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(54) Title: ANTI-AGING COMPOSITIONS COMPRISING BILE ACID-FATTY ACID CONJUGATES

(57) Abstract: The present invention provides topical compositions comprising fatty acid bile acid conjugates (FABACs). The present invention further provides methods of using the disclosed compositions for preventing, attenuating or treating skin aging and symptoms related thereto.

# ANTI-AGING COMPOSITIONS COMPRISING BILE ACID-FATTY ACID CONJUGATES

## FIELD OF THE INVENTION

The present invention relates to topical compositions comprising bile acid-fatty acid conjugates and their use in treatment or prevention of skin conditions relating to aging.

## BACKGROUND OF THE INVENTION

Skin and Aging

The skin is the largest organ of the body and functions primarily to protect the body from external/environmental factors such as opportunistic pathogenic microorganisms, chemicals, UV radiation as well as to assist with temperature modulation.

Skin is subject to constant insult by the above environmental factors as well as by inherent factors. Environmental factors affecting skin include exposure to the sun, smoking and air pollution, while inherent factors include stress and chronological aging. Chronological aging may be caused by sub-chronic inflammation related to normal cellular oxidative stress.

Whether extrinsic or intrinsic, challenges faced by skin result in visible signs such as fine lines, wrinkles, uneven texture and scattered pigmentation. The prevention, elimination or diminution of these signs has become a multi-billion dollar business with treatments ranging from over-the-counter topical creams and moisturizers to a variety of beautifying plastic surgery techniques. Normal chronological aging results in skin thinning, loss of elasticity and general atrophy of the skin. Chronological aging may be hastened by photo-aging, the premature aging of the skin due to exposure to UV radiation. Oxidation may also contribute to the process of skin aging by producing

unstable molecules, known as free radicals, which, when produced in access and/or chronically, may accumulate and damage skin cells.

Western Society is judging elderly looking individuals as less attractive. This is fostering a very significant industry that is supporting the aging population with means to maintain youthful appearance. Premature aging of the skin is associated with wrinkles that can have a profound impact on self-esteem.

Retinoic acid (also known as tretinoin) is currently the only prescribed topical drug with an anti-aging and wrinkle reduction indication. While the effect of retinoic acid on anti-aging marks is significant, especially with reversing wrinkle and damage associated with photo-aging, its use is associated with several major side effects including teratogenicity, primary irritation and photo-sensitivity. Therefore retinoic acid must be used under physician supervision. Retinoids, which are commonly used for anti-aging treatments, have been shown to be cytotoxic for fibroblasts and epithelial cells in the range of 0.6-3x$10^5$ M (Varani et al. *Journal of Investigative Dermatology* (1993) 101, 839–842), and to increase epithelial cell death (Ding et al. Invest Ophthalmol Vis Sci. 2013 Jun 26;54(6):4341-50).

Fatty Acid Bile Acid or Bile Salt conjugates (FABACs), referred to also as Bile Acid Fatty Acid conjugates (BAFACs), are a family of synthetic molecules that may be used to improve conditions related to bile acids or cholesterol metabolism. FABACs are believed to lower blood cholesterol concentration, reduce liver fat levels and dissolve gallstones (Gilat et al., Hepatology 2003; 38: 436-442; and Gilat et al., Hepatology 2002; 35: 597-600).

US Patents 6,384,024, 6,395,722, 6,589,946 disclose use of certain FABACs in dissolving cholesterol gallstones in bile and treating arteriosclerosis. These and additional FABACs were disclosed in US Patents 7,501,403 and US 8,110,564 as well as in US Application Publication US 2012/0214872 for use in treating fatty liver, in reducing blood cholesterol levels and in treating hyperglycemia, diabetes, insulin resistance and obesity. More recently, US Application No. 2012/0157419 disclosed FABACs as useful for treating brain diseases characterized by amyloid plaque deposits (e.g., Alzheimer's disease).

Canadian Patent Application 2,166,427 discloses use of bile acids chenodeoxycholic acid and/or ursodeoxycholic acid for the preparation of a medicament for treatment of atopic dermatitis. WO02/083147 discloses certain bile acid derivatives as Farnesoid X receptor (FXR) ligands for prevention or treatment of FXR-mediated diseases or conditions. Nowhere in the art is it disclosed or suggested that FABACs may be useful for topical administration, and particularly for prevention, treatment or attenuation of disorders associated with skin aging.

There is an unmet need for compositions and methods useful in treating the symptoms associated with aging of the skin, including but not limited to, wrinkles formation.

## SUMMARY OF THE INVENTION

The present invention relates to skin care, particularly cosmetic compositions comprising fatty acid bile acid conjugates (FABACs) and method of use thereof for preventing, attenuating or treating skin aging and symptoms related thereto.

The present invention is based in part on the unexpected discovery that FABACs are able to reduce gene expression levels of keratin 10 and keratin 1 in skin fibroblasts, as exemplified herein below. According to some embodiments, reduced expression of keratin 1 and 10 results in reduced keratinocyte differentiation.

The present invention is further based on the surprising discovery that administration of FABACs does not result in a significant effect on viability of epidermal cells, in contrast to administration of retinoids.

Furthermore, as exemplified herein below, administration of FABACs results in enhanced efflux of cholesterol into skin fibroblasts. Thus, without wishing to be bound by any theory or mechanism, FABACs may act on lipid rafts in skin cells and attenuate keratinocytes differentiation in a mechanism that is similar to that of retinoic acid but without the serious adverse reactions affiliated with retinoic-acid treatment such as teratogenicity, skin irritation and higher susceptibility to sun damage.

According to a first aspect the present invention provides a topical composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the composition is formulated for topical administration. The term "topical administration", as used herein, refers to administration through body surfaces, preferably through skin. According to another embodiment, the composition is formulated in a form selected from the group consisting of: aqueous solution, cream, lotion, water in oil or oil in water emulsion, multiple emulsion, silicone emulsion, microemulsion, nanoemulsion, gel, foam and an aqueous solution with a co-solvent. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the topical composition is a cosmetic composition formulated for topical administration.

According to some embodiments, the term "dermatologically acceptable diluent, carrier or excipient" refers to any diluent, carrier or excipient known in the art to be suitable for application to the skin. According to some embodiments, the at least one dermatologically acceptable diluent, carrier or excipient is cosmetically suitable. According to certain embodiments, the at least one dermatologically acceptable diluent, carrier or excipient is pharmaceutically acceptable. According to certain embodiments, the topical composition comprises at least one pharmaceutically acceptable carrier, diluent or excipient suitable for topical administration, preferably suitable for application to the skin.

According to another embodiment, the bonding member is selected from the group consisting of: NH, P, S, O, and a direct C-C or C=C bond. Each possibility

represents a separate embodiment of the present invention. According to an exemplary embodiment, said bonding member is NH.

According to some embodiments, the FABAC comprises two fatty acid radicals wherein at each occurrence W is independently a fatty acid radical having 6-22 carbon atoms; and X is independently a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention.

According to another embodiment, said one or two fatty acid radicals are independently selected from radicals of a fatty acid selected from the group consisting of: stearic acid, behenic acid, arachidylic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, oleic acid. Each possibility represents a separate embodiment of the present invention. According to yet another embodiment, said one or two fatty acid radical is a radical of stearic acid.

According to another embodiment, said bile acid is selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and derivatives thereof. Each possibility represents a separate embodiment of the present invention. According to yet another embodiment, said bile acid is a cholic acid.

According to some embodiments, the term "bile salt radical" as used herein refers to a bile salt radical of a bile acid selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and derivatives thereof. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the bile salt radical is a bile salt radical of cholic acid.

According to some embodiments, said FABAC is selected from the group consisting of:

3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid;

3 -beta arachidylamido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid; and a combination thereof. Each possibility represents a separate embodiment of the present invention.

According to an exemplary embodiment, said FABAC is 3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid (also referred to herein as "Steamchol").

According to some embodiments, the present invention provides a cosmetic composition comprising at least one FABAC as an active ingredient, preferably Steamchol, wherein the cosmetic composition is formulated for topical administration and further comprises at least one cosmetically acceptable diluent, carrier or excipient suitable for topical administration.

According to another embodiment, the composition of the present invention is useful for preventing or treating a skin condition related to aging. Each possibility represents a separate embodiment of the present invention. According to another embodiment, the composition of the present invention is useful for treating a skin condition related to aging.

According to another aspect, there is provided a method of preventing or treating a skin condition related to aging comprising the step of administering to a subject in need thereof a topical composition, the composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond; thereby preventing or treating the skin condition related to aging. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, there is provided a topical composition for use in preventing or treating a skin condition related to aging, the composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the present invention provides at least one fatty acid bile acid conjugate (FABAC) for use in preparation of a topical composition for treatment of a skin condition associated with altered sebum levels, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond, thereby treating the skin conditions associated with altered sebum levels in said subject. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the topical composition further comprises at least one dermatologically acceptable diluent, carrier or excipient. According to some embodiments, the topical composition is a cosmetic composition.

According to another embodiment, the skin condition related to aging is associated with at least one of chronological aging, photo-aging, skin atrophy or a combination thereof. Each possibility represents a separate embodiment of the present invention.

According to some embodiment, the skin condition related to aging is selected from the group consisting of: fine lines, wrinkles, discoloration, uneven pigmentation sagging, enlarged pores, rough skin, dry skin and stretch marks, uneven tone, blemishes, skin thickening or thinning and a combination thereof. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the skin condition related to aging may be any other aging related skin appearance either associated with chronological and/or environmental aging. Each possibility represents a separate embodiment of the present invention.

According to another embodiment, the skin condition related to aging is wrinkling. According to yet another embodiment, the skin condition related to aging is fine lines. According to some embodiments, the skin condition related to aging is selected from the group consisting of: skin wrinkles, skin atrophy, photo-aging and a combination thereof. Each possibility represents a separate embodiment of the present invention.

Other objects, features and advantages of the present invention will become clear from the following description and drawings.

## BRIEF DESCRIPTION OF THE FIGURES

**Figure 1** shows a process for producing 3β-stearylamido-7α,12α, dihidroxy-5β-cholan-24-oic acid (stearyl amido cholanoic acid also referred herein as "Steamchol"), according to some embodiments.

**Figure 2** depicts comparison of viability of epidermal cell cultures which were untreated (Negative Control), treated with 1% Triton X-100 (Positive Control), with DMSO alone, or with DMSO containing either 0.01%, 0.1%, 1% or 2% of Steamchol.

## DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to topical compositions comprising a fatty acid bile acid conjugate (FABAC) useful as an anti-aging agent. As used herein, the term "anti-aging agent" relates to an agent able to treat or prevent at least one skin condition related

to aging. The invention further relates to methods of preventing, attenuating or treating skin conditions related to aging and symptoms thereof, including, but not limited to, skin wrinkling, through topical administration of the disclosed composition.

Cholesterol is the second most abundant lipid by weight in the *stratum corneum* (after ceramides) and is known to promote the intermixing of different lipid species and regulate their thermodynamic "phase behavior". Keratinocytes require abundant amounts of cholesterol for maintaining a strong barrier and to control cutaneous permeability; hence the regulation of cholesterol homeostasis in the skin is of great importance. ATP-binding cassette transporter (ABCA1) is a membrane transporter for cholesterol efflux playing a pivotal role in regulating cellular cholesterol levels. Lipid rafts existing in cell membranes generally contain 3 to 5-fold the amount of cholesterol found in the surrounding bilayer.

As exemplified herein below, administration of a FABAC compound resulted in elevated levels of ABCA-1 cholesterol transporter in skin cells in parallel to an elevation in cholesterol efflux. Moreover, administration of FABAC was exemplified to significantly down-regulate mRNA levels of keratinocyte differentiation markers keratins 1 and 10 in skin cells.

Without wishing to be bound by any theory or mechanism of action, FABACs show advantageous anti-aging effect by enhancing ABCA1 transporter in fibroblasts and down regulating mRNA levels of the keratinocyte differentiation markers keratins 1 and 10. Thus, FABACs may affect cellular differentiation at epidermal skin layers in a mechanism similar to that of retinoic-acid. As further exemplified below, the mRNA level of ABCA-1 were not elevated as a result of FABAC administration. Thus, without wishing to be bound by theory or mechanism, FABACs may affect differentiation in epidermal skin layers, though without direct effect on nucleus associated retinoic acid receptors. Thus, according to some embodiments, FABAC do not cause the serious adverse reactions affiliated with retinoic-acid treatment such as teratogenicity, skin irritation and higher susceptibility to sun damage.

As exemplified herein below, Steamchol demonstrated very low cellular toxicity in a cytotoxicity assay using a cell culture including fibroblasts and keratinocytes. According to some embodiments, FABCAs, such as, but not limited to, Steamchol, induce no or very limited cell death when topically administered in a composition at a concentration of up to 10% weight volume, possibly up to 5% weight/volume, most typically up to 2% weight/volume. Each possibility represents a separate embodiment of the present invention.

According to one aspect the present invention provides a topical composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention.

The term "FABAC" (synonym BAFAC) as used herein, refers to conjugates of the formula W - X – G (Formula I), wherein G represents a bile acid or bile salt radical thereof, W represents one or two fatty acid radical(s) having 6-22 carbon atoms, and X represents a bonding member between said bile acid and the fatty acid radical(s). According to some embodiments, bonding member X includes, but is not limited to, NH, P, S, O or a direct C=C or C-C bond. Each possibility represents a separate embodiment of the present invention. FABACs are known in the art, and are described, for example, in US Patents 6,384,024, 6,395,722, and 6,589,946, the contents of which are incorporated herein by reference. According to some embodiments, the fatty acid radical(s) comprise specify 8-22 carbon atoms, 14-22 carbon atoms or 18-22 carbon atoms . Each possibility represents a separate embodiment of the present invention. As used herein, the terms “FABACs”, “BAFACs”, “the FABACs” and “the FABACs of the invention” are used

interchangeably. According to some embodiments, the topical composition of the invention comprises at least one FABAC.

A non-limiting general structure of FABACs is set forth below. According to a non-liming example, bile acid is conjugated (e.g. using an amide bond, for example at position 3) with 1-2 fatty acids of any of a number of chain lengths.

According to an exemplary embodiment, the FABAC of the invention is 3β-arachidylamido-7α,12α, dihidroxy-5β-cholan-24-oic acid (Arachidyl Amido Cholanoic Acid; an amide conjugate of cholic acid with arachidic acid; also known as "Aramchol" or "C20 FABAC") or 3β-stearylamido-7α,12α, dihidroxy-5β-cholan-24-oic acid (Stearyl Amido Cholanoic Acid; an amide conjugate of cholic acid with stearic acid; also known as "Steamchol" or "C18 FABAC"). Each possibility represents a separate embodiment of the present invention. According to some embodiment, the FABAC is Steamchol.

In another embodiment, the FABAC of methods and compositions of the present invention has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two radicals of saturated or unsaturated fatty acids having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or a C=C bond. Each possibility represents a separate embodiment of the present invention. According to some embodiments, G represents a radical of a bile acid. According to some embodiments, X represents a bonding member selected from the group consisting of: a heteroatom, a direct C-C bond and a C=C bond. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the FABACs of methods and compositions of the present invention have the formula II:

(W -X -)n G (II)

wherein G represents a bile acid or a bile salt radical; W represents a fatty acid radical having 6-22 carbon atoms; X represents a bonding member comprising a

heteroatom or a direct C-C or C=C bond; and n is an integer 1 or 2. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the heteroatom is selected from the group consisting of: NH, P, S and O. Each possibility represents a separate embodiment of the present invention. In general, the term "heteroatom" includes atoms of any element other than carbon or hydrogen, preferred examples of which include nitrogen, oxygen, sulfur, and phosphorus.

According to one embodiment n is 1. According to another embodiment n is 2, and at each occurrence W is independently a fatty acid radical having 6-22 carbon atoms and X is independently a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention.

In another embodiment, the bonding member of the FABAC is selected from the group consisting of NH, P, S, O, or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the term "Direct bond" refers, to a C-C (single) bond. In another embodiment, the term "Direct bond" refers to a C=C (double) bond. In another embodiment, more than one direct bond is utilized in the FABAC of the invention. In another embodiment, the bond between the bile acid and the fatty acid radical(s) is in the beta configuration. In another embodiment, the bond between the bile acid and the fatty acid radical(s) is in the alpha configuration. In another embodiment, the bonding member is other than an ester bond.

According to some embodiments, the bile acid or bile acid radical of the FABAC is selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid and derivatives thereof. Each type of bile acid or radical thereof represents a separate embodiment of the present invention. The term "radical" as used herein means a chemical moiety comprising one or more unpaired electrons. According to some embodiments, the bile acid or bile acid radical of the FABAC is cholic acid.

In another embodiment, the FABAC comprises a single fatty acid radical. The conjugation of the bile acid with the fatty acid radical may take place at various positions

of the bile acid. In certain embodiments, the conjugation of the bile acid with the fatty acid radical is performed in a position of the bile acid nucleus selected from positions 3, 6, 7, 12 and 24. Each possibility represents a separate embodiment of the present invention. In one embodiment, said conjugation is performed in position 3 of the bile acid nucleus.

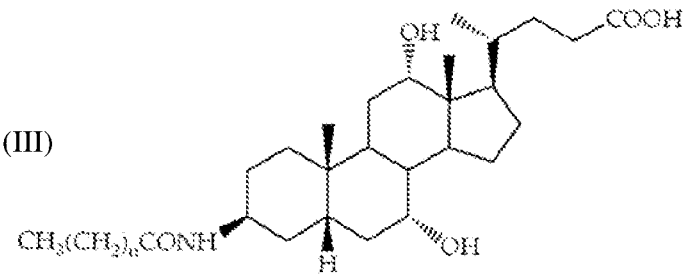
In another embodiment, the FABAC comprises two fatty acid radicals. According to some embodiments, the conjugation of each fatty acid radical to the bile acid nucleus is at two positions selected from the 3, 7, 12 and 24 positions of the bile acid nucleus. Each possibility represents a separate embodiment of the present invention. According to a particular embodiment, the conjugations are at position 3 and 7 of the bile acid nucleus.

In another embodiment, the fatty acid is saturated. In another embodiment, the fatty acid is unsaturated. In another embodiment, the fatty acid is mono-unsaturated. In another embodiment, the fatty acid is poly-unsaturated.

In another embodiment, the fatty acid(s) or fatty acid radical(s) of the FABAC are independently selected from the group consisting of: behenic acid, arachidylic acid, stearic acid, and palmitic acid. Each possibility represents a separate embodiment of the present invention.

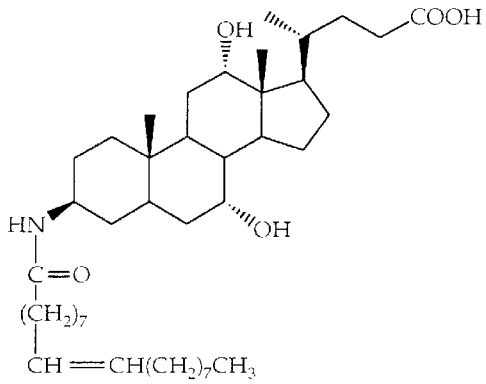
An exemplary embodiment of a FABAC according to the present invention is presented in Formula III herein below. According to some embodiments, in Formula III n=20 or n=18. Each possibility represents a separate embodiment of the present invention.

(III)



According to some embodiments, the one or two fatty acids or fatty acid radicals of the FABACs of the invention are unsaturated fatty acids or fatty acid radicals. Each possibility represents a separate embodiment of the present invention. In another embodiment, the unsaturated fatty acid(s) or unsaturated fatty acid radical(s) of the FABAC are independently selected from the group consisting of: linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, arachidonic acid, palmipoleic acid, oleic acid and elaidic acid. Each possibility represents a separate embodiment of the present invention. A non-limiting example of FABAC comprising an unsaturated fatty acid is 3β-oleylamido-7α,12α-dihidroxy-5β-cholan-24-oic acid, as depicted in Formula IV herein below.

(IV)




In another embodiment, linoleic acid is utilized. In another embodiment, a conjugated linoleic acid is utilized. In another embodiment, a conjugated linoleic acid isomer is utilized. Each possibility represents a separate embodiment of the present invention. The term "conjugated fatty acid", also known as "CFA", refers to polyunsaturated fatty acids in which at least one pair of double bonds are separated by only one single bond.

In another embodiment, the fatty acid is a short-chain fatty acid. In another embodiment, the fatty acid chain length is 6-8 carbons. In another embodiment, the fatty acid is a medium chain fatty acid. In another embodiment, the fatty acid chain length is 8-14 carbons. In another embodiment, the fatty acid chain length is 14-22 carbons. In another embodiment, the fatty acid chain length is 16-22 carbons. In another

embodiment, any other fatty acid chain length known in the art is utilized. Each type of fatty acid or fatty acid radical represents a separate embodiment of the present invention.

