



(51) International Patent Classification:

A61Q 19/02 (2006.01) A61K 8/49 (2006.01)

A61K 8/9789 (2017.01) A61K 8/63 (2006.01)

A61K 8/9794 (2017.01)

(21) International Application Number:

PCT/US2018/029507

(22) International Filing Date:

26 April 2018 (26.04.2018)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201710292478.X 28 April 2017 (28.04.2017) CN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: COMPOSITION FOR TREATING SKIN PIGMENTATION

(57) Abstract: A composition for treating skin pigmentation, a method of forming the composition, and a method of treating skin pigmentation are disclosed. The composition comprises at least one pharmaceutically acceptable additive. The composition further comprises at least one melanin production inhibitor, which may be a depigmentation agent. The melanin production inhibitor is present in an amount effective to inhibit melanin production in human skin cells of a subject that is administered the composition. The melanin production inhibitor is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, *Rhodiola alga* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, *Astragali complanati* semen extract, *Plantaginis* semen extract, *Lycopi herba* extract, *Euryales* semen extract, *Cuscutae* semen extract, *Amomi fructus* extract, *Tara* seed extract, *Platycladi cacumen* extract, *Eucommiae cortex* extract, *Dioscoreae rhizoma* extract, *Cirsii herba* extract, and combinations thereof.



COMPOSITION FOR TREATING SKIN PIGMENTATION

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to and all advantages of Chinese Patent Application No. 201710292478.X filed on 28 April 2017, the content of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] This disclosure provides a composition for treating human skin pigmentation, a method of forming the composition, and a method of treating human skin pigmentation.

BACKGROUND OF THE INVENTION

[0003] Melanin is important for protecting human skin from damage induced by radiation. The accumulation of melanin in human skin cells can result in pigmentation disorders, such as melasma, freckles, ephelides, and senile lentigines, also referred to as liver spots or age spots. Aging and exposure to ultraviolet radiation from the sun can increase the occurrence of these and other types of pigmentation disorders.

[0004] Melanin is produced in a specialized group of cells known as melanocytes, which are located in the basal layer of the epidermis. Melanin production is controlled at least in part by tyrosinase enzymes and is produced by the oxidation of the amino acid tyrosine, followed by polymerization to produce the pigment melanin.

[0005] While melanin is useful in protecting human skin from sun damage, darkening of the skin as a result of melanin production can be aesthetically undesirable to some individuals. Skin lightening treatments and cosmetics are often used by individuals to reduce the appearance of pigmentation disorders, such as freckles or age spots. Conventional cosmetics only temporarily reduce the visibility of the undesirable pigmentation and can be inconvenient to use on a regular basis and on certain parts of the body.

[0006] Conventional skin lightening treatments can decrease the appearance of certain pigmentation disorders, but are often associated with undesirable side-effects. Hydroquinone is one example of a common skin lightener, however higher hydroquinone doses may require a prescription from a dermatologist. In some individuals, hydroquinone may cause undesirable discoloration of the skin. Arbutin is an example of a skin lightener that is derived from plants, such as mulberry, cranberry, bearberry and blueberry leaves. Arbutin is a glycosylated hydroquinone and thus may result in undesirable side effects that are similar to hydroquinone in some individuals.

[0007] While various efforts have been made, there remains an opportunity to provide additional methods and compositions for treating skin pigmentation disorders, particularly in lightening the appearance of dark spots on the skin and optionally preventing the formation of visible dark spots on the skin.

BRIEF SUMMARY OF THE INVENTION

[0008] Disclosed is a composition. The composition can be used for treating human skin pigmentation. The composition comprises at least one pharmaceutically acceptable additive. The composition further comprises at least one melanin production inhibitor. The melanin production inhibitor is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi semen* extract, *Synotis erythropappa* extract, *Astragali complanati semen* extract, *Plantaginis semen* extract, *Lycopi herba* extract, *Euryales semen* extract, *Cuscutae semen* extract, *Amomi fructus* extract, *Tara seed* extract, *Platycladi cacumen* extract, *Eucommiae cortex* extract, *Dioscoreae rhizoma* extract, *Cirsii herba* extract, and combinations thereof. The melanin production inhibitor is present in an amount effective to inhibit melanin production in human skin cells of a subject that is administered the composition.

[0009] A method of forming the composition is also disclosed. The method comprises providing at least one pharmaceutically acceptable additive and providing at least one melanin production inhibitor. The melanin production inhibitor is as described above. The method further comprises combining the pharmaceutically acceptable additive and the melanin production inhibitor to form the composition.

[0010] A method of treating human skin pigmentation of a subject is also disclosed. The method comprises providing a topical composition. The method further comprises applying the topical composition to skin of the subject. The topical composition comprises the composition as described above.

[0011] The composition and methods are useful for providing a composition for treating pigmentation in a human subject's skin. Treating pigmentation in human skin can include inhibiting melanin production in treated human skin cells. Optionally, treating pigmentation in human skin includes decreasing an amount of melanin present in the subject's skin cells following treatment. The methods and compositions disclosed herein for inhibiting melanin production and optionally decreasing an amount of melanin present in a subject's skin cells can be used to visually lighten the subject's skin and optionally inhibit further darkening of the subject's skin.

[0012] According to various embodiments of the invention, a composition for treating pigmentation in human skin includes one or more pharmaceutically acceptable additives and at least one melanin production inhibitor. The at least one melanin production inhibitor can be selected from the group consisting of Cyclovirobuxine D (CAS No. 860-79-7, C₂₆H₄₆N₂O, 402.67g/mol), Lipoic acid (CAS No. 62-46-4, C₈H₁₄O₂S₂, 206.32 g/mol), Nuciferine (CAS No. 475-83-2, C₁₉H₂₁NO₂, 295.38 g/mol), Peimisine (CAS No. 19773-24-

1, $C_{27}H_{41}NO_3$, 427.62 g/mol), Oleuropein (CAS No. 32619-42-4, $C_{25}H_{32}O_{13}$, 540.51 g/mol), *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, *Astragali complanati* semen extract, *Plantaginis* semen extract, *Lycopi herba* extract, *Euryales* semen extract, *Cuscutae* semen extract, *Amomi fructus* extract, *Tara* seed extract, *Platycladi cacumen* extract, *Eucommiae cortex* extract, *Dioscoreae rhizoma* extract, *Cirsii herba* extract, and combinations thereof. The at least one melanin production inhibitor can be present in an amount effective to inhibit melanin production in human skin cells.

[0013] In various embodiments, the at least one melanin production inhibitor is present in an amount effective to inhibit tyrosinase enzyme activity in human skin cells. The at least one melanin production inhibitor for inhibiting tyrosinase enzyme activity can be selected from the group consisting of lipoic acid, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, and combinations thereof.

[0014] In various embodiments, the at least one melanin production inhibitor is present in an amount effective to decrease a concentration of melanin present in human skin cells. The at least one melanin production inhibitor for decreasing a concentration of melanin can be selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, *Rhodiola kirilowii* (Regel) Maxim extract, *Platycladi* semen extract, and combinations thereof.

[0015] In various embodiments, the pharmaceutically acceptable additives can be selected from the group consisting of water, glycerin, waxes, alcohols, vegetable oils, mineral oils, silicones, fatty esters, fatty alcohols, glycols, polyglycols, and combinations thereof. The composition can be provided in a form including at least one of a gel, a cream, an aerosol spray, a dispersion, an oil-in-water emulsion, a water-in-oil emulsion, a water-in-silicone emulsion, a foam, a liquid, a mousse, a pomade, a powder, a solid, and an ointment suitable for topical application to human skin.

[0016] In various embodiments, a blend for inclusion in a topical treatment for human skin includes at least one depigmentation agent. The at least one depigmentation agent can be selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, *Rhodiola kirilowii* (Regel) Maxim extract, *Platycladi* semen extract, and combinations thereof. The at least one depigmentation agent can be present in an amount effective to decrease a concentration of melanin present in human skin cells subsequent to application of the topical treatment on human skin.

[0017] In various embodiments, a blend for inclusion in a topical treatment for human skin includes at least one melanin production inhibitor. The at least one melanin production

inhibitor can be present in an amount effective to inhibit melanin production in human skin cells subsequent to application of the topical treatment on human skin.

[0018] In various embodiments, a method of preparing a composition for treating human skin is provided. The method includes providing one or more pharmaceutically acceptable additives and providing at least one melanin production inhibitor in an amount effective to inhibit melanin production in human skin cells.

[0019] Without being bound or limited by any particular theory, it is thought that the methods and compositions of this disclosure are useful for treating skin pigmentation, and more particular for lightening of the skin and/or inhibiting darkening of the pigmentation of a subject's skin. These and other objects, advantages, and features of the invention will be more fully understood and appreciated by reference to the detailed description and drawings.

[0020] Before the embodiments of the invention are explained in detail, it is to be understood that the invention is not limited to the details of operation or to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention may be implemented in various other embodiments and practiced or carried out in alternative ways not expressly disclosed herein. Also, it is to be understood that the phraseology and terminology used herein are for the purpose of description and should not be regarded as limiting. The use of "including" and "comprising" and variations thereof is meant to encompass the items listed thereafter and equivalents thereof as well as additional items and equivalents thereof. Further, enumeration may be used in the description of various embodiments. Unless otherwise expressly stated, the use of enumeration should not be construed as limiting the invention to any specific order or number of components. Nor should the use of enumeration be construed as excluding from the scope of the invention any additional steps or components that might be combined with or into the enumerated steps or components.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Other advantages of the disclosure will be readily appreciated, as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings wherein:

[0022] Figure 1 is a graph illustrating the cell toxicity of nuciferine according to an embodiment;

[0023] Figure 2 is a graph illustrating the cell toxicity of peimisine according to an embodiment;

[0024] Figure 3 is a graph illustrating the cell toxicity of *Platycladi* semen extract according to an embodiment;

[0025] Figure 4 is a graph illustrating the cell toxicity of *Lycopi herba* extract according to an embodiment;

[0026] Figure 5 is a graph illustrating the percent of melanin synthesis inhibition for cells treated with nuciferine according to an embodiment;

[0027] Figure 6 is a graph illustrating the percent of melanin synthesis inhibition for cells treated with peimisine according to an embodiment;

[0028] Figure 7 is a graph illustrating the percent of melanin synthesis inhibition for cells treated with *Platycladi* semen extract according to an embodiment;

[0029] Figure 8 is a graph illustrating the percent of melanin synthesis inhibition for cells treated with *Lycopi herba* extract according to an embodiment;

[0030] Figure 9 is a graph illustrating the percent of melanin elimination for cells treated with nuciferine according to an embodiment;

[0031] Figure 10 is a graph illustrating the percent of melanin elimination for cells treated with peimisine according to an embodiment; and

[0032] Figure 11 is a graph illustrating the percent of melanin elimination for cells treated with *Platycladi* semen extract according to an embodiment.

