

FORMULATIONS OF DIHYDROKAEMPFEROL

FIELD OF THE INVENTION

The invention is related to formulations of dihydrokaempferol and methods of using the
5 formulations for topical conditions in a subject.

BACKGROUND OF THE INVENTION

Mammalian epidermis and its appendages (e.g., hair, nail, sebaceous and sweat glands) provide a barrier to keep harmful elements out of the body and essential body fluids in. As the first
10 line of defense against the various physical traumas of the environment, the epidermis must protect itself as well as the underlying tissues. The epidermis is also exposed to mutagenic ultraviolet radiation. In non-haired or sparsely haired regions such as most human skin, the epidermis is thicker than that of furred skin, and in these locations the skin functions primarily in a protective role. The constant assaults on the epidermis necessitate self-renewal, making the epidermis a prime
15 example of an adult tissue that undergoes continual and rapid flux.

Aged skin differs from youthful skin both in appearance and in function. The aged epidermis demonstrates decreased keratinocyte proliferation and is physically thinner, but mostly from decline of the rete ridges. In addition to thinning, aging slows wound healing, prolongs epidermal turnover, and impairs barrier formation. The skin appears thin, wrinkled, bruised, and
20 rough. Wrinkling and bruising can also result from aging-related changes in the dermis. The dermis, too, is characteristically thinner in aged persons. Aged fibroblasts are less likely to synthesize normal amounts of collagen, elastin, laminin glycosaminoglycans, and fibronectin. The dermis can, in such cases, lack elasticity, strength, vessel support, remodeling abilities, and ground substances. For example, rete ridges can be effaced, and basal cells can no longer display villous
25 projections into the dermis. Epidermal cell turnover is reduced up to 50% in the aged as compared to youth.

For example, melanocyte numbers can decrease 8-20% per decade. There are fewer Langerhans cells in the aged, and those present are often functionally impaired. Collagen synthesis decreases, for example, up to 30% within 4 years of menopause in women. The numbers of
30 collagen and elastic fibers are also decreased. The dermis can also become less echogenic to ultrasounds, consistent with changes in collagen and elastic tissues.

SUMMARY OF THE INVENTION

The present invention provides, in various embodiments, compositions comprising dihydrokaempferol, and methods of using the compositions, for example for treating, protecting, and/or altering (e.g., improving) the condition and/or aesthetic appearance of skin, including, for example, treating, preventing, ameliorating, reducing and/or eliminating fine lines and/or wrinkles of skin and/or improving the aesthetic appearance of fine lines and/or wrinkles of skin. In certain embodiments, the compositions of the invention lead to increase in skin and/or hair resiliency. In certain embodiments, the compositions of the invention lead to increase in elasticity of the skin. In certain embodiments, the compositions of the invention prevent skin damage. In certain embodiments, the compositions of the invention reduce inflammation. In certain embodiments, the compositions of the invention lead to skin barrier improvement. In certain embodiments, the compositions of the invention support wound healing and epidermal regeneration.

Topical administration of compositions comprising dihydrokaempferol were not known in the field for application on human skin. In particular, the topical administration of dihydrokaempferol for improving the condition of skin, including enhancing the appearance of the skin, by topical administration of a composition comprising an effective amount of dihydrokaempferol was not known in the field. Beneficially, the invention recognizes, for the first time, that topical compositions comprising dihydrokaempferol may be used for improving the condition of the skin or for treatment of any ailment related to the skin of a subject.

In one aspect, the invention provides a composition for topical administration comprising an effective amount of dihydrokaempferol. The effective amount of dihydrokaempferol is an amount of dihydrokaempferol that would be effective in treating, ameliorating, or otherwise impacting the underlying condition of the skin. The invention recognizes that dihydrokaempferol is poorly soluble or insoluble in water. The invention also recognizes that dihydrokaempferol is also poorly soluble or insoluble in oil, for example, dihydrokaempferol is insoluble in Helianthus Annuus (Sunflower) Seed Oil. In addition, dihydrokaempferol is also only minimally soluble in isopropyl myristate and capric/caprylic triglyceride. In certain embodiments of the invention, dihydrokaempferol is dissolved in a solvent selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyl diol, 1,2 heptanediol, and any combinations thereof. In certain preferred

embodiments, dihydrokaempferol is dissolved in dimethyl isosorbide. In certain embodiments, the composition comprising dihydrokaempferol is anhydrous. In certain embodiments, the composition comprises oil as the only solvent.

In certain embodiments, the composition comprising dihydrokaempferol is an emulsion. In certain embodiments, the emulsion is an oil/water emulsion. In certain embodiments, the composition further comprises a solvent. In certain embodiment, the solvent is selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyldiol, 1,2 heptanediol, In certain embodiments, the solvent in the composition is dimethyl isosorbide. In certain embodiments, the solvent in the composition is ethoxydiglycol. In certain embodiments, the solvent in the composition is isopropyl lauroyl sarcosinate. In certain embodiments, the solvent in the composition is 1,2-hexanediol. In certain embodiments, the solvent is propanediol. In certain embodiments, the solvent is isopentyldiol. In certain embodiments, the solvent is 1,2-heptanediol. In certain embodiments, the solvent in the composition is a glycol. In certain embodiments, the glycol is selected from a group consisting of pentylene glycol, butylene glycol, propylene glycol, and any combination thereof.

In certain embodiments, dihydrokaempferol is dissolved in a solvent selected from a group consisting of: 1,2 heptanediol, 1,2 hexanediol, 1,2 propanediol, butylene glycol, C₁₅₋₁₉ alkane, capric/caprylic triglyceride, dibutyl adipate, diisopropyl adipate, dimethyl isosorbide, dipropylene glycol, ethanol, ethoxydiglycol, isoamyl laurate, isohexadecane, isopentyldiol, isopropyl myristate, isopropyl lauroyl sarcosinate, jojoba oil, meadowfoam seed oil, mineral oil, neopentyl glycol diethylhexanoate, octyldodecanol, oleyl alcohol, pentylene glycol, phenylpropanol, polysorbate 20, propanediol, safflower seed oil, squalene, sunflower oil, t-butyl alcohol, tributyl citrate, tributyl-O-acetylcitrate, tri-C₁₅₋₁₉ alkyl citrate, triethyl citrate, triethyl O-acetylcitrate, and triisostearin.

The compositions of the invention are stable under storage in ambient conditions. This is beneficial because the compositions of the invention may be stored prior to administration to the subjects. There were no previously known shelf-stable formulations of dihydrokaempferol. Shelf-storage stable formulations of dihydrokaempferol would provide a convenient option for the composition to be applied to patients suffering from various ailments of the skin and/or seeking options for appearance of the skin.

In certain preferred embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least two (2) years under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least one year under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least six (6) months under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least three (3) months under ambient conditions.

In certain embodiments, the compositions of the invention demonstrate less than about 10% degradation of dihydrokaempferol when stored at 70 °C for one (1) month. In certain embodiments, the compositions of the invention demonstrate less than about 20% degradation of dihydrokaempferol when stored at 70 °C for one (1) month. The high stability of the compositions of the invention at 70 °C demonstrate that the compositions of the invention will be stable under ambient conditions for at least 2 years. In certain embodiments, the compositions comprise dihydrokaempferol dissolved in dimethyl isosorbide, isopropyl lauroyl sarcosinate, and ethoxydiglycol.

Surprisingly, the stability of dihydrokaempferol is dependent on the pH of the composition. The invention recognizes that dihydrokaempferol degrades at a higher rate if the pH of the composition is not in an optimal pH range. Thus, in certain embodiments, the compositions of the invention comprise buffers and/or pH adjusting agents to maintain the pH of the composition in an optimal range to minimize the degradation of dihydrokaempferol under ambient conditions. In certain embodiments, the pH of the composition is from about 4 to about 8. In certain embodiments, the pH of the composition is from about 4 to about 7. In certain embodiments, the pH of the composition is from about 4 to about 6. In certain embodiments, the pH of the composition is from about 4 to about 5. The data pertaining to stability of the compositions of the invention with respect to the pH of the solution is provided in FIG. 1.

In certain embodiments, the pH of the composition is about 4. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 4 have less than 10% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 4 have less than 20% degradation when stored at 50 °C for one (1) month.

In certain embodiments, the pH of the composition is about 5. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 5 have less than 20% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 5 have less than 25% degradation when stored at 50 °C for one (1) month.

In certain embodiments, the pH of the composition is about 6. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 6 have less than 20% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 6 have less than 25% degradation when stored at 50 °C for one (1) month.

In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 5 nM to about 5 mM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 10 nM to about 4 mM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 5 nM to about 2500 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 10 nM to about 2000 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 20 nM to about 1000 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 10 nM to about 20 nM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 5 µM to about 3,750 µM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 50 µM to about 3,000 µM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 50 µM to about 3,000 µM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 500 µM to about 4,500 µM.

In certain embodiments, dihydrokaempferol is present in a concentration of about 0.0001% to about 5.0% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.0001% to about 1.0% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.001% to about 0.5% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.01% to about 0.5% w/w

in the composition of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.1% to about 0.5% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.5% w/w in the compositions of the invention.

5 In certain aspects, the compositions of the invention may be administered as a topical composition on the skin of the subject. The compositions of the invention may be included in any formulation suitable for topical administration. In certain embodiments, the composition of the invention is a fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion,
10 powder, aerosol, color cosmetic, and/or hair treatment. In certain embodiments, the compositions of the invention also include excipients. These excipients may be selected from a group consisting of: solvent, emulsifier, preservative, antioxidant, emollient, thickening agent, penetration enhancer, surfactant, diluent, filler, carrier, and/or pH control agent. In certain embodiments, the preservative in the composition is an antimicrobial preservative or chelating agent. In certain
15 embodiments, the excipients in the composition are selected from the group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyl diol, 1,2 heptanediol, water, glycerin, hydrogenated ethylhexyl olivate, hydrogenated olive oil unsaponifiables, polyglycerol-6-distearate, jojoba esters, polyglyceryl-3-beeswax, cetyl alcohol, cetearyl olivate, sorbitan olivate, hydroxyethyl acrylate/sodium
20 acryloyldimethyl taurate copolymer, helianthus annuus (sunflower) seed oil, caprylic/capric triglyceride, phenoxyethanol, decylene glycol, and 1,2-hexanediol.

The compositions of the invention may be prepared by various methods. As an example, the compositions may be prepared by dissolving, dispersing, etc. dihydrokaempferol as provided herein and optional excipients in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols,
25 ethanol or the like) or a solvent to form a solution, colloid, liposome, emulsion, complexes (including inclusion complexes), coacervate, or suspension. In certain embodiments, the compositions of the current invention can also contain additional excipients such as wetting agents, emulsifying agents, co-solvents, solubilizing agents, pH buffering agents, and the like (e.g., sodium acetate, sodium citrate, cyclodextrins and derivatives, sorbitan monolaurate,
30 triethanolamine acetate, triethanolamine oleate, hydroxyethylpiperazine and the like). In certain embodiments, the compositions of the invention may further include one or more additional

excipients selected from a group consisting of: carriers, excipients, or diluents including, but not limited to, absorbents, anti-irritants, antibacterials, anti-acne agents, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents, silicones, skin-
5 identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, and a preservative.

10 In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, and a preservative.

In certain embodiments, the compositions of the invention comprise dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, a diluent, and a preservative.

15 In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, a thickener, optionally a diluent, and a preservative.

In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, and one or more excipients selected from the group consisting of: diluents, absorbents, antioxidants, emollients, emulsifiers,
20 thickeners, surfactants, and/or preservatives.