According to some embodiments, the FABAC of methods and compositions of the present invention is selected from the group consisting of: 3β-behenylamido-7α, 12α -dihydroxy-5β -cholan-24-oic acid; 3β -arachidylamido-7α, 12 α -dihydroxy-5β -cholan-24-oic acid; 3β -stearylamido-7α, 12α -dihydroxy-5β -cholan-24-oic acid; 3β -palmitylamido-7α, 12α -dihydroxy-5β -cholan-24-oic acid; 3β -myristylamido-7α, 12α -dihydroxy-5β -cholan-24-oic acid; and N-(-carboxymethyl)-3β -stearylamido-7α, 12α -dihydroxy-5β -cholane-24-amide. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the FABAC of methods and compositions of the present invention is selected from the group consisting of:

3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid;

3 -beta arachidylamido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid;

3 -beta arachidonylamido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid; and a combination thereof. Each possibility represents a separate embodiment of the present invention.

In an exemplary embodiment, the FABAC of the methods and compositions of the present invention is 3β-stearoylamido-7α,12α- dihydroxy-5β-cholan-24-oic acid ("Steamchol"). An exemplary embodiment for producing 3β-stearylamido-7α,12α, dihidroxy-5β-cholan-24-oic acid is presented herein in Figure 1. According to some embodiments, the present invention provides methods for producing 3β-stearylamido-7α,12α, dihidroxy-5β-cholan-24-oic acid, including but not limited to the process described in Figure 1.

FABACs as described herein may include pharmaceutically acceptable salts, derivatives and prodrugs. Methods for preparing FABACs and salts, derivatives and prodrugs of FABACs are well known in the art, and are further described in US 6,384,024, 6,395,722 and 6,589,946 and WO 2002/083147, the contents of which are

incorporated herein as if set forth in their entirety. As used herein, the term "bile acid derivative" includes bile acid salts with their pharmaceutically acceptable bases or acids as well as their diastereoisomeric and enantiomeric forms.

According to some embodiments, the present invention provides a topical composition comprising at least one of the FABACs of the invention as an active ingredient and at least one diluent, carrier or excipient suitable for topical administration to skin. According to some embodiments, the present invention provides a cosmetic composition formulated for topical administration to skin, comprising at least one of the FABACs of the invention as an active ingredient and at least one diluent, carrier or excipient suitable for topical administration to skin. According to some embodiments, the at least one diluent, carrier or excipient suitable for topical administration is cosmetically acceptable. According to some embodiments, the at least one diluent, carrier or excipient suitable for topical administration is pharmaceutically acceptable.

According to some embodiments, the present invention provides a topical composition comprising Steamchol as an active ingredient and at least one diluent, carrier or excipient suitable for topical administration to skin. According to some embodiments, the disclosed composition is formulated for topical administration to skin, preferably as a cosmetic composition.

According to some embodiments, the present invention provides the disclosed topical composition for preventing or treating a skin condition related to aging. Each possibility represents a separate embodiment of the present invention. According to another embodiment, the composition of the present invention is useful for treating a skin condition related to aging.

Skin renewal is essential for maintaining healthy homeostasis and it is maintained by controlling the balance between proliferation, differentiation and apoptosis of epidermal cells. The program of epidermal differentiation in keratinocytes appears to be altered upon disruption of cholesterol-enriched domains in the plasma membrane. The mechanism for this cholesterol depletion effect was shown to lead to changes in keratinocytes differentiation. The direct correlation between attenuation of keratinocytes

differentiation and clinically younger appearing skin is not fully elucidated, however a known compound that demonstrated such activity, retinoic acid, is shown to mitigate and even reverse aging damage. The mechanism may be related to a downstream compensation effect leading to accelerated desmosome cleavage and faster skin renewal as well as affects the extracellular matrix in the dermis.

The present invention is based, in part, on the unexpected finding that fatty acid-bile acid conjugates (FABACs) enhance ABCA1 transporter in fibroblasts and down regulate mRNA levels of the keratinocytes differentiation markers keratins 1 and 10. Without wishing to be bound by any theory or mechanism, these two key effects of FABACs provide the basis for their anti-aging effect.

According to another aspect, the present invention provides a method of preventing or treating a skin condition related to aging comprising the step of administering to a subject in need thereof a dermatologically acceptable amount of a topical composition, the composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond; thereby preventing or treating the skin condition related to aging. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the present invention provides a topical composition for use in treating or preventing a skin condition related to aging, the composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the FABAC is Steamchol.

According to some embodiments, the present invention provides a topical composition, preferably a cosmetic topical composition, for use in treating or preventing a skin condition related to aging, comprising at least one FABAC as the active ingredient. According to some embodiments, the present invention provides a topical cosmetic composition for use in treating or preventing a skin condition related to aging comprising Steamchol as the active ingredient.

According to some embodiments, the present invention provides a topical composition, preferably a cosmetic topical composition, for use in treating or preventing skin wrinkles, comprising at least one FABAC as the active ingredient. According to some embodiments, the present invention provides a topical cosmetic composition for use in treating or preventing skin wrinkles comprising Steamchol as the active ingredient.

According to some embodiments, the present invention provides use at least one FABAC of the invention for preparation of a topical composition for treatment or prevention of a skin condition related to aging. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the topical composition further comprises at least one dermatologically acceptable carrier, diluent or excipient, preferably a cosmetically acceptable carrier, diluent or excipient.

The terms "cosmetically acceptable/suitable" and "dermatologically acceptable/suitable", as used herein, relate to elements suitable to come into contact with the skin or human skin appendages without posing a risk of toxicity, intolerance, instability, allergic reaction, and the like. According to some embodiments, the cosmetically or dermatologically acceptable ingredients, such as carriers, diluents and excipients, are those capable of being commingled with anti-aging (e.g., anti-wrinkle) active ingredients such as, but not limited to, the FABACs of the invention such that the

cosmetically or dermatologically acceptable ingredients and the active ingredients do not interact in a way which would substantially reduce the efficacy of the active ingredients for treating a condition related to skin aging.

As used herein, the terms "effective amount" and "dermatologically effective amount" relate to an amount of compound or a composition that is capable of inhibiting, reducing, attenuating or treating at least part of the symptoms of a skin condition related to aging. According to some embodiments, a dermatologically effective amount of a composition relates to an amount sufficient for inhibiting, reducing, attenuating or treating at least part of the symptoms of a skin condition related to aging upon topical administration of the composition to the skin of a subject in need thereof. Each possibility represents a separate embodiment of the present invention.

The specific dose of a compound administered according to this invention will, of course, be determined by the particular circumstances surrounding the case including, for example, the compound administered, the route of administration, the physiological state of the subject, and the severity of the pathological condition being treated. According to a typical embodiment, the disclosed composition is administered in several dosages over a prolonged period of time until a sufficient response has been achieved, such as, but not limited to attenuation or treatment of symptoms of a skin condition related to aging.

According to some embodiments, the composition of the present invention is configured to be topically administered to a subject, preferably by direct application to the skin of a subject. Each possibility represents a separate embodiment of the present invention. In particular embodiments, the subject is a mammal, preferably a human.

Human skin, as a primary protective barrier, protects the vital organs of the body from external insult such as changes in temperature and humidity, ultraviolet rays and contaminants, and plays an important role in the regulation of biological homeostasis such as thermoregulation. However, as skin ages, it shows skin aging signs such as loss of elasticity, keratinization, formation of skin wrinkles and skin contraction. The cause of this skin aging can be classified as internal factors such as cell gene transformation and cell tissue change, and external factors such as ultraviolet (UV) and humidity. Skin aging

effect due to UV is termed "photo-aging". In photo-aging, oxygen free radicals are generated in cells by UV light. The oxygen free radicals in turn accelerate the synthesis of fiber degrading proteases (such as MMP-1, MMP-3, MMP-9, etc.), enzymes that catabolize proteins such as collagen or elastin that form the elasticity-controlling fibers of the skin's foundation. By way of signal transduction systems, the effects of the free radicals may induce an inflammatory reaction, thereby decreasing the elasticity of the dermal layer and producing skin wrinkles.

As used herein, "skin aging" or "a skin condition related to aging" refers to skin conditions associated with aged skin. According to some embodiments, conditions associated with aged skin in a subject are conditions that may be treated or attenuated by reduction of keratinocyte differentiation in the subject's skin. Non-limiting examples of conditions associated with aged skin include, but are not limited to, wrinkles, sun damage, dull appearance of the skin, sagging skin, jowls, keratosis, melasma, and uneven hyperpigmentation. Each possibility represents a separate embodiment of the present invention. According to some embodiments, a method for treating skin aging comprises treating the skin with an effective amount of a topical composition comprising a FABAC compound as defined above. According to some embodiments, the skin condition related to aging is skin wrinkles. According to some embodiments, the skin condition related to aging is skin atrophy.

According to some embodiments, the skin condition related to aging is a skin condition that may be treated and/or attenuated and/or prevented by a reduction in keratinocyte differentiation. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the composition of the invention induces a reduction in keratinocyte differentiation by reducing expression of keratin 1 and/or keratin 10, by enhancing ABCA1 activity or a combination thereof. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the present invention provides a method of treating, attenuating and preventing skin wrinkles in a subject, comprising topically administering to the subject's skin a topical composition comprising at least one FABAC

of the invention as an active ingredient and at least one dermatologically acceptable carrier, diluent or excipient. According to some embodiments, the present invention provides a method of treating, attenuating and preventing skin wrinkles in a subject, comprising topically administering to the subject's skin a topical composition comprising Steamchol as an active ingredient and at least one dermatologically acceptable carrier, diluent or excipient.

In some embodiments the composition of the invention further comprises at least one additional active ingredient other than the FABACs of the invention including, but not limited to, an anti-aging agent. Non-limiting examples of additional active ingredients that may be added to the composition of the invention, include, but are not limited to, retinoic acid and its derivatives, alpha and beta hydroxy acids (e.g., glycolic acid), peptides, anti-oxidants, skin brightening compounds and the like. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the amount of topical composition and frequency of treatment administered to a subject afflicted with skin wrinklesvaries widely depending upon the level of wrinkling already in existence in the subject, the rate of further wrinkle formation, and the level of regulation desired.

The present invention provides, in some embodiments, a method for preventing, retarding, arresting, or reversing atrophy in mammalian skin comprising the step of topically applying to the skin the topical composition of the invention. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the present invention provides a topical composition for treating, preventing, retarding, arresting, or reversing skin atrophy in a subject in need thereof, the composition comprising at least one of the FABACs of the invention as an active ingredient and further comprising at least one dermatologically acceptable carrier, diluent or excipient. Each possibility represents a separate embodiment of the present invention.

As used herein, "atrophy" of skin means the thinning and/or general degradation of the dermis often characterized by a decrease in collagen and/or elastin as well as decreased number and size of fibroblast cells due to reduction in mitosis and access of cells in senescence. Skin atrophy is a natural result of menopause, chronological aging and of photo-aging and often is an undesirable side effect resulting from corticosteroid treatment. Menopause may be physiological menopause or surgery- or treatment-induced menopause.

The present disclosure further provides, according to some embodiments, a method for treating, preventing, attenuating or ameliorating photo-aging or at least part of the symptoms thereof, comprising the step of topically administering the composition of the invention to the skin of a subject afflicted with photo-aging. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the skin condition related to aging is photo-aging. According to some embodiments, the present invention provides the topical composition of the invention for treating, preventing, attenuating or ameliorating photo-aging or at least part of the symptoms thereof. Each possibility represents a separate embodiment of the present invention. As used herein, the term "photo-aging" includes, without limitation, aging of the skin associated with exposure to the sun or other ultraviolet energy sources. Symptoms of photo-aging include, for example, solar lentigo (age spots), solar keratoses dermatoheliosis and combinations thereof. Each possibility represents a separate embodiment of the present invention. The method of treating photo-aging includes, according to some embodiments, topically administering to an individual in need thereof a composition comprising a FABAC compound as defined above.

Herein, the term "treating" includes abrogating, substantially inhibiting, slowing or reversing the progression, substantially ameliorating clinical symptoms, or substantially preventing the appearance of symptoms associated with a skin condition related to aging, such as, but not limited to, skin wrinkles, photo-aging and skin atrophy. According to some embodiments, the term "treating" is further meant to include improvement of skin appearance and texture, improvement of skin hydration,

healing,smoothing of the skin or any combination thereof. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the term "treating" refers to at least partial smoothing of existing wrinkles and/or slowing of deepening of existing wrinkles and/or preventing formation of new wrinkles. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the term "treating" refers to amelioration, arrest or prevention of skin thinning and/or skin degradation. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the term "treating" refers to amelioration, arrest or prevention of photo-aging or at least part of the symptoms thereof. Each possibility represents a separate embodiment of the present invention.

The symptoms of a skin condition related to aging may include, but are not limited to: fine lines, wrinkling, age spots and other discolorations of the skin, sagging skin, growths, dry skin, rough skin, dull skin, acne, alopecia,stretch marks and combinations thereof. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the treatment of a skin condition related to aging such as skin atrophy or photo-aging of the epidermal cells includes treatment of at least part of the symptoms described herein above with respect to aging of epidermal cells. This treatment may further include prevention of at least part of these symptoms, and in particular aging signs, before they occur. As used herein, the term "preventing" may relate to inhibiting appearance of a skin condition related to aging or at least part of its symptoms. Alternatively, the term "preventing" may relate to inhibiting worsening of existing skin conditions related to aging, such as, but not limited to, worsening of existing skin wrinkles.

According to some embodiments, the topical composition of the invention is formulated for application to the skin of a subject in need thereof. According to a non-limiting example, one method of treating the skin of a subject afflicted with symptoms of a skin condition related to aging, such as wrinkles, is via topical application of a safe amount of the topical composition of the invention. According to some embodiments,

symptoms of a skin condition related to aging include, but are not limited to: wrinkles, reduction in skin smoothness, non-even skin tone, impaired skin complexion and the like.The frequency of topical application to the skin may vary widely, depending upon personal needs, but it is suggested as a non-limiting example that topical application of the composition of the invention will range from about once per week to about 10 times daily, preferably from about twice per week to about 4 times daily, more preferably from about 3 times a week to about twice daily, most preferably about once per day. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the topical application would preferably be over a period of from about one month to several years.

"Skin", as used herein, refers to any epidermal surface prone to aging and can also include, without limitation, the surface of the face and neck, hands, elbows, upper arm region, knees, thighs, legs, feet, breasts, chest, stomach, buttocks, and back area. Preferably, the term "skin" refers to the surface of the face and neck.

According to some embodiments, the present invention provides a skin care treatment method for treating the cutaneous signs of aging, such as, but not limited to, wrinkles and skin atrophy and/or for protecting the skin against the harmful effects caused by ultraviolet (UV) radiation, the method comprising: topically applying, to skin or skin appendages to be treated, the topical composition of the present invention.

In some embodiments there is provided a method for slowing the aging process of the human skin, reducing the signs of aging of the human skin or both, the method comprising applying to the skin of a subject afflicted with skin aging the topical composition of the invention. Slowing the aging process of the human skin and reducing the signs of aging of the human skin may include, but is not limited to, improvement of the skin tone, elasticity or contraction, reduction of wrinkles, removal of lines, combating the formation of skin wrinkles, promotion of skin firmness, reduction of skin sensitivity and irritability or any combination thereof. Each possibility represents a separate embodiment of the present invention.

In additional embodiments there is provided a method for protecting and/or improving the state of the skin of a subject and/or treating imperfections of the skin of a subject in need thereof, the method comprising topically administering the composition of the invention to the skin of a subject. In additional embodiments, there is provided a method for protecting the skin of a subject from skin conditions related to aging, comprising the step of administering the topical composition of the invention to the skin of the subject. According to some embodiment, protecting the skin of the subject relates to prevention of further worsening of existing skin conditions related to aging and/or arrest or slowing of existing skin conditions related to aging or symptoms thereof. Each possibility represents a separate embodiment of the present invention.

**Formulations**

According to some embodiments, the topical composition of the invention is formulated as a cosmetic composition comprising at least one FABAC as an active agent. According to some embodiments, the topical composition is formulated for topical administration to the skin of the subject, preferably to skin areas affected by skin conditions associated with aging such as, but not limited to, wrinkled skin or skin affected by photo-aging. As used herein, the term "topical composition" refers to a composition formulated for topical administration to skin.

The compositions of the present invention may be manufactured by processes well known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragger-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

The compositions for use in accordance with the present invention thus may be formulated in conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries, which facilitate processing of the active compounds into preparations which, can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

According to some embodiments, the skin treatment compositions of the invention comprise a dermatologically or cosmetically acceptable carrier to act as a diluent, dispersant or vehicle for at least one FABAC, so as to facilitate its distribution when the composition is applied to the skin. Vehicles other than, or in addition to, water may include liquid or solid emollients, solvents, humectants, thickeners and powders. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the composition of the present invention may be formulated for topical administration in the form of aqueous or non-aqueous solutions, lotions, creams, gels, ointments, foam, mousse, sprays, emulsions, microemulsions, adhesive patches, powders etc. Each possibility represents a separate embodiment of the present invention. The formulation may be oleaginous-based, occlusive composition comprising, for example, white petroleum and or mineral oil. In some embodiments the composition is non-greasy or substantially non-greasy and can be a water-based formulation.

According to some embodiments, there is provided a skin care, cosmetic or dermopharmaceutical composition comprising at least one of the FABACs of the invention or a cosmetic, dermatological or pharmaceutically-acceptable salts and esters thereof, and a cosmetically or dermatologically acceptable diluent, carrier or excipient. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the composition of the invention comprises at least one FABAC. According to some embodiments, the FABAC in the composition of the invention is in an effective amount sufficient to treat, ameliorate, slow down or prevent a skin condition related to aging or at least part of the symptoms thereof. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the effective amount is an amount which induces no or non-significant cytotoxicity in skin cells. According to some embodiments, the FABAC in the composition of the invention is in an effective amount sufficient for treating, attenuating, slowing progression or preventing skin wrinkles and/or skin atrophy and/or photo-aging. Each possibility represents a separate embodiment of the present invention., As used

here, the terms "effective amount" and "effective concentration" are used interchangeably.

According to some embodiments, the effective concentration of the FABAC in the composition is between about, 0.01 to 10% weight/volume, possibly between 0.01 to 5% weight/volume, alternatively between 0.05 to 2% weight/volume FABAC. Each possibility represents a separate embodiment of the present invention. According to typical embodiments, the effectiveness of the composition also depends on the vehicle (i.e., carrier) and its interaction with the *stratum corneum*.

According to some embodiments, the weight/volume concentration of FABAC in the composition of the invention is 0.01%-2%, possibly 0.1%-2%, alternatively 1%-2%. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the weight/volume concentration of FABAC in the composition of the invention is at least 0.01%. According to some embodiments, the FABAC in the composition of the invention is Aramchol. According to some embodiments, the FABAC in the composition of the invention is Steamchol.

In some embodiments the composition of the invention further comprises at least one additional active ingredient other than the FABACs of the invention. Non-limiting examples of such active ingredients include, but are not limited to, the following classes of ingredients: vegetable extracts, oil ingredients, whitening agents, anti-oxidants, coloring agents, healing agents, anti-aging agents, anti-wrinkle agents, soothing agents, anti-radical agents, anti-UV agents (or UV absorbers), agents stimulating the synthesis of dermal macromolecules or the skin's energy metabolism (e.g., skin nutrients), hydrating agents, anti-bacterial agents, anti-fungal agents, anti-inflammatory agents, anesthetic agents, agents modulating cutaneous differentiation, pigmentation or depigmentation, agents stimulating nail or hair growth, combinations thereof etc. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the at least one additional active ingredient is selected from the group consisting of: metal sequestering agents, medicinal agents,

whitening agents, sugars and a combination thereof. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the at least one additional active ingredient is selected from the group consisting of: metal sequestering agents including, but not limited, to disodium edetate, trisodium edetate, sodium citrate, sodium polyphosphate, sodium metaphosphate and gluconic acid; medicinal agents including but not limited to caffeine, tannin, verapamyl, tranexamic acid and derivatives thereof, grabridin, various herbal medicines, tocopherol acetate, glycyrrhizic acid and the derivatives and salts thereof; whitening agent including but not limited to vitamin C, magnesium ascorbic phosphate, glucoside ascorbate, arbutin and kojic acid; sugars including but not limited to glucose, fructose, mannose, sucrose and trehalose. Each possibility represents a separate embodiment of the present invention.

