

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
5 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
10 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
15 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
20 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 OF THE INVENTION

[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 another aspect, provided herein is a method of reducing excess pigmentation in a
30 subject in need thereof, the method comprising administering a composition comprising a
polyamine synthesis inhibitor to the subject.

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

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

DEFINITIONS

5 [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
10 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
15 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
20 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).

25 [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
30 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

as, but not limited to, *Malassezia globosa* and *Malassezia furfur*. Hyperpigmentation commonly appears as brown or reddish-brown patches and is generally caused by chemicals secreted by the yeast. Other infections caused by yeast species, which also present with hyperpigmentation, can be treated according to the method claimed herein.

5 [0013] Hyperpigmentation associated with aging includes solar lentigo, which appears as patches of darkened skin. It results from exposure to UV radiation, which causes local proliferation of melanocytes and accumulation of melanin within the keratinocytes. Solar lentigos are common in people over the age of 40 years. Sometimes it is also known as an “old age spot” or “senile freckle”.

10 [0014] The term “melanin” as used herein is a broad term for a group of natural pigments found in most organisms. Melanin is produced by the oxidation of the amino acid tyrosine, followed by polymerization. Melanin is produced in melanocytes and subsequently transported to the keratinocytes through dendrites. “Melanocyte” refers to melanin-producing cells located in the bottom layer (the stratum basale) of the skin’s epidermis, the middle layer of the eye (the uvea),
15 the inner ear, meninges, bones and heart. Each epidermal melanocyte is associated with a group of neighbouring keratinocytes, forming an epidermal melanocyte unit. “Keratinocyte” refers to the predominant cell type in the epidermis, which constitutes 90% of the cells found in the epidermis. The primary function of keratinocyte is the formation of a barrier against environmental damage. Keratinocytes contribute to protecting body from UV radiation by
20 taking up melanosomes, which are vesicles containing melanin. The melanin is then stored within keratinocytes.

[0015] The term “melanogenesis” as used herein refers to the process of producing melanin by melanocytes. Melanogenesis leads to a long-lasting pigmentation, which is in contrast to the pigmentation that originates from oxidation of existing melanin. Exposure to UV-B radiation
25 causes increased melanogenesis. Melanogenesis can take place in the melanocytes located in the skin.

[0016] As used herein, the singular form “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise. For example, the term “a polyamine synthesis inhibitor” includes a plurality of polyamine synthesis inhibitors, including mixtures and combinations
30 thereof.

[0017] As used herein, the term “about”, in the context of concentrations of components of the formulations, typically means +/- 5% of the stated value, more typically +/- 4% of the stated value, more typically +/- 3% of the stated value, more typically, +/- 2% of the stated value,

even more typically +/- 1% of the stated value, and even more typically +/- 0.5% of the stated value.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] The invention will be better understood with reference to the detailed description when considered in conjunction with the non-limiting examples and the accompanying drawings, in which:

[0019] **FIG. 1** shows the role of ornithine decarboxylase in skin pigmentation. **FIG. 1A** shows the biosynthetic pathway for the polyamines putrescine, spermidine and spermine from the common precursor, ornithine, wherein the first step of the conversion from ornithine to putrescine is catalysed by ornithine decarboxylase (ODC). The compound α -difluoromethylornithine (DFMO), also known as eflornithine, inhibits this pathway by inhibiting ODC. Ornithine decarboxylase in humans is encoded by the *ODCI* gene. **FIG. 1B** is a chart showing *ODCI* mRNA levels in melanocyte samples and shows that expression of *ODCI* is upregulated in the melanocytes in lesional skin from melasma patients compared to melanocytes in non-lesional skin from the same melasma patients. **FIG. 1C** is a paired micrograph of a skin section and a corresponding photograph of human *ex vivo* skin samples which were either untreated or treated with 0.5 mM putrescine (PUT) for 24 hours. Representative micrographs of samples from a single patient are shown here. The top and bottom micrographs on the left show fixed mounts of skin section stained with Fontana-Masson staining to show the melanin and the top and bottom photographs on the right show the corresponding skin samples. As shown in the bottom left micrograph, there are more melanin-containing cells (indicated by the arrows) in the putrescine-treated sample compared to the untreated sample, and the melanin-containing cells are darker, indicating higher amount of melanin in each cell. Overall, the skin contains more melanin after putrescine treatment. **FIG. 1D** is a chart quantifying the amount of melanin in the skin with and without treatment with 0.5 mM putrescine. Quantification of melanin levels was done via image analysis using the ImageJ software.

[0020] **FIG. 2** shows a comparison of the modified Melasma Area Severity Index (mMASI) scores from melasma patients after three months of treatment with either eflornithine in the form of Vaniqa® cream (“Treatment”) (**FIG. 2A**) or hydroquinone 2% cream (“Reference”) (**FIG. 2B**). **FIG. 2C** is a diagram showing how the mMASI score is calculated. The formula is $0.3A(f)D(f) + 0.3A(lm)D(lm) + 0.3A(rm)D(rm) + 0.1A(c)D(c)$, wherein (f) is forehead, (lm) is left malar, (rm) is right malar, (c) is chin, “A” represents “Area” and “D” represents “Darkness”.