In certain embodiments, the excipients included in the composition are water, dimethyl isosorbide, glycerin, caprylic/capric triglyceride, propanediol, sunflower seed oil, ethoxydiglycol, squalane, sodium acrylate copolymer, cetearyl alcohol, phenoxyethanol, glyceryl stearate, capryloyl glycerin/sebacic acid copolymer, diheptyl succinate, naringenin, lecithin, decylene
25 glycol, pentylene glycol, cetearyl glucoside, shea butter, palmitic acid, arachidyl alcohol, behenyl alcohol, arachidyl glucoside, phenethyl alcohol, 1,2-hexanediol, hydrogenated olive oil, olea europaea (olive) fruit oil, olea europaea (olive) oil unsaponifiables, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, citric acid, sodium acetylated hyaluronate, sodium hyaluronate crosspolymer, sodium phytate, hydrolyzed sodium hyaluronate, and/or
30 ethylhexylglycerin.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate antioxidant activity. In certain embodiments, the compositions of the invention, the antioxidant activity of dihydrokaempferol is demonstrated at concentrations of about 0.00625% w/w or higher. Beneficially, the antioxidant activity of compositions comprising dihydrokaempferol is demonstrated in both aqueous and organic solvent systems. Thus, the invention provides compositions which retain antioxidant activity in both aqueous and organic solvents. Advantageously, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for treating and/or preventing oxidation damage. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for treatment of skin and/or hair damaged by reactive oxygen species and protection from other environmental aggressors that may damage the skin of the subject. In certain other embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for prevention of skin and/or hair damage by reactive oxygen species, including the damage caused by environmental aggressors.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate elastase enzyme inhibition. In certain embodiments, the compositions of the invention, the elastase enzyme inhibition activity of dihydrokaempferol is demonstrated at concentrations of about 0.1% w/w or higher. Advantageously, the compositions comprising dihydrokaempferol, demonstrating elastase enzyme inhibition activity, are effective for promoting the elasticity of the skin. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating elastase enzyme inhibition, are effective in reduction of fine lines and/or wrinkles in the skin. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating elastase enzyme inhibition, are effective in prevention of formation of fine lines and/or wrinkles in the skin.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate inhibition of glycation. In certain embodiments, the compositions of the invention, the glycation inhibition activity of dihydrokaempferol is demonstrated at concentrations of about 0.004% w/w or higher. Advantageously, the compositions comprising dihydrokaempferol, demonstrating glycation inhibition activity, are effective for supporting and promoting skin and/or hair resiliency.

In certain aspects, the invention provides methods of treatment of a topical condition by administration of the topical composition comprising an effective amount of dihydrokaempferol. In certain embodiments, the invention provides methods for prevention of fine lines or wrinkles on skin of the subject by administration of the compositions provided herein. In certain
5 embodiments, the invention provides methods for supporting firmness and increasing/maintaining elasticity of skin by administration of the compositions provided herein. In certain embodiments, the invention provides methods for prevention of skin and hair damaged by reactive oxygen species by administration of the compositions provided herein. In certain embodiments, the invention provides methods for protection from environment aggressors on skin by administration
10 of the compositions provided herein. In certain embodiments, the invention provides methods for increase in skin and/or hair resiliency by administration of the compositions provided herein. In certain embodiments, the invention provides methods for prevention of glycation by administration of the compositions provided herein. Glycation is known to be linked with the wrinkling, loss of elasticity, and aging in the skin. In certain embodiments, the invention provides
15 methods of reducing damage in skin by administration of compositions provided herein.

In some embodiments, the invention provides a method of modulating expression of one or more genes in a mammal, comprising administering to the mammal an effective amount of a composition comprising dihydrokaempferol, wherein the one or more genes include at least one gene that is related to a condition of the mammalian epidermis.

20 In some embodiments, the one or more genes include at least one gene that is pro-inflammatory.

In some embodiments, the one or more genes include at least one gene that increases fibroblast growth.

25 In some embodiments, the one or more genes include at least one gene that promotes skin barrier formation.

In some embodiments, the one or more genes include at least one gene that regulates endothelial growth factors.

In some embodiments, the one or more genes include at least one gene that promotes fibroblast and keratinocyte migration.

30 In some embodiments, the one or more genes are selected from the group consisting of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine

Ligand 1 (CXCL1), C-X-C Motif Chemokine Ligand 2 (CXCL2), Fibroblast Growth Factor 2 (FGF2), Transient Receptor Potential Cation Channel Subfamily (TRPV6), Vascular Endothelial Growth Factor A (VEGFA), Thrombospondin 4 (THBS4).

5 In some embodiments, administering the composition causes down-regulation of expression and/or activity of at least one of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), and C-X-C Motif Chemokine Ligand 2 (CXCL2).

10 In some embodiments, administering the composition causes up-regulation of expression and/or activity of at least one of Fibroblast Growth Factor 2 (FGF2), Transient Receptor Potential Cation Channel Subfamily (TRPV6), Vascular Endothelial Growth Factor A (VEGFA), and Thrombospondin 4 (THBS4).

In some embodiments, administering the composition reduces skin inflammation.

In some embodiments, administering the composition increases skin regeneration and wound healing.

15 In some embodiments, administering the composition increases skin barrier function.

In some embodiments, administering the composition increases skin elasticity.

In some embodiments, the composition comprises an emulsion.

20 In some embodiments, the composition comprises a fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, color cosmetic, and/or hair treatment.

In some embodiments, the composition comprises an emulsion.

In some embodiments, the emulsion is an oil in water emulsion.

In some embodiments, the composition has a pH of about 4 to about 8.

25 In some embodiments, the composition comprises about 0.0001% to about 5.0% w/w dihydrokaempferol.

In some embodiments, the composition comprises about 0.1% to about 0.5% w/w dihydrokaempferol.

30 In some embodiments, the composition comprising dihydrokaempferol is administered topically.

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -4.0 to about -7.0 in the expression of Interleukin 6 (IL6).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -5.5 in the expression of Interleukin 6 (IL6).

5 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -1.0 to about -3.0 in the expression of Interleukin 24 (IL24).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -2.0 in the expression of Interleukin 24 (IL24).

10 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -2.0 to about -5.0 in the expression of Tumor Necrosis Factor (TNF).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -3.4 in the expression of Tumor Necrosis Factor (TNF).

15 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -1.0 to about -3.0 in the expression of C-X-C Motif Chemokine Ligand 1 (CXCL1).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -1.9 in the expression of C-X-C Motif Chemokine Ligand 1 (CXCL1).

20 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -3.0 to about -6.0 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about -4.2 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2).

25 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about 1.0 to about 3.0 in the expression of Fibroblast Growth Factor 2 (FGF2).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log₂ fold change of about 1.8 in the expression of Fibroblast Growth Factor 2 (FGF2).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 1.0 to about 4.0 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6).

5 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 2.2 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 1.0 to about 4.0 in the expression of Vascular Endothelial Growth Factor A (VEGFA).

10 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 2.3 in the expression of Vascular Endothelial Growth Factor A (VEGFA).

In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 2.0 to about 5.0 in the expression of Thrombospondin 4 (THBS4).

15 In some embodiments, administering the composition comprising dihydrokaempferol leads to a log2 fold change of about 3.3 in the expression of Thrombospondin 4 (THBS4).

Additional features and advantages of embodiments of the present invention are described further below. This summary section is meant merely to illustrate certain features of embodiments of the invention, and is not meant to limit the scope of the invention in any way. The failure to
20 discuss a specific feature or embodiment of the invention, or the inclusion of one or more features in this summary section, should not be construed to limit the invention as claimed.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing summary, as well as the following detailed description, will be better
25 understood when read in conjunction with the appended drawings. For the purposes of illustrating the compositions and methods of the present application, there are shown in the drawings certain embodiments. It should be understood, however, that the application is not limited to the precise embodiments shown.

FIG. 1 shows pH stability data for compositions comprising dihydrokaempferol according
30 to various embodiments of the present invention.

FIG. 2 shows images of human dermal fibroblasts (hDF) treated with compositions comprising dihydrokaempferol according to various embodiments of the present invention.

FIG. 3 shows a KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway map illustrating differential gene expression of genes involved in the cellular senescence pathway in normal human epidermal keratinocytes treated with 1% dihydrokaempferol.

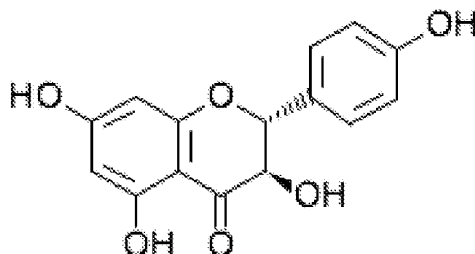
FIG. 4 shows a full list of differentially expressed genes related to specific pathways.

DETAILED DESCRIPTION

Dihydrokaempferol

Dihydrokaempferol (DHK) is a naturally occurring flavonoid that can be found in European plum, wood of *Pinus sibirica*, and *Olea europaea* (Venditti et al. 2013, Natural Product Research 27(4-5):340-349).

The invention provides compositions of dihydrokaempferol (molecular weight 288.3 g/mol; CAS 480-20-66; synonyms aromadendrin, aromodendrin). The chemical structure of dihydrokaempferol is provided below:



Dihydrokaempferol has demonstrated anti-inflammatory activity in both macrophage cell lines and in skin (Venditti et al. 2013; Lee et al. 2013, Biomolecules and Therapeutics 21(3):216-221).

Additionally, dihydrokaempferol has been shown to function as an antioxidant, anti-diabetic, and as a treatment for severe acute pancreatitis in mice (Venditti et al. 2013; Liang et al. 2020, Life Sciences 261:118340).

With respect to skin and aging, dihydrokaempferol upregulates Sirtuin-1 to reduce oxidative stress and reduce inflammatory response and subsequent inflammatory cascades (Zhang et al. 2021, The American Journal of Chinese Medicine, 49(3):705-718).

In addition to anti-aging and anti-inflammatory benefits, dihydrokaempferol also increases
5 PPAR- γ 2 expression to stimulate glucose uptake, effectively decreasing insulin resistance (Zhang et al. 2011, Pharmacology, 88:266-74).

Compositions of dihydrokaempferol

In one aspect, the invention provides compositions comprising dihydrokaempferol. In
10 certain embodiments, the invention provides compositions comprising dihydrokaempferol that are suitable for administration on the skin of the subject.

In one aspect, the invention provides a composition for topical administration comprising an effective amount of dihydrokaempferol. The effective amount of dihydrokaempferol is an amount of dihydrokaempferol that would be effective in treating, ameliorating, or otherwise
15 impacting the underlying condition of the skin. The invention recognizes that dihydrokaempferol is poorly soluble or insoluble in water. The invention also recognizes that dihydrokaempferol is also poorly soluble or insoluble in oil, for example, dihydrokaempferol is insoluble in Helianthus Annuus (Sunflower) Seed Oil. In addition, dihydrokaempferol is also only minimally soluble in isopropyl myristate. In certain embodiments of the invention, dihydrokaempferol is dissolved in a
20 solvent selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyldiol, 1,2 heptanediol, and any combinations thereof. In certain preferred embodiments, dihydrokaempferol is dissolved in dimethyl isosorbide. In certain embodiments, the composition comprising dihydrokaempferol is anhydrous. In certain embodiments, the composition comprises oil as the only solvent. In certain
25 preferred embodiments, dihydrokaempferol is dissolved in dimethyl isosorbide. In certain embodiments, the composition comprising dihydrokaempferol is anhydrous. In certain embodiments, the composition comprises oil as the only solvent.

In certain embodiments, dihydrokaempferol is dissolved in a solvent selected from a group consisting of: 1,2 heptanediol, 1,2 hexanediol, 1,2 propanediol, butylene glycol, C₁₅₋₁₉ alkane,
30 capric/caprylic triglyceride, dibutyl adipate, diisopropyl adipate, dimethyl isosorbide, dipropylene glycol, ethanol, ethoxydiglycol, isoamyl laurate, isohexadecane, isopentyldiol, isopropyl

myristate, isopropyl lauroyl sarcosinate, jojoba oil, meadowfoam seed oil, mineral oil, neopentyl glycol diethylhexanoate, octyldodecanol, oleyl alcohol, pentylene glycol, phenylpropanol, polysorbate 20, propanediol, safflower seed oil, squalene, sunflower oil, t-butyl alcohol, tributyl citrate, tributyl-O-acetylcitrate, tri-C₁₅₋₁₉ alkyl citrate, triethyl citrate, triethyl O-acetylcitrate, and triisostearin.

Table 1, provided below, provides solubility data for dihydrokaempferol in various solvents.

