARY

[0004] In one aspect, provided herein is a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, for reducing excess pigmentation.

[0005] In one example, provided herein is a method of reducing excess pigmentation in a subject in need thereof, the method comprising administering a composition comprising a polyamine synthesis inhibitor to the subject.

[0006] In another example, provided herein is the composition described herein for use in treating excess pigmentation.

[0007] In another example, provided herein is the use of the composition described herein in the manufacture of a medicament for treating excess pigmentation.

[0007a] In another aspect, provided herein is the use of a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, in the manufacture of a medicament for treating or reducing excess pigmentation in a subject in need thereof, wherein the subject has melasma, solar lentigo, post-inflammatory hyperpigmentation, hyperpigmentation associated with inflammation, infection, aging, ochronosis, or a combination thereof, and wherein the composition is to be administered to the subject.

[0007b] In another aspect, provided herein is the composition described herein for use in therapy.

[0007c] In another aspect, provided herein is a method of cosmetically reducing excess pigmentation in a subject, the method comprising administering a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid to the subject.

DEFINITIONS

[0008] The term “excess pigmentation” refers to any state wherein the amount of pigmentation in the skin is deemed undesirably high. For example, an area of skin may have increased pigmentation compared to the rest of the skin surrounding said area, thus, said increased pigmentation may be considered as “excessive”, and said area has “excess pigmentation”. The terms “excess pigmentation” and “hyperpigmentation” can be used interchangeably. Excess pigmentation is generally caused by increased or abnormally high amounts of the skin pigment melanin in the skin or in the epidermis. Excess pigmentation can be associated with various physiological causes, such as inflammatory responses, yeast infections, pregnancy, hormonal changes, genetics, sun exposure and aging, etc. Excess pigmentation can be ameliorated by reduction of melanin in the skin or epidermis, for example, through reducing melanin production by melanocytes in the skin.

[0009] Some examples of excess pigmentation may include increased pigmentation caused by natural processes, such as aging, due to genetics, due to hormonal changes, benign skin lesions comprising excess pigmentation (e.g., in moles and freckles). Excess pigmentation may also be caused by pigmentation disorders such as hyperpigmentation disorders. Hyperpigmentation disorders may be caused directly or indirectly by medical conditions, and include but are not limited to melasma (also known as chloasma), lentigo (plural: lentigines) (e.g., solar and non-

solar lentigo), post-inflammatory hyperpigmentation (PIH), fungal infection (e.g., tinea versicolor), inflammation, or underlying medical conditions (e.g., acanthosis nigricans), drug-induced hyperpigmentation (e.g., ochronosis).

[0010] Melasma, also known as chloasma or the mask of pregnancy, appears as dark, irregular well demarcated hyper-pigmented macules to patches, commonly found on the upper cheek, nose, lips, upper lip, forehead, and other parts of the body that are exposed to the sun.

[0011] Post-inflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring after cutaneous inflammation or injury. PIH results from the overproduction of melanin or an irregular dispersion of pigment after cutaneous inflammation. PIH typically manifests as macules or patches in the same distribution as the initial inflammatory process.

[0012] Hyperpigmentation can also be associated with fungal infection, which is then considered to be a type of a skin condition known as tinea versicolor, also termed pityriasis versicolor. It can be caused by infection with fungi, for example, of the genus *Malassezia*, such

CLAIMS

What is claimed is:

1. A composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, for reducing excess pigmentation.
2. The composition of claim 1, wherein the polyamine synthesis inhibitor is an ornithine decarboxylase (ODC) inhibitor.
3. The composition of claim 2, wherein the ornithine decarboxylase inhibitor is selected from the group consisting of eflornithine, allicin, myricetin, 7,8-dihydroxyflavone, baicalein, and any combination thereof.
4. The composition of any one of claims 1 to 3, wherein the tyrosinase inhibitor is selected from the group consisting of hydroquinone, arbutin, azelaic acid, L-ascorbic acid, ellagic acid, kojic acid, tranexamic acid, and any combination thereof.
5. The composition of any one of claims 1 to 4, wherein the corticosteroid is selected from the group consisting of fluocinolone acetonide, betamethasone, clobetasol, desonide, hydrocortisone, triamcinolone, and any combination thereof.
6. The composition of any one of claims 2 to 5, wherein the concentration of the ornithine decarboxylase inhibitor in the composition is 0.05% to 15% w/w, the concentration of the tyrosinase inhibitor in the composition is 1% to 5% w/w, and the concentration of the corticosteroid in the composition is 0.005% to 0.015% w/w.
7. The composition of any one of claims 2 to 6, wherein the ornithine decarboxylase inhibitor is eflornithine, the tyrosine kinase inhibitor is hydroquinone, and the corticosteroid is fluocinolone acetonide.
8. The composition of claim 7, wherein the concentration of the eflornithine in the composition is 9.5% to 11.5% w/w.
9. The composition of claim 7, wherein the concentration of the hydroquinone in the composition is about 4% w/w.
10. The composition of claim 7, wherein the concentration of the fluocinolone acetonide in the composition is about 0.01% w/w.
11. The composition of any one of claims 1 to 10, wherein the composition is formulated for topical administration.
12. The composition of claim 11, wherein the composition is formulated as an aqueous hydrogel, an ointment, a cream, or a lotion.
13. The composition of any one of claims 1 to 12, wherein the composition further comprises one or more excipients.

14. Use of a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, in the manufacture of a medicament for treating or reducing excess pigmentation in a subject in need thereof, wherein the subject has melasma, solar lentigo, post-inflammatory hyperpigmentation, hyperpigmentation associated with inflammation, infection, aging, ochronosis, or a combination thereof, and wherein the composition is to be administered to the subject.

15. The use of claim 14, wherein the degree of pigmentation is reduced after administration of the composition.

16. The use of claim 15, wherein the degree of pigmentation is assessed using the modified Melasma Area Severity Index (mMASI), Physician Global Assessment (Physician IGA), Patient Global Assessment (Patient IGA) or any combination thereof, wherein after the administration of the composition:

    (i) the mMASI score of the subject is reduced;

    (ii) the Physician IGA score is improved by at least 1 grade;

    (iii) the Patient IGA score is improved by at least 1 grade; or

    (iv) any combination thereof of (i) to (iii).

17. The use of any one of claims 14 to 16, wherein one or more polyamines selected from the group consisting of putrescine, spermidine, spermine, or combinations thereof is reduced in the skin of the subject at the site of administration of the composition.

18. The use of any one of claims 14 to 17, wherein the composition is to be administered to the subject daily.

19. The use of any one of claims 14 to 18, wherein a fingertip unit is to be administered to the subject once daily, preferably at night, for at least 3 months.

20. The use of any one of claims 14 to 19, wherein one or more additional therapies for reducing excess pigmentation is to be further administered to the subject.

21. The use of claim 20, wherein the composition is to be administered to the subject before, after, or at the same time as the further administration of the one or more additional therapies for reducing excess pigmentation.

22. The composition of any one of claims 1 to 13 for use in therapy.

23. A method of cosmetically reducing excess pigmentation in a subject, the method comprising administering a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid to the subject.

24. The method of claim 23, wherein the degree of pigmentation is reduced after administration of the composition.

25. The method of any one of claims 23 and 24, wherein one or more polyamines selected from the group consisting of putrescine, spermidine, spermine, or combinations thereof is reduced in the skin of the subject at the site of administration of the composition.
26. The method of any one of claims 23 to 25, further comprising administering to the subject one or more additional cosmetic treatments for reducing excess pigmentation.
27. The method of claim 26, comprising administering the composition to the subject before, after, or at the same time as administering the one or more additional cosmetic treatments for reducing excess pigmentation.
28. The method of any one of claims 23 to 27, wherein the excess pigmentation in the subject is due to natural genetics, natural hormonal changes due to aging, or post-recovery scars.