[0021] FIG. 3 is a chart showing the assessment of melasma severity using the Physician Global Assessment (i.e., Physician IGA) (FIG. 3A) and Patient Global Assessment (i.e., Patient IGA) (FIG. 3B) after 3 months of treatment with either the composition described herein (labelled “Active”) or Tri-Luma® (labelled “Reference”). In both figures, a score of 0 = no melasma, 1 = mild melasma, 2 = moderate melasma and 3 = severe melasma. The y-axis indicates the proportion of patients, and the x-axis indicates the day of visit to the clinic, which is also the time at which the assessments were conducted.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The inventors of the present disclosure have set out to provide compositions suitable for reducing excess pigmentation and for inducing or promoting lightening of the skin. Also provided are alternative methods for reducing excess pigmentation and for inducing or promoting lightening of the skin.

[0023] In one aspect, provided herein is a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, for reducing excess pigmentation.

[0024] An inhibitor of a substance may be a molecule or compound that reduces an existing level of a substance. The reduction in level of a substance may be the result of various processes, for example, directly or indirectly preventing synthesis of the substance, directly or indirectly reducing the rate of synthesis of the substance, or directly or indirectly increasing the rate of degradation (e.g., by increasing catabolism) of the substance. Thus, an example of a polyamine synthesis inhibitor may be a molecule or compound that prevents or reduces the synthesis of a polyamine.

[0025] The most common polyamines in humans and other mammals are putrescine, spermidine, and spermine. In the first step of the biosynthetic pathway for production of said polyamines, ornithine is converted by the enzyme ornithine decarboxylase (ODC) to putrescine. Putrescine is then converted to spermidine, and spermidine to spermine. Thus, a suitable polyamine synthesis inhibitor may be any inhibitor that inhibits the rate of production of putrescine, spermidine, spermine, or any combination thereof via said biosynthetic pathway.

[0026] In one example, the polyamine synthesis inhibitor is an ornithine decarboxylase (ODC) inhibitor.

[0027] It is understood by those skilled the art that inhibition of an enzyme may comprise reversible or irreversible inhibition. Reversible inhibition refers to a temporary inhibition of enzymatic activity of an enzyme, generally due to an inhibitor binding reversibly to the enzyme. Irreversible inhibition refers to permanent inhibition of enzymatic activity of an enzyme,

generally due to an inhibitor binding irreversibly to the enzyme. An example of this type of inhibitor are small molecules and compounds that are capable of binding reversibly or irreversibly to an enzyme.

[0028] The ornithine decarboxylase enzyme in humans is encoded by the *ODCI* gene. Thus, suitable inhibitors of the ornithine decarboxylase may include, for example, any small molecule or compound capable of inhibiting ornithine decarboxylase enzymatic activity by binding, either reversibly or irreversibly, to the ornithine decarboxylase enzyme.

[0029] Some examples of ornithine decarboxylase inhibitors include but are not limited to eflornithine, allicin, myricetin, 7,8-dihydroxyflavone, and baicalein.

[0030] In one example, the ornithine decarboxylase inhibitor is selected from the group consisting of eflornithine, allicin, myricetin, 7,8-dihydroxyflavone, baicalein, and any combination thereof.

[0031] Suitable inhibitors of tyrosinase may include any small molecule or compound capable of reducing tyrosinase enzymatic activity by binding, either reversibly or irreversibly, to the tyrosinase enzyme.

[0032] Examples of tyrosinase inhibitors include but are not limited to hydroquinone, arbutin, azelaic acid, L-ascorbic acid, ellagic acid, kojic acid, and tranexamic acid.

[0033] In one example, 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.

[0034] A corticosteroid is a steroid hormone that is produced in the adrenal cortex, including derivatives and synthetic analogues thereof. While corticosteroids have effect on myriad physiological functions, this invention refers particularly to corticosteroids that affect skin pigmentation, for example, any corticosteroid that has an effect on inflammation in the skin.

[0035] Examples of suitable corticosteroids include but are not limited to fluocinolone, betamethasone, clobetasol, desonide, hydrocortisone and triamcinolone.

[0036] In one example, the corticosteroid is selected from the group consisting of fluocinolone acetonide, betamethasone, clobetasol, desonide, hydrocortisone, triamcinolone, and any combination thereof.

[0037] Formulations of the compositions described herein may comprise one or more active ingredients (“actives”) which are functionally active in reducing pigmentation. For example, the formulations may comprise one or more actives, wherein the actives are one or more of a polyamine synthesis inhibitor, an ornithine decarboxylase inhibitor, a tyrosinase inhibitor, and

a corticosteroid. In some examples, the formulations comprise eflornithine, hydroquinone, and fluocinolone acetonide as actives.

[0038] The actives present in formulations of the compositions described herein may be present in their free forms or as pharmaceutically acceptable salts thereof, hydrates thereof, 5 solvates thereof, and combinations thereof. For example, the compositions described herein may comprise an ornithine decarboxylase inhibitor, such as eflornithine, in its free form or as a pharmaceutically acceptable salt, hydrate, solvate, or combination thereof. The term “salt(s)” as used herein, refers to acid or basic salts. Methods of obtaining suitable pharmaceutically acceptable salts, hydrates, solvates, and combinations thereof are well known to those skilled 10 in the art, for example as discussed in *Handbook of Pharmaceutical Salts: Properties, Selection, and Use* (P. Heinrich Stahl, Camille G. Wermuth (Eds.), Verlag Helvetica Chimica Acta, Zurich (2008)). Salts of the actives may be formed, for example, by reacting said actives with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization. Such acid salts and base 15 salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

[0039] Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, 20 fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like.

