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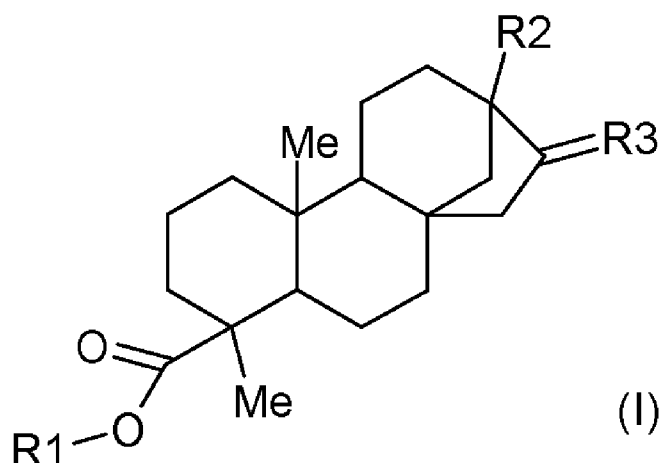
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(54) Title: TOPICAL USE OF STEVIOL OR DERIVATIVES IN HAIR CARE



(57) Abstract: The present invention relates to the use of steviol and/or isosteviol, or a salt, ester, a diester, or an ether thereof as depicted in formula (I), wherein R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups, R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ alkyl group, -OH group, a -O-C(O)-C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group, R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl), wherein the enhancement of the appearance of hair is selected from the group consisting of: restoring hair color and delaying the onset of greyness in hair, lessening hair loss, restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and thinning, maintaining of the natural hair color, increasing hair shininess, glossiness or volume.



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Topical Use of Steviol or Derivatives in Hair Care

The present invention relates to the use of steviol and/or isosteviol, and/ or a salt, an ester, a diester, or an ether thereof for application to skin, skin having hair, scalp, hair of a human, or fur of an animal for the overall enhancement of the hair, particularly for restoring hair color and delaying the onset of greyness in hair, lessening hair loss, restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and thinning, maintaining of the natural hair color, increasing hair shininess, glossiness or volume. This invention also relates to a method for stimulating hair growth, and/or preventing the graying of hair, or restoring or maintaining the natural hair color.

BACKGROUND OF THE INVENTION

The hair is composed of a protein called keratin. The hair itself is arranged in three layers, an outer cuticle, middle cortex and central medulla. If the hair is colored, it is due to the presence of pigments – either eumelanin (black or brown) or pheomelanin (red or yellow). If these pigments are lacking, the hair is white. Canities is the term given to grey hair, it is an illusion created by the mixture of white and colored hairs. Hair grows from a follicle. The walls of the follicle form the outer root sheath of the hair. The lower part of the follicle widens out to form the hair bulb that contains the germinal matrix, the source of hair growth. Dermal tissue projects into the follicle base to form the dermal papilla, and this has a network of capillary blood vessels to supply oxygen, energy, and the amino-acids needed for growth.

Correcting the effects of aging as far as possible is a preoccupation of ever-increasing importance.

It therefore remains a long awaited need in the hair care industry to prevent hair loss, to stimulate hair growth, to prevent age related graying of the hair, to prevent loss of natural coloration of the hair, and to promote restoration of the natural hair color.

Stevia extracts have been described in (JP 11193219 A) as having hair growing and regeneration effect, however, steviol as well as phloretin, which are known inhibitors of cellular glucose transport have been claimed to also inhibit hair growth when applied topically (EP 0 711 541 A1).

DETAILED DESCRIPTION OF THE INVENTION

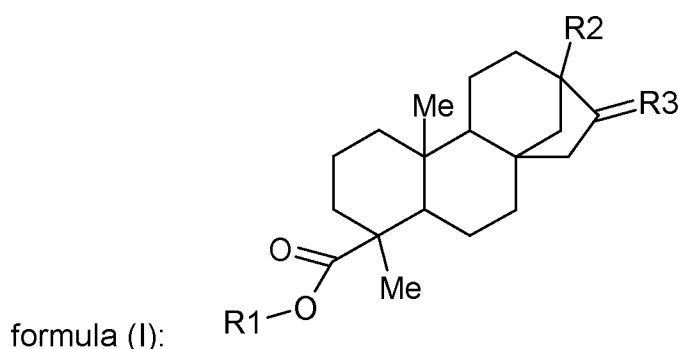
The inventors of the present application now surprisingly found that steviol and/or isosteviol and derivatives as described below with formula (I) have a great potential for use in topical hair care applications for stimulating hair growth, preventing hair loss, and enhancing the overall appearance, eg. thickness, volume, shininess and glossiness of hair of an animal including human. Thus, one aspect of this invention is a method of enhancing an animal's, including a human's, hair comprising administering a topically applied composition comprising steviol and/or isosteviol, an ester, a diester, or an ether derivative for a time sufficient and in an amount effective to enhance the overall appearance, eg. thickness, volume, shininess and glossiness of hair in an animal including human, and observing or appreciating the result.

Another embodiment of this invention is the use of steviol and/or isosteviol, an ester, a diester, or an ether derivative thereof in the manufacture of topical or cosmetic composition which stimulates hair growth and enhances the overall appearance of hair of an animal including human, eg. thickness, volume, shininess and glossiness.

In a further embodiment, the compound of formula (I) below is combined with at

least one additional active substance selected from the group consisting of: anti-oxidants, light screening agents, colorants, and biological actives.

Therefore, the present invention provides the topical use of a compound of formula (I) or a salt thereof,



wherein

R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,

R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group, and

R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),

for enhancement of the appearance of hair of an animal including human,

wherein the enhancement of the appearance of hair is selected from the group consisting of: restoring hair color and delaying the onset of greyness in hair, lessening hair loss, restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and thinning, maintaining of the natural hair color, increasing hair shininess, glossiness or volume.

It is to be understood that formula (I) as depicted above encompasses all possible stereoisomers.