Table 1

Solvent	Solubility (% w/w)
Ethoxydiglycol	25.00
Dimethyl Isosorbide	20.00
Isopropyl Lauroyl sarcosinate	10.00
1,2 hexanediol	10.00
Phenylpropanol	0.00
1,2 hexanediol	2.50
Propanediol	5.00
Butylene glycol	5.00
Pentylene glycol	5.00
Isopentyldiol	5.00
1,2 heptanediol	5.00
Sunflower Oil	0.00
Squalene	0.00
Jojoba Oil	0.00
C9-12 Alkane	0.00
C15-19 Alkane	0.00
Capric/Caprylic Triglyceride	0.00
Di(propylene glycol) dibenzoate	0.00
Isoamyl Laurate	0.00
Isopropyl Myristate	0.00
Neopentyl Glycol Dihexanoate	0.00
Tri C12-13 alkyl citrate	0.00

Tributyl citrate	0.00
Tributyl-O-acetylcitrate	0.00
Triethyl Citrate	0.00
Triethyl-O-acetylcitrate	0.00
Triisostearin	0.00
Phenylpropanol	0.00
3-methyl-1,3-butanediol	0.00
Oleyl Alcohol	0.00
1,2 Propanediol	0.00

As evident from the data provided in Table 1, dihydrokaempferol is soluble in dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, pentylene glycol, 1,2 hexanediol, propanediol, butylene glycol, phenylpropanol, isopentyldiol, 1,2 heptanediol, and any combinations thereof. However, dihydrokaempferol is minimally soluble in a number of other commonly used solvents.

In certain embodiments, the composition comprising dihydrokaempferol is an emulsion. In certain embodiments, the emulsion is an oil/water emulsion. In certain embodiments, the composition further comprises a solvent. In certain embodiment, the solvent is selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, pentylene glycol, 1,2 hexanediol, propanediol, butylene glycol, phenylpropanol, isopentyldiol, 1,2 heptanediol, and any combinations thereof. In certain embodiments, the solvent in the composition is dimethyl isosorbide. In certain embodiments, the solvent in the composition is ethoxydiglycol. In certain embodiments, the solvent in the composition is isopropyl lauroyl sarcosinate. In certain embodiments, the solvent in the composition is 1,2 hexanediol. In certain embodiments, the solvent in the composition is propanediol. In certain embodiments, the solvent in the composition is 1,2 hexanediol. In certain embodiments, the solvent in the composition is isopentyldiol. In certain embodiments, the solvent in the composition is 1,2 heptanediol. In certain embodiments, the solvent in the composition is a glycol. In certain embodiments, the glycol is selected from a group consisting of pentylene glycol, butylene glycol, propylene glycol, and any combination thereof.

The compositions of the invention are wherein the composition are stable under storage in ambient conditions. This is beneficial because the compositions of the invention may be stored

prior to administration to the subjects. There were no previously known shelf-stable formulations of dihydrokaempferol. Shelf-storage stable formulations of dihydrokaempferol would provide a convenient option for the composition to be applied to patients suffering from various ailments of the skin and/or seeking options for appearance of the skin.

5 In certain preferred embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least two (2) years under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least one year under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least
10 six (6) months under ambient conditions. In certain embodiments, the composition of the invention, comprising dihydrokaempferol, are stable under storage for at least three (3) months under ambient conditions.

In certain embodiments, the compositions of the invention demonstrate less than about 10% degradation of dihydrokaempferol when stored at 70 °C for one (1) month. In certain
15 embodiments, the compositions of the invention demonstrate less than about 20% degradation of dihydrokaempferol when stored at 70 °C for one (1) month. The high stability of the compositions of the invention at 70 °C demonstrate that the compositions of the invention will be stable under ambient conditions for at least 2 years. In certain embodiments, the compositions comprise dihydrokaempferol dissolved in dimethyl isosorbide, isopropyl lauroyl sarcosinate, and
20 ethoxydiglycol.

Surprisingly, the stability of dihydrokaempferol is dependent on the pH of the composition. The invention recognizes that dihydrokaempferol degrades at a higher rate if the pH of the composition is not in an optimal pH range. Thus, in certain embodiments, the compositions of the invention comprise buffers and/or pH adjusting agents to maintain the pH of the composition in
25 an optimal range to minimize the degradation of dihydrokaempferol under ambient conditions. In certain embodiments, the pH of the composition is from about 4 to about 8. In certain embodiments, the pH of the composition is from about 4 to about 7. In certain embodiments, the pH of the composition is from about 4 to about 6. In certain embodiments, the pH of the composition is from about 4 to about 5. The data pertaining to stability of the compositions of the
30 invention with respect to the pH of the solution is provided in FIG. 1.

In certain embodiments, the pH of the composition is about 4. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 4 have less than 10% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 4 have less than 20% degradation when stored at 50 °C for one (1) month.

In certain embodiments, the pH of the composition is about 5. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 5 have less than 20% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 5 have less than 25% degradation when stored at 50 °C for one (1) month.

In certain embodiments, the pH of the composition is about 6. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 6 have less than 20% degradation when stored at 50 °C for one (1) month. In certain embodiments, the compositions comprising dihydrokaempferol and a pH of about 6 have less than 25% degradation when stored at 50 °C for one (1) month.

Table 2, provided below, provides stability data for compositions comprising dihydrokaempferol in various solvents, when stored at 70 °C for up to one (1) month.

Table 2

Dihydrokaempferol stability at 70 °C					
Solvent	Concentration (% w/w)			% Degradation	
	Initial	1 week	1 month	1 week	1 month
Dimethyl isosorbide	6.66	6.33	6.04	95%	91%
Isopropyl lauroyl sarcosinate	8.40	8.14	7.71	97%	92%
Ethoxydiglycol	7.74	7.27	6.54	94%	84%

As evident from the data provided in Table 2, the compositions comprising dihydrokaempferol demonstrate good stability and minimal degradation. The representative data provided in Table 2, with dihydrokaempferol dissolved in various solvents, demonstrates the compositions of the invention, comprising dihydrokaempferol are stable when tested under

accelerated conditions. Thus, the compositions of the invention will also be stable for storage for at least 2 years under ambient conditions.

In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 5 nM to about 5 mM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 10 nM to about 4 mM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 5 nM to about 2500 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 10 nM to about 2000 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 20 nM to about 1000 nM. In certain embodiments, the compositions of the invention comprise dihydrokaempferol in a concentration of about 10 nM to about 20 nM. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 5 μ M to about 3,750 μ M. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 50 μ M to about 3,000 μ M. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 50 μ M to about 3,000 μ M. In certain embodiments, the compositions of the inventions comprise dihydrokaempferol in a concentration of about 500 μ M to about 4,500 μ M.

In certain embodiments, dihydrokaempferol is present in a concentration of about 0.0001% to about 5.0% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.0001% to about 1.0% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.001% to about 0.5% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.01% to about 0.5% w/w in the composition of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.1% to about 0.5% w/w in the compositions of the invention. In certain embodiments, dihydrokaempferol is present in a concentration of about 0.5% w/w in the compositions of the invention.

In certain aspects, the compositions of the invention may be administered as a topical composition on the skin of the subject. The compositions of the invention may be included in any formulation suitable for topical administration. In certain embodiments, the composition of the invention is a fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel,

hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, color cosmetic, and/or hair treatment. In certain embodiments, the compositions of the invention also include excipients. These excipients may be selected from a group consisting of: solvent, emulsifier, preservative, antioxidant, emollient, thickening agent, penetration enhancer, surfactant, diluent, filler, carrier, and/or pH control agent. In certain embodiments, the preservative in the composition is an antimicrobial preservative or chelating agent.

The compositions of the invention may be prepared by various methods. As an example, the compositions may be prepared by dissolving, dispersing, etc. dihydrokaempferol as provided herein and optional excipients in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) or a solvent to form a solution, colloid, liposome, emulsion, complexes (including inclusion complexes), coacervate, or suspension. In certain embodiments, the compositions of the current invention can also contain additional excipients such as wetting agents, emulsifying agents, co-solvents, solubilizing agents, pH buffering agents, and the like (e.g., sodium acetate, sodium citrate, cyclodextrins and derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, hydroxyethylpiperazine and the like). In certain embodiments, the compositions of the invention may further include one or more additional excipients selected from a group consisting of: carriers, excipients, or diluents including, but not limited to, absorbents, anti-irritants, antibacterials, anti-acne agents, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents, silicones, skin-identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, and a preservative.

In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, and a preservative.

In certain embodiments, the compositions of the invention comprise dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, a diluent, and a preservative.

In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, a thickener, optionally a diluent, and a preservative.

5 In certain embodiments, the compositions of the invention comprise: dihydrokaempferol, in an oil/water emulsion, a solvent for solubilizing dihydrokaempferol, and one or more excipients selected from the group consisting of: diluents, absorbents, antioxidants, emollients, emulsifiers, thickeners, surfactants, and/or preservatives.

10 In certain embodiments, the excipients included in the composition are water, dimethyl isosorbide, glycerin, caprylic/capric triglyceride, propanediol, sunflower seed oil, ethoxydiglycol, squalane, sodium acrylate copolymer, cetearyl alcohol, phenoxyethanol, glyceryl stearate, capryloyl glycerin/sebacic acid copolymer, diheptyl succinate, lecithin, decylene glycol, pentylene glycol, cetearyl glucoside, shea butter, palmitic acid, arachidyl alcohol, behenyl alcohol, arachidyl glucoside, phenethyl alcohol, 1,2-hexanediol, hydrogenated olive oil, olea europaea (olive) fruit oil, olea europaea (olive) oil unsaponifiables, hydroxyethyl acrylate/sodium acryloyldimethyl
15 taurate copolymer, citric acid, sodium acetylated hyaluronate, sodium hyaluronate crosspolymer, sodium phytate, hydrolyzed sodium hyaluronate, and/or ethylhexylglycerin.

The compositions of the invention may be prepared by various methods. As an example, the compositions may be prepared by dissolving, dispersing, etc dihydrokaempferol as provided herein and optional excipients in a carrier (e.g., water, saline, aqueous dextrose, glycerol, glycols, ethanol or the like) or a solvent to form a solution, colloid, liposome, emulsion, complexes
20 (including inclusion complexes), coacervate, or suspension. In certain embodiments, the compositions of the current invention can also contain auxiliary substances such as wetting agents, emulsifying agents, co-solvents, solubilizing agents, pH buffering agents, and the like (e.g., sodium acetate, sodium citrate, cyclodextrins and derivatives, sorbitan monolaurate, triethanolamine acetate, triethanolamine oleate, hydroxyethylpiperazine and the like). In certain
25 embodiments, the compositions of the invention may further include one or more additional excipients selected from a group consisting of: carriers, excipients, or diluents including, but not limited to, absorbents, anti-irritants, antibacterials, anti-acne agents, antioxidants, coloring agents/pigments, emollients (moisturizers), emulsifiers, film-forming/holding agents, fragrances, leave-on exfoliants, prescription drugs, preservatives, scrub agents, silicones, skin-
30

identical/repairing agents, slip agents, sunscreen actives, surfactants/detergent cleansing agents, penetration enhancers, and thickeners.

Absorbents are substances which are added to topical products to take up water and oil-soluble dissolved or finely dispersed substances. Topical absorbents can also be used as thickeners in a wide variety of formulations including facial creams, lipsticks, shampoos and calamine lotions. In some embodiments, absorbents may include, but are not limited to, alcohol (ethyl alcohol, methanol, isopropyl alcohol, SD alcohol [especially denatured alcohol] and benzyl alcohol), alumina (aluminum oxide), aluminum chlorohydrate, aluminum hydroxide, aluminum magnesium silicate, aluminum silicate, aluminum starch octenylsuccinate, aluminum sulfate, ammonium chloride, bentonite, bismuth oxychloride, boron nitride, calcium carbonate, carnauba wax, charcoal, China clay, clay, Copernicia cerifera wax, cornstarch, fuller's earth, hydrolyzed corn starch, iron powder, kaolin, lithium magnesium sodium silicate, magnesium, magnesium carbonate, magnesium hydroxide, montmorillonite, nylon-12, rice starch, silica, silicate, silk powder, silt, sodium carbonate, sodium polyacrylates, and zeolite.

Anti-irritants are substances which are added to topical products to reduce inflammation, especially, the inflammation resulting from the application of the product itself. The excipients included as anti-irritants that perform the function of anti-irritants or anti-inflammatories may have more than one function. For example, many antioxidants also function as anti-irritants. In some embodiments, anti-irritants and/or antioxidants may include, but are not limited to, Acacia senegal, acetylsalicylic acid, *Achillea millefolium*, adenosine, citric acid, adenosine triphosphate, Aloe barbadensis, aloe barbadensis leaf juice extract, aloe extract, aloe juice, hydrogenated olive oil, hydrogenated palm glycerides, hydrolyzed silk, hydroquinone, aloe vera, and/or alpha bisabolol.