The compositions of the present invention may be present in the forms of aqueous or hydro alcoholic solution, solubilized systems, emulsions, powders, oils, aqueous or anhydrous gels, serum, foam, ointments, aerosols, water-oil two-phase systems, water-oil-powder three-phase systems, etc. Each possibility represents a separate embodiment of the present invention. In some embodiments the composition is applied in a form selected from the group consisting of: a facial cleanser, spray, salve, ointment, lotions, emulsions, creams, gels, essences (beauty lotions), packs patches and masks. Each possibility represents a separate embodiment of the present invention.

In other embodiments, such as in the case of makeup cosmetics, the composition may be used with a wide range of types of cosmetics such as foundations. In additional embodiments, the composition is applied in the form of a toiletry product, e.g., body soap, facial soap, etc. According to some embodiments, the composition may be formulated as a quasi-drug. Further, in the case of quasidrugs, the composition may be formulated for a wide range of applications such as various ointments. The types or forms of the anti-aging agent of the present invention are not limited to these forms and types.

The types or forms of the compositions of the present invention are not limited to these forms and types. In any case, the person skilled in the art will ensure that these

additives, the amounts thereof and the selected formulation are selected so as not to be detrimental to the desired, advantageous properties of the composition according to the invention.

According to another embodiment, the composition is formulated as a topical formulation in a form selected from the group consisting of: aqueous solution, cream, lotion, water in oil or oil in water emulsion, multiple emulsion, silicone emulsion, microemulsion, nanoemulsion, gel, foam and an aqueous solution with a co-solvent. Each possibility represents a separate embodiment of the present invention.

Non-limiting examples of suitable topical formulations of the disclosed composition are as follows:

Lotions and Creams

According to some embodiments, the topical composition of the invention is formulated as a lotion. The lotions contain an effective concentration of one or more FABAC compound as described herein. The compositions of the present invention may also include at least one or more emollient, which can function as either or both a lubricating and thickening agent. The emollients can comprise in total from about 0.1% to about 50%, preferably from about 1% to about 10%, by weight of the composition. Any emollients known to those of skill in the art as suitable for application to human skin may be used. These include, but are not limited to: hydrocarbon oils and waxes, including mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene; silicone oils; triglyceride fats and oils, including those derived from vegetable, animal and marine source; including jojoba oil and shea butter; acetoglyceride esters, such as acetylated monoglycerides; ethoxylated glycerides, such as ethoxylated glyceryl monostearate; fatty acids, fatty alcohols and derivatives thereof. Each possibility represents a separate embodiment of the present invention. Other suitable emollients include lanolin and lanolin derivatives; polyhydric alcohols and poly ether derivatives; polyhydric alcohol esters; wax esters; vegetable waxes; phospholipids, such as lecithin and derivatives; sterols, including, but not limited to, cholesterol and

cholesterol fatty acid esters; amides, such as fatty acid amides, ethoxylated fatty acid amides, and solid fatty acid alkanolamides. Each possibility represents a separate embodiment of the present invention.

The lotions may further contain from about 1% to about 10%, more preferably from 2% to 5%, of an emulsifier. Each possibility represents a separate embodiment of the present invention. The emulsifiers may be nonionic, anionic, cationic or a mixture thereof. Each possibility represents a separate embodiment of the present invention. Suitable emulsifiers are known to those with skill in the art. Other conventional components of such lotions and creams may be included. One such additive is a thickening agent at a level from 1% to 10% of the composition. Examples of suitable thickening agents include, but are not limited to: cross-linked carboxypolymethylene polymers, ethyl cellulose, polyethylene glycols, gum tragacanth, gum karaya, xanthan gums, bentonite and other clays, hydroxy ethyl cellulose, and hydroxypropyl cellulose. Each possibility represents a separate embodiment of the present invention.

According to some embodiments, the lotions and creams are formulated by simply admixing all of the components together. According to some embodiments, the FABAC is dissolved, suspended or otherwise uniformly dispersed in the mixture.

Solutions and Suspensions

According to some embodiments, the composition is formulated as a solution. According to some embodiments, the composition is formulated as a suspension. According to some embodiments, the solutions, which may be aqueous or non-aqueous, are formulated to contain an effective concentration of one or more FABAC compound as disclosed herein.

Suitable organic materials which may be useful as the solvent or a part of a solvent system in the solution are as follows: propylene glycol, polyethylene glycol, polypropylene glycol, glycerin, sorbitol esters, 1,2,6-hexanetriol, ethanol, isopropanol,

diethyl tartrate, butanediol, and mixtures thereof. Each possibility represents a separate embodiment of the present invention. Such solvent systems can also contain water.

According to some embodiments, the composition is formulated as an emulsion. When the compositions of the invention are formulated as an emulsion, the proportion of the fatty phase may range from about 5% to about 80% by weight, and preferably from about 5% to about 50% by weight, relative to the total weight of the composition. Each possibility represents a separate embodiment of the present invention. Oils, emulsifiers and co-emulsifiers incorporated in the composition in emulsion form are selected from among those known to those with skill in the cosmetic or dermatological field.

The compositions formulated as solutions or suspensions may be applied directly to the skin, or, may be formulated as an aerosol and applied to the skin as a spray, foam or mousse. Each possibility represents a separate embodiment of the present invention. The aerosol compositions may further contain from about 20% to 80%, preferably from 30% to 50%, of a suitable propellant. Each possibility represents a separate embodiment of the present invention. Examples of such propellants may be, but are not limited to, the chlorinated, fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane may also be used as propellant gases. These propellants are used as known in the art in a quantity and under a pressure suitable to expel the contents of the container. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount.

Gels and Solids

According to some embodiments, the composition is formulated as a gel. Gel compositions may be formulated by simply admixing a suitable thickening agent to the previously described solution or suspension compositions. Examples of suitable thickening agents have been previously described with respect to the lotions. According to some embodiments, the gelled compositions contain an effective concentration of at least one FABABC compound. According to some embodiments, the composition further comprises from about 5% to about 75% of an organic solvent as

previously described; from about 0.5% to about 20% of a thickening agent, and the balance being water or other aqueous carrier.

In other embodiments the compositions formulated as solutions, suspensions lotions and gels of the present invention are formulated as a foam or mousse for dermal application. Each possibility represents a separate embodiment of the present invention. Relevant carriers for formulation as a foam or mousse are taught, for example, in International Patent Application Publication No. WO 2004/037225 and US Patent No. 6,730,288.

According to some embodiments, the composition is formulated as a solid form. Compositions of solid forms may be formulated as stick-type compositions intended for application to the lips or other parts of the body. The solids may also contain from about 50% to about 98% of the previously described emollients. This composition may contain from about 1% to about 20%, of a suitable thickening agent, and, if desired or needed, emulsifiers and water or buffers. Thickening agents previously described with respect to lotions are suitably employed in the compositions in solid form. Other ingredients, such as preservatives, including methyl-paraben or ethyl-paraben, perfumes, dyes or the like, that are known in the art to provide desirable stability, fragrance or color, or other desirable properties, to compositions for application to the skin.

According to some embodiments, the composition of the present invention is effective to prevent and/or treat skin disorders associated with aging including, but not limited to, reduction in skin elasticity, generation of wrinkles, skin discoloration, skin sagging due to cutaneous aging caused by normal and photo-aging, and combinations thereof. Each possibility represents a separate embodiment of the present invention.

Additives

According to some embodiments, the composition of the present invention further comprises at least one additive selected from the group consisting of: a diluent, a preservative, an abrasive, an anticaking agent, an antistatic agent, a binder, a buffer, a

dispersant, an emollient, an emulsifier, a co-emulsifiers, a humectant or emollient agent, a fiberous material, a film forming agent, a fixative, a foaming agent, a foam stabilizer, a foam booster, a gellant, a lubricant, a moisture barrier agent, a plasticizer, a preservative, a propellant, a stabilizer, a surfactant, a suspending agent, a thickener, a chelating agent, a sequestering agent, a conditioning agent, a wetting agent, a liquefier and a combination thereof. Each possibility represents a separate embodiment of the present invention.

For any agent, combination of agents and composition used within the scope of the invention, the dermatologically effective amount or dose can be estimated initially from cell culture assays. For example, a dose can be formulated in animal models to achieve a circulating concentration range that includes the $IC_{50}$ as determined in cell culture (e.g., the concentration of the test compound, which achieves a half-maximal inhibition of the epidermal cells proliferation). Such information can be used to more accurately determine useful doses in humans.

Other examples of additives may include sunscreen agents and tanning agents. Sunscreen agents may include those materials commonly employed to block ultraviolet light. Illustrative compounds are the derivatives of PABA, cinnamate and salicylate. For example, octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone are also known as parsol MCX and benzophenone-3, respectively. The amount of sunscreen agents employed in the compositions can vary depending upon the degree of UV radiation protection desired. The sunscreen agent added to the composition must be compatible with the active compound but in general the composition may comprise from about 1% to about 20%, of a sunscreen agent. Exact amounts will vary depending upon the sunscreen agent chosen and the desired Sun Protection Factor (SPF).

The composition of the present invention may further comprise an anti-oxidant/radical scavenger. The inclusion of an anti-oxidant/radical scavenger may increase the benefits of the composition. The anti-oxidant/radical scavenger may be added to the compositions of the present invention in a concentration range of about 0.1% to about 10% total weight of the composition. Anti-oxidants/radical scavengers include, but are not limited to, ascorbic acid (vitamin C) and its salts, and tocopherol (vitamin E).

Certain vitamin A metabolites, as well as agonists, derivatives and pro-drugs of vitamin A, may be incorporated into the compositions of the present invention. Examples of vitamin A agents that are useful in the context of the present invention include, without limitation, the well-known variety of retinol, retinoic acid and retinoic acid receptor (RAR) agonists. Each possibility represents a separate embodiment of the present invention. RAR agonists may include, without limitation, chromans, thiochromans, tetrahydroquinolines, substituted tetrahydronaphthalenes, substituted dihydronaphthalenes, trisubstituted phenyls, aromatic tetracyclic compounds, substituted cyclohexanes, substituted cyclohexenes, substituted cyclohexanedienoic acids, substituted adamentanes, substituted diaryl, heteroaryl compounds, combinations thereof and many more. Each possibility represents a separate embodiment of the present invention.

Vitamin C, or ascorbic acid is a very potent antioxidant and may even be protective against UVA and UVB rays. Studies suggest that topical vitamin E, particularly alpha tocopherol (a form of vitamin E) cream decreased skin roughness, length of facial lines, and wrinkle depth. Studies on mice have also reported reductions in UV-induced skin cancer with its use. Vitamin K may also be useful for treating capillary damage. According to some embodiments, the composition further includes at least one of: vitamin C, vitamin E, vitamin K and any combination thereof. Each possibility represents a separate embodiment of the present invention.

Green and black tea and extracts thereof are suitable as additives. Other plant derived agents which may be used as additives to the composition include, but are not limited to, pomegranate and soy extracts, aloe, ginger, grape seed extract, and coral extracts.

Color correctors and foundations are suitable additives and may be desired when blemishes are prominent or when a more even tone of skin is desired. For example, green neutralizers may mask red lesions; yellow may camouflage dark circles and bruises; and white may help to minimize apparent wrinkles. Liquid and press powder foundations may also be included. Other possible additives include glycosaminoglycans, such as hyaluronic acid and the like.

**Product Packaging and Kits**

In use, a small quantity of the composition, for example from about 0.1 ml to about 100 ml, is applied to exposed areas of the skin, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the skin using the hand, fingers or a suitable device. The product may be specifically formulated for use as a hand or facial treatment.

When formulated the composition can be packaged in a suitable container to suit its viscosity and intended use by the consumer. For example, a lotion or cream can be packaged in a bottle, or a propellant-driven aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar. The invention accordingly also provides, according to some embodiments, a closed container containing a dermatologically or cosmetically acceptable composition as herein defined. The shape of the container is not limited in this invention, and can be a tube, a pump dispenser, a compressed dispenser, a bottle, a spray, a sachet or the like.

In some embodiments, the compounds or compositions of the invention are provided in packs in a form ready for administration. In other embodiments, the compounds or compositions are provided in concentrated form in packs, optionally with the diluent required to make final solution(s) for administration. In still other embodiments, the product contains a compound useful in the invention in solid form and, optionally, a separate container with a suitable solvent or carrier for the compound useful in the invention.

According to some embodiments, the present invention provides a kit comprising the composition of the invention in a first suitable container. According to some embodiments, the present invention provides a kit comprising at least one FABAC of the invention in a first suitable container. According to some embodiments, the kit further comprises at least one container other than the first container. According to some embodiments, said at least one other container comprises at least one diluent, excipient,

carrier, solvent or additive. Each possibility represents a separate embodiment of the present invention. According to some embodiments, the composition of the invention is formed by combining the content of a first container comprising at least one FABAC and the content of said at least one other container. According to some embodiments, the kit further comprises instructions for use and/or preparation of the composition of the invention. Each possibility represents a separate embodiment of the present invention.

In still other embodiments, the above packs/kits include other components, e.g., instructions for dilution, mixing and/or administration of the product, other containers, syringes, needles, etc. Each possibility represents a separate embodiment of the present invention. Other such pack/kit components will be readily apparent to one of skill in the art.

The following examples are presented in order to more fully illustrate some embodiments of the invention. They should, in no way be construed, however, as limiting the broad scope of the invention.

## EXAMPLES

### Example 1. Cytotoxicity assay

Study Overview

Full-thickness Epiderm cultures (EFT-400, MatTek) were used to determine toxicity in response to topical application of a test material (Steamchol). A previous viability assay was conducted at concentrations of 40.0, 13.3, 4.4, 1.5 ug/mL and vehicle alone (DMSO); no toxicity was observed.

Experimental Procedures

The test material was provided as a powder. Test solutions were prepared by adding the appropriate amount of powdered material to 1 mL DMSO. Lower concentrations were made by serial dilution with 100% DMSO. The final test material concentrations and treatments are listed below:

- 2% Steamchol (20,000 ug/mL)
- 1% Steamchol (10,000 ug/mL)
- 0.1% Steamchol (1000 ug/mL)
- 0.01% Steamchol (100 ug/mL)
- vehicle control (100% DMSO)
- untreated control

Full-thickness skin cultures (EFT-400) were maintained as required to ensure viability; the cultures were equilibrated at 37°C and 5% $CO_2$ for 24 hours prior to application of test materials. Test material was applied to the surface of each culture using sterile techniques (10 µL applied to each culture). Two cultures were assigned to each treatment group. Two EFT cultures served as an untreated control (also referred to as negative control in Figure 2), and two other EFT cultures served as a positive control (100 µL 1% Triton X-100).

Following a 24-hour incubation period with the test material, cultures were processed for cell toxicity analysis using an MTT [(3-4,5-dimethylthiazole-2-yl) 2,5-diphenyltetrazoliumbromide] assay (reagents purchased from MatTek). Viable tissues converted MTT into a blue formazan salt that was detected by measuring absorbance at a specific wavelength of light ($A_{570}$). Percent viability was calculated by comparing the $A_{570}$ reading of the test cultures to the $A_{570}$ of the untreated control culture, using the following formula: [Treated $A_{570}$ / Untreated $A_{570}$] * 100.

Results

None of the concentrations tested produced any significant effects on cell viability (Figure 2; Table 1). Cell viability was near 100% compared to the untreated control for all dilutions of Steamchol tested. These results show an advantageous affect of FABACs over retinoids which have been shown to be cytotoxic for fibroblasts and epithelial cells in the range of $0.6\text{-}3*10^5$ M (Varani et al. *Journal of Investigative Dermatology* (1993) 101, 839–842), and increase epithelial cell death (Ding et al. Invest Ophthalmol Vis Sci. 2013 Jun 26;54(6):4341-50).

**Table 1. Cell Viability following a 24-hour Exposure to Steamchol**

| Test compound | Cell Viability |
|---|---|
| Untreated Cells (Negative Control) | 100% |
| Positive control | 6.8 % |
| DMSO vehicle | 101.0 % |
| 2% Steamchol | 93.89 % |
| 1% Steamchol | 96.88% |
| 0.1% Steamchol | 99.98 % |
| 0.01% Steamchol | 100.41 % |

**Example 2. Effect of Steamchol or Aramchol on cholesterol efflux and ABCA1 mRNA and protein levels**

Steamchol was incubated with human skin fibroblasts for 20 hours to measure cholesterol loading in the presence of [$^3$H] cholesterol. After series of washing and adding efflux containing cholesterol acceptors, medium was collected and centrifuged and cell associated cholesterol was compared to effluxed cholesterol in the presence and absence of the similar FABAC. This research project also included quantification of mRNA of ABCA1 and direct measurement of ABCA1. Results demonstrated that cholesterol efflux in fibroblasts was significantly enhanced and that ABCA1 protein concentration increased approximately 2 fold when efflux took place in the presence of FABAC as compared to untreated cells.

Similarly, cells were pre-incubated with [$^3$H] cholesterol, washed four times and then placed in an incubation medium with or without Aramchol for 20 hours. Following the incubation, radioactivity was measured separately in the medium and in the cells.

Cholesterol efflux percentage was calculated as radioactivity in medium divided by the total radioactivity (cells+medium). Results demonstrated that cholesterol efflux in fibroblasts was significantly enhanced and that ABCA1 protein concentration increased approximately 2 fold when efflux took place in the presence of Aramchol as compared to untreated cells.

**Example 3. Effect of Steamchol on gene expression in skin culture**

A full-thickness *in vitro* skin culture model, Epiderm FT (MatTek, MA), was treated with Steamchol. Steamchol in DMSO (0.5%, 5000 ug/mL) was applied to the surface of each test culture and cells were collected 24 hours post-application. Control cells were similarly treated with DMSO without Steamchol.

Tissues were collected in RNAlater for gene expression analysis. Gene expression was analyzed using validated Taqman gene expression assays in Taqman Low Density Array (TLDA) format. 94 genes that regulate a variety of known functions in skin were analyzed including the ABCA1 and SCD1 genes. The experimental set up was conducted in a 96-well format using validated Taqman gene expression assays. Each gene was assayed in duplicates. Statistics were carried out using the StatMiner software v4.2 (unpaired t-tests, $p \leq 0.05$, N=4) to compare the Steamchol group to the DMSO control group.

The effect of Steamchol on gene expression in the Epiderm FT culture revealed that out of the 94 selected genes in the panel, two genes, KRT 1 (keratin 1) and KRT 10 (keratin 10) demonstrated statistically significant deviation of more than two fold when compared to cells treated with DMSO (see Table 2 below). No significant change in mRNA levels of ABCA1 was observed. As shown in table 2, Steamchol significantly inhibits the expression of keratins 1 and 10 which are known markers for keratinocyte differentiation.

**Table 2: Fold change of keratin 1 and 10 gene expression after treatment with FABAC**

| Gene ID | Gene Name | Fold Change |
|---|---|---|
| KRT10 | keratin 10 | -2.60 |
| KRT1 | keratin 1 | -2.49 |

In the basal layer of the epidermis where keratinocytes are mitotically active they express keratins 5 and 14. As the cell becomes suprabasal, keratins 1 and 10 are expressed while keratins 5 and 14 shut down. As the cells continue to move outward to the granular layer, they become filled with granules containing a variety of differentiation proteins; Loricin, Profilaggrin, Involucrin. Transgultaminase, an enzyme that cross-links keratins and other proteins into the impermeable cell envelop is also synthesized in this layer. Finally, the keratinocytes die and their dead, flattened squamous form composes the stratum corneum.

The effect on keratinocytes differentiation is thought to be reversible and recovery from cholesterol depletion is believed to occur when the stimulus is removed. Without wishing to be bound by any theory or mechanism of action, FABACs enhance the transport activity of ABCA1 protein, causing depletion in cholesterol levels at the lipid rafts, thereby reducing expression of keratins 1 and 10.

The activity of a fatty acid-bile acid conjugate was demonstrated herein, for the first time, to be similar to the effects known to be induced by retinoic acid. Both compounds affect differentiation markers at the spinous epidermal level and at the dermal extracellular matrix level. While retinoic acid acts via activation of nuclear receptor, a fatty acid-bile acid conjugate is presumed to induce organizational changes at the cell membrane level that lead to cascades similar to those of retinoic acid. In two different unrelated studies a fatty acid-bile acid conjugate was demonstrated to activate ABCA1 cell transporter and down regulate keratin 1 and 10 expression in human epidermal model. These two activities support reduction in keratinocytes differentiation, triggering a

compensation mechanism at the epidermis and dermis levels and eventually leading to tissue rejuvenation, and possibly stronger extracellular matrix foundation that potentially leads to clinical manifestation of younger skin appearance.