In the above definition of compounds of formula (I), the term alkoxy refers to methoxy- and ethoxy- groups. Preferably, the term alkyl amino and dialkylamino refers to methylamino-, dimethylamino-, ethylamine- or diethylamino- groups.

5 In the above definition of compounds of formula (I), preferred R1 groups are hydrogen, methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, isobutyl, pentyl, neopentyl, hexyl, 2-ethyl-hexyl, heptyl, and octyl. Independently of R1, preferred R2 groups are, methyl, ethyl, propyl, isopropyl, butyl, sec. butyl, isobutyl, pentyl, neopentyl, hexyl, 2-ethyl-hexyl, heptyl, octyl, hydroxy, methyloxy, ethyloxy, propyloxy, isopropoxyloxy, butyloxy, sec. butyloxy, isobutyloxy, pentyloxy, neopentyloxy, hexyloxy, 2-ethyl-hexyloxy, heptyloxy, octyloxy, -O-C(O) methyl, -O-C(O) ethyl, -O-C(O) propyl, -O-C(O) isopropyl, -O-C(O) butyl, -O-C(O) sec. butyl, -O-C(O) isobutyl, -O-C(O) pentyl, -O-C(O) neopentyl, -O-C(O) hexyl, -O-C(O) 2-ethyl-hexyl, -O-C(O) heptyl, -O-C(O) octyl. -COO methyl, -COO ethyl, -COO propyl, -COO isopropyl, -COO butyl, -COO sec. butyl, -COO isobutyl, -COO pentyl, -COO neopentyl, -COO hexyl, -COO 2-ethyl-hexyl, -COO heptyl, and -COO octyl. Independently of R1 and R2, preferred R3 groups are oxygen, CH₂, CH-CH₃, CH-C₂H₅, CH-C₃H₇, CH-C₄H₉. It is well understood that any lower alkyl group containing three or more carbon atoms can be either straight chain or branched chain.

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In a preferred embodiment, R1 is selected from hydrogen and a saturated, straight C₁-C₅ alkyl group, preferred R2 groups are selected from hydroxy, methyl, ethyl, propyl, methyloxy, ethyloxy, propyloxy, -O-CO-CH₃, -O-CO-C₂H₅, and -O-CO-C₃H₇, and preferred R3 groups are selected from CH₂, CH-CH₃, and O.

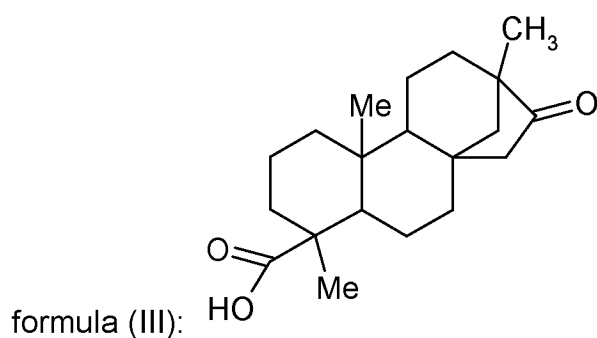
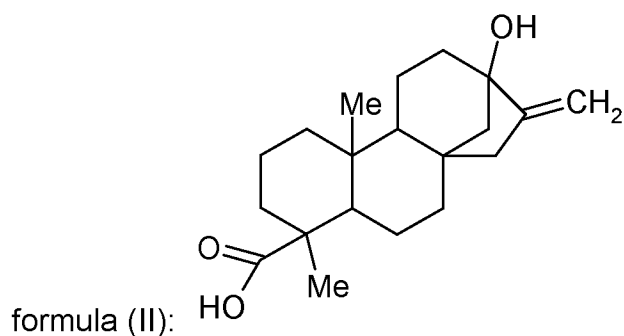
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In another preferred embodiment, R1 is selected from hydrogen or a saturated, straight C₁-C₃ alkyl group, R2 is selected from hydroxy, methyl, methyloxy, ethyloxy, and propyloxy, and preferred R3 groups are selected from CH₂, CH-CH₃, and O.

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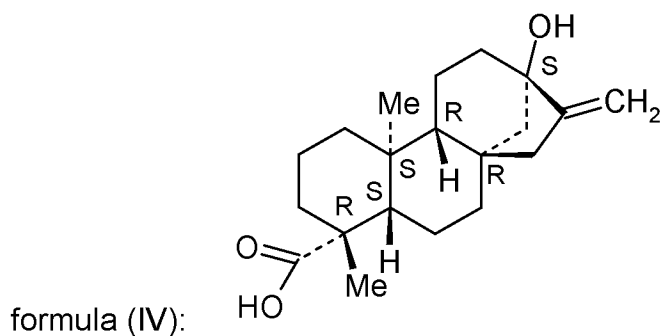
In a further preferred embodiment, R1 is hydrogen or a saturated, straight or branched C₁-C₃ alkyl group, R2 is hydroxy or a methyl group, and R3 is a CH₂ or O group.

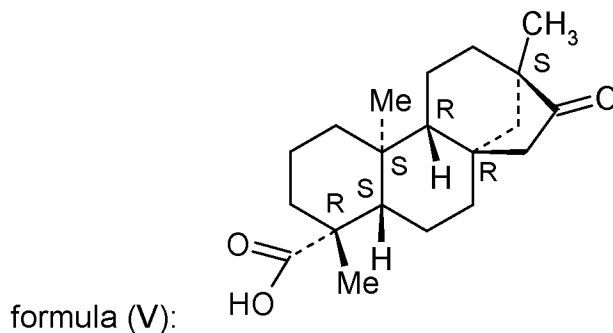
In the most preferred embodiment, R1 is hydrogen, R2 is hydroxy, and R3 is CH₂, or R2 is methyl and R3 is O corresponding to the compound of formula (II) steviol (CAS number: 471-80-7) and the compound of formula (III) Isosteviol (CAS number 27975-19-5).



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Even more preferred compounds according to the present invention are steviol and isosteviol with the stereochemistry as depicted in formula (IV) and formula (V).





Most preferred compound for all embodiments of the present invention is steviol.