In certain embodiments, the compositions of the invention may further include humectants. Humectants (or moisturizers) are important cosmetic ingredients that prevent loss of moisture thereby retaining the skin's natural moisture. Some humectants also can actively attract moisture. In certain embodiments, the humectants may be selected from a group consisting of sodium hyaluronate, sodium acetylated hyaluronate, hydrolyzed sodium hyaluronate, propylene glycol, hexylene glycol, panthenol, pentylene glycol, and butylene glycol.

In certain embodiments, the compositions of the invention may further include slip agents. The term "slip agent" is used to describe a range of ingredients which can help other ingredients spread over the skin and penetrate into the skin. Slip agents can also have humectant (hygroscopic)

properties. In some embodiments, slip agents may include, but are not limited to, amodimethicone, bis-PEG-18 methyl ether dimethyl silane, bis-phenylpropyl dimethicone, butylene glycol, cetyl dimethicone, cetyl dimethicone copolyol, cetyl PEG/PPG-10/1-dimethicone, cyclohexasiloxane, cyclomethicone, cyclopentasiloxane, cyclotetrasiloxane, decylene glycol, diisostearyl trimethylolpropane siloxy silicate, dimethicone, dimethicone copolyol, dimethicone crosspolymer, dimethiconol, dipropylene glycol, hexylene glycol, hydrolyzed silk, isododecane, methicone, methyl trimethicone, methylsilanol mannuronate, methylsilanol PEG-7 glyceryl cocoate, Good, PEG-10 dimethicone, PEG-10 dimethicone/vinyl dimethicone crosspolymer, PEG-12 dimethicone, PEG/PPG-18/18 dimethicone, PEG/PPG-20/15 dimethicone, pentylene glycol, phenyl trimethicone, polymethylsilsesquioxane, PPG-3 benzyl ether myristate, silica dimethyl silylate, silk powder, siloxane, simethicone, sorbitol, stearyl dimethicone, stearyl methicone, triethoxycaprylsilane, trimethylsiloxysilicate, xylitol, and zinc stearate.

In certain embodiments, the compositions of the invention may further include diluents, and/or carriers. Diluents and/or carriers may include, but are not limited to, polyethylene glycols (such as PEG200, PEG300, PEG400, PEG540, PEG600, PEG1450 or mixtures thereof) and coconut oils (such as propylene glycol dicaprate, coco-caprylate/caprate, propylene glycol dicaprylate/dicaprate, caprylic/capric triglyceride, caprylic/capric/lauric triglyceride, caprylic/capric/linoleic triglyceride, tricaprin, tricaprylin, glyceryl trioleate, neopentyl glycol dicaprylate/dicaprate, caprylic/capric/palmitic/stearic triglyceride, or mixtures thereof).

In certain embodiments, the compositions of the invention may further include emollients. Emollients are supple, waxlike, lubricating, thickening substances which are added to cosmetic/dermatological products to prevent water loss and have a softening and soothing effect on the skin. In some embodiments, emollients may include, but are not limited to, 10-hydroxydecanoic acid, acetyl glyceryl ricinoleate, acetylated castor oil, acetylated hydrogenated cottonseed glyceride, acetylated lanolin, acetylated lanolin alcohol, acetylated palm kernel glycerides, agar, algae extract, algin, almond oil, squalane, squalene, α -glucan oligosaccharide, amodimethicone, *Anacystis nidulans* extract, apricot kernel oil, arachidic acid, arachidonic acid, arachidyl alcohol, arachidyl propionate, C₁₀₋₃₀ cholesterol/lanosterol esters, C₁₂₋₁₅ alkyl benzoate, C₁₂₋₁₈ acid triglyceride, C₁₈₋₃₆ acid triglyceride, candelilla wax, *Cannabis sativa* L. oil, caprylic/capric triglyceride, caprylyl methicone, carrot oil, *Carthamus tinctorius*

oil, *Carya illinoensis* oil, castor isostearate succinate, castor oil, *Caulerpa taxifolia* extract, and/or cephalin.

In certain embodiments, the compositions of the invention may further include film-forming/holding agents. Film-Forming/Holding agents are substances which are added to cosmetic/dermatological products to help leave a pliable, cohesive, and continuous covering over the skin. This film has water-binding properties and leaves a smooth feel on skin. In some embodiments, film-forming/holding agents may include, but are not limited to, acrylate, acrylates copolymer, acrylates/C₁₀₋₃₀ alkyl acrylate crosspolymer, acrylates/dimethicone copolymer, adipic acid/neopentyl glycol/trimellitic anhydride copolymer, allyl methacrylates crosspolymer, carnauba wax, cellulose gum, Copernicia cerifera wax, dextrin, diisopropyl adipate, glyceryl polymethacrylate, hydrolyzed wheat protein, hydroxyethylcellulose, locust bean, neopentyl glycol diheptanoate, PEG-40 hydrogenated castor oil, polyacrylamide, polyacrylate-17, polyglucuronic acid, polyglyceryl methacrylate, polyisobutene, polymethyl methacrylate, polyquaternium-10, polyquaterniums, polyvinyl alcohol, polyvinylpyrrolidone, propylene carbonate, PVM/MA (polyvinyl methyl ether/maleic acid) decadiene crosspolymer, PVP [poly(vinylpyrrolidone)] copolymer, PVP/dimethylaminoethyl-methacrylate, sodium carbomer, sodium polyacrylate, styrene/acrylates copolymer, triethoxycaprylylsilane crosspolymer, VA (vinyl acetate)/crotonates, VA/crotonates copolymer, VP (vinylpyrrolidone)/eicosene copolymer, and VP/hexadecene copolymer.

In certain embodiments, the compositions of the invention may further include excipients related to the fragrance of the formulation. Fragrance ingredients are a single or a blend of volatile and/or fragrant plant oils (or synthetically derived oils) that impart aroma and odor to cosmetic/dermatological products. The level of fragrance to use varies according to the product type. In some embodiments, the composition of the formulation may contain up to about 0.01% fragrance by weight. In some embodiments, fragrances (e.g., synthetic and fragrant plant extracts) may include, but are not limited to, *Acacia farnesiana* extract, *Aerocarpus santalinus*, amyl cinnamate, amyl salicylate, amyris oil, *Anethum graveolens*, *Angelica archangelica* root oil, anisaldehyde, anise, balm mint extract, balsam peru, bay leaf oil, bergamot oil, bitter orange flower, bois de rose oil, bois oil, *Boswellia carterii*, butylphenyl methylpropional, *cananga* extract, *Cananga odorata*, cardamom, cedarwood, cherry extract, *Citrus aurantifolia*, *Citrus aurantium*, *Citrus aurantium* extract, *Citrus medica limonium*,

clary oil, *Commiphora* myrrha extract, coriander, Cucurbita pepo, cyclamen aldehyde, dill extract, ethyl vanillin, eugenol, farnesol, farnesyl acetate, Ferula galbaniflua, fir needle oil, floralozone, *Foeniculum vulgare* extract, frankincense extract, *galbanum*, *Gardenia florida* extract, grapefruit oil, guaiac wood, *Guaiacum officinale*, hedione, hexyl cinnamal, hyssop, *Illicium verum*, Iris florentina extract, jasmine oil, *Jasminum grandiflorum*, jonquil extract, *Laurus nobilis*, lauryl lactate, lavandin oil, *Lavandula angustifolia*, *Lavandula officinalis*, lavender extract and oil, lemon, lemon balm, lemongrass oil, *Levisticum officinale* root extract, lime oil and extract, limonene, linalool, *Litsea cubeba*, mandarin orange oil or extract, marjoram, *Melissa officinalis*, *Mentha piperita*, *Mentha spicata*, *Mentha viridis*, menthol, menthone, menthoxypropanediol, and menthyl lactate.

In certain embodiments, the composition of the invention may further include preservatives. Preservatives are substances which prevent bacterial, microbial or fungal contamination of cosmetic/dermatological products thereby increasing the product's shelf life and consumer safety. Some of these agents also have stabilizing effects able to preserve the function of various active ingredients including anti-oxidants (vitamins), emulsifiers and surfactants. In some embodiments, preservatives may include, but are not limited to, 1,2-hexanediol, benzoic acid, benzothionium chloride, borax, bronopol, butylparaben, caprylyl glycol, chlorophene, chloroxylenol, chlorphenesin, decylene glycol, dehydroacetic acid, diazolidinyl urea, DMDM hydantoin, ethylhexylglycerin, ethylparaben, formaldehyde-releasing preservative, Germaben II, hoelen, hydroxyacetophenone, imidazolidinyl urea, iodopropynyl butylcarbamate, isobutylparaben, methylchloroisothiazolinone, methyldibromo glutaronitrile, Methylisothiazolinone, methylparaben, o-cymen-5-ol, phenoxyethanol, phenoxyisopropanol, phytosphingosine, polyaminopropyl biguanide, potassium sorbate, propylparaben, quaternium-15, sodium benzoate, sodium citrate, sodium dehydroacetate, sodium hexametaphosphate, sodium hydroxymethylglycinate, phenethyl alcohol, sodium lactobionate, sodium metabisulfite, sodium sulfite, sorbic acid, caprylyl glyceryl ether, caprylhydroxamic acid, and *styrax benzoin*.

In certain aspects of the invention, the pharmaceutical composition is an emulsion. The emulsion compositions of the invention may further include emulsifiers. Emulsifiers are substances which are added to cosmetic/dermatological products to help keep unlike ingredients (such as oil and water) from separating in an emulsion. There are 2 types of emulsifiers. Oil-in-water (o/w) emulsifiers keep oil drops packed in water, while water-in-oil (w/o) emulsifiers keep

water drops packed in oil. W/O emulsifiers are used for a fatty feel (e.g., night & sun protection creams). O/W emulsifiers are used more in moisturizing products (e.g., body lotions, day creams).

In certain embodiments, the compositions of the invention may further include surfactants. Surfactants are compounds that lower surface tension or interfacial tension. Reducing the surface
 5 tension allows a liquid to spread easier while reducing the interfacial tension (interfacial meaning between two faces) between water and an oil/lipid allows them to mix. Surfactants may have a be anionic, amphoteric, non-ionic, and/or quaternary agents. Surfactants form the base of all personal cleansing products and can also have wetting, conditioning, defatting, emulsifying, & thickening effects. In some embodiments, emulsifiers, surfactants, and detergents may include, but are not
 10 limited to, ammonium laureth sulfate, ammonium lauryl sulfate, arachidyl glucoside, behenic acid, bis-PEG-18 methyl ether dimethyl silane, C₂₀₋₄₀ pareth-40, cocamidopropyl betaine, cocamidopropyl dimethylamine, cocamidopropyl hydroxysultaine, coco-glucoside, coconut oil, decyl glucoside, dicetyl phosphate, dihydrocholeth-30, disodium cocoamphodiacetate, disodium cocoyl glutamate, disodium lauraminopropionate, glyceryl behenate, hydrogenated vegetable
 15 glycerides citrate, isohexadecane, isostearamide DEA, lauramphocarboxyglycinate, laureth-23, laureth-4, laureth-7, lauryl PEG-9 polydimethylsiloxylethyl dimethicone, lauryl alcohol, lauryl glucoside, magnesium laureth sulfate, magnesium oleyl sulfate, myristic acid, nonoxynols, oleic acid, oleyl 10, palm kernel acid, palmitic acid, PEG-60 almond glycerides, PEG-75 shea butter glycerides, PEG 90M, PEG-10 dimethicone, PEG-10 dimethicone/vinyl dimethicone
 20 crosspolymer, PEG-10 rapeseed sterol, PEG-100 stearate, PEG-12 dimethicone, PEG-120 methyl glucose dioleate, PEG-20 methyl glucose sesquistearate, PEG-40 stearate, PEG-60 hydrogenated castor oil, PEG-7 glyceryl cocoate, PEG-8, PEG-80 sorbitan laurate, PEG/PPG-17/6 copolymer (polyethylene glycol/polypropylene glycol-17/6 copolymer), PEG/PPG-18/18 dimethicone, PEG/PPG-20/15 dimethicone, poloxamer 184, Poloxamer 407, poloxamers, polyglyceryl-3
 25 beeswax, polyglyceryl-4 isostearate, polyglyceryl-6 isostearate, polysorbate 20, polysorbate 60, polysorbate 80, potassium cetyl phosphate, potassium hydroxide, potassium myristate, PPG-12 buteth-16, PPG-26-Buteth-26, *Salvia officinalis*, *Saponaria officinalis* extract, soapwort, sodium C₁₄₋₁₆ olefin sulfonate, sodium cetaryl sulfate, sodium cocoamphoacetate, sodium cocoate, sodium cocoyl glutamate, sodium cocoyl isethionate, sodium dilauramidoglutamide lysine,
 30 sodium hexametaphosphate, sodium hydroxide, sodium laureth sulfate, sodium laureth-13 carboxylate, sodium lauroamphoacetate, sodium lauroyl lactylate, sodium lauroyl sarcosinate,

sodium lauryl glucose carboxylate, sodium lauryl sulfate, sodium methyl cocoyl taurate, sodium methyl taurate, sodium myreth sulfate, sodium palm kernelate, sodium palmate, sodium PEG-7 olive oil carboxylate, sodium trideceth sulfate, steareth-20, TEA-lauryl sulfate (triethanolamine-lauryl sulfate), and tribehenin PEG-20 esters.