[0040] Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, 25 lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and 30 dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

[0041] It is to be understood that formulations of the compositions described herein may be formulated with each of the actives in free form or as a pharmaceutically acceptable salt, hydrate, solvate, or combination thereof, in equivalent molar concentrations. For example, in a

composition comprising 12.45% w/w eflornithine hydrochloride monohydrate, the molar concentration of eflornithine in said composition is equivalent to about 9.58% w/w eflornithine free base (i.e., its free form). Accordingly, the compositions described herein are to be formulated to achieve the desired molar concentrations of the free form of the actives.

5 **[0042]** Unless otherwise stated, the actives referred to herein are the free form of the actives. For example, unless otherwise stated, it would be understood that the term “eflornithine” refers to the free form of eflornithine, the term “hydroquinone” refers to the free form of hydroquinone, and the term “fluocinolone acetonide” refers to the free form of fluocinolone acetonide.

10 **[0043]** The ornithine decarboxylase inhibitor, tyrosinase inhibitor and corticosteroid may be present in the composition in a range of concentrations that are effective for reducing pigmentation in the skin.

[0044] In one example, the concentration of the ornithine decarboxylase inhibitor in the composition is about 0.05% to 15% w/w, the concentration of the tyrosinase inhibitor in the
15 composition is about 1% to 5% w/w, and the concentration of the corticosteroid in the composition is about 0.005% to 0.015% w/w.

[0045] In some examples, the concentration of the ornithine decarboxylase inhibitor in the composition is about 0.05% to 0.1% w/w, about 0.1% to 0.2% w/w, about 0.2% to 0.3% w/w, about 0.3% to 0.4% w/w, about 0.4% to 0.5% w/w, about 0.5% to 0.6% w/w, about 0.6% to
20 0.7% w/w, about 0.7% to 0.8% w/w, about 0.8% to 0.9% w/w, about 0.9% to 1.0% w/w, about 1.0% to 2.0% w/w, about 2.0% to 3.0% w/w, about 3.0% to 4.0% w/w, about 4.0% to 5.0% w/w, about 5.0% to 6.0% w/w, about 6.0% to 7.0% w/w, about 7.0% to 8.0% w/w, about 8.0% to 9.0% w/w, about 9.0% to 10.0% w/w, about 10.0% to 11.0% w/w, about 11.0% to 12.0% w/w, about 12.0% to 13.0% w/w, about 13.0% to 14.0% w/w, or about 14.0% to 15.0% w/w.

25 **[0046]** In one example, the ornithine decarboxylase inhibitor is eflornithine.

[0047] In one example, the concentration of the eflornithine in the composition is about 9.5% to 11.5% w/w. In yet another example, the concentration of the eflornithine in the composition is about 9.5% to 9.6% w/w, for example, 9.58% w/w.

[0048] In some examples, the concentration of the tyrosinase inhibitor in the composition is
30 about 1.0% to 2.0% w/w, about 2.0% to 3.0% w/w, about 3.0% to 4.0% w/w or about 4.0% to 5.0% w/w.

[0049] In one example, the tyrosinase inhibitor is hydroquinone.

[0050] In one example, the concentration of the hydroquinone in the composition is about 4% w/w.

- 5 [0051] In some examples, the concentration of the corticosteroid in the composition is about 0.005% to 0.006% w/w, about 0.006% to 0.007% w/w, about 0.007% to 0.008% w/w, about 0.008% to 0.009% w/w, about 0.009% to 0.01% w/w, about 0.010% to 0.011% w/w, about 0.011% to 0.012% w/w, about 0.012% to 0.013% w/w, about 0.013% to 0.014% w/w or about 0.014% to 0.015% w/w.
- [0052] In one example, the corticosteroid is fluocinolone acetonide.
- [0053] In one example, the concentration of the fluocinolone acetonide in the composition is about 0.01% w/w.
- 10 [0054] The compositions described herein may be formulated in a format suitable for administration to the skin of a subject. Suitable formats for administration to the skin include any format that allows the skin or cells in the skin to be contacted with the composition. For example, the composition may be formulated for administration intradermally, cutaneously, subcutaneously, topically, transdermally, or any combination thereof.
- [0055] In one example, the composition is formulated for topical administration.
- 15 [0056] The compositions can be provided in various forms, the non-limiting examples of which include pastes, powders, dressings, creams, plasters, solutions, patches, gels, suspensions, aqueous liquid suspensions, non-aqueous liquid suspensions, oil-in-water emulsions, a water-in-oil liquid emulsions, solutions, sterile solids, crystalline solids, amorphous solids, solids for reconstitution or combinations thereof.
- 20 [0057] In one example, the composition is formulated as an aqueous hydrogel, an ointment, a cream, or a lotion.
- [0058] The compositions described herein may comprise one or more adjuvants, excipients, or any combinations thereof. An excipient is a substance that serves as a vehicle or medium for the active ingredient in the composition but is itself inactive. Some examples of suitable
- 25 excipients include but is not limited to solvents, emollients and/or emulsifiers, oil bases, preservatives, antioxidants, tonicity adjusters, penetration enhancers and solubilizers, chelating agents, buffering agents, surfactants, one or more polymers, and combinations thereof. An adjuvant is a substance that enhances the effect of the active ingredient in the composition but is itself not an active substance.
- 30 [0059] In one example, the composition further comprises one or more excipients selected from the group consisting of purified water, glycerin, 2-hydroxyethyl cellulose, Pluronic® F127 (poloxamer 407), butylated hydroxytoluene, caprylyl glycol, citric acid, ascorbic acid, sodium metabisulfite, and sodium citrate.