- 5 The salts of steviol, steviol derivatives and/or isosteviol, and isosteviol derivatives may be formed by any cosmetically acceptable cation which means any metal cation as well as any organic cation that is not toxic to the skin and/or does not cause allergic reactions. Examples of such cations are ammonium salts and alkyl ammonium salts, alkali cations such as sodium and potassium ions and alkaline
10 earth metal cations such as calcium and magnesium ions.

Steviol, isosteviol, salts and esters thereof are particularly preferred as they can then be easily transported to hair follicles.

- 15 The compounds used according to the present invention can either be sourced from chemical suppliers like e.g. Sigma or can be prepared by chemical synthesis according to known methods to a person skilled in the art such as e.g.: by deglycosylation of the respective glucosides (e.g.: stevioside or rebaudiosides A and C) and, in case of the derivatives or salts, further derivatisation (esterification/ amida-
20 tion, etherification/ salt formation). Such methods are well known in the art and are e.g.: disclosed in Yingyong Huaxue (1993), 10(4), 35-8: Synthesis of steviol derivatives and their bioactivity, Russian Journal of General Chemistry (2009), 79(10), 2197-2200: O-Alkylation of diterpenoid steviol in the system KOH-DMSO, or Tao et al. Synthesis and bioactivity of Isosteviol derivatives; Chinese Chemical
25 Letters (2005) 16: 1441-1444.

The compositions according to the invention are especially attractive, since many people, including animal owners and handlers, have a special interest in cosmetic treatments considered as "natural" with mild effects and without major side effects.

As used throughout the specification and claims, the following definitions apply:

5 The term "effective amount" means an amount necessary to obtain a desired physiological effect.

The term "Hair" as used according to the invention refers to both, hair of a human being as well as animal fur.

10 The term 'hair of an animal including human' relates to all parts of the body of an animal as well as of a human having hair such as the fur of animals as well as the eyelashes, the eyebrows, the beard or the scalp hair of a human. Most preferably the term relates to the hair on the scalp of humans (male or female of any age).

15 The term "skin having hair" relates to all parts of the skin of a human having hair such as in particular the scalp and the face (eyelashes, the eyebrows, beard). Most preferably the topical compositions are applied to the scalp of humans (male or female of any age).

20 "Topical composition" as used herein denotes any composition suitable for the topical application to mammalian keratinous tissue such as skin having hair, particularly to the human scalp or to animal skin having fur.

25 "Preventing" as used herein is not intended to mean that the event will never occur, but means delaying the onset of the condition or event, and/or lessening the severity of the condition or event when it does occur.

"Chronic administration" is meant to convey that administration of the active ingredient regularly occurs over an extended period of time, for example once or twice
30 per day for a time of at least about two weeks, preferably for at least one month, and more preferably at least two months. Alternatively, the regular administration can be every two days, every three days, or once per week or twice per week.

"Extended period of time" means substantially daily for a period of time of at least about two weeks, preferably at least about a month, and even more preferably for at least about two months.

- 5 "Observing" or "appreciating" may be done by either the individual who administers or applies the active ingredient topically, or may be done by a third party. The post-administration condition may be compared with the pre-administration condition and analyzed either using a standard test, or by subjective analysis.
- 10 "Enhanced Appearance" means that the hair has improved at least one of the following qualities:
- Color (i.e. retention/restoration of natural color vs. greyness),
 - Hair alopecia (i.e. hair is retained, hair loss is stopped or slowed; or hair is re-growing),
 - 15 ○ Hair thickness (progression of hair thinning is slowed, halted, or reversed),
 - Skin wounds/injuries are healing or healed,
 - Hair shininess or glossiness (hair appears less dull and more shiny/glossy),
 - Hair has more volume.
- 20 In a preferred embodiment, the invention provides the use of compounds of formula (I) according to the present invention for the enhancement of the appearance of hair, wherein the enhancement of the appearance of hair is selected from the group consisting of: lessening hair loss, restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-
- 25 associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and thinning. More preferably, the enhancement of the appearance of hair is selected from the group consisting of: restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, and counteracting age-associated hair thinning.
- 30 Compounds of formula (I) according to the present invention may either be used in therapeutic or non-therapeutic topical applications.

In a preferred embodiment, the use according to the present invention is non therapeutic.

In a further embodiment, the compound of formula (I) is combined with at least one additional active substance selected from the group consisting of antioxidants, light screening agents, colorants, and biological actives.

Antioxidants

Based on the invention all known antioxidants usually formulated into hair care compositions can be used. Especially preferred are antioxidants chosen from the group consisting of amino acids (e.g. glycine, histidine, tyrosine, tryptophan) and their derivatives, imidazole (e.g. urocanic acid) and derivatives, peptides such as D,L-carnosine, D-carnosine, L-carnosine and derivatives (e.g. anserine), carotenoids, carotenes (e.g. α -carotene, β -carotene, lycopene) and derivatives, chlorogenic acid and derivatives, lipoic acid and derivatives (e.g. dihydrolipoic acid), aurothioglucose, propylthiouracil and other thiols (e.g. thioredoxine, glutathione, cystine, cystamine and its glycosyl-, N-acetyl-, methyl-, ethyl-, propyl-, amyl-, butyl- and lauryl-, palmitoyl-, oleyl-, γ -linoleyl-, cholesteryl- and glycerylester) and the salts thereof, dilaurylthiodipropionate, distearylthiodipropionate, thiodipropionic acid and its derivatives (ester, ether, peptides, lipids, nucleotides, nucleosides and salts) as well as sulfoximine compounds (such as buthioninsulfoximine, homocysteinesulfoximine, buthioninsulfone, penta-, hexa-, heptathioninsulfoximine) in very low compatible doses (e.g. pmol to μ mol/ kg), additionally (metal)-chelators (such as α -hydroxyfatty acids (citric acid, lactic acid, malic acid), palmitic-, phytinic acid, , lactoferrin), β -hydroxyacids, huminic acid, gallic acid, gallic extracts, bilirubin, biliverdin, EDTA, EGTA and its derivatives, unsaturated fatty acids and their derivatives (such as γ -linoleic acid, linolic acid, oleic acid), folic acid and its derivatives, ubiquinone and ubiquinol and their derivatives, tocopherol and derivatives (such as vitamin-E-acetate), mixtures of nat. vitamin E, vitamin A and derivatives (vitamin-A-palmitate and -acetate) as well as coniferylbenzoate, rutinic acid and derivatives, α -glycosylrutin, ferulic acid, furfurylidene-glucitol, carnosine, butylhydroxytoluene, butylhydroxyanisole, trihydroxybutyrophenone, urea and its derivatives, mannose and derivatives, zinc and