DETAILED DESCRIPTION OF THE INVENTION

[0033] A skin treatment composition, a method for forming a skin treatment composition, and a method of using a composition for skin treatment (e.g. lightening skin of a subject) are disclosed. The skin treatment composition may simply be referred to hereinafter as “the composition.” The composition and methods are useful for providing a composition for treating skin pigmentation in a human subject.

[0034] As used herein, “treating skin pigmentation” refers to inhibiting melanin production in human skin cells and/or decreasing an amount of melanin present in human skin cells. The term “depigmentation agent” is used to refer to a compound, a plant extract, or a combination of materials that is/are capable of decreasing an amount of melanin present in a skin cell and/or reducing the pigmentation effect of melanin already present in a skin cell. The term “melanin production inhibitor” is used to refer to a compound, a plant extract, or a combination of materials that is/are capable of inhibiting the production of melanin in a skin cell. Treating skin pigmentation can include lightening of a subject’s skin, lightening of a dark spot or mole on a subject’s skin, inhibiting an increase in pigmentation in the subject’s skin (also referred to as “darkening”), and/or inhibiting formation of a dark spot or mole on the subject’s skin. Other potential non-limiting benefits are described herein.

[0035] The composition includes at least one component capable of inhibiting melanin production in a subject’s skin cells. Optionally, the composition includes at least one depigmentation agent for decreasing a concentration of existing melanin in a subject’s skin

cell(s). In certain embodiments, the composition includes a depigmentation agent different from the melanin production inhibitor. In various embodiments, the composition includes a combination of one or more melanin production inhibitors and one or more depigmentation agents. In certain embodiments, the composition includes a component that is both a melanin production inhibitor and a depigmentation agent.

[0036] In various embodiments, the melanin production inhibitor is a compound capable of inhibiting the production of melanin in skin cells. In certain embodiments, the compound for inhibiting the production of melanin in skin cells is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, and combinations thereof. In specific embodiments, the melanin production inhibitor comprises or is cyclovirobuxine D. In other specific embodiments, the melanin production inhibitor comprises or is lipoic acid. In yet other specific embodiments, the melanin production inhibitor comprises or is nuciferine. In further specific embodiments, the melanin production inhibitor comprises or is peimisine. In yet further specific embodiments, the melanin production inhibitor comprises or is oleuropein.

[0037] In various embodiments, the melanin production inhibitor is a plant extract capable of inhibiting the production of melanin in skin cells. In certain embodiments, the plant extract for inhibiting the production of melanin in skin cells is selected from the group consisting of an extract (or extracts) of *Rhodiola algida*, *Rhodiola kirilowii* (Regel) Maxim, *Glycyrrhizae Radix et Rhizoma* (including *Glycyrrhiza inflata* Bat.), *Cirsii japonici herba* (including *Cirsium japonicum* Fisch. ex DC), *Platycladi semen* (including *Platycladus orientalis* L. Franco), *Synotis erythropappa*, *Astragali complanati semen* (including *Astragalus complanatus* R. Br.), *Plantaginis semen* (including *Plantago asiatica* L. and *Plantago depressa* Willd.), *Lycopi herba* (including *Lycopus lucidus* turcz. Var. *hirtus* Regel), *Euryales semen* (including *Euryale ferox* Salisb.), *Cuscutae semen* (including *Cuscuta australis* R. Br. and *Cuscuta chinensis* Lam.), *Amomi fructus* (including *Amomum villosum* Lour., *Amomum villosum* Lour. var. *xanthioides* T.L. Wu et Senjen, and *Amomum longiligulare* T.L. Wu), *Tara seed* (including *Caesalpinia spinose* Kuntze), *Platycladi cacumen* (including *Platycladus orientalis* L. Franco), *Eucommiae cortex* (including *Eucommiae cortex* and *Eucommia ulmoides* Oliv.), *Dioscoreae rhizoma* (including *Dioscorea opposita* Thunb.), *Cirsii herba* (including *Cirsium setosum* (Willd.) MB), and combinations thereof. In further embodiments, the composition includes a combination of compound(s) and/or plant extract(s) capable of inhibiting the production of melanin in skin cells.

[0038] In various embodiments, the depigmentation agent is a compound capable of decreasing an amount of existing melanin present in skin cells. In certain embodiments, the

depigmentation agent compound is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, and combinations thereof.

[0039] In various embodiments, the depigmentation agent is a plant extract capable of decreasing an amount of melanin present in skin cells. In certain embodiments, the depigmentation agent plant extract is selected from the group of an extract (or extracts) of *Rhodiola kirilowii* (Regel) Maxim, *Platycladi* semen, and combinations thereof.

[0040] In various embodiments, the composition includes a compound or plant extract that is both a melanin production inhibitor and a depigmentation agent. Examples of components that exhibit both melanin production inhibition capabilities and depigmentation capabilities include cyclovirobuxine D, lipoic acid, nuciferine, peimisine, *Rhodiola kirilowii* (Regel) Maxim extract, and *Platycladi* semen extract. It is to be appreciated that combinations of such components may be used.

[0041] In various embodiments, the composition includes at least one melanin production inhibitor and/or depigmentation agent and optionally consists essentially of a melanin production inhibitor and/or depigmentation agent. As used herein, the phrase "consisting essentially of" generally encompasses the specifically recited elements/components for a particular embodiment. Further, the phrase "consisting essentially of" generally encompasses and allows for the presence of additional or optional elements/components that do not materially impact the basic and/or novel characteristics of that particular embodiment. In certain embodiments, "consisting essentially of" allows for the presence of ≤ 10 , ≤ 5 , or ≤ 1 , weight percent (wt.%) of additional or optional components based on the total weight of the skin treatment composition.

[0042] In various embodiments, the composition includes one or more pharmaceutically acceptable additives that are inactive ingredients. Examples of inactive ingredients include, but are not limited to, fragrances; preservatives; alcohols, such as ethanol, propyl alcohol and benzyl alcohol; glycerin; binders; flow agents; glyceryl triacetate; vegetable oils, such as hydrogenated vegetable oils; mineral oils; water; silicones, such as silicone oils; silicon dioxide; waxes, such as carnauba wax and beeswax; fatty esters and fatty alcohols; glycols and polyglycols; and combinations thereof. If utilized to form the composition, the inactive ingredient(s) can be used in various amounts and combined with the melanin production inhibitor and/or depigmentation agent to form a composition that is suitable for topical application to human skin. It is to be further appreciated that the amounts of actives described herein can be normalized with respect to 100 parts by weight of the composition to account for the presence of inactive ingredients (if utilized).

[0043] As used herein, reference to "plant extract" generally refers to an extract containing material from any species within the identified genus, unless the particular species is

identified. Unless otherwise identified, any part of the plant may be used to obtain the extract used in the composition including, but not limited to, the root, stem, rhizome, leaf, flower, fruit, and/or extracts of these parts. The plant extract may be commercially obtained from various resources. In addition, suitable plant extracts can be obtained by using any conventional extraction technique including, but not limited to, one or more techniques described further below.

[0044] The melanin production inhibitor can be present in the composition in an amount effective to inhibit melanin production when topically applied to a human skin cell. Optionally, the melanin production inhibitor is present in the composition in an amount effective to inhibit tyrosinase enzyme activity in human skin cells. In various embodiments, the concentration of the melanin production inhibitor is about 20 percent by weight (% wt.) or less. Optionally, multiple melanin production inhibitors are combined or blended for use in a skin treatment composition. When multiple melanin production inhibitors are combined, the individual concentration or combined concentration of each melanin production inhibitor may be an amount effective to inhibit melanin production when topically applied to a human skin cell. Optionally, the individual concentration or combined concentration of each melanin production inhibitor is an amount effective to inhibit tyrosinase enzyme activity in human skin cells.

[0045] In various embodiments, the amount of melanin production inhibitor(s) present in the composition can depend upon several factors, including the desired level of melanin inhibition, the melanin inhibiting level in a particular compound, plant extract, or composition, and other factors. In certain embodiments, the melanin production inhibitor(s) is(are) present an amount of from about 0.01 to about 20 part(s) by weight ("pbw") based on 100 pbw of the composition. In further embodiments, the melanin production inhibitor(s) is(are) present in an amount of from about 0.05 to about 15 pbw, optionally about 0.1 to about 10 pbw, or optionally about 1 to about 5 pbw, based on 100 pbw of the composition. Various subranges and amounts between about 0.01 and about 20 pbw, as well as amounts that are less than or greater than these amounts, are also contemplated.

[0046] The depigmentation agent can be present in the composition in an amount effective to decrease a concentration of melanin present in a human skin cell. Optionally, the depigmentation agent is present in an amount effective to inhibit melanin production and decrease a concentration of melanin in a human skin cell. In various embodiments, the concentration of the depigmentation agent is about 20 percent by weight (% wt.) or less. Optionally, depigmentation agents are combined or blended for use in a skin treatment composition. When multiple depigmentation agents are combined, the individual

concentration or combined concentration of each depigmentation agent may be an amount effective to decrease a concentration of existing melanin present in human skin cells.

[0047] In various embodiments, the amount of depigmentation agent(s) present in the composition can depend upon several factors, including the desired level of melanin inhibition, the melanin inhibiting level in a particular compound, plant extract, or composition, and other factors. In certain embodiments, the depigmentation agent(s) is(are) present in an amount of from about 0.01 to about 20 pbw based on 100 pbw of the composition. In further embodiments, the melanin production inhibitor(s) is(are) present in an amount of from about 0.05 to about 15 pbw, optionally about 0.1 to about 10 pbw, or optionally about 1 to about 5 pbw, based on 100 pbw of the composition. Various subranges and amounts between about 0.01 and about 20 pbw, as well as amounts that are less than or greater than these amounts, are also contemplated.

[0048] The plant extracts can be obtained via conventional extraction methods understood in the art, such as by water (e.g. steam) extraction or by solvent (e.g. alcohol) extraction. The composition of this disclosure is not limited to a particular extraction method, nor is extraction required since suitable extracts (e.g. standardized extracts) are readily available from a number of commercial suppliers. Exemplarily extraction methods are described below.

[0049] To obtain an extract, a polar solvent such as an alcohol (e.g. methanol, ethanol, butylene glycol), an ether (e.g. ethyl ether), a ketone (e.g. acetone), an ester (e.g. ethyl acetate), water, or mixtures thereof, can be used as a solvent. Certain extracts can be also obtained by further extracting the extract from the polar solvent with a non-polar solvent. Suitable non-polar solvents include, but are not limited to, ethyl acetate, hexane, dichloromethane, chloroform, or mixtures thereof.