- 5 In certain embodiments, the compositions of the invention may further include one or more thickeners. Thickeners are substances which are added to cosmetic/dermatological products to enhance the consistency, volume and viscosity of cosmetic products, thereby providing more stability and better performance. While some thickeners have also emulsifying or gelling properties, the majority of thickeners have the ability to retain water on the skin and act therefore
- 10 as moisturizers. Thickeners can be completely natural like waxes but also synthetic or semi-synthetic. In some embodiments, thickeners may include, but are not limited to, Acacia senegal, acetyl glyceryl ricinoleate, acetylated castor oil, acetylated hydrogenated cottonseed glyceride, acetylated palm kernel glycerides, acrylates/steareth-20 methacrylate copolymer, agar, *Ahnfeltia concinna* extract, *Ahnfeltia* extract, *Alaria esculenta*, algae, algae extract, algin,
- 15 alkyloamides, *Althaea rosea*, *Althea officinalis*, alumina, aluminum hydroxide, aluminum stearate, ammonium acryloyldimethyltaurate/VP copolymer, *Anacystis nidulans* extract, arachidic acid, arachidonic acid, arachidyl alcohol, arachidyl propionate, arrowroot, artemia extract, *Ascophyllum nodosum*, ascorbyl methylsilanol pectinate, Asparagopsis armata extract, beeswax, behenic acid, behentrimonium chloride, behenyl alcohol, bis-diglyceryl polyacyladipate, bismuth oxychloride,
- 20 C₁₂₋₁₅ alkyl benzoate, C₁₂₋₁₈ acid triglyceride, C₁₃₋₁₄ isoparaffin, C₁₈₋₃₆ acid triglyceride, candelilla wax, caprylic/capric triglyceride, carbomer, carbopol, carnauba wax, carrageenan, Caulerpa taxifolia extract, cellulose, Cellulose gum, cephalin, Cera alba, ceresin, cetareth-20, cetearyl alcohol, cetearyl ethylhexanoate, cetearyl glucoside, cetearyl octanoate, cetyl alcohol, cetyl dimethicone copolyol, cetyl hydroxyethylcellulose, cetyl palmitate, cetyl PEG/PPG-10/1-
- 25 dimethicone, *Chlorella*, *Chondrus crispus*, cocamide DEA and MEA, cocoglycerides, *Codium tomentosum* extract, Copernicia cerifera wax, *Corallina officinalis* extract, *Corallina*, DEA oleth-10 phosphate, diethanolamine (DEA), di-PPG-3 myristyl ether adipate, dimethicone crosspolymer, dimethicone/vinyl dimethicone crosspolymer, polyacrylate crosspolymer, ammonium 2 acrylamido-2-methylpropane sulfonic acid crosspolymer, sodium polyacryloyldimethyl taurate,
- 30 tara gum and/or dimer dilinoleyl dimer dilinoleate.

In certain embodiments, the compositions of the invention may further include one or more chelators. Chelating agents are any of numerous ingredients that bind with metal ions or metallic compounds, preventing them from adhering to a surface (such as skin, hair, or clothing) or causing contamination, such as in the case of trace amounts of iron. In some embodiments, chelators may include, but are not limited to tetrasodium EDTA, sodium phytate, and/or teathydroxypropyl ethylenediamine.

In certain embodiments, the compositions of the invention include one or more buffers and/or pH-adjustors. The buffer and/or pH adjustor (also referred to as pH control agent) is present in the compositions of the invention to maintain the pH of the solution in an optimal range. In certain embodiments, the one or more buffer and/or pH adjustors are selected from a group consisting of: phosphoric acid/phosphate, citric acid/citrate, tromethamine, histidine, lactic acid, gluconic acid, aspartic acid, glutamic acid, tartaric acid, glutamic acid, succinic acid, malic acid, fumaric acid, and/or α -ketoglutaric.

In certain embodiments, the excipients included in the composition are water, dimethyl isosorbide, glycerin, caprylic/capric triglyceride, propanediol, sunflower seed oil, ethoxydiglycol, squalane, sodium acrylate copolymer, cetearyl alcohol, phenoxyethanol, glyceryl stearate, capryloyl glycerin/sebacic acid copolymer, diheptyl succinate, naringenin, lecithin, decylene glycol, pentylene glycol, cetearyl glucoside, shea butter, palmitic acid, arachidyl alcohol, behenyl alcohol, arachidyl glucoside, phenethyl alcohol, 1,2-hexanediol, hydrogenated olive oil, olea europaea (olive) fruit oil, olea europaea (olive) oil unsaponifiables, hydroxyethyl acrylate/sodium acryloyldimethyl taurate copolymer, citric acid, sodium acetylated hyaluronate, sodium hyaluronate crosspolymer, sodium phytate, hydrolyzed sodium hyaluronate, and/or ethylhexylglycerin.

Table 3 provides a list of excipients along with their concentration ranges, that may be used in the exemplary compositions of the invention.

Table 3

Ingredient	Concentration (% w/w)
Water	30-90
Glycerin	0-20
Propanediol	0-10

Hydrogenated Ethylhexyl Olivat	0-2
Hydrogenated Olive Oil Unsaponifiables	0-2
Polyglyceryl-6 Distearate	0-5
Jojoba Esters	0-2.5
Polyglyceryl-3 Beeswax	0-2
Cetyl Alcohol	0-2
Cetearyl Olivat	0-5
Sorbitan Olivat	0-5
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer	0-5
Helianthus Annuus (Sunflower) Seed Oil	0-10
Caprylic/Capric Triglyceride	0-10
Phenoxyethanol	0-2
Decylene Glycol	0-2
1,2-Hexanediol	0-2
Dihydrokaempferol	0.0001-5
Dimethyl Isosorbide	0-10

Dihydrokaempferol for treatment of topical conditions

Advantageously, it was discovered that dihydrokaempferol impacts the genes and signaling pathways involved in several topical conditions. In one aspect, the invention provides methods of using the compositions for treating, protecting, and/or altering (e.g., improving) the condition and/or aesthetic appearance of skin, including, for example, treating, preventing, ameliorating, reducing and/or eliminating fine lines and/or wrinkles of skin and/or improving the aesthetic appearance of fine lines and/or wrinkles of skin. In certain embodiments, the compositions of the invention lead to increase in skin and/or hair resiliency. In certain embodiments, the compositions of the invention lead to increase in elasticity of the skin. In certain embodiments, the compositions of the invention prevent skin damage. In certain embodiments, the compositions of the invention reduce inflammation. In certain embodiments, the compositions of the invention lead to skin barrier improvement. In certain embodiments, the compositions of the invention support wound healing and epidermal regeneration.

In one aspect, the invention includes a composition for topical administration comprising an effective amount of dihydrokaempferol. The effective amount of dihydrokaempferol is an

amount of dihydrokaempferol that would be effective in treating, ameliorating, or otherwise impacting the underlying condition of the skin.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate antioxidant activity. In certain embodiments, the compositions of the invention, the antioxidant activity of dihydrokaempferol is demonstrated at concentrations of about 0.00005% w/w or higher. Beneficially, the antioxidant activity of compositions comprising dihydrokaempferol is demonstrated in both aqueous and organic solvent systems. Thus, the invention provides compositions which retain antioxidant activity in both aqueous and organic solvents. Advantageously, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for treating and/or preventing oxidation damage. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for treatment of skin and/or hair damaged by reactive oxygen species and protection from other environmental aggressors that may damage the skin of the subject. In certain other embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating antioxidant activity, are effective for prevention of skin and/or hair damage by reactive oxygen species, including the damage caused by environmental aggressors.

As demonstrated from the data provided in Examples 2 and 3, compositions comprising dihydrokaempferol are effective in demonstrating robust antioxidant activity in both aqueous and organic solvent systems. The IC_{50} values for antioxidant activity calculated in aqueous solvent system was 0.0143% w/w. The IC_{50} values for antioxidant activity calculated in organic solvent system was 0.05% w/w. These results demonstrate that compositions comprising dihydrokaempferol have robust antioxidant activity. In certain embodiments, the compositions comprising dihydrokaempferol are useful in treatment of conditions caused by oxidation or excessive oxidation in the skin of the subject. In certain embodiments, the compositions comprising dihydrokaempferol are administered for treatment and/or prevention of skin or hair damage by reaction oxygen species and protection from environmental aggressors.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate elastase enzyme inhibition. In certain embodiments, the compositions of the invention, the elastase enzyme inhibition activity of dihydrokaempferol is demonstrated at concentrations of about 0.1% w/w or higher. The data for elastase enzyme inhibition for the

treatment for enzyme inhibition is provided in Example 4. The IC₅₀ values for elastase enzyme inhibition in compositions comprising dihydrokaempferol is 0.13% w/w. Advantageously, the compositions comprising dihydrokaempferol, demonstrating elastase enzyme inhibition activity, are effective for promoting the elasticity of the skin. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating elastase enzyme inhibition, are effective in reduction of fine lines and/or wrinkles in the skin. In certain embodiments, the compositions of the invention comprising dihydrokaempferol, demonstrating elastase enzyme inhibition, are effective in prevention of formation of fine lines and/or wrinkles in the skin.

In certain aspects of the invention, the compositions comprising dihydrokaempferol demonstrate inhibition of glycation. In certain embodiments, the compositions of the invention, the glycation inhibition activity of dihydrokaempferol is demonstrated at concentrations of about 0.004% w/w or higher. The data for elastase enzyme inhibition for the treatment of glycation inhibition is provided in Example 5. The IC₅₀ values for glycation inhibition by compositions comprising dihydrokaempferol is 0.016% w/w. Advantageously, the compositions comprising dihydrokaempferol, demonstrating glycation inhibition activity, are effective for supporting and promoting skin and/or hair resiliency.

In certain embodiments of the invention, the compositions of the invention, comprising dihydrokaempferol modulate the gene expression of one or more genes that is related to a topical condition. In certain embodiments, administration of composition comprising dihydrokaempferol alters one or more of functions related to the modulated genes, wherein the one or more functions are selected from the group consisting of: (i) formation of fine lines or wrinkles on the skin, (ii) inflammation, (iii) skin elasticity, (iv) wound healing, (v) skin barrier formation, and/or (vi) any combination thereof.

In certain aspects, the invention provides methods of treatment of a topical condition by administration of the topical composition comprising an effective amount of dihydrokaempferol. In certain embodiments, the invention provides methods for prevention of fine lines or wrinkles on skin of the subject by administration of the compositions provided herein. In certain embodiments, the invention provides methods for supporting firmness and increasing/maintaining elasticity of skin by administration of the compositions provided herein. In certain embodiments, the invention provides methods for prevention of skin and hair damaged by reactive oxygen species by administration of the compositions provided herein. In certain embodiments, the

invention provides methods for protection from environment aggressors on skin by administration of the compositions provided herein. In certain embodiments, the invention provides methods for increase in skin and/or hair resiliency by administration of the compositions provided herein. In certain embodiments, the invention provides methods for prevention of glycation by administration of the compositions provided herein. Glycation is known to be linked with the wrinkling, loss of elasticity, and aging in the skin. In certain embodiments, the invention provides methods of reducing damage in skin by administration of compositions provided herein.