derivatives (e.g. ZnO, ZnSO₄), selen and derivatives (e.g. selenomethionin), stilbenes and derivatives (such as stilbenoxide, trans-stilbenoxide) and suitable derivatives (salts, esters, ethers, sugars, nucleotides, nucleosides, peptides and lipids) of the named active ingredients, or enzymes such as superoxide dismutase, catalase or similar, or activators of such enzymes. One or more preservatives/antioxidants may be present in an amount of at least 0.01 wt.-% of the total weight of the composition. Preferably about 0.01 to about 10 wt.-% of the total weight of the composition of the present invention is present. Most preferred, one or more preservatives/ antioxidants are present in an amount about 0.1 to about 1 wt. -%.

Light screening agents

Light screening agents are advantageously selected from UV-A, UV-B and/or broadband filters. Examples of UV-B or broad spectrum screening agents, i.e. substances having absorption maximums between about 290 and 340 nm may be organic or inorganic compounds. Organic UV-B or broadband screening agents are e.g. acrylates such as 2-ethylhexyl 2-cyano-3,3-diphenylacrylate (octocrylene, PARSOL[®] 340), ethyl 2-cyano-3,3-diphenylacrylate and the like; camphor derivatives such as 4-methyl benzylidene camphor (PARSOL[®] 5000), 3-benzylidene camphor, camphor benzalkonium methosulfate, polyacrylamidomethyl benzylidene camphor, sulfo benzylidene camphor, sulphomethyl benzylidene camphor, therephthalidene dicamphor sulfonic acid and the like; Cinnamate derivatives such as ethylhexyl methoxycinnamate (PARSOL[®] MCX), ethoxyethyl methoxycinnamate, diethanolamine methoxycinnamate (PARSOL[®] Hydro), isoamyl methoxycinnamate and the like as well as cinnamic acid derivatives bond to siloxanes; p-aminobenzoic acid derivatives, such as p-aminobenzoic acid, 2-ethylhexyl p-dimethylaminobenzoate, N-oxypropylenated ethyl p-aminobenzoate, glyceryl p-aminobenzoate; benzophenones such as benzophenone-3, benzophenone-4,2,2',4,4'-tetrahydroxy-benzophenone, 2,2'-dihydroxy-4,4'-dimethoxybenzophenone and the like; esters of benzalmalonic acid such as di-(2-ethylhexyl) 4-methoxybenzalmalonate; esters of 2-(4-ethoxy-anilinomethylene)propandioic acid such as 2-(4-ethoxy anilinomethylene) propandioic acid diethyl ester as described in the European Patent Publication EP 0 895 776; organosiloxane compounds

containing benzmalonate groups as described in the European Patent Publications EP 0 358 584 B1, EP 0 538 431 B1 and EP 0 709 080 A1 such as polysilicone-15 (PARSOL® SLX); drometrizole trisiloxane (Mexoryl XL); imidazole derivatives such as e.g. 2-phenyl benzimidazole sulfonic acid and its salts (PARSOL® HS). Salts of
5 2-phenyl benzimidazole sulfonic acid are e.g. alkali salts such as sodium- or potassium salts, ammonium salts, morpholine salts, salts of prim., sec. and tert. amines like monoethanol amine salts, diethanol amine salts and the like; salicylate derivatives such as isopropylbenzyl salicylate, benzyl salicylate, butyl salicylate, ethylhexyl salicylate (PARSOL® EHS, NEO Heliopan OS), isooctyl salicylate or
10 homomenthyl salicylate (homosalate, PARSOL® HMS, NEO Heliopan OS) and the like; triazine derivatives such as ethylhexyl triazone (Uvinul T-150), diethylhexyl butamido triazone (Uvasorb HEB). Encapsulated UV-filters such as encapsulated ethylhexyl methoxycinnamate (Eusolex UV-pearls) or microcapsules loaded with UV-filters as e.g. disclosed in EP 1 471 995 and the like. Inorganic compounds are
15 pigments such as microparticulated TiO₂, ZnO and the like. The term "microparticulated" refers to a particle size from about 5 nm to about 200 nm, particularly from about 15 nm to about 100 nm. The TiO₂ particles may also be coated by metal oxides such as e.g. aluminum or zirconium oxides or by organic coatings such as e.g. polyols, methicone, aluminum stearate, alkyl silane. Such coatings
20 are well known in the art.

Examples of broad spectrum or UV A screening agents i.e. substances having absorption maximums between about 320 and 400 nm may be organic or inorganic compounds e.g. dibenzoylmethane derivatives such as 4-tert. butyl-4'-
25 methoxydibenzoyl-methane (PARSOL® 1789), dimethoxydibenzoylmethane, isopropylidibenzoylmethane and the like; benzotriazole derivatives such as 2,2'-methylene-bis-(6-(2H-benzotriazole-2-yl)-4-(1,1,3,3,-tetramethylbutyl)-phenol (TINOSORB M) and the like; bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S) and the like; phenylene-1,4-bis-benzimidazolsulfonic acids or salts such
30 as 2,2-(1,4-phenylene)bis-(1H-benzimidazol-4,6-disulfonic acid) (Neoheliopan AP); amino substituted hydroxybenzophenones such as 2-(4-diethylamino-2-hydroxybenzoyl)-benzoic acid hexylester (Uvinul A plus) as described in EP 1 046 391; Ionic UV-A filters as described in WO 2005/080341 A1; pigments such as microparticulated ZnO or TiO₂ and the like. The term "microparticulated" refers to a

particle size from about 5 nm to about 200 nm, particularly from about 15 nm to about 100 nm. The particles may also be coated by other metal oxides such as e.g. aluminum or zirconium oxides or by organic coatings such as e.g. polyols, methicone, aluminum stearate, alkyl silane. Such coatings are well known in the art.