[0050] There are a variety of extraction methods that may be used to produce extracts suitable for the composition. These methods include, but are not limited to, the extraction methods disclosed in U.S. Patent 7,897,184, which is hereby incorporated by reference in its entirety and partially reproduced below with respect to some extraction methods. While extraction solvents described specifically mention ethanol, other alcohols such as, but not limited to, isopropyl alcohol, ethyl alcohol, and/or methyl alcohol may be used in addition to or as an alternative to ethanol. Exemplary alcoholic solvents include, but are not limited to, C₁-C₄ alcohols, such as methanol, ethanol, propanol, isopropanol, and butanol; hydro-alcohols or mixtures of alcohol and water, including hydro-ethanol; polyhydric alcohols, such as propylene glycol and butylene glycol; and fatty alcohols. Any of these alcoholic solvents may be used. Other solvents such as, but not limited to, acetone may also be used as an

extraction solvent. Solvent-water blends, e.g. alcohol-water and/or acetone-water blends, of any ratio, may also be used.

[0051] In one example, the extracts can be obtained using an organic solvent extraction technique. In another example, solvent sequential fractionation can be used to obtain the extracts. Total hydro-ethanolic extraction techniques can also be used to obtain the extracts. Generally, this is referred to as a lump-sum extraction. Extracts generated in the process will contain a broad variety of phytochemicals present in the extracted material including fat soluble, liposoluble, and water soluble phytochemicals. Following collection of the extract solution, the solvent will be evaporated, resulting in the extract.

[0052] Total ethanol extraction may also be used. This technique uses ethanol as the solvent. This extraction technique generates an extract that may include fat soluble, liposoluble, and/or lipophilic compounds in addition to water soluble compounds. Total methanol extraction may also be used in a similar manner with similar results.

[0053] Another example of an extraction technique that can be used to obtain the extracts is carbon dioxide supercritical fluid extraction ("SFE"). In this extraction procedure, the material to be extracted is not exposed to any organic solvents. Rather, the extraction solvent is carbon dioxide (CO₂), with or without a modifier, in supercritical conditions (e.g. >31.3°C and >73.8 bar). Those of skill in the art will appreciate that temperature and pressure conditions can be varied to obtain the best yield of extract. This technique generates an extract of fat soluble, liposoluble, and/or lipophilic compounds, similar to total hexane and ethyl acetate extraction techniques, which may also be used.

[0054] The composition can be prepared using various methods. For example, actives of the composition, and optionally one or more inactives, can be mixed or blended and compressed or compounded utilizing various techniques understood in the art. The composition of this disclosure is not limited to a particular order of manufacturing steps or method of manufacture.

[0055] In various embodiments, the composition is administered topically by application to the subject's skin. The subject is typically a human, and can include men and women of various ages. The method/composition of this disclosure is not limited to a particular subject.

[0056] The composition can be in various forms. Examples of suitable forms include solids, gels and liquids. For example, the composition can be formulated for application as a gel, cream, lotion, pomade, mousse, powder, or foam for application to the subject's skin. In another example, the composition can be formulated for spraying onto a subject's skin. The composition can be formulated to be sprayed as either an aerosol spray or pump spray. In still another example, the composition can be formulated for application using a pre-moistened towelette. In another example, the composition can be formulated as a solid that

is rubbed onto the subject's skin. In another example, the composition is formulated for delivery through a patch that is adhered to the subject's skin.

[0057] Other than the melanin production inhibitors and/or the depigmentation agents (i.e., the “actives” or “active ingredients”), the composition can include pharmaceutically acceptable additives that are inactives (or “inactive ingredients”) including, but not limited to, excipients, such as diluents and binders; granulating agents; glidants (or flow aids); fillers; lubricants; preservatives; stabilizers; coatings; disintegrants; fragrances; and pigments. Further examples of inactive ingredients are described above. The active ingredients and the pharmaceutically acceptable additives can be combined or compounded as desired to form an individual dose that provides the desired amount of active ingredient to the human subject when topically applied.

[0058] Optionally, the composition may include one or more additional components such as additives. Suitable additives include those understood in the art, including but not limited to, moisturizers, emollients, emulsifiers, surfactants, oils, extracts, skin protectants, disinfectants, antiseptics, drugs and drug substances, analgesic compounds, anti-neuralgic compound, anti-oxidants, blood circulation promoters, antidepressant compounds, anti-anxiety compounds, anti-stress compounds, sunscreens, insect repellants, preservatives, exfoliants, fragrances, colors, fillers, solvents, vehicles, carriers, other types of additives known to those of skill in the art, and combinations thereof. Such additives may be utilized alone or in combination. In general, the optional additives may be of any type used in personal care products and cosmetic products.

[0059] It is to be appreciated that certain components or additives may be classified under different terms of art and just because a component or additive is classified under such a term does not mean that they are limited to that function. If utilized, the additive or additives may be present in the composition in various amounts. Additional ingredients for optional use in the composition are described in U.S. Patent No. 5,747,006 to Dornoff et al., U.S. Patent Nos. 5,980,904, 6,994,874, 7,060,304, 7,247,321, and 7,364,759 to Leverett et al., and U.S. Publication No. 2017/0252293 to Brumbaugh et al., the disclosures of which are hereby incorporated by reference in their entirety.

[0060] In various embodiments, the method of use may also be referred to as a cosmetic method for skin lightening. Specifically, the composition is useful for and may be used for skin lightening (or whitening). More specifically, the composition can be used for lightening skin of a subject. The subject is typically a human, and can include men and women of various ages. The composition is not limited to a particular subject or location of skin on the subject. For example, a person may apply the composition to their face, neck, arms, hands,

chest, torso, legs, feet, etc., or any combination thereof. Such skin areas may be hyper-pigmented or hypo-pigmented.

[0061] The composition may be applied as needed, daily, several times per day or in any suitable regimen such that the desired outcome is achieved. In the method of this disclosure, the frequency of administration (e.g. topical application) can depend on several factors, including the desired level of skin lightening or the frequency and/or color of dark spots. Generally, a regimen includes application of the composition once or twice daily to include an administration in the morning and/or an administration in the evening. The amount and/or frequency of application of the composition may depend on several factors, including the level of desired results and the specific composition.

INDUSTRIAL APPLICABILITY

[0062] The composition can be used to treat pigmentation in a subject's skin by inhibiting the production of melanin in the subject's skin cells and/or by decreasing a concentration of existing melanin in the subject's skin cells. The composition can be applied to topically to lighten the subject's overall skin appearance and to prevent darkening of the subject's skin as a result of melanin production. Optionally, the composition is applied to a particular area of the subject's skin, such as a dark spot or mole, to lighten the area and/or to prevent further darkening of the area.

[0063] Active ingredients suitable for treating pigmentation in a subject's skin include compounds and plant extracts that are capable of inhibiting the production of melanin skin cells and/or are capable of decreasing a concentration of existing melanin in skin cells. Surprisingly, it was discovered that several compounds and plant extracts are capable of inhibiting the production of melanin skin cells and/or are capable of decreasing a concentration of existing melanin in skin cells to the same degree or greater than conventional skin lightening compounds. In addition, many of the compounds and plant extracts of the composition performed similar to or better than conventional skin lightening compounds in *in vitro* testing, with similar or better toxicity.

[0064] The following examples, illustrating the compositions and methods of this disclosure, are intended to illustrate and not to limit the disclosure.

EXAMPLES

[0065] The effects of the present skin treatment compounds and plant extracts were evaluated in vitro using a B16-F10 (ATCC# CRL-6475) cell model. The B16-F10 cell model is a *mus musculus* (mouse) melanoma skin cell line. The skin treatment compounds and plant extracts were evaluated for cell toxicity, inhibition of melanin synthesis, inhibition of tyrosinase enzyme activity, and elimination of existing melanin in B16-F10 cells. Tables 1

and 2 below list the 5 skin treatment compounds and 17 skin treatment plant extracts evaluated, respectively.

[0066] Table 1: Skin Treatment Compounds

Compounds	
Cyclovirobuxine D	Peimisine
Lipoic acid	Oleuropein
Nuciferine	n/a

[0067] Table 2: Skin Treatment Plant Extracts

Plant Extracts		
<i>Rhodiola algida</i>	<i>Astragali complanati</i> semen	<i>Tara</i> seed
<i>Rhodiola kirilowii</i> (Regel) Maxim	<i>Plantaginis</i> semen	<i>Platycladi cacumen</i>
<i>Glycyrrhizae Radix et Rhizoma</i>	<i>Lycopi herba</i>	<i>Eucommiae cortex</i>
<i>Cirsii japonici herba</i>	<i>Euryales</i> semen	<i>Dioscoreae rhizoma</i>
<i>Platycladi</i> semen	<i>Cuscutae</i> semen	<i>Cirsii herba</i>
<i>Synotis erythropappa</i>	<i>Amomi fructus</i>	n/a

Toxicity

[0068] The toxicity of the skin treatment compounds and plant extracts was evaluated using the CellTiter-Glo® (CTG) Luminescent Cell Viability Assay from Promega Corporation. The assay determines the number of viable cells in culture based on quantitation of the ATP present, which is indicative of the presence of metabolically active cells. Hydroquinone is a conventional skin lightening compound and was therefore selected for use as a positive control in the assay.

[0069] Cells were treated with either a skin treatment compound or plant extract or the positive control (i.e., hydroquinone) at multiple concentrations within the range of 0.01 to 100 ug/mL for 72 hours. The CellTiter-Glo® reagent was added to the cells and the luminescence was obtained according to the assay instructions provided by Promega Corporation. The IC₅₀ was calculated for each skin treatment compound or plant extract and the corresponding positive control. The results are summarized in Table 3 below.