[0060] Those skilled in the art will understand that the excipients in the composition may be present in varying amounts as necessary to support the desired amounts of actives. In some examples, water may be present in the composition at between about 60% to 80% w/w, glycerin may be present in the composition at between about 3% to 10% w/w, 2-hydroxyethyl cellulose may be present in the composition at between about 1% to 5% w/w, Pluronic® F127 (poloxamer 407) may be present in the composition at between about 0.5% to 3% w/w, butylated hydroxytoluene may be present in the composition at between about 0.1% to 0.5% w/w, caprylyl glycol may be present in the composition at between about 0.5% to 2.0% w/w, citric acid may be present in the composition at between about 0.2% to 0.5% w/w, ascorbic acid may be present in the composition at between about 0.2% to 1.0% w/w, sodium metabisulfite may be present in the composition at between about 0.01% to 1.0% w/w, and sodium citrate may be present in the composition at between about 0.1% to 0.5% w/w.

[0061] In some examples, water as an excipient may function as a solvent, thus, a formulation of the composition may comprise certain percentage volume or percentage weight of actives and excipients other than water, and any remaining percentage volume or percentage weight of the composition is made up to 100% by water.

[0062] In one example, the composition is formulated as follows:

Table 1

Ingredient	% w/w	Activity
Eflornithine HCl monohydrate	12.45	Active
Hydroquinone	4	Active
Fluocinolone acetonide	0.01	Active
Purified water	72.37	Excipient
Glycerin	5	Excipient
2-hydroxyethyl cellulose	3	Excipient
Pluronic® F127 (poloxamer 407)	1	Excipient
Butylated hydroxytoluene	0.5	Excipient
Caprylyl glycol	0.5	Excipient
Citric acid	0.32	Excipient
Ascorbic acid	0.3	Excipient
Sodium metabisulfite	0.3	Excipient
Sodium citrate	0.25	Excipient
Total	100.00	

The exemplary formulation described in Table 1 comprises the molar equivalent of 9.58% w/w free base eflornithine, 4% free base hydroquinone, and 0.01% w/w fluocinolone acetonide as actives.

[0063] Accordingly, in one example, the composition described herein comprises 12.45% w/w eflornithine hydrochloride monohydrate (equivalent to 9.58% w/w eflornithine), 4% hydroquinone and 0.01% fluocinolone acetonide as actives, and further comprises 5% w/w glycerin, 3% w/w 2-hydroxyethyl cellulose, 1% w/w Pluronic® F127 (poloxamer 407), 0.5% w/w butylated hydroxytoluene, 0.5% w/w caprylyl glycol, 0.32% w/w citric acid, 0.3% w/w ascorbic acid, 0.3% w/w sodium metabisulfite, 0.25% w/w sodium citrate and 72.37% w/w purified water as excipients.

[0064] Methods for reducing excess pigmentation in a subject are also described herein.

[0065] In one aspect, 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.

[0066] The composition of the method described herein may also comprise one or more active substances suitable for reducing excess pigmentation, in addition to the polyamine synthesis inhibitor. The substances may work synergistically with the polyamine synthesis inhibitor in reducing excess pigmentation. For example, administering a composition comprising the polyamine synthesis inhibitor and one or more other active substances may result in an improved reduction of excess pigmentation compared to administering a composition solely comprising the polyamine synthesis inhibitor or any of the one or more active substances. Alternatively, administering a composition comprising the polyamine synthesis inhibitor and one or more other active substances may reduce excess pigmentation with fewer adverse effects or undesired effects compared to the administering a composition solely comprising the polyamine synthesis inhibitor or any of the one or more active substances. Still further, administering a composition comprising the polyamine synthesis inhibitor and one or more other active substances may result in improved reduction of excess pigmentation and with fewer adverse effects or undesired effects compared to the administering a composition solely comprising the polyamine synthesis inhibitor or any of the one or more active substances.

[0067] In one example, the method of reducing excess pigmentation in a subject in need thereof comprises administering a composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid to the subject.

[0068] In one example, the method comprises administering any one of the compositions described herein to the subject.

[0069] In one example, the degree of pigmentation is reduced after administration of the composition.

[0070] The degree of pigmentation in the subject may be determined by any method known to those skilled in art for measuring or quantifying the degree of pigmentation of the skin. The degree of pigmentation of the skin may be measured by visual inspection, for example by comparing the shade of the skin to a colour palette, or it may be measured using an electronic device capable of measuring skin colour, such as the SkinColorCatch colourimeter. The measurements obtained can then be fitted to a scale for assessing the degree of (alternatively, severity of) excess pigmentation or hyperpigmentation. Suitable scales for assessing the degree of hyperpigmentation are known to those skilled in the art. Some examples of such scales include, but is not limited to, the modified Melasma Area Severity Index (mMASI), the Physician Global Assessment (alternatively referred to as the Physician IGA) and the Patient Global Assessment (alternatively referred to as the Patient IGA). The degree of excess pigmentation or hyperpigmentation may range from “no hyperpigmentation” or “absence of hyperpigmentation” to “intermediate hyperpigmentation” and “severe hyperpigmentation”. “Intermediate” hyperpigmentation may include “mild” or “moderate” hyperpigmentation. It is understood by those skilled in the art that the degree of skin pigmentation is a continuum, and determination of specific degrees of pigmentation will depend on the scale used to determine the degree of pigmentation.