- 5 As dibenzoylmethane derivatives have limited photostability it may be desirable to photostabilize these UV-A screening agents. Thus, the term "conventional UV-A screening agent" also refers to dibenzoylmethane derivatives such as e.g. PARSOL® 1789 stabilized by, e.g. 3,3-Diphenylacrylate derivatives as described in EP 0 514 491 B1 and EP 0 780 119 A1; Benzylidene camphor derivatives as de-
- 10 scribed in the US Patent No. 5,605,680; Organosiloxanes containing benzmalonate groups as described in the EP 0 358 584 B1, EP 0 538 431 B1 and EP 0 709 080 A1.

Colorants

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Based on the invention, all colorants usually formulated into hair care compositions which have an absorption in the visible light of electromagnetic radiation (400 nm to 800 nm) can be used. The absorption is often caused by the following chromophores: Azo- (mono-, di-, tris-, or poly-)stilbene-, carotenoide-, diaryl-

20 methane-, triarylmethane-, xanthene-, acridine-, quinoline-, methine- (also polymethine-) thiazol-, indamine-, indophenol-, azin-, oxazine-, thiazine-, anthraquinone-, indigo-, phthalocyanin and further synthetic, natural and/or inorganic chromophores.

- 25 FD & C and D & C which can be used in hair care compositions according to the invention are e.g. curcumin, riboflavin, lactoflavin, tartrazine, quinoline yellow, cochénille, azorubin, amaranth, ponceau 4R, erythrosine, red 2G, indigotin, chlorophyll, chlorophyllin, caramel, carbo medicinalis, carotenoids, carotin, bixin, norbixin, annatto, orlean, capsanthin, capsorubin, lycopin, xanthophyll, flavoxanthin,
- 30 lutein, kryptoaxanthin, rubixanthin, violaxanthin, rhodoxanthin, canthaxanthin, betanin, anthocyanins without being limited thereto. Examples of dyes are e.g. inorganic pigments such as iron oxide (iron oxide red, iron oxide yellow, iron oxide black etc.) ultramarines, chromium oxide green or carbon black. Other colorants and dyes which can be used in the compositions according to the invention com-

prise natural or synthetic organic pigments, disperse dyes which may be solubilized in solvents like direct hair dyes of the HC type, for example HC red No. 3, HC Blue No. 2 and all other hair dyes listed in International Cosmetic Ingredient Dictionary Handbook, 11th edition, 2006) or the dispersion dyes listed in Color Index International Society of Dyers and Colorist, color varnishes (insoluble salts of soluble dyes, like many Ca-, Ba- or Al-salts of anionic dyes), soluble anionic or cationic dyes such as acid dyes (anionic), basic dyes (cationic), direct dyes, reactive dyes or solvent dyes, fluorescent dyes, fluorescein and isothiocyanates.

10 Biological actives.

Biological actives are advantageously selected from general activators of melanogenesis like tyrosinase activators, peptide hormones, cAMP-activators (caffeine) and neurotrophins.

15

Preferred tyrosinase activators are any substance which increases tyrosinase expression or enzyme activity, like e.g. glycyrrhizin from the root of licorice.

20

Peptide hormones belonging to the group of melanocortins are the preferred peptide hormones including ACTH, alpha-MSH, beta-MSH and gamma-MSH; these peptides are all cleavage products of a large precursor peptide called pro-opiomelanocortin (POMC). Alpha-MSH is the most important melanocortin for pigmentation. The melanocyte-stimulating hormones (collectively referred to as MSH or intermedins) are a class of peptide hormones that in nature are produced by cells in the intermediate lobe of the pituitary gland. They stimulate the production and release of melanin (melanogenesis) by melanocytes in skin and hair. Therefore, they will be advantageously combined with the compounds of the present invention.

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30

In yet another embodiment, the compounds of the present invention are used topically on hair, wherein hair is a mammal's fur. Preferred mammals are horses, dogs and cats.

In a further embodiment, the compound of formula (I) is used in an effective

amount selected in the range of 0.00001 to 20 wt.-%, preferably, 0.0001 to 5 wt.-%, more preferably, 0.001 to 0.5 wt.-% based on the total weight of the topical composition.

- 5 According to the present invention, the compound of formula (I) is used in a topical composition in an amount in the range of 0.00001 to 20 wt.-%, preferably, 0.0001 to 5 wt.-%, more preferably, 0.001 to 0.5 wt.-% based on the total weight of the topical composition.
- 10 The present invention also relates to the use of compounds of formula (I) for increasing the total number of melanocytes in hair follicles and/or for increasing the differentiation and migration of melanocytes from the hair sheath to the hair matrix and/or increasing proliferation of hair cells, and/or increasing the production of melanin, and/or for lengthening hair growth phase (anagen) and/or shortening hair
- 15 resting phase (telogen). Number of melanocytes in the hair follicle can be evaluated by standard methods e.g. immunohistochemical staining of the melanocytes with the pan-melanocyte marker NKI-beteb following by counting the NKI-beteb+ cells.
- 20 Differentiation and migration of melanocytes from the hair sheath to the hair matrix can be measured by immunohistochemical staining of c-kit+ melanocytes in the hair follicle, and by assessing their distribution within the hair follicle.

In another embodiment, the invention further provides the use of a compound of

25 formula (I) according to the present invention, in combination with the use of other ingredients which are conventionally used in topical compositions, such as in particular hair care compositions, generally enhance the appearance of hair, eg. thickness, volume, shininess and glossiness, to prevent the graying of hair and/or restore or maintain the natural hair color, such as 5,6-dihydroxyindoline HBr, 5,6-

30 dihydroxyindoline HBr in combination with 2-methylresorcinol and/or arginine.