Treatment of topical conditions

The current invention recognizes that the compositions comprising dihydrokaempferol is beneficial for treating, protecting and/or improving the condition and/or aesthetic appearance of skin. For example, the compositions of the invention may be effective for altering the aesthetic appearance of skin associated with or affected by, or for treating or preventing, fine lines and/or wrinkles of skin caused by, for example, cellular senescence, environmental damage or dermatoheliosis. The invention also provides methods for stimulating skin cell renewal, increasing cell or tissue regeneration, promoting fibroblast proliferation and synthesizing elastin, collagen, proteoglycans, and/or new connective tissue, thereby reducing or improving the appearance of wrinkles, restoring elasticity, resiliency, and/or suppleness to the skin.

The compositions of the invention provided herein can be useful for improving the aesthetic appearance of skin. Such improvements can include, but are not limited to, all outward visibly and tactilely perceptible manifestations as well as any other macro or micro effects due to skin aging and damage. Such manifestations and effects can be induced or caused by intrinsic factors and/or extrinsic factors, e.g., chronological aging, environmental damage, climate, sun (UV) exposure, smoking, drugs, alcohol consumption, jetlag, night work, changes in circadian rhythm, pregnancy, menopause, genetic factors, nutritional factors and/or deficiencies, dehydration, stress, allergies (e.g., to plants, animals, medications, and other substances), exposure to industrial and/or household chemicals, indoor heating and cooling, various disorders and diseases such as arteriosclerosis, diabetes, heart disease, liver disease, and obesity, thinning of the outer layer of skin, decreases in the number of pigment-containing cells, increases in the size of pigment-containing cells, changes in the connective tissue, and reduction in the strength and elasticity of the skin.

The aesthetic appearance of skin can be improved, for example, by improving the appearance of skin associated with or affected by one or more of wrinkles, dry skin, sensitive skin; wrinkling and sagging; acne; vitiligo (skin condition in which there is a loss of brown color (pigment) from areas of skin); fine lines, wizened skin, thinning of the dermis, the degradation of collagen fibers, flaccid skin, thinned skin, and skin exposed to ultraviolet radiation. In some
5 embodiments, the compositions of the invention can improve the aesthetic appearance of skin by decreasing the appearance of fine lines in the skin; creating a more youthful appearance of the skin; decreasing bags and/or rings around the eyes; increasing or restoring the elasticity, resiliency, and/or suppleness of the skin; increasing the apparent thickness, elasticity, flexibility, radiance,
10 glow, and plumpness of the skin; improving the fineness of the skin texture; improving the appearance of wrinkles, lined, dry, flaky, aged, and/or photodamaged skin; treating or preventing photodamaged skin; reducing the signs of skin aging; reducing the appearance of hyperpigmentation; treating or preventing hyperpigmentation; treating or preventing pigment deposition in the skin (e.g., that caused by UV exposure); reducing the appearance of skin
15 discolorations; and whitening, lightening, and/or bleaching the skin.

In certain embodiments, the compositions may be used for care, treatment, cleansing, and/or protective products for facial or body skin; anti-wrinkle or anti-aging compositions; skin firming compositions; skin lightening compositions; compositions for irritated skin; sunscreen compositions, artificial tanning (self-tanning) compositions or after-sun
20 care compositions; scalp care compositions; shaving preparation compositions; depilatory compositions; or make-up products for the skin of the face or body.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for altering the aesthetic appearance of skin associated with or affected by, or treating or preventing, a skin condition/disorder (e.g., a skin condition/disorder accompanied with a loss of
25 skin elasticity).

In certain embodiments, the compositions comprising dihydrokaempferol are administered for improving the barrier function and viability of the skin.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for altering the aesthetic appearance of skin associated with or affected by wrinkling, sagging,
30 and/or a loss of skin elasticity.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for altering the aesthetic appearance of skin associated with or affected by deteriorations in skin viscoelasticity.

5 In certain embodiments, the compositions comprising dihydrokaempferol are administered for altering the aesthetic appearance of skin associated with or affected by one or more of wrinkles and/or fine lines, wizened skin, a lack of elasticity and/or of tonus of the skin, thinning of the dermis, degradation of collagen fibers, flaccid skin, thinned skin, and the internal degradation of the skin following exposure to ultraviolet radiation.

10 In certain embodiments, the compositions comprising dihydrokaempferol are administered for decreasing the appearance of fine lines and/or wrinkles in the skin.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for decreasing the appearance of bags and/or rings around the eyes.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for reducing the appearance of hyperpigmentation.

15 In certain embodiments, the compositions comprising dihydrokaempferol are administered for improving or increasing one or more of the thickness, elasticity, flexibility, radiance, glow, and plumpness of the skin.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for improving the fineness of skin texture.

20 In certain embodiments, the compositions comprising dihydrokaempferol are administered for improving the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin.

In certain embodiments, the compositions comprising dihydrokaempferol are administered for altering the aesthetic appearance of skin associated with or affected by skin discolorations.

25 Gene expression and/or activity modulation

In certain embodiments of the invention, the compositions of the invention, comprising dihydrokaempferol modulate the gene expression of one or more genes that is related to a topical condition. In certain embodiments, administration of composition comprising dihydrokaempferol alters one or more of functions related to the modulated genes, wherein the one or more functions
30 are selected from the group consisting of: (i) formation of fine lines or wrinkles on the skin, (ii)

inflammation, (iii) skin elasticity, (iv) wound healing, (v) skin barrier formation, and/or (vi) any combination thereof.

In some embodiments, the invention provides a method of modulating expression of one or more genes in a mammal, comprising administering to the mammal an effective amount of a composition comprising dihydrokaempferol, wherein the one or more genes include at least one gene that is related to a condition of the mammalian epidermis. In some embodiments, the one or more genes are selected from the group consisting of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), C-X-C Motif Chemokine Ligand 2 (CXCL2), Fibroblast Growth Factor 2 (FGF2), Transient Receptor Potential Cation Channel Subfamily (TRPV6), Vascular Endothelial Growth Factor A (VEGFA), Thrombospondin 4 (THBS4).

In some embodiments, administering the composition reduces skin inflammation. In some embodiments, the one or more genes include at least one gene that is pro-inflammatory. In some embodiments, administering the composition causes down-regulation of expression and/or activity of at least one of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), and C-X-C Motif Chemokine Ligand 2 (CXCL2).

In some embodiments, administering the composition increases skin regeneration and wound healing. In some embodiments, the one or more genes include at least one gene that increases fibroblast growth. In some embodiments, the one or more genes include at least one gene that regulates endothelial growth factors. In some embodiments, the one or more genes include at least one gene that promotes fibroblast and keratinocyte migration. In some embodiments, administering the composition causes up-regulation of expression and/or activity of at least one of Fibroblast Growth Factor 2 (FGF2), Vascular Endothelial Growth Factor A (VEGFA), and Thrombospondin 4 (THBS4).

In some embodiments, administering the composition improves skin barrier function. In some embodiments, the one or more genes include at least one gene that promotes skin barrier formation. In some embodiments, administering the composition causes up-regulation of expression and/or activity of Transient Receptor Potential Cation Channel Subfamily (TRPV6).

In some embodiments, administering the composition leads to a log₂ fold change of about -4.0 to about -7.0 in the expression of Interleukin 6 (IL6). In some embodiments, administering the composition leads to a log₂ fold change of about -5.5 in the expression of Interleukin 6 (IL6).

In some embodiments, administering the composition leads to a log₂ fold change of about -1.0 to about -3.0 in the expression of Interleukin 24 (IL24). In some embodiments, administering the composition leads to a log₂ fold change of about -2.0 in the expression of Interleukin 24 (IL24).

In some embodiments, administering the composition leads to a log₂ fold change of about
5 -2.0 to about -5.0 in the expression of Tumor Necrosis Factor (TNF). In some embodiments, administering the composition leads to a log₂ fold change of about -3.4 in the expression of Tumor Necrosis Factor (TNF).

In some embodiments, administering the composition leads to a log₂ fold change of about
10 -1.0 to about -3.0 in the expression of C-X-C Motif Chemokine Ligand 1 (CXCL1). In some embodiments, administering the composition leads to a log₂ fold change of about -1.9 in the expression of C-X-C Motif Chemokine Ligand 1 (CXCL1).

In some embodiments, administering the composition leads to a log₂ fold change of about
15 -3.0 to about -6.0 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2). In some embodiments, administering the composition leads to a log₂ fold change of about -4.2 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2).

In some embodiments, administering the composition leads to a log₂ fold change of about
20 1.0 to about 3.0 in the expression of Fibroblast Growth Factor 2 (FGF2). In some embodiments, administering the composition leads to a log₂ fold change of about 1.8 in the expression of Fibroblast Growth Factor 2 (FGF2).

In some embodiments, administering the composition leads to a log₂ fold change of about
25 1.0 to about 4.0 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6). In some embodiments, administering the composition leads to a log₂ fold change of about 2.2 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6).

In some embodiments, administering the composition leads to a log₂ fold change of about
30 1.0 to about 4.0 in the expression of Vascular Endothelial Growth Factor A (VEGFA). In some embodiments, administering the composition leads to a log₂ fold change of about 2.3 in the expression of Vascular Endothelial Growth Factor A (VEGFA).

In some embodiments, administering the composition leads to a log₂ fold change of about
35 2.0 to about 5.0 in the expression of Thrombospondin 4 (THBS4). In some embodiments, administering the composition leads to a log₂ fold change of about 3.3 in the expression of Thrombospondin 4 (THBS4).

Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), and C-X-C Motif Chemokine Ligand 2 (CXCL2) have functions that are pro-inflammatory. In some embodiments, down-regulation of activity and/or expression of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), and/or C-X-C Motif Chemokine Ligand 2 (CXCL2) results in an anti-inflammatory response in the body, particularly in the skin.

Fibroblast Growth Factor 2 (FGF2) functions to increase fibroblast growth. In some embodiments, up-regulation of expression and/or activity of Fibroblast Growth Factor 2 (FGF2) improves skin regeneration and wound healing.

Vascular Endothelial Growth Factor A (VEGFA) regulates endothelial growth factors. In some embodiments, up-regulation of expression and/or activity of Vascular Endothelial Growth Factor A (VEGFA) improves skin regeneration and wound healing.

Thrombospondin 4 (THBS4) promotes fibroblast and keratinocyte migration. In some embodiments, up-regulation of expression and/or activity of Thrombospondin 4 (THBS4) improves skin regeneration and wound healing.

Transient Receptor Potential Cation Channel Subfamily (TRPV6) promotes skin barrier formation. In some embodiments, up-regulation of expression and/or activity of Transient Receptor Potential Cation Channel Subfamily (TRPV6) improves skin barrier function.

Methods of administration

In one aspect, the invention provides methods of administration of the compositions comprising dihydrokaempferol. In certain embodiments, the invention the compositions of the invention are designed for topical administration.

In certain embodiments, the compositions of the invention may be administered as a topical composition on the skin of the subject. The compositions of the invention may be included in any formulation suitable for topical administration. In certain embodiments, the composition of the invention is a fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, color cosmetic, and/or hair treatment.

In certain other embodiments, the compositions comprising dihydrokaempferol may be prepared and used in the form of an aerosol spray, cream, emulsion, solid, liquid, dispersion, foam,

oil, gel, lotion, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, towelette, soap, or other forms commonly employed in the art of topical administration and/or cosmetic and skin care formulation. The compositions can be in an emulsion form. In addition, compounds provided herein used in the compositions provided herein can be used in color cosmetic compositions such as foundation makeups, blushes, eyeshadows, mascaras, concealers, eyeliners, lip colors, nail colors, and so on. Other cosmetic compositions can include perfumes, lipsticks, fingernail and toenail polish, eye and facial makeup, towelettes, deodorants, hand sanitizer, baby products, bath oils, bubble baths, and butters.

In certain embodiments, the compositions comprising dihydrokaempferol are administered on the skin at a concentration of about 100 $\mu\text{g}/\text{cm}^2$ to about 5 mg/cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered on the skin at a concentration of about 200 $\mu\text{g}/\text{cm}^2$ to about 4 mg/cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered on the skin at a concentration of about 400 $\mu\text{g}/\text{cm}^2$ to about 3 mg/cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered on the skin at a concentration of about 1 mg/cm^2 to about 2 mg/cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered on the skin at a concentration of about 2 mg/cm^2 .