[0070] Table 3: Cellular Toxicity for the Skin Lightening Compounds & Plant Extracts vs. Hydroquinone

Skin Treatment Compound/Plant Extract	IC₅₀ (Hydroquinone IC₅₀) ($\mu\text{g/mL}$)
Cyclovirobuxine D	>100 (3.7)
Lipoic acid	>100 (2.2)
Nuciferine	62.2 (1.9)
Peimisine	>50 (3.4)
Oleuropein	90.3 (3.3)
<i>Rhodiola algida</i> extract	>100 (4.4)
<i>Rhodiola kirilowii</i> (Regel) Maxim extract	>100 (5.2)
<i>Glycyrrhizae Radix et Rhizoma</i> extract	74.5 (4.1)
<i>Cirsii japonici herba</i> extract	77.6 (7.0)
<i>Platycladi</i> semen extract	78.8 (8.1)
<i>Synotis erythropappa</i> extract	>100 (5.9)
<i>Astragali complanati</i> semen extract	>100 (5.4)
<i>Plantaginis</i> semen extract	>100 (7.0)
<i>Lycopi herba</i> extract	>100 (6.8)
<i>Euryales</i> semen extract	>100 (3.2)
<i>Cuscutae</i> semen extract	75.9 (4.8)
<i>Amomi fructus</i> extract	>100 (4.2)
Tara seed extract	>100 (4.2)
<i>Platycladi cacumen</i> extract	>100 (9.3)
<i>Eucommiae cortex</i> extract	95.8 (5.0)
<i>Dioscoreae rhizoma</i> extract	>100 (4.5)
<i>Cirsii herba</i> extract	>100 (4.1)

[0071] Referring to the Figures, Figures 1-4 illustrate toxicity curves for Nuciferine, Peimisine, *Platycladi* semen extract, and *Lycopi herba* extract (squares), respectively, compared to a hydroquinone positive control (triangles). The data in Table 3 and Figures 1-4 demonstrates that each of the skin lightening compounds and plant extracts are significantly less toxic than the conventional skin lightening compound hydroquinone.

Melanin Synthesis Inhibition

[0072] The ability of the skin treatment compounds and plant extracts to inhibit melanin synthesis was evaluated. Melanin is the pigment in skin cells that is responsible for coloring

of the skin and various pigmentation disorders, such as age spots and freckles. Inhibition of melanin synthesis may result in lightening of the skin color and/or inhibit further darkening of the skin color. Arbutin is a conventional plant-derived compound used in skin lightening treatments and was therefore selected for use as a positive control.

Procedure

[0073] B16-F10 cells were trypsinized using Trypsin-EDTA (GIBCO Cat. #25200-072) and cell density was determined. The cell slurry was diluted to a concentration of 18,000 cells per milliliter (mL) in a growth media containing RPMI 1640 (GIBCO Cat. #22400-089) supplemented with fetal bovine serum (GIBCO Cat. #10099-141). The diluted cell slurry was dispensed into the wells of a 24 well cell culture plate (BD Falcon Cat. #353047) at 1 mL per well (18,000 cells/well). The cells were incubated overnight at 37 °C and 5 % CO₂ in humid conditions.

[0074] The plated cells were treated by preparing a 200x dilution of each skin lightening compound, plant extract, and arbutin (i.e., the positive control; Sigma Cat. #A4256) in 100% dimethyl sulfoxide (DMSO; Sigma Cat. #D2650). 5 µL of the 200x dilution was added to each well. The treated cells were incubated for 72 hours at 37 °C and 5 % CO₂ in humid conditions. The skin lightening compounds and plant extracts were evaluated at concentrations of 0 (untreated), 10, 50, and 100 µg/mL. Arbutin was evaluated at concentrations of 0 (untreated), 25, 125, and 250 µg/mL.

[0075] When the treatment period was completed, the medium from each well was discarded and the cells were washed once with 1 mL per well of DPBS (Dulbecco's Phosphate-Buffered Saline; Biosera Cat. #LM-S2041). The DPBS wash was removed and 150 µL of 1N sodium hydroxide was added to each well for 30 minutes while the cells were incubated at 80 °C to lyse the cells. Next, 145 µL from each well was transferred to an ultraviolet (UV) plate and the remaining 5 µL was tested to determine the protein concentration. The UV absorbance of each well was determined using a plate reader with the primary wave length set to 400 nm.

[0076] Melanin synthesis inhibition was determined using the UV absorbance at 400 nm according to the following equation:

$$\%Inh = (\text{Max signal} - \text{Compound signal}) / (\text{Max signal} - \text{Min signal}) \times 100$$

[0077] Where “%Inh” is the percent inhibition of melanin synthesis, the “Max signal” is the UV absorption for untreated cells, and the “Min signal” is the UV absorption of cells treated with 500 µg/mL arbutin.

Results

[0078] The results of the melanin synthesis inhibition assay are provided in Table 4 below. The percent of melanin synthesis inhibition for each skin lightening compound and plant

extract at the 100 µg/mL treatment concentration is compared with the percent inhibition for arbutin at the 125 µg/mL treatment concentration.

[0079] Table 4: Melanin Synthesis Inhibition for the Skin Lightening Compounds & Plant Extracts vs. Arbutin

Skin Treatment Compound/Plant Extract	% Melanin Synthesis Inhibition Skin Treatment Compound/Plant Extract (Arbutin)*
Cyclovirobuxine D	53.2 (61.4)
Lipoic acid	30.3** (61.4)
Nuciferine	104.3 (65.3)
Peimisine	62.1 (83.8)
Oleuropein	--
<i>Rhodiola algida</i> extract	52.5 (97.6)
<i>Rhodiola kirilowii</i> (Regel) Maxim extract	60.8 (97.6)
<i>Glycyrrhizae Radix et Rhizoma</i> extract	30.7 (97.4)
<i>Cirsii japonici herba</i> extract	123.7 (49.8)
<i>Platycladi</i> semen extract	91.4 (83.4)
<i>Synotis erythropappa</i> extract	82.0 (91.4)
<i>Astragali complanati</i> semen extract	80.8 (73.2)
<i>Plantaginis</i> semen extract	75.7 (84.4)
<i>Lycopi herba</i> extract	73.8 (84.4)
<i>Euryales</i> semen extract	63.6 (95.1)
<i>Cuscutae</i> semen extract	62.2 (73.2)
<i>Amomi fructus</i> extract	61.6 (95.1)
Tara seed extract	59.8 (96)
<i>Platycladi cacumen</i> extract	59.1 (93.4)
<i>Eucommiae cortex</i> extract	56.1 (97.4)
<i>Dioscoreae rhizoma</i> extract	46.6 (83.4)
<i>Cirsii herba</i> extract	34.4 (95.1)

* % inhibition determined for the skin treatment compound/extract at a 100 µg/mL treatment concentration and arbutin at a 125 µg/mL. Values are the average of two treatment wells.

** % inhibition for lipoic acid at a concentration of 50 µg/mL was 53.9 %, compared to 61.4 % inhibition with treatment of 125 µg/mL arbutin.

-- Data not obtained.

[0080] Figures 5-8 illustrate example melanin synthesis inhibition data for Nuciferine, Peimisine, *Platycladi* semen extract, and *Lycopi herba* extract (squares), respectively, compared to the arbutin positive control (triangles).

[0081] The data in Table 4 and Figures 5-8 demonstrates that many of the skin lightening compounds and plant extracts tested exhibited similar or increased ability to inhibit melanin synthesis production compared to a higher concentration of the positive control, arbutin.

Tyrosinase Enzyme Activity

[0082] The ability of the skin treatment compounds and plant extracts to inhibit tyrosinase enzyme activity was evaluated. Tyrosinase enzyme is involved in melanin production and thus inhibition of tyrosinase may suppress melanin production, which may result in lightening of skin color and/or inhibition of further darkening of skin color. Arbutin is a conventional plant-derived compound used in skin lightening treatments and was therefore selected for use as a positive control.

Procedure

[0083] B16-F10 cells were trypsinized using Trypsin-EDTA and cell density was determined. The cell slurry was diluted to a concentration of 18,000 cells per milliliter (mL) in a growth media containing RPMI 1640 supplemented with fetal bovine serum. The diluted cell slurry was dispensed into the wells of a 24 well cell culture plate (BD Falcon Cat. #353047) at 1 mL per well (18,000 cells/well). The cells were incubated overnight at 37 °C and 5 % CO₂ in humid conditions.

[0084] The plated cells were treated by preparing a 200x dilution of each skin lightening compound, plant extract, and arbutin (positive control) in 100% DMSO. 5 µL of the 200x dilution was added to each well. The treated cells were incubated for 72 hours at 37 °C and 5 % CO₂ in humid conditions. The skin lightening compounds and plant extracts were evaluated at concentrations of 0 (untreated), 10, 50, and 100 µg/mL. Arbutin was evaluated at concentrations of 0 (untreated), 25, 125, and 250 µg/mL.

[0085] When the treatment period was completed, the medium from each well was discarded and the cells were washed once with 1 mL per well of DPBS. The DPBS wash was removed and 80 µL of PBS with 0.1 % Triton-X was added to each well and the cells were frozen at -80 °C to lyse the cells. The cells were frozen and recovered 3 times. The lysed cells were transferred to a V-bottom plate and centrifuged at 3000 rpm for 10 min. at 4 °C. Next, 60 µL of the supernatant for each sample was added to a UV plate and diluted with 140 µL of 3,4-Dihydroxy-L-phenylalanine (L-DOPA; SIGMA Cat. #D9628). The samples were incubated for 1 hour at 37 °C. The UV absorbance of each well was determined using a plate reader with the primary wave length set to 475 nm.

[0086] Tyrosinase inhibition was determined using the UV absorbance at 475 nm according to the following equation:

$$\%Inh = (\text{Max signal} - \text{Compound signal}) / (\text{Max signal} - \text{Min signal}) \times 100$$

[0087] Where “%Inh” is the percent inhibition of tyrosinase, the “Max signal” is the UV absorption for cells treated with L-DOPA, and the “Min signal” is the UV absorption of cells not treated with L-DOPA.

Results

[0088] The results of the tyrosinase enzyme inhibition assay are provided in Table 5 below. The percent of tyrosinase inhibition for each skin lightening compound and plant extract at the 100 µg/mL treatment concentration is compared with the percent inhibition for arbutin at the 125 µg/mL treatment concentration.

[0089] Table 5: Tyrosinase Inhibition for the Skin Lightening Compounds & Plant Extracts vs. Arbutin

Skin Treatment Compound/Plant Extract	% Tyrosinase Inhibition Skin Treatment Compound/Plant Extract (Arbutin)*
Lipoic acid	98.6 (41.8)
<i>Rhodiola algida</i> extract	36.2 (52.8)
<i>Rhodiola kirilowii</i> (Regel) Maxim extract	52.4 (52.8)
<i>Glycyrrhizae Radix et Rhizoma</i> extract	73.3 (13.6)
<i>Cirsii japonici herba</i> extract	63.1 (29.0)
<i>Platycladi</i> semen extract	70.6 (38.3)
<i>Synotis erythropappa</i> extract	56.0 (38.3)

* % inhibition determined for the skin treatment compound/plant extract at a 100 µg/mL treatment concentration and arbutin at a 125 µg/mL. Values are the average of two treatment wells.