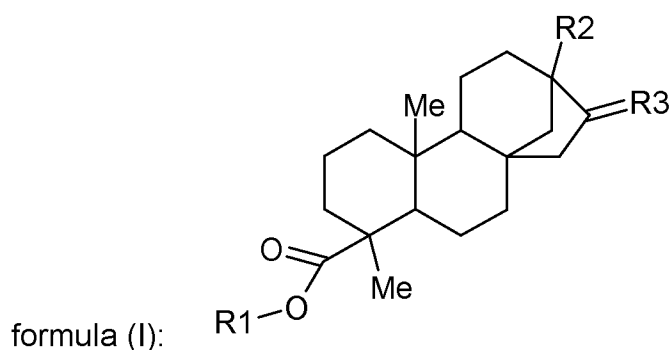
The present invention further provides the use of compounds of formula (I) as described in this invention for elongation of hair follicles, increasing the proliferation of hair follicle cells (outer/inner root sheet, dermal papilla fibroblasts).

Thus, the present invention provides the use of compound of formula (I) for restoring hair color and delaying the onset of greyness in hair, and/or maintaining of the natural hair color.

5

In another embodiment, this invention relates to a method for stimulating hair growth, and/or preventing the greying of hair or restoring or maintaining the natural hair color comprising the steps of applying to skin having hair, for a sufficient time, a topical composition comprising an effective amount a compound of formula (I),

10



wherein

- 15 R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,
- R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group,
- 20 R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),
- and observing the result.

More preferred compounds are steviol and isosteviol in any isomeric form, most preferred are compounds of formula (IV) and formula (V), even most preferred is steviol. Preferred amounts of the compound of formula (I) are selected in the range of 0.00001 to 20 wt.-%, preferably, 0.0001 to 5 wt.-%, more preferably, 0.001 to 0.5 wt.-% based on the total weight of the topical composition.

25

Preferably, the topical composition for the method according to the present invention is a hair care composition, and more preferably, it is a hair tonic, a conditioner, a shampoo, or a styling gel. The topical composition may further comprise at least one additional active substance selected from the group consisting of antioxidants,
5 light screening agents, colorants, and biological actives.

Graying of the Hair

One embodiment of this invention is the prevention of the graying of hair for restoration and/or maintenance of the natural hair color, as shown by the ability of said
10 compounds and derivatives to increase total number of melanocytes in hair follicles, as well as, to increase the differentiation and migration of melanocytes from the hair sheath to the hair matrix.

This invention relates to a method for preventing the graying of hair, delaying the onset of graying, and/or restoring and/or maintaining the natural hair color which comprises the step of applying a topical composition comprising an effective amount of steviol and/or isosteviol, or a salt, an ester, a diester, or an ether thereof as depicted in formula (I) to human or animal skin having hair, and observing the
15 prevention, restoration, or maintenance of natural hair color.
20

Thus the present invention also encompasses a method of topically administering an amount of steviol and/or isosteviol or a salt, an ester, a diester, or an ether thereof and observing or appreciating an increase in the number of melanocytes in
25 hair follicles, and/or increasing the differentiation or migration of melanocytes from the hair sheath to the hair matrix. The observation or appreciation can be done by noticing a decrease in grayness, maintenance of original hair color, or by observing a restoration of original hair color.

The efficacy of the use of compounds of formula (I) in accordance with the present invention for prevention of the greying of hair and/or for restoration and/or maintenance of the natural hair color can be shown by procedures described below:

30

As a reference (control) a hair tress containing approximately 100 hairs is cut neatly above the scalp. The color of the hair within the tress is measured from the near-root part to the tip. This could be either done 1) visually by scoring, 2) with high density photo documentation and scoring, 3) by pigment analysis and determination of the melanin content from hair following hair degradation and melanin extraction. In this later case, melanin can be measured by photometric means, or by chemical reaction (i.e. formation of pyrrole-2,3,5 tricarboxylic acid from eumelanin, and formation of aminohydroxyphenylalanine isomers for pheomelanin, followed by quantitative chromatographic, spectroscopic, or spectrophotometric analysis. It can also be done directly by assessing the pigment status of the hair bulb of plucked hair using light microscopy and the Lickert-Scale of pigmentation.

A sample of a topical composition (2 to 10 mL or mg/ cm², depending on the type of formulation; preferably a leave-on product such as hair tonic, lotion or cream) containing a preferred amount of a compound of formula (I) is then applied at least once a day on the scalp, typically from 1 to 4 times daily for at least three months, especially six months (because normal hair growth rate is about 1 cm/ month) and distributed equally with a massage on the scalp. In one method, the product is not washed out after application. At the end of the treatment period, a second hair sample is taken from the same place on the scalp and analyzed as described above.

A comparison of the melanin content, hair color or degree of graying is made intra-individually before and after the treatment period.

Hair Loss

Also according to this invention, topical applications of steviol and/or isosteviol can:

- lessening hair loss,
- restoring hair growth after the onset of baldness has occurred,
- increasing the thickness of hair,
- counteracting age-associated hair thinning,
- preventing or counteracting premature hair loss,

- delaying the onset or severity of age-associated hair loss, and/or
- delaying the onset or severity of hair thinning.

Thus another aspect of this invention is a method of enhancing hair appearance
5 selected from the group consisting of:

- lessening of hair loss,
 - restoring hair growth after the onset of baldness has occurred,
 - increasing the thickness of hair,
 - counteracting age-associated hair thinning,
 - 10 ○ preventing or counteracting premature hair loss,
 - delaying the onset or severity of age-associated hair loss, and/or
 - delaying the onset or severity of hair thinning
- comprising topically administering steviol and/or isosteviol, and observing the enhancement.

15

The present invention also relates to the use of steviol and/or isosteviol or a salt, an ester, a diester, or an ether thereof as depicted in formula (I) for stimulating dermal papilla region and keratinocytes within the hair follicle in order to increase the total number of keratinocytes responsible for hair growth and/or releasing
20 growth stimulating molecular signals from surrounding cells of the hair follicle and/or migration of progenitor keratinocytes to rebuild hair follicles.