[0071] In one example, 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;
- (ii) the Patient IGA score is improved by at least 1 grade; or
- (iii) any combination thereof of (i) to (iii)

[0072] The methods described herein are suitable for reducing excess pigmentation by reducing melanin content in the affected area, for example in the skin. The melanin content in the skin may be reduced by several methods. For example, melanin content in the skin may be reduced by inhibiting production of melanin, by increased breakdown of melanin, or a combination of inhibiting production and increasing breakdown of melanin. Inhibiting production of melanin may be direct or indirect. For example, the production of melanin may be directly inhibited by the inhibiting the biosynthetic pathway that converts tyrosine into melanin, resulting in less melanin in the affected area. The production of melanin may also be

indirectly inhibited by inhibiting one or more substances that promote melanogenesis, for example, by reducing the level of polyamines in the affected area.

[0073] In one example, one or more polyamines selected from the group consisting of putrescine, spermidine, spermine, or combinations thereof is reduced in the skin of the subject
5 at the site of administration of the composition.

[0074] The amount of polyamine present in the skin can be moderated in response to inflammation and UV exposure, both of which can drive pigmentation. Thus, the method described herein is suitable for treating subjects having conditions comprising excess pigmentation, for example, melasma, post-inflammatory hyperpigmentation, solar lentigo and
10 any other condition comprising excess pigmentation.

[0075] It will also be apparent to those skilled in the art that the present invention may be suitable for treating conditions caused by undesirable or excessive melanin production, conditions caused by a disorder in melanogenesis, conditions caused by excessive polyamines such as putrescine, spermidine and/or spermine, or conditions caused by excess ornithine
15 decarboxylase or by increased ornithine decarboxylase activity.

[0076] The methods described herein may comprise administering the composition to a subject in doses and frequencies that are suitable for reducing skin pigmentation in the subject. In some examples, the composition may be administered at a certain dose and/or frequency initially, and the dose and/or frequency is subsequently adjusted. An adjustment in the dose and/or
20 frequency may be desired for example, to increase the effect of reduction of excess pigmentation or to reduce adverse effects or undesired effect.

[0077] In some examples, the composition may be administered to a subject three times daily, twice daily, once daily, or at any other appropriate interval.

[0078] The composition may be administered to the subject at times of the day that may be
25 beneficial for reducing excess pigmentation, or beneficial for the activity of the active ingredients. For example, administering the composition at night may be preferred so that the subject avoids exposure to sunlight when the active ingredients are effective. In another example, administering the composition at night may be preferred if one or more of the active ingredients are degraded faster when exposed to sunlight. In some examples, the composition
30 may be administered to a subject in the morning or at night.

[0079] In one example, the method comprises administering the composition to the subject daily, preferably at night.

[0080] The composition may be administered at a specified dose. For example, the amount to be administered may be a small fingertip unit.

[0081] The composition may be administered for a duration of time. For example, the composition may be administered for at least 1 week, at least 2 weeks, at least 3 weeks, at least 1 month, at least 2 months or at least 3 months.

[0082] In one example, the method comprises administering a fingertip unit to the subject once
5 daily, preferably at night, for at least 3 months.

[0083] The compositions described herein may be administered to the subject either alone or in combination with one or more other therapies for reducing excess pigmentation. Administration of the compositions described herein in combination with one or more other therapies may result in a synergistic improvement in the effect of reducing excess pigmentation.
10 In other examples, the one or more other therapies may work as an adjuvant to the compositions described herein.

[0084] In one example, the method further comprises administering to the subject one or more additional therapies for reducing excess pigmentation.

[0085] In some examples, the one or more other therapies include but is not limited to an active
15 substance for reducing excess pigmentation, a chemical peel, micro-needling, a LASER treatment or a light treatment, or combinations thereof. Examples of an active substance include but are not limited to a retinoid, niacinamide, a natural topical compound, a tyrosinase inhibitor, a corticosteroid, or combinations thereof.

[0086] In some examples, the compositions described herein may also be administered in
20 combination with a cosmetic camouflage or a cosmetic concealer.

[0087] In one example, the method comprises administering the composition to the subject before, after, or at the same time as administering the one or more additional therapies for reducing excess pigmentation.

[0088] The methods described herein are suitable for reducing excess pigmentation and are
25 thus particularly suitable for treating excess pigmentation in a subject. The term “treat” or “treating” as used herein refers to any measurable or quantifiable reduction in pigmentation, including partial or complete removal of excess pigmentation resulting from administration of the composition. The term “treat” or “treating” as used herein also includes the resolution of excess pigmentation resulting from administration of the composition.

[0089] In some examples, the methods described herein may be used to treat excess
30 pigmentation in a subject therapeutically, such as when the excess pigmentation is due to a hyperpigmentation disorder. In other examples, the methods described herein may be used to treat excess pigmentation in a subject cosmetically, such as when the excess pigmentation is due to natural genetics, natural hormonal changes due to aging, or post-recovery scars.

Accordingly, in some examples, the methods as described herein may be cosmetic methods of reducing excess pigmentation.

[0090] In one example, the subject has excess pigmentation due to melasma, solar lentigo, post-inflammatory hyperpigmentation, hyperpigmentation associated with inflammation,
5 infection, aging, ochronosis, or a combination thereof.

[0091] It will be apparent from the foregoing that the compositions described herein are suitable for use in treating conditions comprising excess pigmentation, particularly excess skin pigmentation.

[0092] In one aspect, provided herein is the composition described herein for use in treating
10 excess pigmentation.

[0093] In another aspect, provided herein is the use of the composition described herein in the manufacture of a medicament for treating excess pigmentation.