Affecting cellular differentiation at the epidermal skin layers has been demonstrated to be the underlying mechanism for anti-aging activity. However, in many cases, such as in that of the retinoic acid, this activity comes with a "price" of serious adverse reactions such as teratogenicity, skin irritation and higher susceptibility to sun damage. This may be since the effect is initiated at the nuclear receptor levels and therefore is profound and slow to recover. The suggested mechanism of action of the FABACs of the invention provides a milder but yet promising biochemical path affecting the organization of lipids in the lipids rafts as a result of cholesterol depletion.

**Example 4. Effect of FABACs on keratinocyte differentiation**

In order to examine the effect of the disclosed FABACs on differentiation of keratinocytes, the highly differentiated full-thickness in vitro skin culture model Epiderm FT (MatTek, MA) is used. Duplicates of skin cultures are treated with three different concentrations of Steamchol in DMSO and three different concentrations of Aramchol in DMSO. One of the tested concentrations is 0.5% (5000 µg/mL) which was efficient in reducing gene expression of KRT1 and KRT10. Two non-treated skin cultures and two cultures treated with vehicle alone (DMSO) are used as negative controls. Two skin cultures treated with retinoic acid are used as a positive control.

The cells are collected 24 hours following application of the compositions to the surface of each test culture. Proteins are extracted from part the cells and subjected to Western Blot and ELISA analyses using primary antibodies specific for Keratin 1, Keratin 10, SCD1 and ABCA-1. Another part of the cells is fixated and subjected to immunohistochemical staining using primary antibodies specific for Keratin 1, Keratin 10, SCD1 and ABCA-1.

Down-regulation in expression of Keratin 1 and/or Keratin 10 is indicative of a decrease in keratinocyte differentiation.

**Example 5. Effect of FABACs on keratinocyte proliferation and expression of Extra Cellular Matrix (ECM) proteins**

In order to examine the effect of the disclosed FABACs on proliferation of keratinocytes and expression of ECM proteins, the highly differentiated full-thickness in vitro skin culture model Epiderm FT (MatTek, MA) is used.

Duplicates of skin cultures are treated with three different concentrations of Steamchol in DMSO and three different concentrations of Aramchol. One of the tested concentrations is 0.5% (5000 μg/mL) which was efficient in reducing gene expression of KRT1 and KRT10. Two non-treated skin cultures and two cultures treated with vehicle alone (DMSO) are used as negative controls. Two skin cultures treated with retinoic acid are used as a positive control.

The cells are collected 24 hours following application of the compositions to the surface of each test culture. Some of the cells are used for assaying cell proliferation using the MTT assay as used in Example 1 herein above. Proteins are extracted from part of the cells and subjected to ELISA analyses using primary antibodies specific for Elastin, Pro-Collagen and Matrix Metalloproteinase 1 (MMP-1). Another part of the cells is fixated and subjected to immunohistochemical staining using primary antibodies specific for Elastin, Pro-Collagen and Matrix Metalloproteinase 1 (MMP-1).

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without undue experimentation and without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation. The means, materials, and steps for carrying out various disclosed functions may take a variety of alternative forms without departing from the invention.

## CLAIMS

1. A topical composition for use in preventing or treating a skin condition related to aging, the composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and at least one dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond.

2. The composition of claim 1, wherein the FABAC comprises two fatty acid radicals wherein at each occurrence W is independently a fatty acid radical having 6-22 carbon atoms; and X is independently a bonding member comprising a heteroatom or a direct C-C or C=C bond.

3. The composition of claim 1, wherein said bonding member is selected from the group consisting of NH, P, S, O, or a direct C-C or C=C bond.

4. The composition of claim 3, wherein said bonding member is NH.

5. The composition of claim 1, wherein said one or two fatty acid radicals are independently selected from the group consisting of: stearic acid, behenic acid, arachidylic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, oleic acid.

6. The composition of claim 5, wherein said one or two fatty acids is a stearic acid.

7. The composition of claim 1, wherein said bile acid is selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and derivatives thereof.

8. The composition of claim 7, wherein said bile acid is a cholic acid.

9. The composition of claim 1, wherein wherein said FABAC is selected from the group consisting of:

3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid,

3 -beta arachidylamido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid, and a combination thereof.

10. The composition of claim 1, wherein said FABAC is 3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid.

11. The composition of claim 1 wherein the skin condition related to aging is associated with at least one of chronological aging, photo-aging, skin atrophy or a combination thereof.

12. The composition of claim 1 wherein the skin condition is selected from the group consisting of: fine lines, wrinkles, discoloration, uneven pigmentation, sagging, enlarged pores, rough skin, dry skin and stretch marks, uneven tone, blemishes, skin thickening or thinning and a combination thereof.

13. The composition of claim 12, wherein the skin condition is wrinkling.

14. The composition of claim 12, wherein the skin condition is fine lines.

15. A method of preventing or treating a skin condition related to aging comprising the step of administering to a subject in need thereof a topical composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and a dermatologically acceptable diluent or carrier, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond

16. The method of claim 15 wherein the FABAC comprises two fatty acid radicals wherein at each occurrence W is independently a fatty acid radical having 6-22 carbon atoms; and X is independently a bonding member comprising a heteroatom or a direct C-C or C=C bond.

17. The method of claim 15, wherein said bonding member is selected from the group consisting of NH, P, S, O, or a direct C-C or C=C bond.

18. The method of claim 17, wherein said bonding member is NH.

19. The method of claim 15, wherein said one or two fatty acid radicals are independently selected from the group consisting of: stearic acid, behenic acid, arachidylic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, oleic acid.

20. The method of claim 19, wherein said one or two fatty acids is a stearic acid.

21. The method of claim 15, wherein said bile acid is selected from the group consisting of: cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and derivatives thereof.

22. The method of claim 21, wherein said bile acid is a cholic acid.

23. The method of claim 15, wherein said FABAC is selected from the group consisting of:

3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid,

3 -beta arachidylamido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid, and

a combination thereof.

24. The method of claim 23, wherein said FABAC is 3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid.

25. The method of claim 15, wherein the skin condition related to aging is associated with at least one of chronological aging, photo-aging, skin atrophy or a combination thereof.

26. The method of claim 15, wherein the skin condition is selected from the group consisting of: fine lines, wrinkles, discoloration, uneven pigmentation, sagging, enlarged pores, rough skin, dry skin and stretch marks, uneven tone, blemishes, skin thickening or thinning and a combination thereof.

27. The method according to claim 26 wherein the skin condition is wrinkling.

28. The method according to claim 26 wherein the skin condition is fine lines.

29. The method of claim 15 wherein the composition is topically administered to a subject in need thereof.

30. A topical composition comprising as an active ingredient a fatty acid bile acid conjugate (FABAC) and a dermatologically acceptable diluent, carrier or excipient, wherein the FABAC has the formula I:

W - X - G (I)

wherein G represents a bile acid or a bile salt radical; W represents one or two fatty acid radicals having 6-22 carbon atoms; and X represents a bonding member comprising a heteroatom or a direct C-C or C=C bond.

31. The topical composition of claim 30, wherein the FABAC comprises two fatty acid radicals wherein at each occurrence W is independently a fatty acid radical having 6-22 carbon atoms; and X is independently a bonding member comprising a heteroatom or a direct C-C or C=C bond.

32. The topical composition of claim 30, wherein said bonding member is selected from the group consisting of NH, P, S, O, or a direct C-C or C=C bond.

33. The topical composition of claim 32, wherein said bonding member is NH.

34. The topical composition of claim 30, wherein said one or two fatty acid radicals are independently selected from the group consisting of: stearic acid, behenic acid, arachidylic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid and oleic acid.

35. The topical composition of claim 30, wherein said bile acid is selected from the group consisting of cholic acid, ursodeoxycholic acid, chenodeoxycholic acid, deoxycholic acid, lithocholic acid, and derivatives thereof.

36. The topical composition of claim 30, wherein said FABAC is 3-beta-stearoyl-amido,7α,12α-dihydroxy-5-beta-cholan-24-oic acid.

37. The topical composition of claim 30, formulated in a form selected from the group consisting of: aqueous solution, cream, lotion, water in oil or oil in water emulsion,

multiple emulsion, silicone emulsion, microemulsion, nanoemulsion, foam, gel and an aqueous solution with a co-solvent.

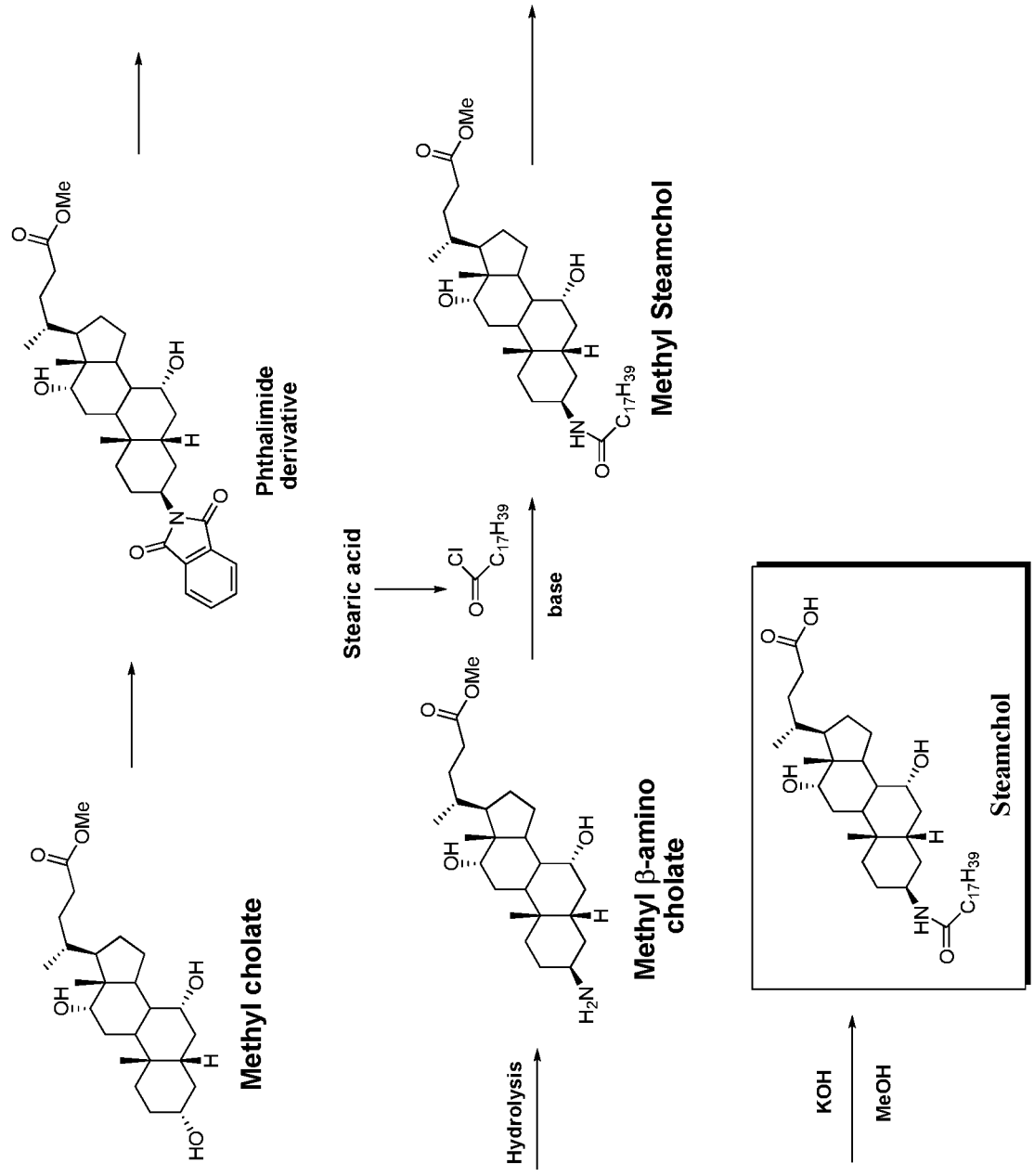

Methyl cholate
Phthalimide derivative
Stearic acid
base
Methyl Steamchol
Hydrolysis
Methyl β-amino cholate
KOH
MeOH
Steamchol

Fig. 1

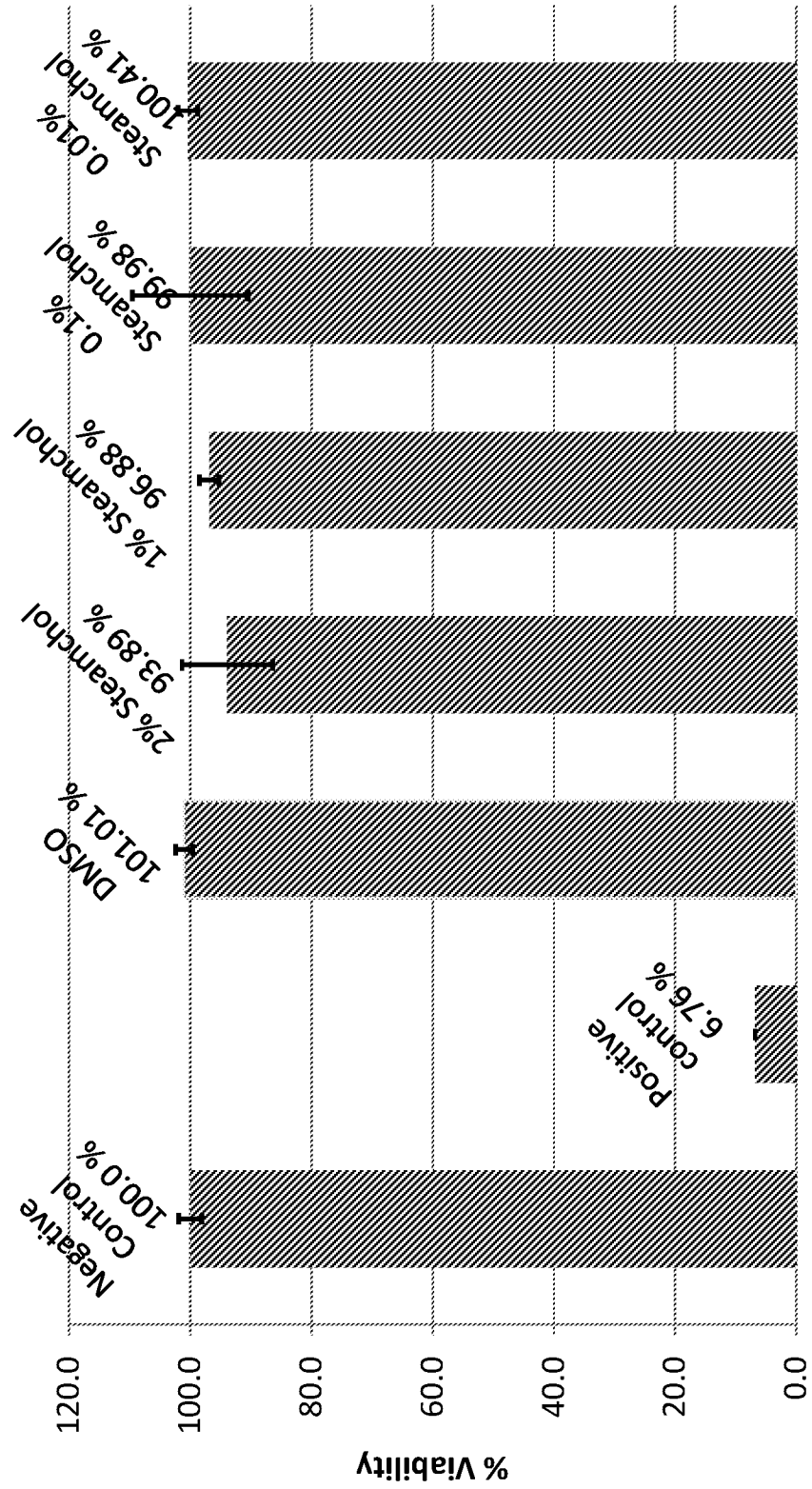

% Viability
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Negative Control 100.0 %
Positive control 6.76 %
DMSO 101.01 %
2% Steamchol 93.89 %
1% Steamchol 96.88 %
0.1% Steamchol 99.98 %
0.01% Steamchol 100.41 %

Fig. 2

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2014/050717

A. CLASSIFICATION OF SUBJECT MATTER

IPC (2014.01) A61K 8/36, A61K 8/63, A61K 31/575, A61Q 19/08, A61P 17/00, C07J 9/00, C07C 53/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC (2014.01) A61K 8/36, A61K 8/63, A61K 31/575, A61Q 19/08, C07J 9/00, C07C 53/42

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: THOMSON INNOVATION, Google Patents, CAPLUS, REGISTRY

Search terms used: bile acid, fatty acid, cholic, stearic, behenic, arachnid, palmic, eicosapent, oleic, conjugate, skin, aging, topical, ointment, cream, lotion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2011256247 A1 NITROMEGA CORP [US]<br>20 Oct 2011 (2011/10/20)<br>abstract , [0006], [0157], claims | 1-5,7,8,11-19,21,22,<br>25-35,37 |
| Y | ES 2296463 A1 UNIV SANTIAGO COMPOSTELA<br>16 Apr 2008 (2008/04/16)<br>page7 ,ex. 6 ,claims 1, 24, 25 | 1-5,7,8,11-19,21,22,<br>25-35,37 |
| A | US 4115313 A LYON IRVING, LYON HARRIETTE<br>19 Sep 1978 (1978/09/19)<br>abstract, example VIII | 1-37 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 29 Oct 2014 | 16 Nov 2014 |
| Name and mailing address of the ISA:<br>Israel Patent Office<br>Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel<br>Facsimile No. 972-2-5651616 | Authorized officer<br>BERKOWITZ Tzipora<br><br>Telephone No. 972-2-5651656 |

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
PCT/IL2014/050717

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| | | ES 2296463 B1 | 16 Feb 2009 |

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权利要求书3页 说明书20页 附图2页

(54)发明名称

包含胆汁酸-脂肪酸缀合物的抗老化组合物

(57)摘要

本发明提供了包含脂肪酸胆汁酸缀合物(FABAC)的局部组合物。本发明还提供了使用公开的组合物用于预防、减弱或治疗皮肤老化和与其相关的症状的方法。

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1.一种用于预防或治疗与老化相关的皮肤状况的局部组合物,所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

W-X-G(I)

其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。

2.如权利要求1所述的组合物,其中所述FABAC包含两个脂肪酸基团,其中在每次出现时W独立地为具有6-22个碳原子的脂肪酸基团;并且X独立地为键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。

3.如权利要求1所述的组合物,其中所述键合成员选自由NH、P、S、O或直接的C-C或C=C键组成的组。

4.如权利要求3所述的组合物,其中所述键合成员是NH。

5.如权利要求1所述的组合物,其中所述一个或两个脂肪酸基团独立地选自由以下组成的组:硬脂酸、山萮酸、二十烷醇酸、棕榈酸、花生四烯酸、二十碳五烯酸、油酸。

6.如权利要求5所述的组合物,其中所述一个或两个脂肪酸是硬脂酸。

7.如权利要求1所述的组合物,其中所述胆汁酸选自由以下组成的组:胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。

8.如权利要求7所述的组合物,其中所述胆汁酸是胆酸。

9.如权利要求1所述的组合物,其中所述FABAC选自由以下组成的组:

3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸、3-β二十烷醇氨基,7α,12α-二羟基-5-β-胆烷-24-酸、及其组合。

10.如权利要求1所述的组合物,其中所述FABAC是3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸。

11.如权利要求1所述的组合物,其中所述与老化相关的皮肤状况与时序老化、光老化、皮肤萎缩或其组合的至少一种相关。

12.如权利要求1所述的组合物,其中所述皮肤状况选自由以下组成的组:细纹、皱纹、变色、不均匀色素沉着、下垂、毛孔粗大、皮肤粗糙、皮肤干燥和妊娠纹、肤色不均、疵点、皮肤变厚或变薄及其组合。

13.如权利要求12所述的组合物,其中所述皮肤状况为起皱纹。

14.如权利要求12所述的组合物,其中所述皮肤状况为细纹。

15.一种预防或治疗与老化相关的皮肤状况的方法,所述方法包括向需要其的受试者施用局部组合物,所述局部组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及皮肤病学可接受的稀释剂或载体,其中所述FABAC具有式I:

W-X-G(I)

其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。

16.如权利要求15所述的方法,其中所述FABAC包含两个脂肪酸基团,其中在每次出现时W独立地为具有6-22个碳原子的脂肪酸基团;并且X独立地为键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。