In certain embodiments, the composition comprising dihydrokaempferol is administered on the affected area of the skin. The affected area of skin is the area of skin to be improved or otherwise suffering from a topical condition. In certain embodiments, the compositions comprising dihydrokaempferol are administered over an area of about 0.5 cm^2 to about 100 cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered over an area of about 1 cm^2 to about 75 cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered over an area of about 10 cm^2 to about 75 cm^2 . In certain embodiments, the compositions comprising dihydrokaempferol are administered over an area of about 50 cm^2 .

In certain embodiments, the compositions comprising dihydrokaempferol are administered for a duration till the desired impact in amelioration or prevention of a topical condition is realized. In certain embodiments, the composition comprising dihydrokaempferol comprises an effective amount of dihydrokaempferol. The effective amount of dihydrokaempferol is an amount of dihydrokaempferol that results in the desired result in the condition of the skin. In certain

embodiments, the composition comprising dihydrokaempferol is administered once a day. In certain embodiments, the composition comprising dihydrokaempferol is administered twice a day. In certain embodiments, the composition comprising dihydrokaempferol is administered thrice a day. In certain embodiments, the composition comprising dihydrokaempferol is administered once every two days. In certain embodiments, the composition comprising dihydrokaempferol is administered once every three days.

EXAMPLES

Example 1: Exemplary composition comprising dihydrokaempferol

Table 4 provides an exemplary composition comprising dihydrokaempferol.

Table 4

Ingredient	Concentration (% w/w)
Water	76.300
Glycerin	5.000
Propanediol	2.000
Hydrogenated Ethylhexyl Olivat	0.500
Hydrogenated Olive Oil Unsaponifiables	0.500
Polyglyceryl-6 Distearate	1.419
Jobba Esters	0.407
Polyglyceryl-3 Beeswax	0.187
Cetyl Alcohol	0.187
Cetearyl Olivat	1.000
Sorbitan Olivat	1.000
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer	1.500
Helianthus Annuus (Sunflower) Seed Oil	3.000
Caprylic/Capric Triglyceride	3.000
Phenoxyethanol	0.700
Decylene Glycol	0.225
1,2-Hexanediol	0.075
Dihydrokaempferol	0.500
Dimethyl Isosorbide	2.500

Example 2: ABTS antioxidant assay

The 2,2-Azinobis [3-ethylbenzothiazoline-6-sulfonic acid]-diammonium salt (ABTS) antioxidant assay is designed to evaluate the antioxidant activity of compositions comprising dihydrokaempferol in an aqueous medium.

5 ABTS+ solution is generated as a free radical and used to measure relative ability of a compound to scavenge free radicals. Reduction of the absorbance at 734 nm was standardized to solvent control as an indication of ABTS+ scavenging.

Table 5, provided below, provides the results from these experiments.

Table 5

Dihydrokaempferol concentration (% w/w)	% Radical Inhibition
0.025	56.17
0.0125	42.49
0.00625	32.55

10

As evident from the results provided in Table 5 above, compositions comprising dihydrokaempferol demonstrate antioxidant activity at concentrations at low as 0.00625% w/w in aqueous systems. The calculated IC₅₀ value is: 0.0143% w/w.

15

Example 3: DPPH Antioxidant Activity assay

The 2,2-diphenyl-1-picrylhydrazyl (DPPH) antioxidant assay is designed to evaluate the antioxidant activity of compositions comprising dihydrokaempferol in an organic medium.

2,2-diphenyl-1-picrylhydrazyl (DPPH) is a stable free radical used to evaluate free radical scavenging capacity of a material. In the presence of an antioxidant DPPH is reduced, resulting in the formation of a colorless solution. Reduction of absorbance at 517 nm is standardized to solvent control as an indication of DPPH scavenging.

Table 6, provided below, provides the antioxidant activity data.

Table 6

Dihydrokaempferol concentration (% w/w)	% Radical Inhibition
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0.063	61.12
0.031	31.00
0.016	16.54

As evident from the results provided in Table 6 above, compositions comprising dihydrokaempferol demonstrate antioxidant activity at concentrations at low as 0.016% w/w in organic solvent systems, supporting treatment/prevention of skin and hair damaged by reactive oxygen species and protection from environmental aggressors. The calculated IC₅₀ value is: 0.05% w/w.

Example 4: Elastase enzyme inhibition

The assay was conducted to evaluate the elastase enzyme inhibition activity of compositions comprising dihydrokaempferol.

Neutrophil infiltration and neutrophil elastase are both increased in the skin in response to UV stress. Neutrophil elastase has been shown to activate MMP-1 and MMP-2 collagenase in response to low dose UV exposure, harming the extracellular matrix and contributing to photoaging and wrinkle formation. The activity of elastase can be further upregulated in the presence of reactive oxygen species. Therefore, inhibition of this enzyme, particularly in combination with antioxidant activity, is effective in delaying wrinkle development and aiding in maintaining skin integrity. This assay measures release of 4-nitroaniline from an Me-Suc-Ala-Ala-Pro-Val-pNA by human neutrophil elastase and can be quantified at 405 nm by comparing to solvent control.

Table 7 provides the elastase inhibition activity of compositions comprising dihydrokaempferol.

Table 7

Dihydrokaempferol concentration (% w/w)	% Enzyme Inhibition
0.500	81.52

0.100	29.65
0.020	0.00

As evident from the data provided in Table 7, compositions comprising dihydrokaempferol inhibit elastase enzyme activity as low as 0.1% w/w, supporting fine line/wrinkle reduction and prevention and support of skin firmness/elasticity. The calculated IC₅₀ value is: 0.13% w/w.

5

Example 5: Glycation inhibition assay

The assay was conducted to evaluate the glycation inhibition activity of compositions comprising dihydrokaempferol.

Nonenzymatic glycation can occur when glucose reacts with proteins, forming a Schiff
10 base intermediate that subsequently undergoes Amadori rearrangement to form glycosylated proteins, when they react with skin proteins to form Advanced Glycation End products (AGE). AGE formation can result in loss of skin elasticity and impaired cellular function. The glycation inhibition ability of a compound is measured by change in fluorescence at excitation/emission of 360 nm/420 nm relative to solvent control.

15 Table 8 provides the data for glycation inhibition.

Table 8

Dihydrokaempferol concentration (% w/w)	% Glycation Inhibition
0.100	82.42
0.033	64.87
0.011	42.23
0.004	25.05

As evident from the data provided in Table 8, compositions comprising dihydrokaempferol
20 inhibit glycation as low as 0.004% w/w, supporting skin elasticity, glycation prevention, and support of skin/hair resiliency. The IC₅₀ value calculated for glycation inhibition is 0.016% w/w.

Example 6: Anti-Inflammatory Activity

Normal Human Epidermal Keratinocytes (NHEK) were stressed with a cocktail of lipopolysaccharide (LPS) and Polyinosinic-polycytidylic acid sodium salt (Poly:IC), external aggressors capable of inducing an inflammatory response. Stressed cells were subsequently treated with test articles and incubated for 24 hours. Reduction in inflammatory markers was measured by ELISA and % reduction calculated relative to solvent control.

Table 9 shows the measurements of IL-6 concentration in stimulated (stressed) normal human epidermal keratinocytes.

Table 9

Test Article	IL-6 (pg/ml)	% Reduction vs Treated	p-value
Unstimulated Control	3.1	--	1.76E-06
Stimulated Control	1276.1	0.000	1
0.001% DHK	838.7	31.32	0.0167
0.002% DHK	687.5	43.70	0.0003
0.003% DHK	430.0	64.79	0.0002

As evident from the data provided in Table 9, dihydrokaempferol shows anti-inflammatory properties by reducing inflammatory markers IL-6 up to 64.79% *in vitro*.

Example 7: Skin Barrier Improvement

Human dermal fibroblasts (hDF) were treated with test article of interest. Barrier markers of interest were measured by flow cytometry. The results are shown in Table 10.

Table 10

Protein	Test Article	% Total Population
Filaggrin	Solvent Control	6.75
Filaggrin	0.003% DHK	42.2
Loricrin	Solvent Control	1.69

Loricrin	0.003% DHK	19.3
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As evident from the data provided in Table 10, dihydrokaempferol increases barrier proteins *in vitro*.

5

Example 8: Wound Healing

Human dermal fibroblasts (hDF) were plated in the presence of a growth-preventing insert. The insert was subsequently removed and regrowth measured by image analysis.

FIG. 2 shows images of the plates at T0, 24 hours, and 48 hours, for solvent control and treatment with compositions comprising 0.003% DHK. Table 11 shows the measurements of regrowth by image analysis.

10

Table 11

Test Article	Closure Rate 24 hr	Closure Rate 48 hr
Solvent Control	2.08	1.85
0.003% DHK	4.17	9.40

As evident from the data provided in FIG. 2 and Table 11, dihydrokaempferol increases fibroblast regrowth rate to support wound healing and epidermal regeneration.

15

Example 9: Anti-Aging

Human dermal fibroblasts (hDF) were treated with test article of interest. Elastin was quantified by ELISA. The results are provided in Table 12.

20

Table 12

Test Article	Elastin (ng/ml)	p-value
Solvent control	0.0	1
0.001% DHK	23.1	0.017
0.003% DHK	16.6	0.021
0.005% DHK	15.9	0.007

As evident from the data provided in Table 12, dihydrokaempferol increases elastin protein *in vitro*, supporting anti-aging and improvement in skin elasticity.

Example 10: Dihydrokaempferol Gene Expression

5 FIG. 3 shows a KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway map illustrating differential gene expression of genes involved in the cellular senescence pathway in normal human epidermal keratinocytes treated with compositions comprising 1% DHK. Log2fold changes are detailed in FIG. 4. Table 13, provided below, highlights certain examples of differential gene expression in normal human epidermal keratinocytes treated with compositions
10 comprising 1% DHK.

Table 13

Gene Name	Gene Function	Log2 Fold Change	Interpretation
Interleukin 6 (IL6)	Pro-inflammatory	-5.54	Anti-inflammatory
Interleukin 24 (IL24)	Pro-inflammatory	-2.01	Anti-inflammatory
Tumor Necrosis Factor (TNF)	Pro-inflammatory	-3.39	Anti-inflammatory
C-X-C Motif Chemokine Ligand 1 (CXCL1)	Pro-inflammatory	-1.91	Anti-inflammatory
C-X-C Motif Chemokine Ligand 2 (CXCL2)	Pro-inflammatory	-4.19	Anti-inflammatory
Fibroblast Growth Factor 2 (FGF2)	Increase fibroblast growth	1.82	Improve skin regeneration and wound healing
Transient Receptor Potential Cation Channel Subfamily (TRPV6)	Promotes skin barrier formation	2.19	Improve skin barrier function
Vascular Endothelial Growth Factor A (VEGFA)	Endothelial growth factors	2.32	Improve skin regeneration and wound healing
Thrombospondin 4 (THBS4)	Promotes fibroblast and keratinocyte migration	3.30	Improve skin regeneration and wound healing

Incorporation by Reference

References and citations to other documents, such as patents, patent applications, patent publications, journals, books, papers, web contents, publicly accessible databases, have been made
5 throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

Various modifications of the invention and many further embodiments thereof, in addition
10 to those shown and described herein, will become apparent to those skilled in the art from the full contents of this document, including references to the scientific and patent literature cited herein. The subject matter herein contains important information, exemplification and guidance that can be adapted to the practice of this invention in its various embodiments and equivalents thereof.

CLAIMS

1. A composition for topical administration comprising an effective amount of dihydrokaempferol.
- 5 2. The composition of claim 1, wherein the composition comprises an emulsion.
3. The composition of claim 2, wherein the emulsion is an oil/water emulsion.
- 10 4. The composition of claim 1, wherein the composition further comprises a solvent.
5. The composition of claim 4, wherein the solvent is a cosmetic solvent.
- 15 6. The composition of claim 5, wherein the solvent is selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyldiol, 1,2 heptanediol, and any combinations thereof.
- 20 7. The composition of claim 6, wherein the solvent is dimethyl isosorbide.
8. The composition of claim 6, wherein the solvent is ethoxydiglycol.
9. The composition of claim 6, wherein the solvent is isopropyl lauroyl sarcosinate.
- 25 10. The composition of claim 6, wherein the solvent is 1,2 hexanediol.
11. The composition of claim 6, wherein the solvent is propanediol.
12. The composition of claim 6, wherein the solvent is isopentyldiol.
- 30 13. The composition of claim 6, wherein the solvent is 1,2 heptanediol.
14. The composition of claim 6, where in the solvent is a glycol.