[0090] The data in Table 5 demonstrates that many of the skin lightening compounds and plant extracts tested exhibited similar or increased ability to inhibit tyrosinase enzyme activity compared to a higher concentration of the positive control, arbutin.

Melanin Elimination

[0091] The ability of the skin treatment compounds and plant extracts to eliminate existing melanin within skin cells was evaluated. Melanin is the pigment in skin cells that is responsible for coloring of the skin and various pigmentation disorders, such as age spots and freckles. Elimination of existing melanin inside a cell may result in lightening of the skin color and/or inhibit further darkening of the skin color. Arbutin is a conventional plant-derived

compound used in skin lightening treatments and was therefore selected for use as a positive control.

Procedure

[0092] B16-F10 cells were trypsinized using Trypsin-EDTA and cell density was determined. The cell slurry was diluted to a concentration of 18,000 cells per milliliter (mL) in a growth media containing RPMI 1640 supplemented with fetal bovine serum. The diluted cell slurry was dispensed into the wells of a 24 well cell culture plate at 1 mL per well (18,000 cells/well). The cells were incubated overnight at 37 °C and 5 % CO₂ in humid conditions.

[0093] Following the overnight incubation, the medium was discarded and replaced with 1mL per well of growth media including 50 µM forskolin (Sigma Cat.#F6886) and 10 µM 8-Methoxypsoralen (8-MOP; Alfa Aesar Cat. #A17108). The cells were then incubated for 72 hours at 37 °C and 5 % CO₂ in humid conditions.

[0094] The plated cells were treated by preparing a 200X dilution of each skin lightening compound, plant extract, and arbutin (positive control) in 100% DMSO. The medium in each well was discarded and replaced with 1 mL/well. 5 µL of the 200X dilution was added to each well. The treated cells were incubated for 72 hours at 37 °C and 5 % CO₂ in humid conditions. The skin lightening compounds and plant extracts were evaluated at concentrations of 0 (untreated), 10, 50, and 100 µg/mL. Arbutin was evaluated at concentrations of 0 (untreated), 25, 125, and 250 µg/mL.

[0095] When the treatment period was completed, the medium from each well was discarded and the cells were washed once with 1 mL per well of DPBS. The DPBS wash was removed and 150 µL of 1N sodium hydroxide was added to each well for 30 minutes while the cells were incubated at 80 °C to lyse the cells. Next, 145 µL from each well was transferred to a UV plate and the remaining 5 µL was tested to determine the protein concentration. The UV absorbance of each well was determined using a plate reader with the primary wave length set to 400 nm.

[0096] Melanin elimination was determined using the UV absorbance at 400 nm according to the following equation:

$$\%Inh = (\text{Max signal} - \text{Compound signal})/(\text{Max signal} - \text{Min signal}) \times 100$$

[0097] Where “%Inh” is the percent of melanin eliminated from the cell, the “Max signal” is the UV absorption for cells treated with forskolin and 8-MOP, and the “Min signal” is the UV absorption of untreated cells.

Results

[0098] The results of the melanin elimination assay are provided in Table 6 below. The percent decrease of melanin following treatment with each skin lightening compound and

plant extract at the 100 µg/mL treatment concentration is compared with the percent decrease for cells treated with arbutin at the 125 µg/mL treatment concentration.

[0099] Table 6: Melanin Elimination for the Skin Lightening Compounds & Plant Extracts vs. Arbutin

Skin Treatment Compound/Plant Extract	% Melanin Elimination Skin Treatment Compound/Plant Extract (Arbutin)*
Cyclovirobuxine D	92.4 (31.2)
Lipoic acid	65.7 (31.2)
Nuciferine	34.1 (37.5)
Peimisine	23.8 (50.4)
Oleuropein	37.0 (50.4)
<i>Rhodiola kirilowii</i> (Regel) Maxim extract	43.1 (70.6)**
<i>Glycyrrhizae Radix et Rhizoma</i> extract	72.3 (21.2)

* % inhibition determined for the skin treatment compound/plant extract at a 100 µg/mL treatment concentration and arbutin at a 125 µg/mL. Values are the average of two treatment wells.

** % inhibition determined for the skin treatment compound/plant extract at a 100 µg/mL treatment concentration and hydroquinone at a 100 µg/mL. Values are the average of two treatment wells.

[00100] Figures 9-11 illustrate example melanin elimination data for Nuciferine, Peimisine, and *Platycladi* semen extract (squares), respectively, compared to the arbutin positive control (triangles). The data in Table 6 and Figures 9-11 demonstrates that many of the skin lightening compounds and plant extracts tested exhibited similar or increased ability to eliminate existing melanin within cells compared to a higher concentration of the positive control, arbutin. The ability to eliminate melanin indicates that these compounds and plant extracts may be used in a skin treatment composition as a depigmentation agent to diminish or even eliminate skin spots and undesired skin pigmentation.

[00101] The data in Tables 3-5 demonstrates that several of the skin lightening compounds and plant extracts of this disclosure are capable of inhibiting melanin production in cells to a degree similar to a conventional skin lightening compound, and sometimes better than the conventional skin lightening compound, with similar or less toxicity to the cells. Thus, these skin lightening compounds and plant extracts may be used for treating skin pigmentation disorders. The data in Tables 3 and 6 demonstrates that several of the skin lightening compounds and plant extracts of this disclosure are capable of decreasing the concentration of existing melanin in cells to a degree similar to a conventional skin lightening compound,

and sometimes better than the conventional compound, with similar or less toxicity to the cells. These skin lightening compounds and plant extracts may be used as depigmentation agents in a skin treatment composition.

[00102] An exemplary skin treatment composition can include a combination of nuciferine and peimisine present individually or in combination in an amount effective to inhibit melanin production in human skin cells. The skin treatment composition can include one or more pharmaceutically acceptable additives to form a composition suitable for topical application on a subject's skin. Optionally, nuciferine and peimisine are present individually or in combination in an amount effective to inhibit tyrosinase activity in human skin cells. Optionally, nuciferine and peimisine are present individually or in combination in an amount effective to decrease a concentration of existing melanin present in human skin cells. In various embodiments, nuciferine and peimisine are present in a skin treatment composition in an amount effective to visibly lighten a subject's skin following topical treatment of the subject's skin according to a predetermined treatment schedule. In various embodiments, nuciferine and peimisine are combined to form a blend that can be included in a skin treatment composition for lightening a subject's skin.

[00103] Another exemplary skin treatment composition can include a combination of *Platycladi* semen extract and *Lycopi herba* extract present individually or in combination in an amount effective to inhibit melanin production in human skin cells. The skin treatment composition can include one or more pharmaceutically acceptable additives to form a composition suitable for topical application on a subject's skin. Optionally, the *Platycladi* semen extract and *Lycopi herba* extract are present individually or in combination in an amount effective to inhibit tyrosinase activity in human skin cells. Optionally, the *Platycladi* semen extract and *Lycopi herba* extract are present individually or in combination in an amount effective to decrease a concentration of existing melanin present in human skin cells. In various embodiments, the *Platycladi* semen extract and *Lycopi herba* extract are present in a skin treatment composition in an amount effective to visibly lighten a subject's skin following topical treatment of the subject's skin according to a predetermined treatment schedule. In various embodiments, the *Platycladi* semen extract and *Lycopi herba* extract are combined to form a blend that can be included in a skin treatment composition for lightening a subject's skin.

[00104] The following additional embodiments are provided, the numbering of which is not to be construed as designating levels of importance.

[00105] Embodiment 1 relates to a composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is selected from the

group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, *Astragali complanati* semen extract, *Plantaginis* semen extract, *Lycopi herba* extract, *Euryales* semen extract, *Cuscutae* semen extract, *Amomi fructus* extract, *Tara* seed extract, *Platycladi cacumen* extract, *Eucommiae cortex* extract, *Dioscoreae rhizoma* extract, *Cirsii herba* extract, and combinations thereof; and wherein the melanin production inhibitor is present in an amount effective to inhibit melanin production in human skin cells of a subject that is administered the composition.

[00106] Embodiment 2 relates to the composition of Embodiment 1, wherein the melanin production inhibitor is present in an amount effective to inhibit tyrosinase enzyme activity in human skin cells of the subject.

[00107] Embodiment 3 relates to the composition of Embodiment 1 or 2, wherein the melanin production inhibitor is selected from the group consisting of lipoic acid, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, and combinations thereof.

[00108] Embodiment 4 relates to the composition of any one of Embodiments 1 to 3, comprising a combination of at least two melanin production inhibitors, optionally at least three melanin production inhibitors.

[00109] Embodiment 5 relates to the composition of any one of Embodiments 1 to 4, wherein the melanin production inhibitor is present in an amount of no greater than about 20 percent by weight based on 100 parts by weight of the composition.

[00110] Embodiment 6 relates to the composition of Embodiment 1 or 2, wherein the melanin production inhibitor is present in an amount effective to decrease a concentration of melanin present in human skin cells of the subject.

[00111] Embodiment 7 relates to the composition of Embodiment 6, wherein the melanin production inhibitor is further defined as a depigmentation agent, and wherein the depigmentation agent is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, *Rhodiola kirilowii* (Regel) Maxim extract, *Platycladi* semen extract, and combinations thereof.

[00112] Embodiment 8 relates to the composition of Embodiment 7, comprising a combination of at least two depigmentation agents, optionally at least three depigmentation agents.

[00113] Embodiment 9 relates to the composition of Embodiment 7 or 8, wherein the depigmentation agent is present in an amount of no greater than about 20 percent by weight based on 100 parts by weight of the composition.

[00114] Embodiment 10 relates to the composition of any one of Embodiments 1 to 9, further comprising a depigmentation agent different from the melanin production inhibitor.

[00115] Embodiment 11 relates to the composition of any one of Embodiments 1 to 10, wherein the pharmaceutically acceptable additive is selected from the group consisting of water, glycerin, waxes, alcohols, vegetable oils, mineral oils, silicones, fatty esters, fatty alcohols, glycols, polyglycols, and combinations thereof.

[00116] Embodiment 12 relates to the composition of any one of Embodiments 1 to 11, further defined as a topical composition for administration to human skin.

[00117] Embodiment 13 relates to the composition of Embodiment 12, wherein the topical composition is in the form of a gel, a cream, an aerosol spray, a dispersion, an oil-in-water emulsion, a water-in-oil emulsion, a water-in-silicone emulsion, a foam, a liquid, a mousse, a pomade, a powder, a solid, or an ointment suitable for topical application to human skin.

[00118] Embodiment 14 relates to use of the composition according to any one of Embodiments 1 to 13 for treating human skin pigmentation.