17.如权利要求15所述的方法，其中所述键合成员选自由NH、P、S、O或直接的C-C或C＝C键组成的组。

18.如权利要求17所述的方法，其中所述键合成员是NH。

19.如权利要求15所述的方法，其中所述一个或两个脂肪酸基团独立地选自由以下组成的组：硬脂酸、山萮酸、二十烷醇酸、棕榈酸、花生四烯酸、二十碳五烯酸、油酸。

20.如权利要求19所述的方法，其中所述一个或两个脂肪酸是硬脂酸。

21.如权利要求15所述的方法，其中所述胆汁酸选自由以下组成的组：胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。

22.如权利要求21所述的方法，其中所述胆汁酸是胆酸。

23.如权利要求15所述的方法，其中所述FABAC选自由以下组成的组：

3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸、3-β-二十烷醇氨基,7α,12α-二羟基-5-β-胆烷-24-酸、及其组合。

24.如权利要求23所述的方法，其中所述FABAC是3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸。

25.如权利要求15所述的方法，其中所述与老化相关的皮肤状况与时序老化、光老化、皮肤萎缩或其组合的至少一种相关。

26.如权利要求15所述的方法，其中所述皮肤状况选自由以下组成的组：细纹、皱纹、变色、不均匀色素沉着、下垂、毛孔粗大、皮肤粗糙、皮肤干燥和妊娠纹、肤色不均、疵点、皮肤变厚或变薄及其组合。

27.如权利要求26所述的方法，其中所述皮肤状况是起皱纹。

28.如权利要求26所述的方法，其中所述皮肤状况是细纹。

29.如权利要求15所述的方法，其中所述组合物局部施用至需要其的受试者。

30.一种局部组合物，所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及皮肤病学可接受的稀释剂、载体或赋形剂，其中所述FABAC具有式I：

W-X-G(I)

其中G代表胆汁酸或胆汁盐基团；W代表具有6-22个碳原子的一个或两个脂肪酸基团；并且X代表键合成员，所述键合成员包含杂原子或直接的C-C或C＝C键。

31.如权利要求30所述的局部组合物，其中所述FABAC包含两个脂肪酸基团，其中在每次出现时W独立地为具有6-22个碳原子的脂肪酸基团；并且X独立地为键合成员，所述键合成员包含杂原子或直接的C-C或C＝C键。

32.如权利要求30所述的局部组合物，其中所述键合成员选自由NH、P、S、O或直接的C-C或C＝C键组成的组。

33.如权利要求32所述的局部组合物，其中所述键合成员是NH。

34.如权利要求30所述的局部组合物，其中所述一个或两个脂肪酸基团独立地选自由以下组成的组：硬脂酸、山萮酸、二十烷醇酸、棕榈酸、花生四烯酸、二十碳五烯酸、油酸。

35.如权利要求30所述的局部组合物，其中所述胆汁酸选自由以下组成的组：胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。

36.如权利要求30所述的局部组合物，其中所述FABAC是3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸。

37.如权利要求30所述的局部组合物，所述局部组合物以选自由以下组成的组的形式配制：水性溶液、霜剂、洗液、油包水乳液或水包油乳液、多重乳液、硅酮乳液、微米乳液、纳米乳液、泡沫、凝胶和具有共溶剂的水性溶液。

# 包含胆汁酸-脂肪酸缀合物的抗老化组合物

## 发明领域

[0001] 本发明涉及包含胆汁酸-脂肪酸缀合物的局部组合物以及其在治疗或预防与老化相关的皮肤状况中的用途。

[0002] 发明背景

[0003] 皮肤和老化

[0004] 皮肤是身体的最大器官，并且主要功能是保护身体免于外部/环境因素诸如机会病原微生物、化学品、UV辐射，以及帮助体温调节。

[0005] 皮肤经受着以上环境因素以及内在因素带来的持续不断的损害。影响皮肤的环境因素包括暴露于阳光、吸烟和空气污染，而内在因素包括压力和时序老化。时序老化可以由与正常细胞氧化压力相关的亚慢性炎症引起。

[0006] 不论是外在还是内在，皮肤面临的挑战导致可见的迹象诸如细纹、皱纹、纹理不均匀以及散布的色素沉着。预防、消除或减少这些迹象已经成为数十亿美元的商业，治疗范围从非处方的局部霜剂和保湿霜到多种美容整形外科技术。正常的时序老化导致皮肤变薄、失去弹性和皮肤的总体萎缩。时序老化可能被光老化加速，光老化是由于暴露于UV照射的皮肤提早老化。氧化也可通过产生不稳定的称为自由基的分子有助于皮肤老化的进程，所述分子当在近处和/或慢性产生时可积累并损害皮肤细胞。

[0007] 西方社会判断衰老外貌的个人比较没有吸引力。这培育了一个非常显著的产业，其为衰老人群提供保持年轻外貌的方法。皮肤的提早老化与皱纹相关，皱纹能够对自尊具有深远的影响。

[0008] 视黄酸(也称为维甲酸)是目前唯一规定的具有抗老化和皱纹减少适应症的局部用药。视黄酸对抗老化标记的影响显著的同时，特别是具有逆转皱纹以及与光老化相关的损害，它的使用与一些主要的副作用相关，所述副作用包括致畸性、原发性刺激以及光敏感。因此视黄酸必须在医生的监督下使用。通常用于抗老化治疗的类视黄醇已经表现出在0.6-3x10$^{5}$M的范围对成纤维细胞和上皮细胞的细胞毒性(Varani等Journal of Investigative Dermatology(1993)101,839-842)，以及增加上皮细胞的死亡(Ding等Invest Ophthalmol Vis Sci.2013Jun 26;54(6):4341-50)。

[0009] 脂肪酸胆汁酸或胆汁盐缀合物(FABAC)，也被称为胆汁酸脂肪酸缀合物(BAFAC)，是可用于改善与胆汁酸或胆固醇代谢相关的状况的合成分子家族。FABAC被认为降低血液胆固醇浓度，降低肝脏脂肪水平以及溶解胆结石(Gilat等,Hepatology 2003;38:436-442;和Gilat等,Hepatology 2002;35:(597-600)。

[0010] 美国专利6,384,024,6,395,722,6,589,946公开了某些FABAC在溶解胆汁中的胆固醇胆结石以及治疗动脉硬化中的用途。美国专利7,501,403和US 8,110,564以及美国申请公布US2012/0214872中公开了这些和另外的FABAC用于治疗脂肪肝、降低血液胆固醇水平和治疗高血糖症、糖尿病、胰岛素耐受以及肥胖症。最近，美国申请号2012/0157419公开了FABAC可用于治疗以淀粉样蛋白斑沉积为特征的脑疾病(例如阿尔兹海默症)。

[0011] 加拿大专利申请2,166,427公开了胆汁酸鹅去氧胆酸和/或熊脱氧胆酸用于制备

用于治疗特应性皮炎的药物的用途。WO02/083147公开了某些胆汁酸衍生物如法尼酯X受体(FXR)配体用于预防或治疗FXR-介导的疾病或状况。本领域并未公开或表明FABAC可以用于局部施用,并且特别是用于预防、治疗或减轻与皮肤老化相关的紊乱。

[0012] 对可用于治疗与皮肤的老化相关的症状的组合物和方法存在尚未满足的需求,所述症状包括但不限于皱纹形成。

[0013] 发明概述

[0014] 本发明涉及皮肤护理,特别是包含脂肪酸胆汁酸缀合物(FABAC)的美容组合物以及其用于预防、减轻或治疗皮肤老化以及与其相关的症状的使用方法。

[0015] 本发明部分基于出乎意料的发现:FABAC能够降低皮肤成纤维细胞中角蛋白10和角蛋白1的基因表达水平,如下文所示。根据一些实施方案,角蛋白1和10的表达降低导致降低的角质形成细胞的分化。

[0016] 本发明还基于出乎意料的发现:与类视黄醇施用不同,FABAC的施用不会导致对表皮细胞的生存力的显著影响。

[0017] 此外,如下文所示,FABAC的施用导致增强的胆固醇流出到皮肤成纤维细胞中。因此,不希望受到任何理论或机制的约束,FABAC可作用于皮肤细胞中的脂筏并减弱角质形成细胞分化,其机制类似于视黄酸的机制,但是没有视黄酸治疗带来的严重的副作用,诸如致畸性、皮肤刺激性和更高的对阳光损害的敏感性。

[0018] 根据第一方面,本发明提供了一种局部组合物,所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0019] W-X-G(I)

[0020] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述组合物被配制成用于局部施用。用于本文时,术语“局部施用”是指通过身体表面优选通过皮肤施用。根据另一个实施方案,所述组合物以选自由以下组成的组的形式配制:水性溶液、霜剂、洗液、油包水乳液或水包油乳液、多重乳液、硅酮乳液、微米乳液(microemulsion)、纳米乳液(nanoemulsion)、凝胶、泡沫和具有共溶剂的水性溶液。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述局部组合物是配制成用于局部施用的美容组合物。

[0021] 根据一些实施方案,术语“皮肤病学可接受的稀释剂、载体或赋形剂”是指本领域已知的适用于应用至皮肤的任何稀释剂、载体或赋形剂。根据一些实施方案,所述至少一种皮肤病学可接受的稀释剂、载体或赋形剂是美容方面适用的。根据某些实施方案,所述至少一种皮肤病学可接受的稀释剂、载体或赋形剂是药学上可接受的。根据某些实施方案,所述局部组合物包含至少一种适用于局部施用的优选适用于施用至皮肤的药学上可接受的载体、稀释剂或赋形剂。

[0022] 根据另一个实施方案,所述键合成员选自由以下组成的组:NH、P、S、O以及直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。根据一个示例性实施方案,所述键合成员是NH。

[0023] 根据一些实施方案,FABAC包含两个脂肪酸基团,其中在每次出现时W独立地为具

有6-22个碳原子的脂肪酸基团;并且X独立地为键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。

[0024] 根据另一个实施方案,所述一个或两个脂肪酸基团独立地选自选自由以下组成的组的脂肪酸的基团:硬脂酸、山嵛酸、二十烷醇酸(arachidylic acid)、棕榈酸、花生四烯酸、二十碳五烯酸、油酸。每种可能性代表本发明的单独实施方案。根据又另一实施方案,所述一个或两个脂肪酸基团是硬脂酸的基团。

[0025] 根据另一实施方案,所述胆汁酸选自由以下组成的组:胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。每种可能性代表本发明的单独实施方案。根据又一个实施方案,所述胆汁酸是胆酸。

[0026] 根据一些实施方案,用于本文的术语"胆汁酸基团"是指选自由以下组成的组的胆汁酸的胆汁盐基团:胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述胆汁酸基团是胆酸的胆汁盐基团。

[0027] 根据一些实施方案,所述FABAC选自由以下组成的组:

[0028] 3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸;

[0029] 3-β二十烷醇氨基,7α,12α-二羟基-5-β-胆烷-24-酸;及其组合。每种可能性代表本发明的单独实施方案。

[0030] 根据一个示例性实施方案,所述FABAC是3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸(在本文中也被称为"Steamchol")。

[0031] 根据一些实施方案,本发明提供了一种美容组合物,所述组合物包含至少一种FABAC作为活性成分,优选Steamchol,其中所述美容组合物配制成用于局部施用并还包含至少一种适用于局部施用的美容上可接受的稀释剂、载体或赋形剂。

[0032] 根据另一个实施方案,本发明的组合物可用于预防或治疗与老化相关的皮肤状况。每种可能性代表本发明的单独实施方案。根据另一个实施方案,本发明的组合物可用于治疗与老化相关的皮肤状况。

[0033] 根据另一个方面,提供了一种预防或治疗与老化相关的皮肤状况的方法,所述方法包括向需要其的受试者施用局部组合物,所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0034] W-X-G(I)

[0035] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键;从而预防或治疗与老化相关的皮肤状况。每种可能性代表本发明的单独实施方案。

[0036] 根据一些实施方案,提供了一种用于预防或治疗与老化相关的皮肤状况的局部组合物,所述局部组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0037] W-X-G(I)

[0038] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表

本发明的单独实施方案。

[0039] 根据一些实施方案,本发明提供了至少一种用于制备用于治疗与改变的皮脂水平相关的皮肤状况的脂肪酸胆汁酸缀合物(FABAC),其中所述FABAC具有式I:

[0040] W-X-G(I)

[0041] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键;从而治疗所述受试者中与改变的皮脂水平相关的皮肤状况。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述局部组合物还包含至少一种皮肤病学可接受的稀释剂、载体或赋形剂。根据一些实施方案,所述局部组合物是美容组合物。

[0042] 根据另一个实施方案,所述与老化相关的皮肤状况与时序老化、光老化、皮肤萎缩或其组合的至少一种相关。每种可能性代表本发明的单独实施方案。

[0043] 根据一些实施方案,所述与老化相关的皮肤状况选自由以下组成的组:细纹、皱纹、变色、不均匀色素沉着、下垂、毛孔粗大、皮肤粗糙、皮肤干燥和妊娠纹、肤色不均、疵点、皮肤变厚或变薄及其组合。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述与老化相关的皮肤状况可为与时序和/或环境老化相关的任何其它老化相关的皮肤外观。每种可能性代表本发明的单独实施方案。

[0044] 根据另一个实施方案,所述与老化相关的皮肤状况是起皱纹。根据又另一实施方案,所述与老化相关的皮肤状况是细纹。根据一些实施方案,所述与老化相关的皮肤状况选自由以下组成的组:皮肤皱纹、皮肤萎缩、光老化及其组合。每种可能性代表本发明的单独实施方案。

[0045] 本发明的其他目的、特征和优势将从下文的描述和附图变得清楚。

[0046] 附图简述

[0047] 图1示出了根据一些实施方案,用于产生3β-硬脂酰氨基-7α,12α,二羟基-5β-胆烷-24-酸(硬脂酰氨基胆烷酸,在本文中也被称为“Steamchol”)的方法。

[0048] 图2描绘了未处理的(阴性对照)、用1%Triton X-100(阳性对照)处理的、用单独的DMSO处理的、或用含有0.01%、0.1%、1%或2%的Steamchol的DMSO处理的上皮细胞培养物的生存力的比较。

[0049] 发明详述

[0050] 本发明涉及可用作抗老化剂的包含脂肪酸胆汁酸缀合物(FABAC)的局部组合物。用于本文时,术语“抗老化剂”涉及能够治疗或预防至少一种与老化相关的皮肤状况的试剂。本发明还涉及通过局部施用公开的组合物预防、减轻或治疗与老化相关的皮肤状况及其症状的方法,所述皮肤状况及其症状包括但不限于皮肤起皱纹。

[0051] 胆固醇是角质层中以重量计第二丰富的脂质(在神经酰胺之后),被认为提高不同脂质种类的混合并调节它们的热力学“相行为”。角质形成细胞需要大量的胆固醇用于维持强屏障并以控制皮肤渗透性;因此在皮肤中胆固醇体内稳态的调节非常重要。ATP-结合盒转运子(ABCA1)是在调节细胞胆固醇水平中起关键作用的用于胆固醇流出的膜转运子。细胞膜中存在的脂筏通常含有在周围双层膜中存在的胆固醇的量的3至5倍。

[0052] 如下文所示,FABAC化合物的施用导致皮肤细胞中ABCA-1胆固醇转运子的水平的提高,并行于胆固醇流出的提高。此外,例证了FABAC的施用显著下调了皮肤细胞中角质形

成细胞分化标志物角蛋白1和10的mRNA水平。

[0053] 不希望受到任何理论或作用机制的约束,FABAC通过增强成纤维细胞中ABCA1转运子并下调角质形成细胞分化标志物角蛋白1和10的mRNA水平表现出有利的抗老化效应。因此,FABAC可以以类似于视黄酸的机制的机制影响表皮皮肤层的细胞分化。如下文进一步例证的,ABCA-1的mRNA水平并未由于FABAC的施用而提高。因此,不希望受到理论或机制的约束,FABAC可以影响表皮皮肤层中的分化,而不会对核相关视黄酸受体产生直接影响。因此,根据一些实施方案,FABAC不会引起视黄酸治疗带来的严重不良反应,诸如致畸性、皮肤刺激性和更高的对阳光损害的敏感性。

[0054] 如下文例证的,在使用包括成纤维细胞和角质形成细胞在内的细胞培养物的细胞毒性测定中证实了Steamchol具有非常低的细胞毒性。根据一些实施方案,FABCA诸如,但不限于Steamchol,当在组合物中以最高达10%重量体积、可能最高达5%重量/体积,最通常最高达2%重量/体积的浓度局部施用时,不引起或引起非常有限的细胞死亡。每种可能性代表本发明的单独实施方案。

[0055] 根据一个方面,本发明提供了一种局部组合物,所述局部组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0056] W-X-G(I)

[0057] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。

[0058] 本文使用的术语"FABAC"(同义词BAFAC)是指式W-X-G(式I)的缀合物,其中G代表胆汁酸或其胆汁盐基团,W代表具有6-22个碳原子的一个或两个脂肪酸基团,并且X代表在所述胆汁酸和所述脂肪酸基团之间的键合成员。根据一些实施方案,键合成员X包括但不限于NH、P、S、O、或直接的C=C或C-C键。每种可能性代表本发明的单独实施方案。FABAC是在本领域中已知的,并且在例如美国专利6,384,02、6,395,722和6,589,946中描述,所述专利的内容在此以引用的方式并入。根据一些实施方案,所述脂肪酸基团包含指定8-22个碳原子、14-22个碳原子或18-22个碳原子。每种可能性代表本发明的单独实施方案。用于本文时,术语"FABAC"、"BAFAC"、"所述FABAC"和"本发明的FABAC"可以互换使用。根据一些实施方案,本发明的局部组合物包含至少一种FABAC。

[0059] FABAC的一个非限制性通用结构在下文示出。根据一个非限制性实例,胆汁酸与1-2个具有大量链长的任意一个链长的脂肪酸缀合(例如使用酰胺键,例如在位置3)。

[0060] 根据一个示例性实施方案,本发明的FABAC是3β-二十烷醇氨基-7α,12α,二羟基-5β-胆烷-24-酸(二十烷醇氨基胆烷酸;胆烷酸与二十烷醇酸的酰胺缀合物;也称为"Aramchol"或"C20FABAC")或3β-硬脂酰氨基-7α,12α,二羟基-5β-胆烷-24-酸(硬脂酰氨基胆烷酸;胆烷酸与硬脂酸的酰胺缀合物;也称为"Steamchol"或"C18 FABAC")。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述FABAC是Steamchol。

[0061] 在另一个实施方案中,本发明的方法和组合物的FABAC具有式I:

[0062] W-X-G(I)

[0063] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个饱和或不

饱和脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。根据一些实施方案,G代表胆汁酸的基团。根据一些实施方案,X代表选自由以下组成的组的键合成员:杂原子、直接的C-C键和C=C键。每种可能性代表本发明的单独实施方案。

[0064] 根据一些实施方案,本发明的方法和组合物的FABAC具有式II:

[0065] (W-X-)nG(II)

[0066] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键;并且n是整数1或2。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述杂原子选自由以下组成的组:NH、P、S和O。每种可能性代表本发明的单独实施方案。一般来说,术语"杂原子"包括除了碳或氢之外的任何元素的原子,其优选实例包括氮、氧、硫和磷。

[0067] 根据一个实施方案,n是1。根据另一个实施方案,n是2,并且在每次出现时W独立地为具有6-22个碳原子的脂肪酸基团;并且X独立地为键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。

[0068] 在另一个实施方案中,所述FABAC的键合成员选自由NH、P、S、O或直接的C-C或C=C键组成的组。每种可能性代表本发明的单独实施方案。根据一些实施方案,术语"直接的键"是指C-C(单)键。在另一个实施方案中,术语"直接的键"是指C=C(双)键。在另一个实施方案中,多于一个直接的键用于本发明的FABAC中。在另一个实施方案中,胆汁酸和脂肪酸基团之间的键是β构型。在另一个实施方案中,胆汁酸和脂肪酸基团之间的键是α构型。在另一个实施方案中,所述键合成员不是酯键。

[0069] 根据一些实施方案,所述FABAC的胆汁酸或胆汁酸基团选自由以下组成的组:胆酸、熊脱氧胆酸、鹅脱氧胆酸、脱氧胆酸、石胆酸以及其衍生物。胆汁酸或其基团的每种类型代表本发明的单独实施方案。本文使用的术语"基团"意指包含一个或更多个未成对电子的化学部分。根据一些实施方案,所述FABAC的胆汁酸或胆汁酸基团是胆酸。