15. The composition of claim 15, wherein the glycol is selected from a group consisting of pentylene glycol, butylene glycol, propylene glycol, and any combination thereof.
- 5 16. The composition of claim 1, which is stable under storage for at least two (2) years under ambient conditions.
17. The composition of claim 1, which is stable under storage for at least one (1) year under ambient conditions.
- 10 18. The composition of claim 1, which is stable under storage for at least six (6) months under ambient conditions.
19. The composition of claim 1, which is stable under storage for at least three (3) months under ambient conditions.
- 15 20. The composition of claim 1, wherein the composition demonstrates less than about 10% degradation when stored at 70 °C for one (1) month.
21. The composition of claim 1, wherein the composition demonstrates less than about 20% degradation when stored at 70 °C for one (1) month.
- 20 22. The composition of claim 1, wherein the pH of the composition is from about 4 to about 8.
23. The composition of claim 1, wherein the pH of the composition is from about 4 to about 7.
- 25 24. The composition of claim 1, wherein the pH of the composition is from about 4 to about 6.
- 30 25. The composition of claim 1, wherein the pH of the composition is from about 4 to about 5.
26. The composition of claim 1, wherein the composition of pH is about 4.

27. The composition of claim 26, wherein the composition demonstrates less than about 10% degradation when stored at 50 °C for one (1) month.
- 5 28. The composition of claim 1, wherein the composition of pH is about 5.
29. The composition of claim 28, wherein the composition demonstrates less than about 20% degradation when stored at 50 °C for one (1) month.
- 10 30. The composition of claim 1, wherein the composition of pH is about 6.
31. The composition of claim 30, wherein the composition demonstrates less than about 20% degradation when stored at 50 °C for one (1) month.
- 15 32. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.0001% to about 5.0% w/w.
33. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.0001% to about 1.0% w/w.
- 20 34. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.001% to about 0.5% w/w.
35. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.01% to about 0.5% w/w.
- 25 36. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.1% to about 0.5% w/w.
- 30 37. The composition of claim 1, wherein dihydrokaempferol is present in a concentration of about 0.5% w/w.
38. The composition of claim 1, wherein the composition is selected from a group consisting of: fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel,

hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, color cosmetic, hair treatment, and any combination thereof.

39. The composition of claim 1, wherein the composition further comprises one or more
 5 excipients selected from a group consisting of: solvent, emulsifier, preservative, antioxidant, emollient, thickening agent, penetration enhancer, surfactant, diluent, filler, carrier, and/or pH control agent.
40. The composition of claim 39, wherein the preservative is an antimicrobial preservative or
 10 chelating agent.
41. The composition of claim 1, wherein dihydrokaempferol is encapsulated.
42. The composition of claim 1, wherein the composition further comprises one or more
 15 excipients selected from a group consisting of: dimethyl isosorbide, ethoxydiglycol, glycol, isopropyl lauroyl sarcosinate, 1,2 hexanediol, propanediol, phenylpropanol, isopentyl diol, 1,2 heptanediol, water, glycerin, hydrogenated ethylhexyl olivate, hydrogenated olive oil unsaponifiables, polyglycerol-6-distearate, jojoba esters, polyglyceryl-3-beeswax, cetyl alcohol, cetearyl olivate, sorbitan olivate, hydroxyethyl
 20 acrylate/sodium acryloyldimethyl taurate copolymer, helianthus annuus (sunflower) seed oil, caprylic/capric triglyceride, phenoxyethanol, decylene glycol, and 1,2-hexanediol.
43. The composition of claim 1, wherein the composition is:

Ingredient	Concentration % w/w
Water	30-90
Glycerin	0-20
Propanediol	0-10
Hydrogenated Ethylhexyl Oliviate	0-2
Hydrogenated Olive Oil Unsaponifiables	0-2
Polyglyceryl-6 Distearate	0-5
Jojoba Esters	0-2.5
Polyglyceryl-3 Beeswax	0-2
Cetyl Alcohol	0-2

Cetearyl Olivat	0-5
Sorbitan Olivat	0-5
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer	0-5
Helianthus Annuus (Sunflower) Seed Oil	0-10
Caprylic/Capric Triglyceride	0-10
Phenoxyethanol	0-2
Decylene Glycol	0-2
1,2-Hexanediol	0-2
Dihydrokaempferol	0.0001-5
Dimethyl Isosorbide	0-10

44. The composition of claim 1, wherein the composition is:

Ingredient	Concentration % w/w
Water	76.300
Glycerin	5.000
Propanediol	2.000
Hydrogenated Ethylhexyl Olivat	0.500
Hydrogenated Olive Oil Unsaponifiables	0.500
Polyglyceryl-6 Distearate	1.419
Jojoba Esters	0.407
Polyglyceryl-3 Beeswax	0.187
Cetyl Alcohol	0.187
Cetearyl Olivat	1.000
Sorbitan Olivat	1.000
Hydroxyethyl Acrylate/Sodium Acryloyldimethyl Taurate Copolymer	1.500
Helianthus Annuus (Sunflower) Seed Oil	3.000
Caprylic/Capric Triglyceride	3.000
Phenoxyethanol	0.700
Decylene Glycol	0.225
1,2-Hexanediol	0.075
Dihydrokaempferol	0.500
Dimethyl Isosorbide	2.500

45. A method of treating or preventing a topical condition in a subject by administration of a composition comprising an effective amount of dihydrokaempferol.
- 5 46. The method of claim 45, wherein the administration of the composition prevents fine lines or wrinkles on skin of the subject.
47. The method of claim 45, wherein the administration of the composition leads to supporting firmness and elasticity of skin of the subject.
- 10 48. The method of claim 45, wherein the administration of the composition leads to the prevention of skin and hair damaged by reactive oxygen species.
49. The method of claim 45, wherein the administration of the composition leads to protection from environment aggressors on skin.
- 15 50. The method of claim 45, wherein the administration of the composition leads to supporting skin elasticity.
51. The method of claim 45, wherein the topical condition is glycation.
- 20 52. The method of claim 45, wherein the administration of the composition leads increase in skin and/or hair resiliency.
53. The method of claim 45, wherein the administration of the composition leads to increase in elasticity of skin.
- 25 54. The method of claim 45, wherein the administration of the composition leads to prevention of skin damage.
- 30 55. The method of claim 45, wherein the topical condition is a wound.
56. The method of claim 55, wherein the administration of the composition leads to healing of the wound.

57. The method of claim 45, wherein the composition is administered topically.
58. The method of claim 45, wherein the composition is a composition from any of claims 1 - 44.
59. The method of claim 45, wherein the topical condition is inflammation.
60. The method of claim 49, wherein administering the composition leads to reduction in inflammation.
61. A method of modulating expression of one or more genes in a mammal, comprising administering to the mammal an effective amount of a composition comprising dihydrokaempferol, wherein the one or more genes include at least one gene that is related to a condition of the mammalian epidermis.
62. The method of claim 61, wherein the one or more genes include at least one gene that is pro-inflammatory.
63. The method of claim 61, wherein the one or more genes include at least one gene that increases fibroblast growth.
64. The method of claim 61, wherein the one or more genes include at least one gene that promotes skin barrier formation.
65. The method of claim 61, wherein the one or more genes include at least one gene that regulates endothelial growth factors.
66. The method of claim 61, wherein the one or more genes include at least one gene that promotes fibroblast and keratinocyte migration.
67. The method of claim 61, wherein the one or more genes are selected from the group consisting of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), C-X-C Motif Chemokine Ligand 2 (CXCL2), Fibroblast Growth Factor 2 (FGF2), Transient Receptor Potential Cation Channel

Subfamily (TRPV6), Vascular Endothelial Growth Factor A (VEGFA), Thrombospondin 4 (THBS4).

- 5 68. The method of claim 61, wherein administering the composition causes down-regulation of expression and/or activity of at least one of Interleukin 6 (IL6), Interleukin 24 (IL24), Tumor Necrosis Factor (TNF), C-X-C Motif Chemokine Ligand 1 (CXCL1), and C-X-C Motif Chemokine Ligand 2 (CXCL2).
- 10 69. The method of claim 61, wherein administering the composition causes up-regulation of expression and/or activity of at least one of Fibroblast Growth Factor 2 (FGF2), Transient Receptor Potential Cation Channel Subfamily (TRPV6), Vascular Endothelial Growth Factor A (VEGFA), and Thrombospondin 4 (THBS4).
- 15 70. The method of claim 61, wherein administering the composition reduces skin inflammation.
71. The method of claim 61, wherein administering the composition increases skin regeneration and wound healing.
- 20 72. The method of claim 61, wherein administering the composition increases skin barrier function.
73. The method of claim 61, wherein administering the composition increases skin elasticity.
- 25 74. The method of claim 61, wherein the composition comprises an emulsion.
75. The method of claim 61, wherein the composition comprises a fluid, emulsion, encapsulation, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, 30 color cosmetic, and/or hair treatment.
76. The method of claim 61, wherein the composition comprises an emulsion.
77. The method of claim 76, wherein the emulsion is an oil in water emulsion.

78. The method of claim 61, wherein the composition has a pH of about 4 to about 8.
79. The method of claim 61, wherein the composition comprises about 0.0001% to about
5 5.0% w/w dihydrokaempferol.
80. The method of claim 61, wherein the composition comprises about 0.1% to about 0.5%
w/w dihydrokaempferol.
- 10 81. The method of claim 61, wherein the composition is administered topically.
82. The method of claim 61, wherein administering the composition leads to a log2 fold
change of about -4.0 to about -7.0 in the expression of Interleukin 6 (IL6).
- 15 83. The method of claim 1, wherein administering the composition leads to a log2 fold
change of about -5.5 in the expression of Interleukin 6 (IL6).
84. The method of claim 61, wherein administering the composition leads to a log2 fold
change of about -1.0 to about -3.0 in the expression of Interleukin 24 (IL24).
- 20 85. The method of claim 61, wherein administering the composition leads to a log2 fold
change of about -2.0 in the expression of Interleukin 24 (IL24).
86. The method of claim 61, wherein administering the composition leads to a log2 fold
25 change of about -2.0 to about -5.0 in the expression of Tumor Necrosis Factor (TNF).
87. The method of claim 61, wherein administering the composition leads to a log2 fold
change of about -3.4 in the expression of Tumor Necrosis Factor (TNF).
- 30 88. The method of claim 61, wherein administering the composition leads to a log2 fold
change of about -1.0 to about -3.0 in the expression of C-X-C Motif Chemokine Ligand 1
(CXCL1).

89. The method of claim 61, wherein administering the composition leads to a log2 fold change of about -1.9 in the expression of C-X-C Motif Chemokine Ligand 1 (CXCL1).
- 5 90. The method of claim 1, wherein administering the composition leads to a log2 fold change of about -3.0 to about -6.0 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2).
- 10 91. The method of claim 61, wherein administering the composition leads to a log2 fold change of about -4.2 in the expression of C-X-C Motif Chemokine Ligand 2 (CXCL2).
92. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 1.0 to about 3.0 in the expression of Fibroblast Growth Factor 2 (FGF2).
- 15 93. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 1.8 in the expression of Fibroblast Growth Factor 2 (FGF2).
94. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 1.0 to about 4.0 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6).
- 20 95. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 2.2 in the expression of Transient Receptor Potential Cation Channel Subfamily (TRPV6).
- 25 96. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 1.0 to about 4.0 in the expression of Vascular Endothelial Growth Factor A (VEGFA).
- 30 97. The method of claim 61, wherein administering the composition leads to a log2 fold change of about 2.3 in the expression of Vascular Endothelial Growth Factor A (VEGFA).

98. The method of claim 61, wherein administering the composition leads to a log₂ fold change of about 2.0 to about 5.0 in the expression of Thrombospondin 4 (THBS4).
99. The method of claim 61, wherein administering the composition leads to a log₂ fold change of about 3.3 in the expression of Thrombospondin 4 (THBS4).
- 5