[0094] The invention illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus,
15 for example, the terms "comprising", "including", "containing", etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope
20 of the invention claimed. Thus, it should be understood that although the present invention has been specifically disclosed by specific embodiments and optional features, modification and variation of the inventions embodied therein herein disclosed may be resorted to by those skilled in the art, and that such modifications and variations are considered to be within the scope of this invention.

[0095] The invention has been described broadly and generically herein. Each of the narrower species and sub-generic groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0096] Throughout this disclosure, certain embodiments may be disclosed in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the disclosed ranges. Accordingly, the description of a range should be considered to have specifically disclosed all the possible sub-ranges as well as individual numerical values within that range.

For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed sub-ranges such as from 1 to 3, from 1 to 4, from 1 to 5, from 2 to 4, from 2 to 6, from 3 to 6 etc., as well as individual numbers within that range, for example, 1, 2, 3, 4, 5, and 6. This applies regardless of the breadth of the range.

- 5 [0097] Other embodiments are within the following claims and non- limiting examples. In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby described in terms of any individual member or subgroup of members of the Markush group.

10 **EXPERIMENTAL EXAMPLES**

[0098] The following examples illustrate methods by which aspects of the invention may be practiced or materials suitable for practice of certain embodiments of the invention may be prepared.

15 **Example 1: Effect of putrescine on skin pigmentation**

[0099] The inventors of the present disclosure found that the polyamines, for example putrescine, spermidine, and spermine, may promote skin pigmentation by promoting melanogenesis in melanocytes in the skin. As it is known in the art that ornithine decarboxylase (ODC) is a rate limiting enzyme in the biosynthesis of putrescine (FIG. 1A), the inventors
20 sought to determine whether ODC was associated with melanogenesis. Microarray analysis was performed on laser captured micro-dissected melanocytes isolated from lesional and non-lesional epidermal skin from three female patients with melasma. The scattergram of the fold change in the expression of ODC1 mRNA shows that *ODC1* mRNA was higher in melanocytes from lesional skin compared to non-lesional skin in melasma patients (FIG. 1B), suggesting
25 that higher levels of ODC was indeed associated with increased skin pigmentation.

[0100] To further investigate the theory that increased levels of putrescine in the skin causes increased skin pigmentation, the inventors treated a human *ex vivo* skin sample with putrescine. Normal skin tissue treated with 0.5 mM putrescine for 24 hours. had close to two-fold greater melanin levels compared to untreated normal skin tissue (FIG. 1C and 1D), indicating that
30 increased levels of putrescine is indeed associated with increased skin pigmentation. Taken together, the results suggest that inhibiting polyamine synthesis by inhibiting the rate-limiting enzyme, ornithine decarboxylase, may be effective in reducing skin pigmentation.

Example 2: Effect of ODC1 inhibitors on skin pigmentation

[0101] Eflornithine (alternatively, DFMO) is an inhibitor of ODC enzymatic activity and has been demonstrated to reduce polyamine levels in human subjects. Eflornithine hydrochloride cream is sold under the trade name Vaniqa®. To determine whether inhibiting ODC1 may
5 reduce skin pigmentation, a double blind, split face, non-inferiority trial was conducted where the effect of eflornithine (in the form of a Vaniqa® cream comprising 11.5% eflornithine free base) was compared with the current gold-standard for treating melasma, hydroquinone (in the form of a hydroquinone 2% cream). Melasma patients were treated for three months with twice daily applications. A total of 15 patients were recruited and included for analysis. Both
10 eflornithine and hydroquinone treatments produced significant improvements in the total modified Melasma Area Severity Index (mMASI) score at visits 2 and 3 compared with visit 1 (FIG. 2A and 2B). As a non-inferiority trial, this shows that eflornithine is at least as effective as hydroquinone in the treatment of melasma.

Example 3: Effect of eflornithine in combination with hydroquinone and fluocinolone in treating melasma

[0102] The results of the non-inferiority trial indicated that eflornithine may be suitable for treating melasma. As such, a composition for treating melasma comprising a combination of eflornithine, hydroquinone, and fluocinolone was formulated. The composition, “eflornithine
20 combination”, was formulated as a cream comprising 12.45% w/w eflornithine hydrochloride monohydrate (equivalent to 9.58% w/w eflornithine free base), 4% w/w hydroquinone, and 0.01% w/w fluocinolone acetate as actives. The efficacy of eflornithine combination was compared to Tri-Luma® cream (comprising 4% hydroquinone, 0.05% tretinoin, and 0.01% fluocinolone as actives) for treating melasma via a clinical trial.

[0103] A total of 30 patients were recruited from the outpatient clinic at the Singapore National Skin Centre for the trial. After a washout period of 2 weeks, patients were asked to apply eflornithine 9.58% + hydroquinone 4% + fluocinolone 0.01% cream once a day on one side of the face and tretinoin 0.05% + hydroquinone 4% + fluocinolone 0.01% cream once a day on the other side of the face over a three-month period. All patients were also educated on the need
25 for sun protection and were prescribed a standard commercially available sunscreen of SPF 50 and PA +++.

[0104] Efficacy assessments were measured both quantitatively and qualitatively. Quantitative assessments included the measurement of modified MASI score of each side of face on Day 0, 56 and 84. mMASI were scored clinically by 3 dermatologists who were blinded to the

treatment allocations. In addition, improvement in melanin index were also measured thrice via SkinColorCatch over a fixed area of skin. In terms of qualitative assessment, 3 dermatologists who were blinded to the treatment allocation assessed the degree of improvement via clinical photographs taken on Day 0, 56 and 84. Patient Global Assessment (alternatively referred to as the Patient IGA) scores and Physician Global Assessment (alternatively referred to as the Physician IGA) scores were also obtained. For each side of the face, patient and physician were asked to grade the severity of melasma from a score of 0 (cleared), 1 (mild), 2 (moderate) to 3 (severe).