[0070] 在另一个实施方案中,所述FABAC包含单个脂肪酸基团。所述胆汁酸与所述脂肪酸基团的缀合可以发生在胆汁酸的多个位置。在某些实施方案中,所述胆汁酸与所述脂肪酸基团的缀合形成于选自位置3、6、7、12和24的胆汁酸核心位置。每种可能性代表本发明的单独实施方案。在一个实施方案中,所述缀合形成于胆汁酸核心的位置3。

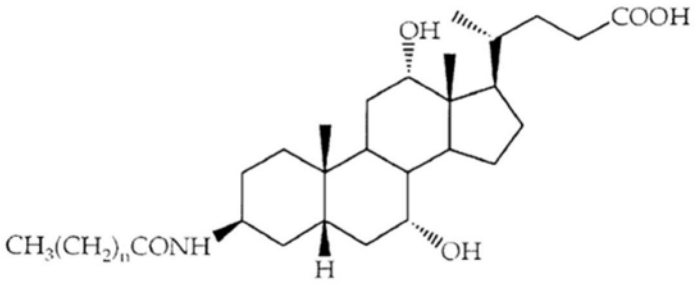
[0071] 在另一个实施方案中,所述FABAC包含两个脂肪酸基团。根据一些实施方案,每个脂肪酸基团与胆汁酸核心的缀合在选自胆汁酸核心的3、7、12和24位置的两个位置上。每种可能性代表本发明的单独实施方案。根据一个特定的实施方案,所述缀合在胆汁酸核心的位置3和7上。

[0072] 在另一个实施方案中,所述脂肪酸是饱和的。在另一个实施方案中,所述脂肪酸是不饱和的。在另一个实施方案中,所述脂肪酸是单不饱和的。在另一个实施方案中,所述脂肪酸是多不饱和的。

[0073] 在另一个实施方案中,所述FABAC的脂肪酸或脂肪酸基团独立地选自由以下组成的组:山萮酸、二十烷醇酸、硬脂酸和棕榈酸。每种可能性代表本发明的单独实施方案。

[0074] 根据本发明,FABAC的一个示例性实施方案在下文式III中示出。根据一些实施方案,在式III中n=20或者n=18。每种可能性代表本发明的单独实施方案。

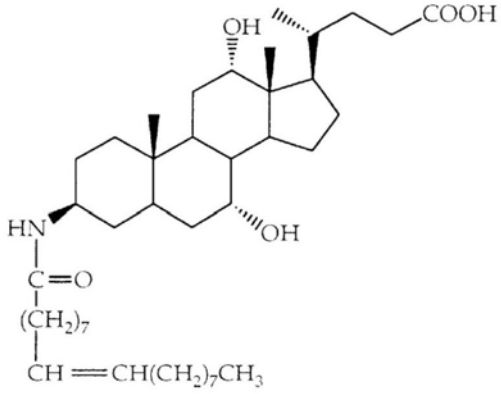
[0075]




(III)

[0076] 根据一些实施方案，本发明的FABAC的一个或两个脂肪酸或脂肪酸基团是不饱和的脂肪酸或脂肪酸基团。每种可能性代表本发明的单独实施方案。在另一个实施方案中，所述FABAC的不饱和脂肪酸或不饱和脂肪酸基团独立地选自由以下组成的组：亚麻酸、二十碳五烯酸、二十二碳六烯酸、花生四烯酸、棕榈油酸(palmipoleic acid)、油酸和反油酸。每种可能性代表本发明的单独实施方案。包含不饱和脂肪酸的FABAC的非限制性实例是3β-油烯基氨基-7α,12α-二羟基-5β-胆烷-24-酸，如下文式IV所描绘的。

[0077]




(IV)

[0078] 在另一个实施方案中，利用亚油酸。在另一个实施方案中，利用共轭亚油酸。在另一个实施方案中，利用共轭亚油酸的异构体。每种可能性代表本发明的单独实施方案。术语“共轭脂肪酸”，也称为“CFA”，是指其中至少一对双键仅被一个单键分开的多不饱和脂肪酸。

[0079] 在另一个实施方案中，所述脂肪酸是短链脂肪酸。在另一个实施方案中，所述脂肪酸链长为6-8个碳。在另一个实施方案中，所述脂肪酸是中链脂肪酸。在另一个实施方案中，所述脂肪酸链长为8-14个碳。在另一个实施方案中，所述脂肪酸链长为14-22个碳。在另一个实施方案中，所述脂肪酸链长为16-22个碳。在另一个实施方案中，利用本领域中已知的任何其它脂肪酸链长。每种类型的脂肪酸或脂肪酸基团代表本发明的单独实施方案。

[0080] 根据一些实施方案，本发明的方法和组合物的FABAC选自由以下组成的组：3β-山嵛醇氨基-7α,12α-二羟基-5β-胆烷-24-酸；3β-二十烷醇氨基-7α,12α-二羟基-5β-胆烷-24-酸；3β-硬脂酰氨基-7α,12α-二羟基-5β-胆烷-24-酸；3β-棕榈酰氨基-7α,12α-二羟基-5β-胆烷-24-酸；3β-肉豆蔻基氨基-7α,12α-二羟基-5β-胆烷-24-酸；和N-(-羧甲基)-3β-硬脂酰氨基-7α,12α-二羟基-5β-胆烷-24-酰胺。每种可能性代表本发明的单独实施方案。

[0081] 根据一些实施方案，本发明的方法和组合物的FABAC选自由以下组成的组：

[0082] 3-β-硬脂酰-氨基,7α,12α-二羟基-5-β-胆烷-24-酸；

[0083] 3-β二十烷醇氨基,7α,12α-二羟基-5-β-胆烷-24-酸；

[0084] 3-β花生酰基氨基,7α,12α-二羟基-5-β-胆烷-24-酸;及其组合。每种可能性代表本发明的单独实施方案。

[0085] 在一个示例性实施方案中,本发明的方法和组合物的FABAC是3β-硬脂酰氨基-7α,12α-二羟基-5β-胆烷-24-酸("Steamchol")。产生3β-硬脂酰氨基-7α,12α-二羟基-5β-胆烷-24-酸的一个示例性实施方案在本文图1中示出。根据一些实施方案,本发明提供了用于产生3β-硬脂酰氨基-7α,12α-二羟基-5β-胆烷-24-酸的方法,包括但不限于在图1中描述的方法。

[0086] 本文描述的FABAC可以包括药学上可接受的盐、衍生物和前药。用于制备FABAC和FABAC的盐、衍生物和前药的方法是本领域熟知的,并且还在美国6,384,024、6,395,722和6,589,946以及WO 2002/083147中描述,所述专利的内容如同其全文示出在此并入。用于本文时,术语"胆汁酸衍生物"包括与其药学上可接受的碱或酸的胆汁酸盐以及其非对应异构和对映异构形式。

[0087] 根据一些实施方案,本发明提供了一种局部组合物,所述局部组合物包含至少一种本发明的FABAC作为活性成分以及至少一种适用于局部施用至皮肤的稀释剂、载体或赋形剂。根据一些实施方案,本发明提供了一种配制成用于局部施用至皮肤的美容组合物,所述美容组合物包含至少一种本发明的FABAC作为活性成分以及至少一种适用于局部施用至皮肤的稀释剂、载体或赋形剂。根据一些实施方案,所述至少一种适用于局部施用的稀释剂、载体或赋形剂是美容上可接受的。根据一些实施方案,所述至少一种适用于局部施用的稀释剂、载体或赋形剂是药学上可接受的。

[0088] 根据一些实施方案,本发明提供了一种局部组合物,所述组合物包含Steamchol作为活性成分以及至少一种适用于局部施用至皮肤的稀释剂、载体或赋形剂。根据一些实施方案,公开的组合物配制成用于局部施用至皮肤,优选作为美容组合物。

[0089] 根据一些实施方案,本发明提供了用于预防或治疗与老化相关的皮肤状况的公开的局部组合物。每种可能性代表本发明的单独实施方案。根据另一个实施方案,本发明的组合物可用于治疗与老化相关的皮肤状况。

[0090] 皮肤更新对于维持健康的体内稳态是至关重要的,并且其通过控制表皮细胞的增殖、分化和凋亡之间的平衡维持。角质形成细胞的表皮分化的程序表现为在质膜中富集胆固醇的结构域破坏之后被改变。表明这种胆固醇消耗效应的机制导致角质形成细胞分化的改变。未能完全阐明角质形成细胞分化的衰减与临床上呈现年轻的皮肤之间的直接相关性,但是表明被证明具有这样活性的已知化合物,视黄酸,减轻并且甚至逆转老化损伤。该机制可能与下游代偿效应相关,导致加快的桥粒分裂和更快的皮肤更新以及影响真皮中的细胞外基质。

[0091] 本发明部分基于意料之外的发现:脂肪酸-胆汁酸缀合物(FABAC)增强成纤维细胞中的ABCA1转运体,并下调角质形成细胞分化标志物角蛋白1和10的mRNA水平。不希望受到任何理论或机制的约束,FABAC的这两个关键效应为它们的抗老化效应提供了基础。

[0092] 根据另一个方面,本发明提供了一种预防或治疗与老化相关的皮肤状况的方法,所述方法包括向需要其的受试者施用皮肤病学可接受的量的局部组合物的步骤,所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0093] W-X-G(I)

[0094] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键;从而预防或治疗与老化相关的皮肤状况。每种可能性代表本发明的单独实施方案。

[0095] 根据一些实施方案,本发明提供了一种用于预防或治疗与老化相关的皮肤状况的局部组合物,所述组合物包含脂肪酸胆汁酸缀合物(FABAC)作为活性成分以及至少一种皮肤病学可接受的稀释剂、载体或赋形剂,其中所述FABAC具有式I:

[0096] W-X-G(I)

[0097] 其中G代表胆汁酸或胆汁盐基团;W代表具有6-22个碳原子的一个或两个脂肪酸基团;并且X代表键合成员,所述键合成员包含杂原子或直接的C-C或C=C键。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述FABAC是Steamchol。

[0098] 根据一些实施方案,本发明提供了用于治疗或预防与老化相关的皮肤状况的局部组合物,优选美容局部组合物,所述组合物包含至少一种FABAC作为活性成分。根据一些实施方案,本发明提供了用于治疗或预防与老化相关的皮肤状况的局部美容组合物,所述组合物包含Steamchol作为活性成分。

[0099] 根据一些实施方案,本发明提供了用于治疗或预防皮肤皱纹的皮肤状况的局部组合物,优选美容局部组合物,所述组合物包含至少一种FABAC作为活性成分。根据一些实施方案,本发明提供了用于治疗或预防皮肤皱纹的局部美容组合物,所述组合物包含Steamchol作为活性成分。

[0100] 根据一些实施方案,本发明提供了至少一种本发明的FABAC用于制备用于治疗或预防与老化相关的皮肤状况的局部组合物的用途。每种可能性代表本发明的单独实施方案。根据一些实施方案,所述局部组合物还包含至少一种皮肤病学可接受的载体、稀释剂或赋形剂,优选美容可接受的载体、稀释剂或赋形剂。

[0101] 用于本文时,术语"美容可接受的/适合的"和"皮肤病学可接受的/适合的"涉及适用于与皮肤或人类皮肤附属物接触而不会造成毒性、不耐受、不稳定性、变应性反应等危险的成分。根据一些实施方案,美容或皮肤病学可接受的成分,诸如载体、稀释剂和赋形剂,是能够与抗老化(例如抗皱纹)的活性成分混合以使得所述美容或皮肤病学可接受的成分与所述活性成分不会以会基本上降低活性成分的治疗与皮肤老化相关的状况的效能的方式相互作用的那些,所述抗老化的活性成分诸如,但不限于,本发明的FABAC。

[0102] 用于本文时,术语"有效量"和"皮肤病学有效量"涉及能够抑制、减少、减弱或治疗与老化相关的皮肤状况的至少部分症状的化合物或组合物的量。根据一些实施方案,组合物的皮肤病学有效量是指将所述组合物局部施用至需要其的受试者的皮肤后足以抑制、减少、减弱或治疗与老化相关的皮肤状况的至少部分症状的量。每种可能性代表本发明的单独实施方案。

[0103] 当然,根据本发明施用的化合物的具体剂量将取决于病例周围的特定环境,包括,例如,施用的化合物、施用途径、受试者的生理状态以及治疗的病理状态的严重性。根据一个典型的实施方案,公开的组合物在很长一段时间以若干剂量施用直至已经实现足够的响应,诸如,但不限于减弱或治疗与老化相关的皮肤状况的症状。

[0104] 根据一些实施方案,本发明的组合物被配置为局部施用至受试者,优选通过直接

施用至受试者的皮肤。每种可能性代表本发明的单独实施方案。在具体的实施方案中，受试者是哺乳动物，优选人。

[0105] 人的皮肤，作为主要保护性屏障，保护身体的重要器官免于外部损害，诸如温度和湿度的改变、紫外线和污染，并且在生物体内稳态的调节诸如体温调节中起到重要的作用。但是，随着皮肤变老，其表现出皮肤老化的迹象，诸如失去弹性、角质化、形成皮肤皱纹和皮肤收缩。该皮肤老化的原因能够被分类为内部因素诸如细胞基因转化和细胞组织改变，以及外部因素诸如紫外线(UV)和湿度。由UV引起的皮肤老化效应被称为“光老化”。在光老化中，UV光在细胞中产生氧自由基。氧自由基反过来加速纤维降解蛋白酶(诸如MMP-1、MMP-3、MMP-9等)的合成，所述纤维降解蛋白酶是催化形成皮肤基础的弹性控制纤维的蛋白质诸如胶原蛋白或弹性蛋白的酶。通过信号转导系统，自由基的效应可以诱导炎症反应，从而降低皮层的弹性并且产生皮肤皱纹。

[0106] 用于本文时，“皮肤老化”或“与老化相关的皮肤状况”是指与老化的皮肤相关的皮肤状况。根据一些实施方案，受试者中与老化的皮肤相关的状况是可以通过减少受试者皮肤中的角质形成细胞分化而被治疗或减弱的状况。与老化的皮肤相关的状况的非限制性实例包括，但不限于，皱纹、阳光损害、暗沉的皮肤外观、皮肤下垂、双下巴、角化病、黄褐斑和不规则的色素沉着过度。每种可能性代表本发明的单独实施方案。根据一些实施方案，用于治疗皮肤老化的方法包括使用有效量的如上文所限定的包含FABAC化合物的局部组合物治疗皮肤。根据一些实施方案，所述与老化相关的皮肤状况是皮肤皱纹。根据一些实施方案，所述与老化相关的皮肤状况是皮肤萎缩。

[0107] 根据一些实施方案，所述与老化相关的皮肤状况是可以通过降低角质形成细胞分化而被治疗和/或减弱和/或预防的皮肤状况。每种可能性代表本发明的单独实施方案。根据一些实施方案，本发明的组合物通过降低角蛋白1和/或角蛋白10的表达、通过增强ABCA1的活性或者其组合引起角质形成细胞分化的降低。每种可能性代表本发明的单独实施方案。

[0108] 根据一些实施方案，本发明提供了治疗、减弱和预防受试者中皮肤皱纹的方法，所述方法包括向受试者的皮肤局部施用局部组合物，所述局部组合物包含至少一种本发明的FABAC作为活性成分以及至少一种皮肤病学可接受的载体、稀释剂或赋形剂。根据一些实施方案，本发明提供了治疗、减弱和预防受试者中皮肤皱纹的方法，所述方法包括向受试者的皮肤局部施用局部组合物，所述局部组合物包含Steamchol作为活性成分以及至少一种皮肤病学可接受的载体、稀释剂或赋形剂。

[0109] 在一些实施方案中，本发明的组合物还包含至少一种除了本发明的FABAC之外的额外的活性成分，所述额外的活性成分包括，但不限于，抗老化剂。可以被添加到本发明的组合物中的额外的活性成分的非限制性实例包括，但不限于，视黄酸及其衍生物、α和β羟基酸(例如羟基乙酸)、肽、抗氧化剂、皮肤增白化合物及类似物。每种可能性代表本发明的单独实施方案。

[0110] 根据一些实施方案，施用至遭受皮肤皱纹的受试者的局部组合物的量和治疗频率取决于已经在所述受试者中存在的起皱纹的水平、进一步皱纹形成的速度以及所需调节的水平而广泛地变化。

[0111] 在一些实施方案中，本发明提供了用于预防、减慢、阻止或逆转哺乳动物皮肤萎缩

的方法，所述方法包括向皮肤局部施用本发明的局部组合物的步骤。每种可能性代表本发明的单独实施方案。根据一些实施方案，本发明提供了用于治疗、预防、减慢、阻止或逆转需要其的受试者中皮肤萎缩的局部组合物，所述组合物包含至少一种本发明的FABAC作为活性成分并且还包含至少一种皮肤病学可接受的载体、稀释剂或赋形剂。每种可能性代表本发明的单独实施方案。

[0112] 用于本文时，皮肤“萎缩”意指通常以胶原蛋白和/或弹性蛋白减少以及由于有丝分裂降低的成纤维细胞的数目和大小降低和细胞接近衰老为特征的皮肤变薄和/或总体退化。皮肤萎缩是更年期、时序老化和光老化的自然结果，并且通常是皮质甾类治疗引起的不需要的副作用。更年期可以是生理更年期或者外科手术或治疗引起的更年期。

[0113] 根据一些实施方案，本公开内容还提供了用于治疗、预防、减弱或减轻光老化或其至少部分症状的方法，所述方法包括局部施用本发明的组合物至患有光老化的受试者的皮肤的步骤。每种可能性代表本发明的单独实施方案。根据一些实施方案，所述与老化相关的皮肤状况是光老化。根据一些实施方案，本发明提供了用于治疗、预防、减弱或减轻光老化或其至少部分症状的本发明的局部组合物。每种可能性代表本发明的单独实施方案。用于本文时，术语“光老化”包括，但不限于，与暴露于太阳下或其他紫外能源相关的皮肤老化。光老化的症状包括，例如，日光性着色班(老年斑)、日光性角质阳光老化(solar keratoses dermatoheliosis)及其组合。每种可能性代表本发明的单独实施方案。根据一些实施方案，治疗光老化的方法包括向需要其的个体局部施用如本文所限定的包含FABAC化合物的组合物。

[0114] 在此，术语“治疗”包括终止、基本上抑制、减慢或逆转与老化相关的皮肤状况的进展，基本上减轻与老化相关的皮肤状况的临床症状，或基本上阻止与老化相关的皮肤状况相关的症状的出现，所述与老化相关的皮肤状况诸如，但不限于，皮肤皱纹、光老化和皮肤萎缩。根据一些实施方案，术语“治疗”还意欲包括改善皮肤外观和纹理、提高皮肤含水量、愈合、使皮肤光滑或其任意组合。每种可能性代表本发明的单独实施方案。根据一些实施方案，术语“治疗”是指使现有皱纹至少部分光滑和/或减慢现有皱纹加深和/或阻止新皱纹形成。每种可能性代表本发明的单独实施方案。根据一些实施方案，术语“治疗”是指减轻、阻止或预防皮肤变薄和/或皮肤退化。每种可能性代表本发明的单独实施方案。根据一些实施方案，术语“治疗”是指减轻、阻止或预防光老化或其至少部分症状。每种可能性代表本发明的单独实施方案。

[0115] 与老化相关的皮肤状况的症状可包括，但不限于：细纹、起皱纹、老年斑和其它皮肤变色、皮肤下垂、赘生物、皮肤干燥、皮肤粗糙、皮肤暗沉、痤疮、脱发、妊娠纹及其组合。每种可能性代表本发明的单独实施方案。

[0116] 根据一些实施方案，与老化相关的皮肤状况诸如皮肤萎缩或表皮细胞的光老化的治疗包括上文所述的与表皮细胞老化相关的至少部分症状的治疗。该治疗可还包括在其发生之前预防这些症状的至少部分，并且特别是老化迹象。用于本文时，术语“预防”可涉及抑制与老化相关的皮肤状况或者其至少部分症状的出现。或者，术语“预防”可涉及抑制现存的与老化相关的皮肤状况的恶化，诸如，但不限于，现存皮肤皱纹的恶化。

[0117] 根据一些实施方案，本发明的局部组合物配制成用于施用至需要其的受试者的皮肤。根据一个非限制性实例，一种治疗遭受与老化相关的皮肤状况的症状诸如皱纹的受试

者的皮肤的方法是通过局部施用安全量的本发明的局部组合物。根据一些实施方案，与老化相关的皮肤状况的症状包括，但不限于：皱纹、皮肤光滑度降低、肤色不均、皮肤肤色受损等。局部施用至皮肤的频率可取决于个人需求而广泛变化，但是作为一个非限制性实例建议本发明的组合物的局部施用将在从约每周一次至约每天10次的范围内，优选从约每周两次至约每天4次，更优选从约每周3次至约每天两次，最优选约每天一次。每种可能性代表本发明的单独实施方案。根据一些实施方案，局部施用优选在从约一个月至数年的时期内。