[00119] Embodiment 15 relates to a method of forming the composition according to any one of Embodiments 1 to 13, the method comprising: providing at least one pharmaceutically acceptable additive; providing at least one melanin production inhibitor; and combining the pharmaceutically acceptable additive and the melanin production inhibitor to form the composition.

[00120] Embodiment 16 relates to a method of treating human skin pigmentation of a subject, the method comprising: providing a topical composition; and applying the topical composition to skin of the subject; wherein the topical composition comprises the composition according to any one of Embodiments 1 to 13.

[00121] Embodiment 17 relates to the method of Embodiment 16, further defined as a cosmetic method for skin lightening.

[00122] The terms “comprising” or “comprise” are used herein in their broadest sense to mean and encompass the notions of “including,” “include,” “consist(ing) essentially of,” and “consist(ing) of.” The use of “for example,” “e.g.,” “such as,” and “including” to list illustrative examples does not limit to only the listed examples. Thus, “for example” or “such as” means “for example, but not limited to” or “such as, but not limited to” and encompasses other similar or equivalent examples. The term “about” as used herein serves to reasonably encompass or describe minor variations in numerical values measured by instrumental analysis or as a result of sample handling. Such minor variations may be in the order of ± 0 -

10, ± 0.5 , or $\pm 0.2.5$, % of the numerical values. Further, The term “about” applies to both numerical values when associated with a range of values. Moreover, the term “about” may apply to numerical values even when not explicitly stated.

[00123] Generally, as used herein a hyphen “-” or dash “—” in a range of values is “to” or “through”; a “>” is “above” or “greater-than”; a “ $\geq$ ” is “at least” or “greater-than or equal to”; a “<” is “below” or “less-than”; and a “ $\leq$ ” is “at most” or “less-than or equal to.” On an individual basis, each of the aforementioned applications for patent, patents, and/or patent application publications, is expressly incorporated herein by reference in its entirety in one or more non-limiting embodiments.

[00124] It is to be understood that the appended claims are not limited to express and particular compounds, compositions, or methods described in the detailed description, which may vary between particular embodiments which fall within the scope of the appended claims. With respect to any Markush groups relied upon herein for describing particular features or aspects of various embodiments, it is to be appreciated that different, special, and/or unexpected results may be obtained from each member of the respective Markush group independent from all other Markush members. Each member of a Markush group may be relied upon individually and or in combination and provides adequate support for specific embodiments within the scope of the appended claims.

[00125] It is also to be understood that any ranges and subranges relied upon in describing various embodiments of the present invention independently and collectively fall within the scope of the appended claims, and are understood to describe and contemplate all ranges including whole and/or fractional values therein, even if such values are not expressly written herein. One of skill in the art readily recognizes that the enumerated ranges and subranges sufficiently describe and enable various embodiments of the present invention, and such ranges and subranges may be further delineated into relevant halves, thirds, quarters, fifths, and so on. As just one example, a range “of from 0.1 to 0.9” may be further delineated into a lower third, i.e., from 0.1 to 0.3, a middle third, i.e., from 0.4 to 0.6, and an upper third, i.e., from 0.7 to 0.9, which individually and collectively are within the scope of the appended claims, and may be relied upon individually and/or collectively and provide adequate support for specific embodiments within the scope of the appended claims. In addition, with respect to the language which defines or modifies a range, such as “at least,” “greater than,” “less than,” “no more than,” and the like, it is to be understood that such language includes subranges and/or an upper or lower limit. As another example, a range of “at least 10” inherently includes a subrange of from at least 10 to 35, a subrange of from at least 10 to 25, a subrange of from 25 to 35, and so on, and each subrange may be relied upon individually and/or collectively and provides adequate support for specific embodiments within the scope

of the appended claims. Finally, an individual number within a disclosed range may be relied upon and provides adequate support for specific embodiments within the scope of the appended claims. For example, a range “of from 1 to 9” includes various individual integers, such as 3, as well as individual numbers including a decimal point (or fraction), such as 4.1, which may be relied upon and provide adequate support for specific embodiments within the scope of the appended claims.

[00126] The present invention has been described herein in an illustrative manner, and it is to be understood that the terminology which has been used is intended to be in the nature of words of description rather than of limitation. Many modifications and variations of the present invention are possible in light of the above teachings. The present invention may be practiced otherwise than as specifically described within the scope of the appended claims. The subject matter of all combinations of independent and dependent claims, both single and multiple dependent, is herein expressly contemplated.

CLAIMS

What is claimed is:

1. A composition for treating human skin pigmentation, the composition comprising:
 - at least one pharmaceutically acceptable additive; and
 - at least one melanin production inhibitor;
 wherein the melanin production inhibitor is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, oleuropein, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, *Astragali complanati* semen extract, *Plantaginis* semen extract, *Lycopi herba* extract, *Euryales* semen extract, *Cuscutae* semen extract, *Amomi fructus* extract, *Tara* seed extract, *Platycladi cacumen* extract, *Eucommiae cortex* extract, *Dioscoreae rhizoma* extract, *Cirsii herba* extract, and combinations thereof; and
 - wherein the melanin production inhibitor is present in an amount effective to inhibit melanin production in human skin cells of a subject that is administered the composition.
2. The composition of claim 1, wherein the melanin production inhibitor is present in an amount effective to inhibit tyrosinase enzyme activity in human skin cells of the subject.
3. The composition of claim 1 or 2, wherein the melanin production inhibitor is selected from the group consisting of lipoic acid, *Rhodiola algida* extract, *Rhodiola kirilowii* (Regel) Maxim extract, *Glycyrrhizae Radix et Rhizoma* extract, *Cirsii japonici herba* extract, *Platycladi* semen extract, *Synotis erythropappa* extract, and combinations thereof.
4. The composition of any one of claims 1 to 3, comprising a combination of at least two melanin production inhibitors, optionally at least three melanin production inhibitors.
5. The composition of any one of claims 1 to 4, wherein the melanin production inhibitor is present in an amount of no greater than about 20 percent by weight based on 100 parts by weight of the composition.
6. The composition of claim 1 or 2, wherein the melanin production inhibitor is present in an amount effective to decrease a concentration of melanin present in human skin cells of the subject.
7. The composition of claim 6, wherein the melanin production inhibitor is further defined as a depigmentation agent, and wherein the depigmentation agent is selected from the group consisting of cyclovirobuxine D, lipoic acid, nuciferine, peimisine, *Rhodiola kirilowii* (Regel) Maxim extract, *Platycladi* semen extract, and combinations thereof.
8. The composition of claim 7, comprising a combination of at least two depigmentation agents, optionally at least three depigmentation agents.

9. The composition of claim 7 or 8, wherein the depigmentation agent is present in an amount of no greater than about 20 percent by weight based on 100 parts by weight of the composition.
10. The composition of any one of claims 1 to 9, wherein the pharmaceutically acceptable additive is selected from the group consisting of water, glycerin, waxes, alcohols, vegetable oils, mineral oils, silicones, fatty esters, fatty alcohols, glycols, polyglycols, and combinations thereof.
11. The composition of any one of claims 1 to 10, further defined as a topical composition for administration to human skin.
12. The composition of claim 11, wherein the topical composition is in the form of a gel, a cream, an aerosol spray, a dispersion, an oil-in-water emulsion, a water-in-oil emulsion, a water-in-silicone emulsion, a foam, a liquid, a mousse, a pomade, a powder, a solid, or an ointment suitable for topical application to human skin.
13. Use of the composition according to any one of claims 1 to 12 for treating human skin pigmentation.
14. A method of forming the composition according to any one of claims 1 to 12, the method comprising:
 - providing at least one pharmaceutically acceptable additive;
 - providing at least one melanin production inhibitor; and
 - combining the pharmaceutically acceptable additive and the melanin production inhibitor to form the composition.
15. A method of treating human skin pigmentation of a subject, the method comprising:
 - providing a topical composition; and
 - applying the topical composition to skin of the subject;
 - wherein the topical composition comprises the composition according to any one of claims 1 to 12.