[0105] Eligible patients were adults aged 25-70 with a diagnosis of melasma. Other inclusion criteria included skin type 3 and 4, provision of written informed consent as well as similar melasma severity scale score on both sides of the face at baseline. Exclusion criteria include pregnant or lactating patients, patients known to be uncooperative as well as patients with known contact allergy to any of the ingredients in topical medication such as such as eflornithine hydrochloride, hydroquinone, fluocinolone acetonide, tretinoin, methyparaben, polyethylene glycol.

[0106] For statistical analysis, the hypothesis H_1 is that there is a difference between the changes in mMASI score across the two treatments if either of the combination is better than the other. The values of the mMASI scores at the initial visit (Day 0) differ between the sides of the face (left $\neq$ right). Hence, we take the difference values between the left and right sides of the face, computed using the following formula:

$$\begin{aligned} \text{Difference}_X &= \text{Reduction}_{\text{Active},X} - \text{Reduction}_{\text{Reference},X} \\ &= (mMASI_{\text{Day } 0, \text{Active}} - mMASI_{\text{Day } X, \text{Active}}) - (mMASI_{\text{Day } 0, \text{Reference}} - mMASI_{\text{Day } X, \text{Reference}}) \end{aligned}$$

[0107] A positive difference value indicates that there was a larger reduction in the mMASI value on the active treatment side to compared to the reference treatment side. Wilcoxon signed rank tests were used to test the hypotheses.

Results

[0108] Of the 30 patients who were recruited into the trial, 3 dropped out, one due to adverse effects from Tri-Luma® application and 2 due to failure to follow up. The melasma severity across both sides of the face were similar (according to mMASI score) at the beginning of the trial.

[0109] Table 2 shows the mean MASI (mMASI) scores for the eflornithine combination group (Active) versus the Tri-Luma® group (Reference) at day 0 were approximately equal (Active = 2.29 vs. Reference = 2.28), indicating that the severity of the melasma was similar on both

side of the face at the start of the trial. With active treatment, the mMASI score of the patients decreased from 2.29 to 1.14 (1.13 reduction) on Day 56 and further decrease to 0.77 (1.49 reduction) on Day 84. On the other hand, mMASI score for reference treatment only decreased to 1.53 (0.72 reduction) on Day 56 and 1.25 (0.99 reduction) on Day 84. These results show that the eflornithine combination is better in improving severity of melasma than Tri-Luma® and the effect can be seen as early as Day 56.

Table 2: mMASI scores, eflornithine combination (Active) vs. Tri-Luma® (Reference).

mMASI Score – mean (standard deviation)			
Day of Visit	n	Treatment	
		Active	Reference
Day 0	30	2.29 (1.36)	2.28 (1.30)
Day 56	29	1.14 (0.89)	1.53 (1.05)
Day 84	27	0.77 (0.83)	1.25 (0.84)
Reduction in mMASI Score – mean (standard deviation)			
Period	n	Active	Reference
Day 0 – Day 56	29	1.13 (0.84)	0.72 (0.91)
Day 0 – Day 84	27	1.49 (1.10)	0.99 (0.87)

[0110] Table 3 presents the difference in reduction in mMASI score between the active and reference treatments with statistical analysis of the difference values.

Table 3: Statistical analysis of the reduction in mMASI scores.

Difference in mMASI Score Reduction – mean (standard deviation)					
Period	n	Active*	Reference*	Wilcoxon Signed Rank Test	Estimate (Pseudomedian)†
Day 0 – Day 56	29^	2.29 (1.36)	2.28 (1.30)	T = 166.5, p-value = 0.004†	0.60 (95% CI: 0.15, 0.90)
Day 0 – Day 84	27^	1.14 (0.89)	1.53 (1.05)	T = 200.5, p-value = 0.003†	0.75 (95% CI: 0.30, 1.05)
^Observations with missing data were removed from the set. *Descriptive statistics are presented as median (interquartile range). †Values not exact due the presence of ties and zero differences.					

[0111] The Physician Global Assessment score is an assessment method that is conducted by a skilled practitioner. Referring to FIG. 3A, in the active treatment (eflornithine) group, a shift towards lower values in the distribution of physician IGA values was observed on days 56 and

84, with a sharp decrease in the proportion of higher values (IGA values of 2 and 3) from 68.96% on day 0 to 18.52% on day 84 (proportions have been converted to percentages throughout this paragraph for easier understanding). An increase in the proportion of lower values (IGA values of 0 and 1) was observed on both days 56 and 84, with an increase from 31.03% on day 0 to 81.49% on day 84. In the reference treatment (Tri-Luma®) group, a shift towards lower physician IGA values was observed on days 56 and 84. However, the magnitude of the shift appeared to be smaller, with no changes in the proportion of 0 values across both days, even though the change in severe values (IGA value of 3) proportion is identical to the active treatment group. The overall proportion of higher values in the reference treatment group remained large by day 84, comprising 51.85% of the observations.