Veterinary Uses

25 In another aspect of this invention, the topical formulation of a compound of formula (I) is administered to a non-human animal, which is preferably a mammal.

In a preferred aspect of this invention, the non-human animal is a mammal, such as a companion animal (dog, cat, ferret) or an animal which is used in the fur industry (minks, chinchillas or the like), or an animal which is shown in competition
30 (such as dogs, horses, cats, rabbits and other farm animals). Supplementing the animal's normal bathing or grooming regime with steviol and or isosteviol, a salt, an ester, a diester, or an ether -containing compositions of this invention will enhance the appearance of the animals' fur. Thus another aspect of this invention is

a veterinary topical composition containing a fur-enhancing amount of steviol and/or isosteviol or a salt, an ester, a diester, or an ether derivative thereof.

Another aspect of this invention is a shampoo or other topical formulation especially designed for a show animal which comprises steviol and/or isosteviol or a salt, an ester, a diester, or an ether derivative thereof. This should be applied to the animal daily for at least one month, and preferably for at least two months prior to the competition in order for its fur to be at its optimal condition.

In a further embodiment the invention relates to the use of a compound of formula (I) such as particularly steviol and/or isosteviol or a salt thereof for fur grooming (so the fur no longer appears neglected, and looks better groomed).

Dosages

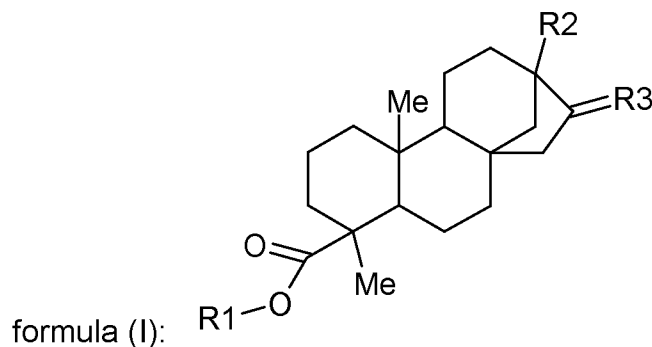
The physiological effect may be achieved by one single dose or by repeated doses. The dosage administered may, of course, vary depending upon known factors, such as the physiological characteristics of the particular composition; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and/or the effect desired and can be adjusted by a person skilled in the art.

An effective amount will typically be at least 0.00001 wt.-% based on the total weight of the topical composition. Preferably, the topical compositions contain the compound of formula (I) according to the present invention in an amount of 0.00001 to 20 wt.-%, more preferably in an amount from 0.0001 to 5 wt.-%, even more preferably in an amount from 0.001 to 0.5 wt.-%, based on the total weight of the composition.

The topical compositions are applied at least several times per week, preferably at least once per day, and more preferably applied at least twice a day such as e.g. once in the morning and once in the evening. Applications should be for a chronic period of time, i.e. at least one week, preferably for at least two weeks, and more preferably for at least 4 weeks in order to observe results.

Formulations

The present invention is also providing a hair care composition comprising a compound of formula (I),



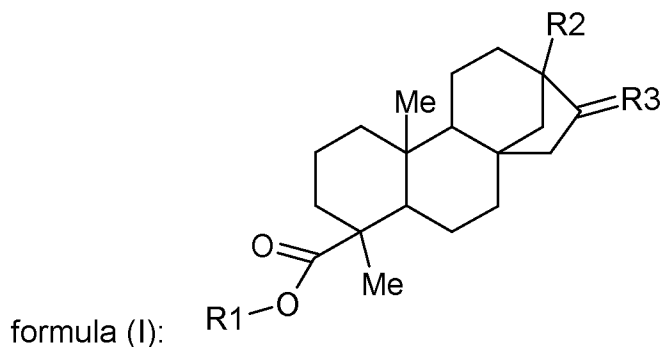
wherein

- 10 R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,
- R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group,
- 15 R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),
- and at least one conventional hair care carrier.

20 In a preferred embodiment, the present invention is also providing a hair care composition comprising a compound of formula (I) as described above, and at least one conventional hair care carrier, wherein the pH of the composition is below 7, preferably below 6, more preferably below 5, even more preferably below 4.

25 In another embodiment, the hair care composition according to the present invention further comprises an antioxidant selected from the group of antioxidants usually formulated in hair care, and as described above, and/or, a light screening agent selected from UV-A, UV-B, and/or broad band UV filters as described in the present application.

The present invention is also providing a hair care composition comprising a compound of formula (I),



5 wherein

R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,

10 R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group,

R3, is independently CH₂, O, or CH-(C₁-C₇ alkyl),

and at least one conventional hair care carrier, and an antioxidant selected from the group of antioxidants usually formulated into hair care and/or a light screening agent selected from UV-A, UV-B and/or broadband filters as described in the pre-
 15 sent application.

The present invention further provides a composition as described above which is a gel, a lotion, a tincture, a spray, a mousse, a cleansing composition, a shampoo,
 20 or a foam.

In particular the topical compositions are hair care compositions such as conditioners, treatments, tonics, styling gels, mousses, shampoos, hair sprays, pomades, setting lotions, coloring and permanent waving compositions. Of particular
 25 interest for the purpose of the present invention are tonics, conditioners, treatments, and styling gels which may be in the form of a gel, a lotion, a tincture, a spray, a mousse, a cleansing composition or a foam and which may be applied according to individual needs, e.g., once daily as a lotion, tincture, mousse or spray; or once or twice weekly as a conditioner or treatment.

The typical composition used in the method for preventing the graying of hair as well as for restoring and/or maintaining the natural hair color according to the present invention may further comprise other ingredients which are conventionally used in topical compositions such as 5,6-dihydroxyindoline HBr, 5,6-dihydroxyindoline HBr in combination with 2-methylresorcinol and/or arginine.