1/6

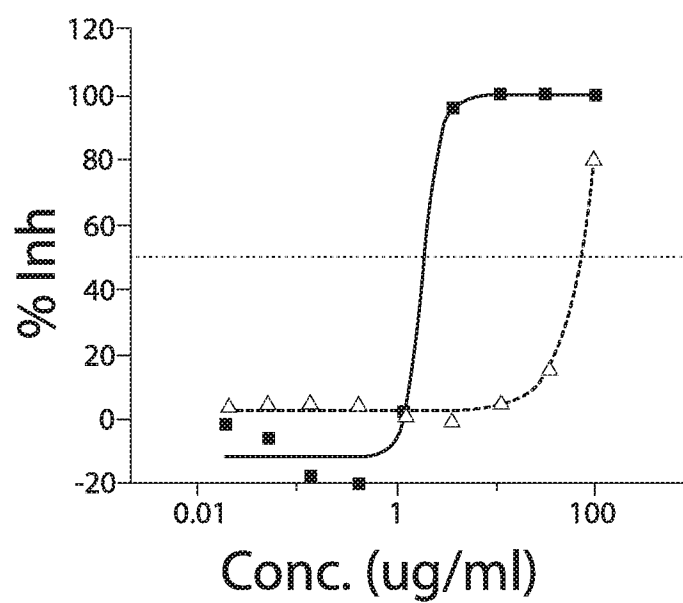


Fig. 1

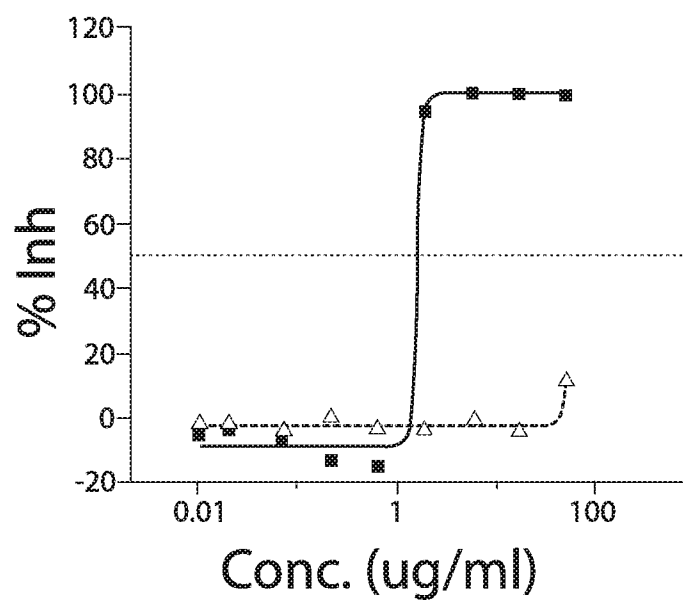


Fig. 2

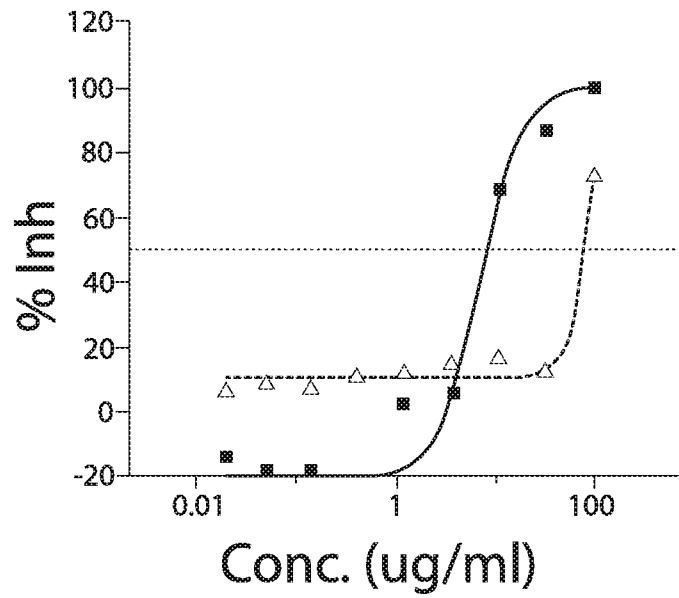


Fig. 3

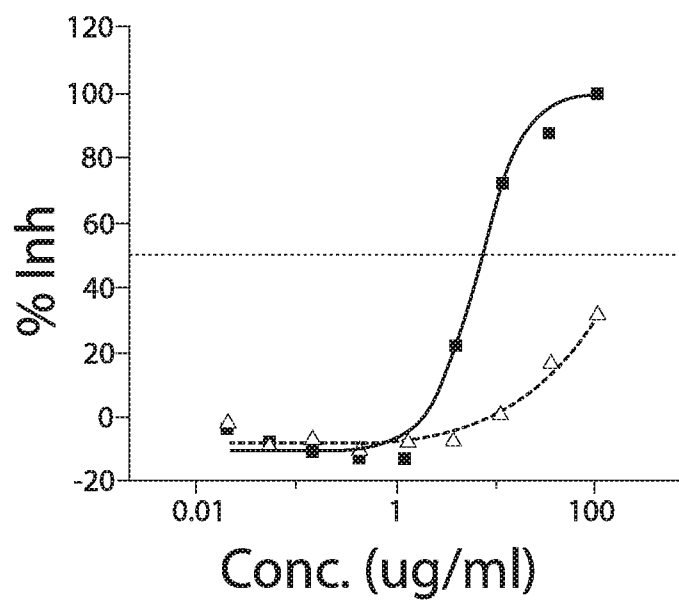


Fig. 4

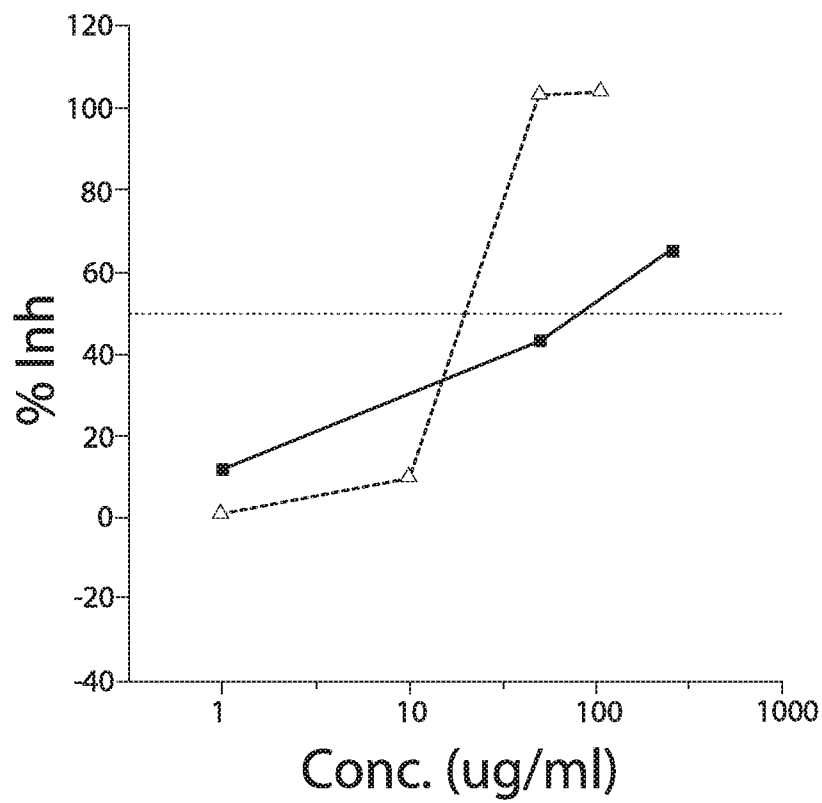


Fig. 5

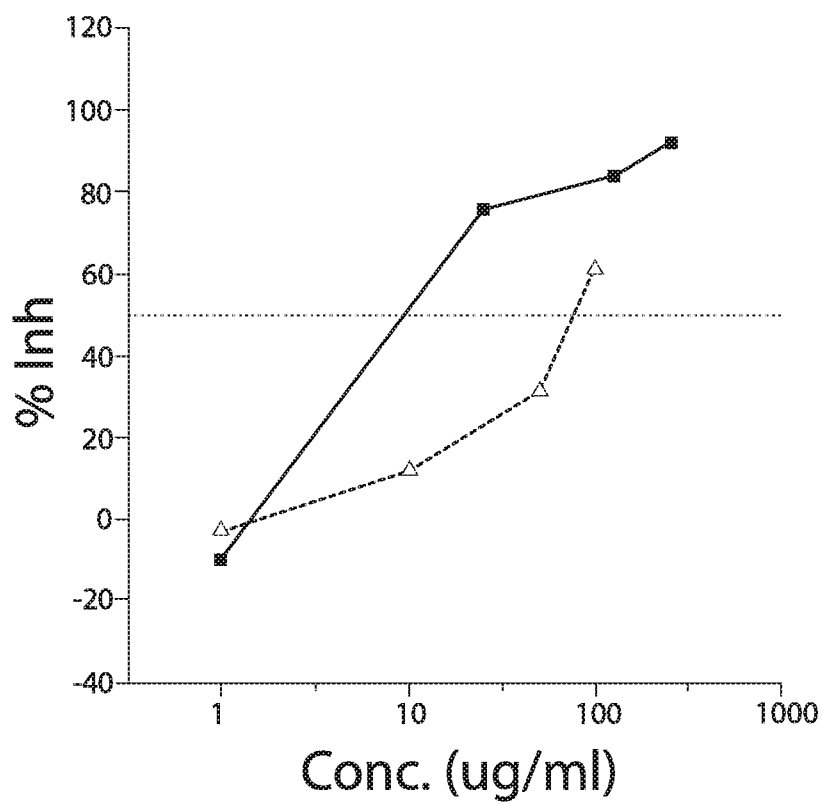


Fig. 6

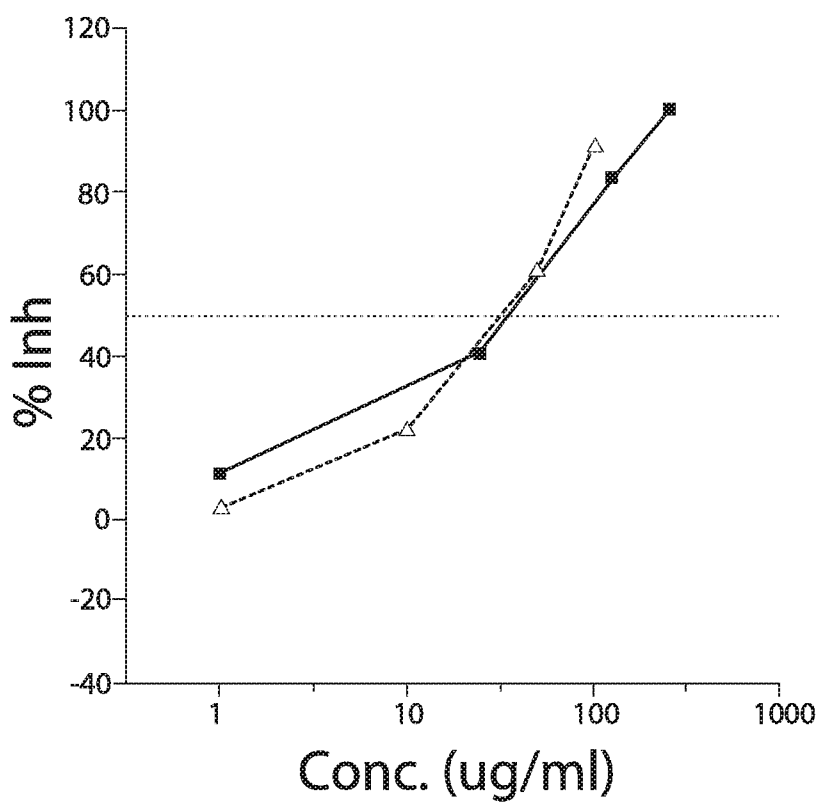


Fig. 7

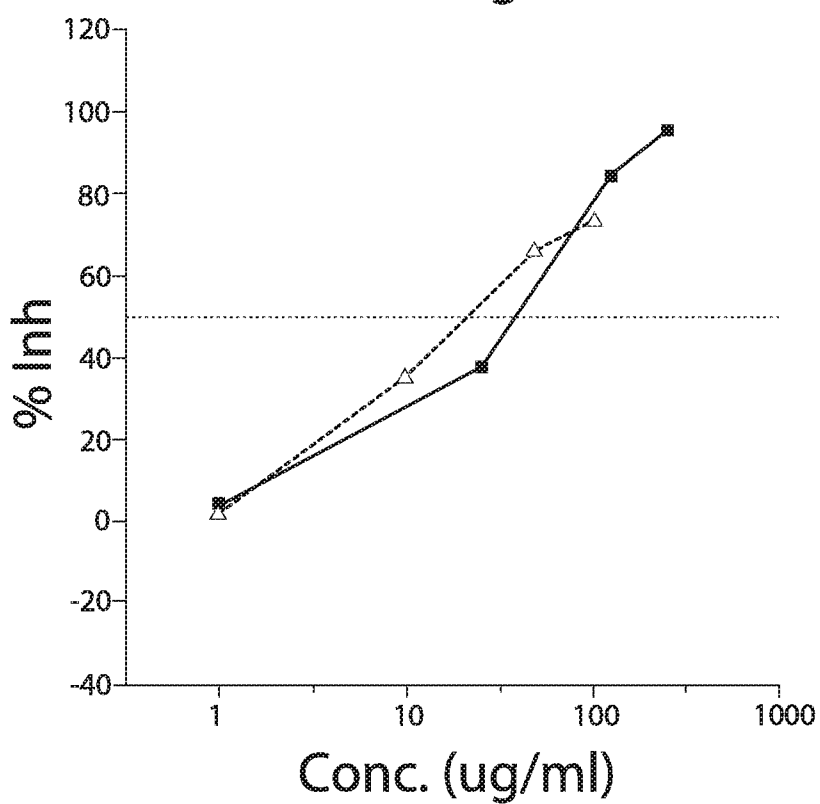


Fig. 8

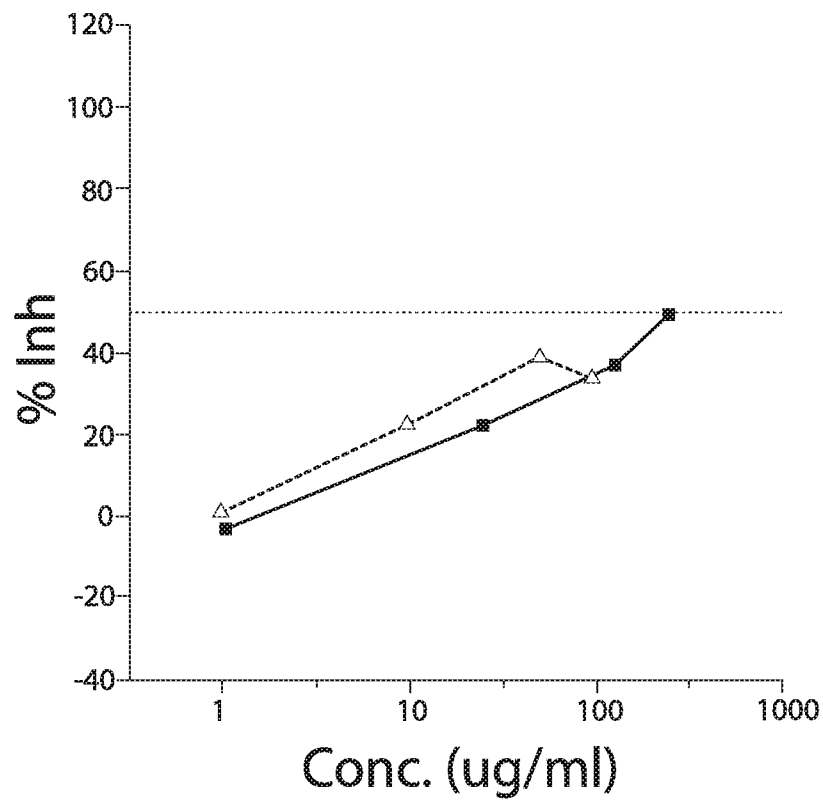


Fig. 9

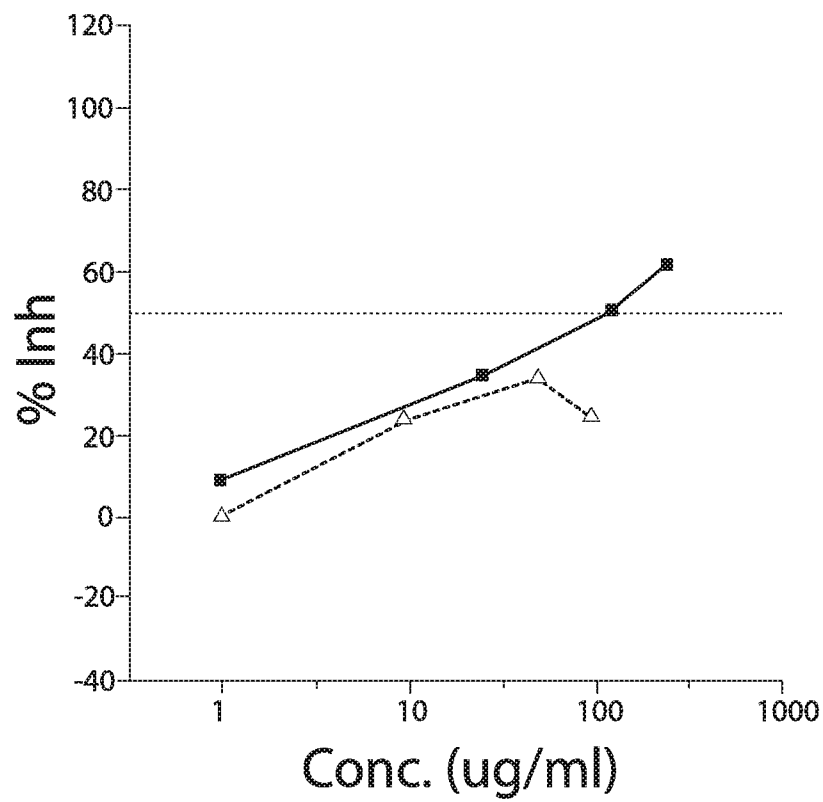


Fig. 10

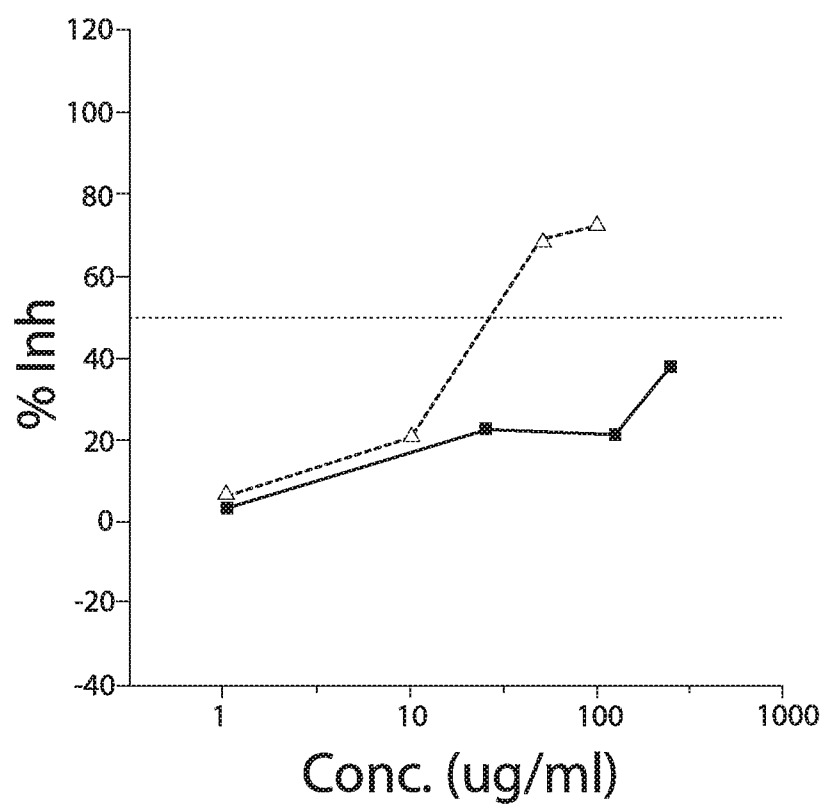


Fig. 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/029507

A. CLASSIFICATION OF SUBJECT MATTER INV. A61Q19/02 A61K8/9789 A61K8/9794 A61K8/49 A61K8/63 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61Q A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EP0-Internal, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 2010 0052092 A (KIM CHEONG TAEK [KR]) 19 May 2010 (2010-05-19) paragraphs [0001], [0008], [0010], [0015], [0018] - [0020], [0025] - [0060] -----	1,2,5-7, 9-15 1,2,4-15
Y	CN 1 827 112 A (CAO MINGCHENG [CN]) 6 September 2006 (2006-09-06) claim 1 -----	1,2,5-7, 9-12
X	CN 1 583 064 A (SHANDONG CHINESE MEDICAL AND M [CN]) 23 February 2005 (2005-02-23) page 4, line 38 - line 50 claim 7 -----	1,2,5-7, 9-12
A	WO 99/20290 A1 (UNIV NICE SOPHIA ANTIPOLIS [FR]; ARKOPHARMA LABORATOIRES [FR]; DELLAMO) 29 April 1999 (1999-04-29) pages 3,10 ----- -/--	1,2,4-15
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents :		
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family	
Date of the actual completion of the international search 13 June 2018	Date of mailing of the international search report 30/08/2018	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Olausson Boulois, J	

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/029507

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CN 105 434 217 A (QINGDAO SHENGJIA INF TECH CO) 30 March 2016 (2016-03-30) claim 1 -----	1,2,4-15
Y	DATABASE GNPD [Online] MINTEL; 31 October 2016 (2016-10-31), ANONYMOUS: "Sun protector SPF 50+/PA+++", XP002781861, Database accession no. 4356985 page 1 -----	1,2,4-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/029507

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 4-15(all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 4-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is cyclovirobuxine D.

2. claims: 1-15(partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is lipoic acid.