[0118] 用于本文时，“皮肤”是指任何有老化倾向的表皮表面，并且还能够包括，不限于，面部和颈部、手、肘、上臂区域、膝盖、大腿、小腿、足、乳房、胸部、腹部、臀部和背部区域的表面。优选地，术语“皮肤”是指脸部和颈部的表面。

[0119] 根据一些实施方案，本发明提供了用于治疗老化的皮肤迹象和/或用于保护皮肤免于由紫外线(UV)照射引起的有害影响的皮肤护理治疗方法，所述方法包括：向待治疗的皮肤或皮肤附属物局部施用本发明的局部组合物，所述老化的皮肤征象诸如，但不限于，皱纹和皮肤萎缩。

[0120] 在一些实施方案中，提供了用于减慢人类皮肤的老化进程、减少人类皮肤的老化迹象或二者的方法，所述方法包括向患有皮肤老化的受试者的皮肤施用本发明的局部组合物。减慢人类皮肤的老化进程和减少人类皮肤的老化迹象可以包括，但不限于，改善肤色、弹性或紧缩性，减少皱纹、去除细纹、对抗皮肤皱纹的形成、提高皮肤紧实度、降低皮肤敏感性和过敏性或其任意组合。每种可能性代表本发明的单独实施方案。

[0121] 在另外的实施方案中，提供了用于保护和/或改善受试者皮肤状态和/或治疗需要其的受试者皮肤的瑕疵的方法，所述方法包括局部施用本发明的组合物至受试者的皮肤。在另外的实施方案中，提供了用于保护受试者皮肤免于与老化相关的皮肤状况的方法，所述方法包括施用本发明的局部组合物至所述受试者皮肤的步骤。根据一些实施方案，保护受试者皮肤涉及预防现存的与老化相关的皮肤状况的进一步恶化和/或阻止或减慢现存的与老化相关的皮肤状况或其症状。每种可能性代表本发明的单独实施方案。

[0122] 制剂

[0123] 根据一些实施方案，本发明的局部组合物被配制为包含至少一种FABAC作为活性试剂的美容组合物。根据一些实施方案，所述局部组合物被配制成用于局部施用至受试者的皮肤，优选至受到与老化相关的皮肤状况影响的皮肤区域，诸如，但不限于，起皱纹的皮肤或受光老化影响的皮肤。用于本文时，术语“局部组合物”是指被配制成用于局部施用至皮肤的组合物。

[0124] 本发明的组合物可以通过本领域熟知的方法制造，例如借助于常规的混合、溶解、粒化、包衣制造、磨细、乳化、包封、包埋或冻干方法。

[0125] 因此根据本发明使用的组合物可以使用促进将活性化合物加工成可以在药学上使用的制剂的一种或更多种生理学上可接受的载体(包括赋形剂和助剂)以常规方式配制。适当的制剂取决于选择的施用途径。

[0126] 根据一些实施方案，本发明的皮肤治疗组合物包含皮肤病学或美容上可接受的载体以充当用于至少一种FABAC的稀释剂、分散剂或媒介物，以当组合物施用至皮肤时促进其分散。除了水之外或除了水的媒介物可以包括液体或固体润肤剂、溶剂、润湿剂、增稠剂和粉末。每种可能性代表本发明的单独实施方案。

[0127] 根据一些实施方案，本发明的组合物可以配制成用于以水性或非水性溶液、洗剂、霜剂、凝胶、软膏、泡沫剂、摩丝、喷雾、乳液、微米乳液、贴片、粉末等的形式局部施用。每种可能性代表本发明的单独实施方案。制剂可以是油基、闭合的组合物，所述组合物包含，例如，白凡士林和或矿物质油。在一些实施方案中，所述组合物是不油腻的或者基本上不油腻的，并且能够是基于水的制剂。

[0128] 根据一些实施方案，提供了皮肤护理、美容或皮肤医学组合物，所述组合物包含至少一种本发明的FABAC或其美容、皮肤医学或药学上可接受的盐和酯，以及美容或皮肤医学上可接受的稀释剂、载体或赋形剂。每种可能性代表本发明的单独实施方案。

[0129] 根据一些实施方案，本发明的组合物包含至少一种FABAC。根据一些实施方案，本发明的组合物中的FABAC是以足以治疗、减轻、减慢或预防与老化相关的皮肤状况或其至少部分症状的有效量。每种可能性代表本发明的单独实施方案。根据一些实施方案，有效量是在皮肤细胞中不引起或引起不显著的细胞毒性的量。根据一些实施方案，本发明的组合物中的FABAC是以足以治疗、减弱、减慢皮肤皱纹和/或皮肤萎缩和/或光老化的进程或预防皮肤皱纹和/或皮肤萎缩和/或光老化的有效量。每种可能性代表本发明的单独实施方案。用于本文时，术语“有效量”和“有效浓度”可以相互交换使用。

[0130] 根据一些实施方案，组合物中FABAC的有效浓度在约0.01％至10％重量/体积之间，可能是在0.01％至5％重量/体积之间，或者在0.05％至2％重量/体积FABAC之间。每种可能性代表本发明的单独实施方案。根据典型的实施方案，组合物的有效性还取决于媒介物(vehicle)(即载体(carrier))和其与角质层的相互作用。

[0131] 根据一些实施方案，本发明的组合物中FABAC的重量/体积浓度为0.01％-2％，可能是0.1％-2％，或者是1％-2％。每种可能性代表本发明的单独实施方案。根据一些实施方案，本发明的组合物中FABAC的重量/体积浓度为至少0.01％。根据一些实施方案，本发明的组合物中的FABAC为Aramchol。根据一些实施方案，本发明的组合物中的FABAC为Steamchol。

[0132] 在一些实施方案中，本发明的组合物还包含至少一种除了本发明的FABAC之外的额外的活性成分。这类活性成分的非限制性实例包括，但不限于，以下种类的成分：植物提取物、油成分、增白剂、抗氧化剂、着色剂、愈合剂、抗老化剂、抗皱剂、舒缓试剂、抗自由基试剂、抗UV试剂(或UV吸收剂)、促进皮肤大分子合成或皮肤能量代谢的试剂(例如，皮肤营养品)、保湿剂、抗细菌剂、抗真菌剂、抗炎症剂、麻醉剂、调节皮肤分化、色素沉着或色素减褪的试剂、促进指甲或毛发生长的试剂、其组合等。每种可能性代表本发明的单独实施方案。

[0133] 根据一些实施方案，所述至少一种额外的活性成分选自由以下组成的组：金属螯合剂、药物制剂、增白剂、糖和其组合。每种可能性代表本发明的单独实施方案。

[0134] 根据一些实施方案，所述至少一种额外的活性成分选自由以下组成的组：金属螯合剂，包括但不限于依地酸二钠、依地酸三钠、柠檬酸钠、聚磷酸钠、偏磷酸钠和葡糖酸；药物制剂，包括但不限于咖啡因、单宁、维拉帕米，凝血酸及其衍生物、光甘草定(grabridin)、多种草药、维生素E、甘草酸及其衍生物和盐；增白剂，包括但不限于维生素C、抗坏血酸磷酸镁、抗坏血酸葡糖苷、熊果苷和曲酸；糖，包括但不限于葡萄糖、果糖、甘露糖、蔗糖和海藻糖。每种可能性代表本发明的单独实施方案。

[0135] 本发明的组合物可以以水性或水醇溶液、增溶系统、乳液、粉末、油、含水或无水凝

胶、浆液、泡沫剂、软膏剂、气雾剂、水-油两相系统、水-油-粉末三相系统等的形式存在。每种可能性代表本发明的单独实施方案。在一些实施方案中，所述组合物以选自由以下组成的组的形式施用：洁面乳、喷雾、药膏、软膏、洗剂、乳液、霜剂、凝胶、精华(驻颜柔肤液)、包裹的贴片(packs patches)和面膜。每种可能性代表本发明的单独实施方案。

[0136] 在其它实施方案中，诸如在化妆品的情况下，所述组合物可以与大范围类型的化妆品诸如粉底一起使用。在另外的实施方案中，所述组合物以浴室用品例如沐浴皂、洁面皂等的形式施用。根据一些实施方案，所述组合物可以配制成医药部外品。此外，在医药部外品的情况下，所述组合物可以配制成用于大范围的应用诸如多种软膏。本发明的抗老化剂的类型或形式不限于这些形式和类型。

[0137] 本发明的组合物的类型或形式不限于这些形式和类型。在任何情况下，本领域技术人员会确保，选择这些添加剂、其量和选择的剂型目的是不会有害于根据本发明的组合物的所需有利性质。

[0138] 根据另一个实施方案，所述组合物以选自由以下组成的组的形式配制为局部剂型：水溶液、霜剂、洗液、油包水或水包油乳液、多重乳液、硅酮乳液、微米乳液、纳米乳液、凝胶、泡沫和具有共溶剂的水溶液。每种可能性代表本发明的单独实施方案。

[0139] 公开的组合物的合适的局部制剂的非限制性实例如下：

[0140] 洗液和霜剂

[0141] 根据一些实施方案，本发明的局部组合物配制为洗液。洗液含有有效浓度的一种或更多种如本文所描述的FABAC化合物。本发明的组合物还可包含至少一种或更多种润肤剂，所述润肤剂能够起润滑剂和增稠剂之一或二者的作用。以组合物的重量计，润肤剂总计可组成从约0.1％至约50％，优选从约1％至约10％。可以使用本领域技术人员已知适用于应用至人类皮肤的任何润肤剂。这些包括，但不限于：烃油和蜡，包括矿物油、凡士林油、石蜡、矿蜡、地蜡、微晶蜡、聚乙烯和鲨烷；硅酮油；甘油三酯脂肪和油，包括衍生自植物、动物和海产来源的那些；包括荷荷芭油和牛油树籽油；乙酸甘油酯，诸如乙酰化单甘酯；乙氧基化甘油，诸如乙氧基化单硬脂酸甘油酯；脂肪酸，脂肪醇及其衍生物。每种可能性代表本发明的单独实施方案。其它合适的润肤剂包括羊毛脂和羊毛脂衍生物；多元醇和聚醚衍生物；多元醇酯；蜡酯；植物蜡；磷脂，诸如卵磷脂和衍生物；甾醇类，包括，但不限于，胆固醇和胆固醇脂肪酸酯；酰胺，诸如脂肪酸酰胺、乙氧基化脂肪酸酰胺和固体脂肪酸烷醇酰胺。每种可能性代表本发明的单独实施方案。

[0142] 洗液还可含有从约1％至约10％，更优选从2％至5％的乳化剂。每种可能性代表本发明的单独实施方案。乳化剂可以是非离子的、阴离子的、阳离子的或其混合物。每种可能性代表本发明的单独实施方案。本领域的技术人员已知适合的乳化剂。可以包含这类洗液和霜剂的其它常规成分。一种这样的添加剂是从组合物的1％至10％水平的增稠剂。合适的增稠剂的实例包括，但不限于：交联的聚羧乙烯聚合物、乙基纤维素、聚乙二醇、黄蓍胶、刺梧桐胶、黄原胶、膨润土和其它粘土、羟乙基纤维素和羟丙基纤维素。每种可能性代表本发明的单独实施方案。

[0143] 根据一些实施方案，洗液和霜剂通过将所有成分简单混合在一起配制。根据一些实施方案，将FABAC溶解、悬浮或者以其他方式均匀分散在混合物中。

[0144] 溶液和悬液

[0145] 根据一些实施方案，组合物配制成溶液。根据一些实施方案，组合物配制成悬液。根据一些实施方案，可以为水性或非水性的溶液配制成含有有效浓度的一种或更多种如本文所公开的FABAC化合物。

[0146] 可以用作溶液中的溶剂或溶剂系统的一部分的合适的有机物质如下：丙二醇、聚乙二醇、聚丙二醇、甘油、山梨醇酯、1,2,6-己三醇、乙醇、异丙醇、酒石酸二乙酯、丁二醇及其混合物。每种可能性代表本发明的单独实施方案。这样的溶剂系统还可含有水。

[0147] 根据一些实施方案，组合物配制成乳液。当本发明的组合物配制成乳液时，脂肪相相对于组合物的总重量的比例可以在以重量计从约5％至约80％的范围内，并且优选以重量计从约5％至约50％。每种可能性代表本发明的单独实施方案。掺入乳液形式的组合物中的油、乳化剂和共乳化剂选自美容或皮肤病学领域技术人员已知的那些。

[0148] 配制成溶液或悬液的组合物可以直接应用至皮肤，或者，可以配制成气雾剂并作为喷雾、泡沫剂或摩丝应用至皮肤。每种可能性代表本发明的单独实施方案。气雾剂组合物还可含有从约20％至80％，优选从30％至50％的合适的推进剂。每种可能性代表本发明的单独实施方案。这样的推进剂的实例可以为，但不限于，氯化的、氟化的和氯氟化的较低分子量的烃。一氧化二氮、二氧化碳、丁烷和丙烷也可以用作推进剂气体。这些推进剂如本领域所已知的量和在适合排出容器中的内含物的压力下使用。在加压的气雾剂的情况下，剂量单位可以通过提供阀门以递送计量的量确定。

[0149] 凝胶和固体

[0150] 根据一些实施方案，组合物配制成凝胶。凝胶组合物可以通过简单的混合合适的增稠剂至先前描述的溶液或悬液组合物配制。合适的增稠剂的实例之前已经关于洗液被描述。根据一些实施方案，形成凝胶的组合物含有有效浓度的至少一种FABAC化合物。根据一些实施方案，组合物还包含从约5％至约75％的如先前所描述的有机溶剂；从约0.5％至约20％的增稠剂，并且其余为水或其他水性载体。

[0151] 在其它实施方案中，本发明的配制成溶液、悬液洗液和凝胶的组合物配制成泡沫剂或摩丝用于皮肤应用。每种可能性代表本发明的单独实施方案。用于配制成泡沫剂或摩丝的相关载体在例如国际专利申请公布号WO2004/037225和美国专利号6,730,288中教导。

[0152] 根据一些实施方案，组合物配制成固体形式。固体形式的组合物可以配制成棍状样式的组合物，意欲用于应用至嘴唇或身体的其它部位。固体还可以含有从约50％至约98％的先前描述的润肤剂。该组合物可以含有从约1％至约20％的合适的增稠剂，并且，如果期望或需要的话，含有乳化剂和水或缓冲液。之前描述的关于洗液的增稠剂适合在固体形式的组合物中采用。本领域已知的提供需要的稳定性、香味或颜色、或其他需要的性质的其它成分至组合物中用于应用至皮肤，所述其它成分诸如防腐剂(包括对羟基苯甲酸甲酯或对羟基苯甲酸乙酯)、香料、染料或类似物。

[0153] 根据一些实施方案，本发明的组合物有效地预防和/或治疗与老化相关的皮肤紊乱，所述与老化相关的皮肤紊乱包括，但不限于，由于正常老化和光老化引起的皮肤老化引起的皮肤弹性降低、产生皱纹、皮肤变色、皮肤下垂以及其组合。每种可能性代表本发明的单独实施方案。

[0154] 添加剂

[0155] 根据一些实施方案，本发明的组合物还包含至少一种选自由以下组成的组的添加

剂:稀释剂、防腐剂、研磨剂、防结块剂、抗静电剂、粘合剂、缓冲液、分散剂、润肤剂、乳化剂、共乳化剂、润湿剂或润肤剂试剂、纤维材料、膜形成剂、固定剂、发泡剂、泡沫稳定剂、泡沫促进剂、胶凝剂、润滑剂、防潮剂、增塑剂、防腐剂、推进剂、稳定剂、表面活性剂、悬浮剂、增稠剂、螯合剂(chelating agent)、螯合剂(sequestering agent)、调节剂、润湿剂、液化剂及其组合。每种可能性代表本发明的单独实施方案。

[0156] 对于本发明范围内使用的任何试剂、试剂的组合和组合物,皮肤病学有效量或剂量能够从细胞培养物测定中最初估计。例如,可以在动物模型中配制一个剂量以达到包括如在细胞培养物中确定的$IC_{50}$(例如,实现最大抑制表皮细胞增殖的一半的测试化合物的浓度)的循环浓度范围。此类信息可用来更精确地确定在人类中的有用的剂量。

[0157] 添加剂的其它实例可以包括防晒剂和鞣剂。防晒剂可包括通常用于阻断紫外光的那些材料。示例性化合物是PABA的衍生物、肉桂酸酯和水杨酸酯。例如,能使用甲氧基肉桂酸辛酯和2-羟基-4-甲氧基苯甲酮(也称为氧苯酮)。甲氧基肉桂酸辛酯和2-羟基-4-甲氧基苯甲酮也被分别称为parsol MCX和苯甲酮-3。组合物中采用的防晒剂的量能够取决于需要的UV照射保护的程度变化。添加到组合物中的防晒剂必须与活性化合物相容,但是一般情况下组合物可以包含从约1%至约20%的防晒剂。精确的量会取决于选择的防晒剂和需要的防晒系数(SPF)变化。

[0158] 本发明的组合物还可包含抗氧化剂/自由基清除剂。包含抗氧化剂/自由基清除剂可以增加组合物的益处。抗氧化剂/自由基清除剂可以在约0.1%至约10%组合物总重量的浓度范围内添加到本发明的组合物中。抗氧化剂/自由基清除剂包括,但不限于,抗坏血酸(维生素C)及其盐,以及生育酚(维生素E)。

[0159] 某些维生素A代谢物,以及维生素A的激动剂、衍生物和前药,可以加入本发明的组合物中。在本发明的情况下有用的维生素A试剂的实例包括,但不限于,熟知的多种类视黄醇、视黄酸和视黄酸受体(RAR)激动剂。每种可能性代表本发明的单独实施方案。RAR激动剂可以包括,但不限于,色满类、硫代色满类、四氢喹啉、取代的四氢化萘、取代的二氢化萘、三取代的苯、芳香四环化合物、取代的环己烷、取代的环己烯、取代的环己二烯酸、取代的金刚烷、取代的二芳基、杂芳基化合物、其组合以及更多。每种可能性代表本发明的单独实施方案。

[0160] 维生素C或抗坏血酸是一种非常有效的抗氧化剂并且甚至可以抵抗UVA和UVB射线。研究表明,局部维生素E,特别是α生育酚(维生素E的一种形式)霜剂降低皮肤的粗糙度、面部细纹的长度以及皱纹深度。对小鼠的研究也已经报道了使用它会减少UV诱导的皮肤癌。维生素K也可对于治疗毛细管损伤有用。根据一些实施方案,组合物还包含以下的至少一种:维生素C、维生素E、维生素K和其任意组合。每种可能性代表本发明的单独实施方案。

[0161] 绿茶和红茶及其提取物适用于作为添加剂。可以作为添加剂用至组合物的其它植物来源的试剂包括,但不限于,石榴和大豆提取物、芦荟、姜、葡萄籽提取物和珊瑚提取物。

[0162] 调色底霜和粉底是合适的添加剂并且当瑕疵显著或者当需要更加均匀的肤色时可以是期望的。例如,绿色中和剂可以遮盖红色损伤;黄色可以掩盖黑眼圈和青肿;并且白色可以帮助最小化明显的皱纹。还可以包括液体和压粉粉底。其它可能的添加剂包括葡糖氨基葡聚糖,诸如透明质酸和类似物。

[0163] 产品包装和试剂盒

[0164] 使用时，小量的组合物，例如从约0.1ml至约100ml，从合适的容器或涂药器应用于暴露的皮肤区域，并且，如果需要的话，然后用手、手指或合适的装置将其延展到皮肤上和/或擦进皮肤。产品可以特别配制成用作手或面部处理。

[0165] 当配制时，组合物可以包装到合适的容器中以适合其粘度和消费者的预期用途。例如，洗液或霜剂可以包装到瓶子、推进剂驱动的气雾剂装置或装有适合手指操作的泵的容器中。当组合物是霜剂时，其能够简单地保存在不可变形的瓶子或挤压容器中，诸如管或有盖的罐子。因此，根据一些实施方案，本发明还提供了含有本文定义的皮肤医学或美容可接受的组合物的密闭的容器。容器的形状在本发明中没有限制，并且能够是管、泵分配器、压缩分配器、瓶子、喷雾器、小袋或类似物。