[0112] In the Patient Global Assessment, patients are provided with guidance to conduct the assessment individually. Referring to FIG. 3B, it is observed that, similar to the analysis of physician IGA values, a shift towards lower values on days 56 and 84 is observed for both active and reference treatment groups. However, the overall magnitude of this shift appears to be smaller in the reference treatment group compared to the active group, as evidently, the active treatment group has a larger number of lower IGA values (e.g., IGA score of 0 or 1). The proportion of the higher values in the active group decreased over the duration of the trial. Accordingly, the proportion of lower values in the active group increased from 3.33% of the observations at the beginning of the trial to 66.67% by day 84. By day 84, there were no “Severe” observations in the active group. The reference group had no instances of “0” scores on day 84, although the proportion of “Mild” values (IGA value of 1) increased from 3.33% to 48.15%.

Safety and irritability of combination creams

[0113] Table 4 shows that none of the trial subjects suffered from skin irritation at the start of the clinical trial (Day 0). At Day 56, a total of 4 trial subjects (13.3%) in the active group and 10 trial subjects (33.3%) in the reference group suffered from severity 1 or severity 2 skin irritation. At Day 84, 3 trial subjects (10%) in active group and 8 trial subjects (26.7%) in the reference group suffered from severity 1 or severity 2 skin irritation. This indicates that eflornithine combination has minimal side effects when compared to Tri-Luma®. This is surprising, because both formulations comprise 4% hydroquinone, and while tretinoin is not present in the active (eflornithine) formulation, it is also not the main active ingredient in Tri-Luma®. Thus, it appears that the use of eflornithine in combination with hydroquinone may have some effect in reducing the side effects of hydroquinone use.

Table 4: Adverse events during the trial

Time Point	Treatment	Severity of Adverse Event		
		0 (No irritation)	1 (Mild irritation)	2 (Irritation, requiring alternate day application)
Day 0	Active	30	0	0
	Reference	30	0	0
Day 56	Active	25	3	1
	Reference	19	5	5
Day 84	Active	24	2	1
	Reference	19	3	5

[0114] The incidence and severity of the adverse events (AEs) differed between the two treatment groups. The active treatment observed a total of 7 AEs, which were predominantly mild irritation (71.43%). In contrast, the reference group observed a higher total number of 18 AEs, with a larger proportion of severe irritation (55.56%). This suggests the reference treatment is linked to both greater incidence and severity of AEs than the active treatment

Example 4: Permeation of the eflornithine composition to the skin and topical formulation of the composition

[0115] An *in vitro* permeation experiment was conducted with native human skin explants and studied for 8 hours after a single application. Eflornithine was found in both the epidermis and dermis, at $2.91 \pm 2.248 \mu\text{g}$ and $12.80 \pm 3.409 \mu\text{g}$ respectively. No eflornithine was recovered in receptor fluid containing phosphate buffered saline (PBS). This suggested that eflornithine was able to permeate the *stratum corneum* (SC) and was retained in the dermal layer within 8 hours of application. Similarly, hydroquinone was found in the epidermis, dermis and receptor fluid, at $1.87 \pm 0.224 \mu\text{g}$, $2.77 \pm 0.912 \mu\text{g}$ and $4.10 \pm 5.488 \mu\text{g}$ respectively. A minimal amount of hydroquinone penetrated the SC and permeated the skin in the first few hours only, before reaching an equilibrium. Fluocinolone acetonide could not be detected because it is not soluble in PBS. The permeation experiment result suggests that the two main active ingredients, eflornithine and hydroquinone are able to cross the skin barrier and reached the skin cells responsible for melanin production. A topical formulation of the eflornithine composition was developed (Table 1) and can be kept at room temperature (25 °C) for 90 days.

CLAIMS

What is claimed is:

1. A composition comprising a polyamine synthesis inhibitor, a tyrosinase inhibitor and a corticosteroid, for reducing excess pigmentation.
- 5 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.
- 10 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.
- 15 6. The composition of any one of claims 2 to 5, wherein the concentration of the ornithine decarboxylase inhibitor in the composition is about 0.05% to 15% w/w, the concentration of the tyrosinase inhibitor in the composition is about 1% to 5% w/w, and the concentration of the corticosteroid in the composition is about 0.005% to 0.015% w/w.
- 20 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 about 9.5% to 11.5% w/w.
- 25 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.
- 30 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. 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.
15. The method of claim 14, comprising administering to the subject the composition of any one of claims 1 to 13.
16. The method of claims 14 or 15, wherein the degree of pigmentation is reduced after administration of the composition.
17. The method of claim 16, 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).
18. The method of any one of claims 14 to 17, 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.
19. The method of any one of claims 14 to 18, comprising administering the composition to the subject daily.
20. The method of any one of claims 14 to 19, comprising administering a fingertip unit to the subject once daily, preferably at night, for at least 3 months.
21. The method of any one of claims 14 to 20, further comprising administering to the subject one or more additional therapies for reducing excess pigmentation.
22. The method of claim 21, comprising administering the composition to the subject before, after, or at the same time as administering the one or more additional therapies for reducing excess pigmentation.
23. The method of any one of claims 14 to 22, wherein the subject has melasma, solar lentigo, post-inflammatory hyperpigmentation, hyperpigmentation associated with inflammation, infection, aging, ochronosis, or a combination thereof.
24. The composition of any one of claims 1 to 13 for use in treating excess pigmentation.
25. Use of the composition of any one of claims 1 to 13 in the manufacture of a medicament for treating excess pigmentation.

26. The composition for use according to claim 24 or the use of claim 25, wherein the excess pigmentation is melasma, solar lentigo, post-inflammatory hyperpigmentation, hyperpigmentation associated with inflammation, infection, aging, or ochronosis.
27. The composition for use according to claim 24 or the use of claim 25, wherein the
5 composition is to be administered to a subject.