3. claims: 1, 2, 4-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is nuciferine.

4. claims: 1, 2, 4-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is peimisine.

5. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is oleuropein.

6. claims: 1-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Rhodiola algida extract.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1-15(partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Rhodiola kirilowii* (Regel) Maxim extract.

8. claims: 1-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Glycyrrhizae Radix et Rhizoma* extract.

9. claims: 1-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Cirsii japonici herba* extract.

10. claims: 1-15(partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Platycladi semen* extract.

11. claims: 1-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Synotis erythropappa* extract.

12. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising: at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is *Astragali complanati semen* extract.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

13. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Plantaginis semen extract.

14. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Lycopi herba extract.

15. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Euryales semen extract.

16. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Cuscutae semen extract.

17. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Amomi fructus extract.

18. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Tara seed extract.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

19. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Platycladi cacumen extract.

20. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Eucommiae cortex extract.

21. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Dioscoreae rhizoma extract.

22. claims: 1, 2, 4-6, 8-15(all partially)

A composition for treating human skin pigmentation, the composition comprising:at least one pharmaceutically acceptable additive; and at least one melanin production inhibitor; wherein the melanin production inhibitor is Cirsii herba extract.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/029507

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
KR 20100052092 A	19-05-2010	NONE	

CN 1827112 A	06-09-2006	NONE	

CN 1583064 A	23-02-2005	NONE	

WO 9920290 A1	29-04-1999	AU 9545698 A	10-05-1999
		FR 2769840 A1	23-04-1999
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