[0166] 在一些实施方案中，本发明的化合物或组合物在以即时施用形式的包装中提供。在其它实施方案中，化合物或组合物以浓缩形式在包装中提供，任选地与制造用于施用的最终溶液所需的稀释剂一起。在仍然其它实施方案中，产品包含固体形式的在本发明中有用的化合物，以及，任选地，含有对于在本发明中有用的化合物合适的溶剂或载体的单独容器。

[0167] 根据一些实施方案，本发明提供了包含本发明的组合物在第一合适的容器中的试剂盒。根据一些实施方案，本发明提供了包含至少一种本发明的FABAC在第一合适的容器中的试剂盒。根据一些实施方案，试剂盒还包含除了所述第一容器之外的至少一个容器。根据一些实施方案，所述至少一个其它容器包含至少一种稀释剂、赋形剂、载体、溶剂或添加剂。每种可能性代表本发明的单独实施方案。根据一些实施方案，本发明的组合物通过合并包含至少一种FABAC的第一容器的内含物与所述至少一个其它容器的内含物形成。根据一些实施方案，试剂盒还包含用于使用和/或制备本发明的组合物的说明书。每种可能性代表本发明的单独实施方案。

[0168] 在仍然其它实施方案中，以上包装/试剂盒包含其它组件，例如，用于稀释、混合和/或施用产品的说明书、其它容器、注射器、针等。每种可能性代表本发明的单独实施方案。其它这类包装/试剂盒组件对于本领域技术人员是容易明显的。

[0169] 以下实施例是为了更充分地说明本发明的一些实施方案而呈现。然而，其不应以任何方式被解释为限制本发明的宽范围。

## 实施例

[0170] 实施例1.细胞毒性测定

[0171] 研究综述

[0172] 全厚度表皮培养物(EFT-400,MatTek)用于确定响应于局部应用测试材料(Steamchol)的毒性。之前的生存力测定以40.0、13.3、4.4、1.5ug/mL的浓度和单独的媒介物(DMSO)进行;未观察到毒性。

[0173] 实施程序

[0174] 测试材料作为粉末提供。通过添加合适的量的粉末状材料至1mL的DMSO制备测试溶液。通过用100％DMSO系列稀释制备较低浓度。最终测试材料浓度和处理在下面列出：

[0175] • 2％Steamchol(20,000ug/mL)

[0176] • 1％Steamchol(10,000ug/mL)

[0177] • 0.1％Steamchol(1000ug/mL)

[0178] • 0.01％Steamchol(100ug/mL)

[0179] • 媒介物对照(100％DMSO)

[0180] • 未处理对照

[0181] 根据确保生存力的需要保持全厚度皮肤培养物(EFT-400);在应用测试材料之前在37℃和5％$CO_2$下持续24小时平衡培养物。使用无菌技术将测试材料应用到每个培养物的表面(10μL应用至每个培养物)。将两个培养物分配至每个处理组。两个EFT培养物充当未处理对照(在图2中也称为阴性对照),并且两个其它的EFT培养物充当阳性对照(100μL 1％Triton X-100)。

[0182] 用测试材料孵育24小时的时期之后,使用MTT[(3-4,5-二甲基噻唑-2-基)2,5-二苯基四唑溴化物]测定(试剂购买自MatTek)处理培养物用于细胞毒性分析。有生存力的组织将MTT转化为蓝色甲臜盐,所述蓝色甲臜盐能够通过在特定光波长下测量吸光度($A_{570}$)检测。通过比较测试培养物的$A_{570}$读数和未处理的对照培养物的$A_{570}$,使用下式计算生存力百分数:[处理的$A_{570}$/未处理的$A_{570}$]*100。

[0183] 结果

[0184] 测试的浓度都未对细胞生存力产生任何显著的影响(图2;表1)。所有测试的Steamchol的稀释物与未处理的对照相比的细胞生存力接近100％。这些结果表明FABAC相对于类视黄醇的有利效应,已经表明类视黄醇在0.6-3*$10^5$M的范围内对成纤维细胞和上皮细胞具有细胞毒性(Varani等Journal of Investigative Dermatology(1993)101,839-842),并增加上皮细胞的死亡(Ding等Invest Ophthalmol Vis Sci.2013Jun 26;54(6):4341-50)。

[0185] 表1.暴露于Steamchol后24小时的细胞生存力

[0186]

| 测试化合物 | 细胞生存力 |
|---|---|
| 未处理的细胞(阴性对照) | 100% |
| 阳性对照 | 6.8 % |
| DMSO 媒介物 | 101.0 % |
| 2% Steamchol | 93.89 % |
| 1% Steamchol | 96.88% |
| 0.1% Steamchol | 99.98 % |

[0187]

| | |
|---|---|
| 0.01% Steamchol | 100.41 % |

[0188] 实施例2.Steamchol或Aramchol对胆固醇流出以及ABCA1的mRNA和蛋白质水平的作用

[0189] 将Steamchol与人类皮肤成纤维细胞孵育20小时以测量在[$^3$H]胆固醇存在的情况下胆固醇的荷载。系列洗涤和添加含有胆固醇受体的流出物后,收集培养基并离心,并在存在和不存在类似的FABAC的情况下将细胞结合的胆固醇与流出的胆固醇作比较。该研究项目还包括ABCA1的mRNA的定量和ABCA1的直接测量。结果证实,与未处理的细胞相比,当流出发生在FABAC存在的情况下时,成纤维细胞中的胆固醇流出物显著增加,并且ABCA1蛋白浓

度增加了大约2倍。

[0190] 类似地，将细胞用[$^3$H]胆固醇预孵育，洗涤四次并且然后置于含有或不含有Aramchol的孵育培养基中20小时。孵育后，分别测量培养基中和细胞中的放射性。胆固醇流出百分数计算为培养基中的放射性除以总放射性(细胞+培养基)。结果证实，与未处理的细胞相比，当流出发生在Aramchol存在的情况下时，成纤维细胞中的胆固醇流出显著增加，并且ABCA1蛋白浓度增加了大约2倍。

[0191] 实施例3.Steamchol对皮肤培养物中基因表达的作用

[0192] 使用Steamchol处理全厚度体外皮肤培养物模型Epiderm FT(MatTek,MA)。将DMSO中的Steamchol(0.5％,5000ug/mL)应用到每个测试培养物的表面，应用24小时后收集细胞。用不含有Steamchol的DMSO类似地处理对照细胞。

[0193] 将组织收集在RNAlater中用于基因表达分析。使用以Taqman低密度阵列(TLDA)格式的验证的Taqman基因表达测定分析基因表达。分析调控皮肤中多个已知功能的94个基因，包括ABCA1和SCD1基因。使用验证的Taqman基因表达测定以96孔形式进行测试设置。每个基因测定两份。使用StatMiner软件v4.2(未成对t-检验，$p<0.05$，$N=4$)进行统计学分析以比较Steamchol组和DMSO对照组。

[0194] Steamchol对Epiderm FT培养物中基因表达的作用表明，组中94个选择的基因中，有2个基因KRT 1(角蛋白1)和KRT 10(角蛋白10)展示出当与用DMSO处理的细胞相比多于两倍的统计学上显著偏离(参见下表2)。未观察到ABCA1的mRNA水平的显著变化。如表2所示，Steamchol显著抑制角蛋白1和10的表达，角蛋白1和10是已知的角质形成细胞分化的标志物。

[0195] 表2.用FABAC处理之后角蛋白1和10基因表达的变化倍数。

[0196]

| 基 因 ID | 基因名称 | 变化倍数 |
|---|---|---|
| KRT10 | 角蛋白 10 | -2.60 |
| KRT1 | 角蛋白 1 | -2.49 |

[0197] 在角质形成细胞有丝分裂活跃的表皮的基底层中，它们表达角蛋白5和14。当细胞成为基底上层时，表达角蛋白1和10，同时关闭角蛋白5和14。随着细胞继续向外移动到颗粒层，它们变得被含有多种分化蛋白(Loricin、丝聚合蛋白原、内皮蛋白)的颗粒体充满。谷氨酰胺转移酶，一种将角蛋白和其它蛋白质交联到不能渗透的细胞包膜中的酶，也在该层中合成。最后，角质形成细胞死亡并且它们的死亡变平的鳞状形式构成角质层。

[0198] 对角质形成细胞分化的作用被认为是可逆的，并且从胆固醇消耗的恢复被认为发生在刺激物被去除时。不希望受到任何理论或作用机制的约束，FABAC增强ABCA1蛋白的转运活性，引起脂筏处胆固醇水平的消耗，从而减少角蛋白1和10的表达。

[0199] 本文第一次证实了脂肪酸-胆汁酸缀合物的活性类似于已知的被视黄酸诱导的效应。这两种化合物在棘层表皮水平和表皮细胞外基质水平上影响分化标志物。尽管视黄酸经由核受体的活化起作用，推测脂肪酸-胆汁酸缀合物在细胞膜的水平上引起组织结构的变化，这导致类似于视黄酸的那些的级联。在两个不同、不相关的研究中，证实脂肪酸-胆汁酸缀合物在人类表皮模型中激活ABCA1细胞转运子并且下调角蛋白1和10的表达。这两个活

性支持了角质形成细胞分化的减少，在表皮和真皮水平上引发补偿机制，并且最终导致组织恢复活力以及可能更强的细胞外基质基础，这可能导致更年轻的皮肤外观的临床表现。

[0200] 已经证实影响表皮皮肤层处的细胞分化是抗老化活性的根本机制。但是，在许多情况下，诸如在视黄酸的情况下，该活性伴随严重不良反应的“代价”一起发生，所述不良反应诸如致畸性、皮肤刺激性和更高的对阳光损害的敏感性。这可能是由于该效应在核受体水平上开始，并且从而是深远的并且恢复缓慢。本发明的FABAC的表明的作用机制提供了更温和但却有前景的生物化学途径，作为胆固醇消耗的结果其影响脂筏中脂质的组织结构。

[0201] 实施例4.FABAC对角质形成细胞分化的作用

[0202] 为了检测公开的FABAC对角质形成细胞的分化的作用，使用高度分化的全厚度体外皮肤培养物模型Epiderm FT(MatTek,MA)。用在DMSO中的三种不同浓度的Steamchol和在DMSO中的三种不同浓度的Aramchol处理皮肤培养物，重复两次。测试的浓度之一是0.5％(5000μg/mL)，其在降低KRT1和KRT10的基因表达中有效。使用两个未处理的皮肤培养物和两个用单独媒介物(DMSO)处理的培养物作为阴性对照。使用视黄酸处理的两个皮肤培养物作为阳性对照。

[0203] 组合物应用至每个测试培养物表面24小时后收集细胞。从部分细胞中提取蛋白质并使用对角蛋白1、角蛋白10、SCD1和ABCA-1特异的第一抗体对所述蛋白质进行蛋白印迹和ELISA分析。固定另一部分细胞并使用对角蛋白1、角蛋白10、SCD1和ABCA-1特异的第一抗体进行免疫组织化学染色。

[0204] 角蛋白1和/或角蛋白10表达的下调指示角质形成细胞分化的降低。

[0205] 实施例5.FABAC对角质形成细胞增殖和细胞外基质(ECM)蛋白表达的作用

[0206] 为了检测公开的FABAC对角质形成细胞增殖和ECM蛋白表达的作用，使用高度分化的全厚度体外皮肤培养物模型Epiderm FT(MatTek,MA)。

[0207] 用在DMSO中的三种不同浓度的Steamchol和三种不同浓度的Aramchol处理皮肤培养物，重复两次。测试的浓度之一是0.5％(5000μg/mL)，其在降低KRT1和KRT10的基因表达中有效。使用两个未处理的皮肤培养物和两个用单独媒介物(DMSO)处理的培养物作为阴性对照。使用视黄酸处理的两个皮肤培养物作为阳性对照。

[0208] 组合物应用至每个测试培养物表面24小时后收集细胞。使用如上文实施例1中使用的MTT测定，使用一些细胞用于测定细胞增殖。从部分细胞中提取蛋白质，并使用对弹性蛋白、前胶原和基质金属蛋白酶1(MMP-1)特异的第一抗体对所述蛋白质进行ELISA分析。固定另一部分细胞并使用对弹性蛋白、前胶原和基质金属蛋白酶1(MMP-1)特异的第一抗体进行免疫组织化学染色。

[0209] 具体实施方案的以上描述将如此完全地揭示本发明的一般性质，以致其他人可通过应用现有的知识，容易地为各种应用修改和/或调整此类具体实施方案而不需要过度实验和不偏离一般概念，且因此，此类调整和修改应当并且预期被包含在公开的实施方案的等价物的含义和范围内。应理解的是，本文采用的措辞或术语是为了描述而非限制的目的。用于进行各种公开的功能的手段、材料和步骤可采取多种替代形式而不偏离本发明。

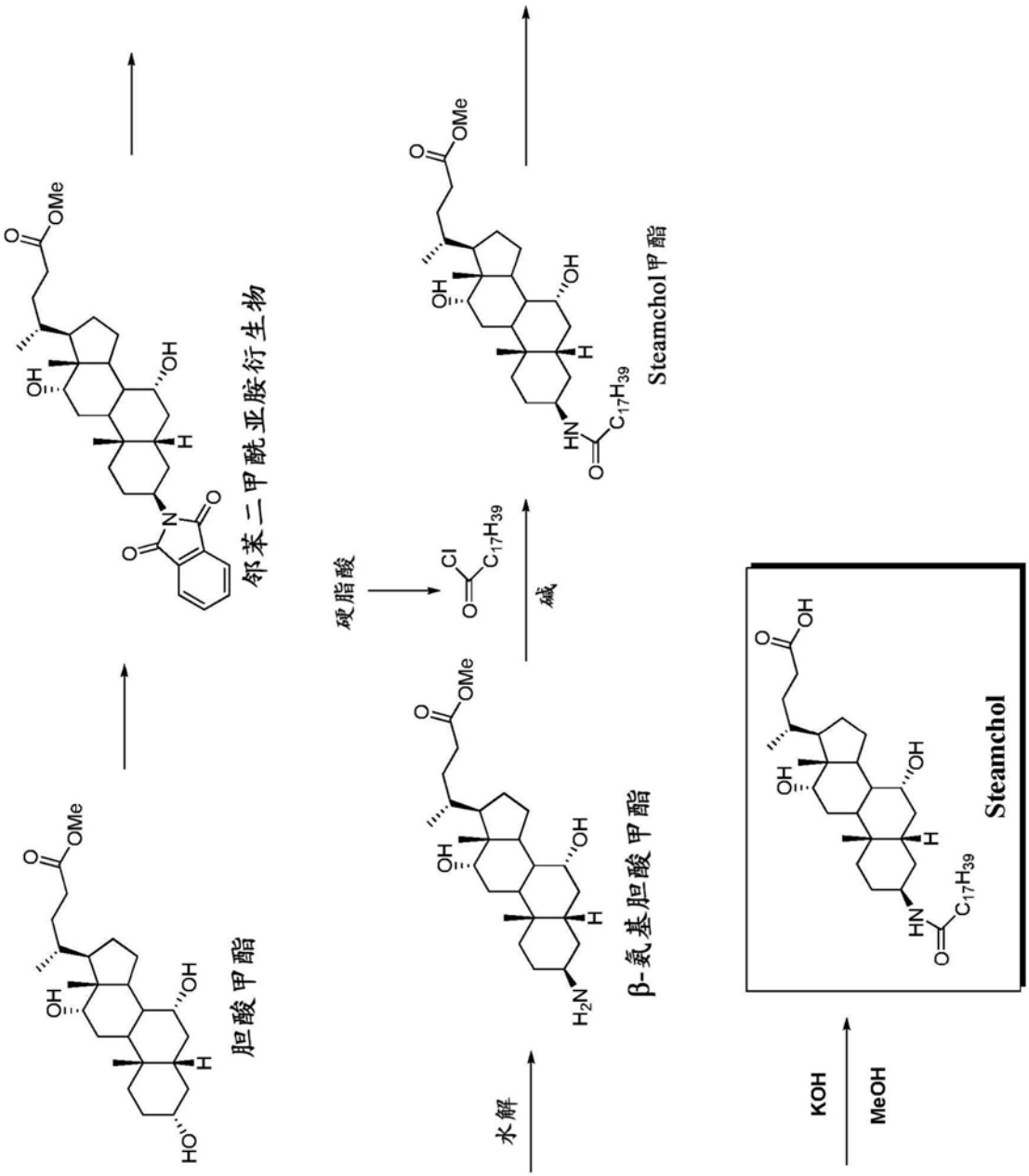

胆酸甲酯
邻苯二甲酰亚胺衍生物
硬脂酸
碱
水解
β-氨基胆酸甲酯
Steamchol甲酯
KOH
MeOH
Steamchol

图1

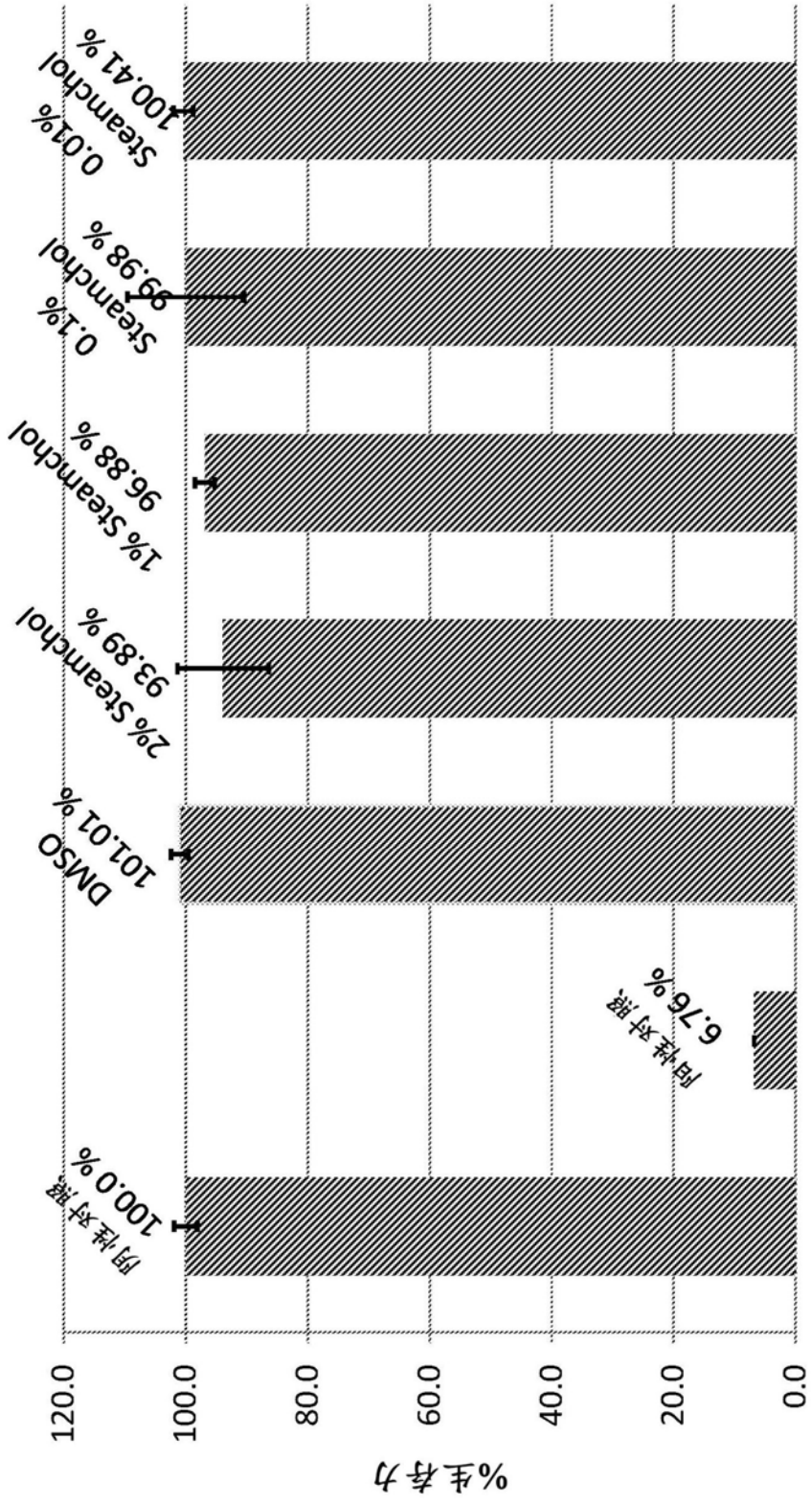

%生存力
120.0
100.0
80.0
60.0
40.0
20.0
0.0
阴性对照
100.0 %
阳性对照
6.76 %
DMSO
101.01 %
2% Steamchol
93.89 %
1% Steamchol
96.88 %
0.1% Steamchol
99.98 %
0.01% Steamchol
100.41 %

图2