In accordance with the present invention, a compound of formula (I) with the definitions and preferences as given above is useful in topical compositions such as in particular hair care compositions which further contain carriers and/or excipients or diluents conventionally used in topical, respectively, hair care compositions.

The compound of formula (I) may be combined with suitable auxiliary agents which are conventionally used in hair care compositions such as disclosed in general terms in Ullmann's Encyclopedia of Industrial Chemistry (1989), Vol. A 12, Hair Preparations, and more specifically, e.g., in International Patent Application No. WO 00/06094, WO 00/07550 and WO 01/06994.

Thus, the use of a compound of formula (I) according to the present invention may be combined with the use of further ingredients to protect the hair against detrimental environmental impact and to improve the health of the hair.

The compounds of formula (I) according to the present invention may be incorporated into conventional hair care compositions as described below:

The hair care compositions may comprise additional cosmetic or dermatological adjuvants and/or additives (cosmetic carrier) which are preferably selected from

- 1.) Water
- 2.) Water soluble organic solvents, preferably C1-C4-Alkanols
- 3.) Oils, fatty substances, waxes
- 4.) Various esters different to 3) of C6-C30 monocarboxylic acids with mono-, di-, or trivalent alcohols
- 5.) Saturated acyclic and cyclic hydrocarbons
- 6.) Fatty acids
- 7.) Fatty alcohols

- 8.) Silicone oils
9.) Surface active ingredients
and mixtures thereof.

5 The hair care compositions can contain further adjuvants and additives such as preservatives, antioxidants, silicones, thickeners, softeners, anionic, cationic, non-ionic or amphoteric emulsifiers, light screening agents, antifoaming agents, moisturizers, fragrances, surfactants, fillers, sequestering agents, anionic, cationic, nonionic or amphoteric polymers or mixtures thereof, propellants, acidifying or basifying agents, dyes, colorants, pigments or nanopigments, light stabilizers, insect repellents, antibacterial agents, or any other ingredients usually formulated into hair care compositions. The necessary amounts of the adjuvants and additives can, based on the desired product, easily be chosen by a skilled artisan in this field and will be illustrated in the examples, without being limited hereto.

15

Preferably the hair care compositions are in the form of cosmetic hair-treatment preparations, e.g. hair tonics, conditioners, hair-care preparations, e.g. pretreatment preparations, styling creams, styling gels, pomades, hair rinses, treatment packs, intensive hair treatments e.g. leave-on and rinse-off deep conditioners, hair-structuring preparations, e.g. hair-waving preparations for permanent waves (hot wave, mild wave, cold wave), hair-straightening preparations, liquid hair-setting preparations, hair foams, hairsprays, bleaching preparations, e.g. hydrogen peroxide solutions, lightening shampoos, bleaching creams, bleaching powders, bleaching pastes or oils, temporary, semi-permanent or permanent hair colorants, preparations containing self-oxidizing dyes, or natural hair colorants, such as henna or chamomile.

25

Preferred hair care compositions are leave-on compositions selected from hair tonics, conditioners, treatments, and styling gels.

30

Based on the application the hair care preparations may be in the form of a (aerosol) spray, (aerosol) foam, gel, gel spray, cream, lotion, liquid or a wax. Hair sprays comprise as well aerosol sprays as pump sprays without propellant. Hair foams comprise as well aerosol foams as pump foams without propellant. Hair

sprays and hair foams comprise mainly or exclusively water soluble or water dispersible components. If the components used in hair sprays or hair foams according to the invention are water dispersible, then they may be in the form of micro dispersions with particle sizes of usually 1-350 nm, preferably 1-250 nm. The solid content of such preparations is typically in the range of 0.5 to 20 wt.-% of the total weight of the preparation. Such micro dispersions normally do not need further emulsifiers or tensides for their stabilization.

An exemplary hair gel with the compound of the present invention may comprise:

1. 0.1 to 20 wt.-% preferably 1 to 10 wt.-% of at least one hair polymer;
2. 0 to 10 wt.-% of at least one carrier (solvent), selected from C2-C5 alcohols, preferably ethanol;
3. 0.01 to 5 wt.-%, preferably 0.2 to 3 wt.-% of at least one thickener;
4. 0 to 50 wt.-% of a propellant;
5. 0 to 10 wt.-%, preferably 0.1 to 3 wt.-% of a styling polymer different to 1.), preferably a water soluble non-ionic polymer;
6. 0 to 1 wt.-% of at least one refatter, preferably selected from glycerine and glycerine derivatives;
7. 0 to 30 wt.-% of other customary additives e.g. a silicone component
8. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention,
9. water ad 100 wt.-%

An exemplary conditioner preparation according to the present invention may comprise:

1. 0.05 to 10 wt.-% of a hair polymer
 2. 5 to 95 wt.-% of water
 3. 5 to 50 wt.-% of surfactant
 4. 0 to 5 wt.-% of an additional conditioning agent
 5. 0 to 10 wt.-% other customary additives
 6. up to 20 wt.-% of a compound of formula (I)
- all ingredients adding up to 100 wt.-%.

An exemplary styling composition with the compound of the present invention may comprise:

1. 0.1 to 10 wt.-% of at least one hair polymer;
2. 20 to 99 wt.-% water and/or alcohol;
- 5 3. 0 to 70 wt.-% of at least one propellant;
4. 0 to 20 wt.-% of customary additives;
5. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention.

10 An exemplary styling gel with the compound of the present invention may comprise:

1. 0.1 to 10 wt.-% of a hair polymer;
2. 60 to 99.85 wt.-% of water and/or alcohol;
3. 0.05 to 10 wt.-% of a gel former;
- 15 4. 0 to 20 wt.-% of other customary additives.
5. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention.

20 An exemplary hair care composition (spray) with the compound of the present invention may comprise:

1. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention,
2. 30 to 99.5 wt.-%, preferably 40 to 99 wt.-%, of at least one solvent chosen from water, water-miscible solvents and mixtures thereof;
- 25 3. 0 to 70 wt.-% of propellant;
4. 0.1 to 10 wt.-% of at least one water-soluble or water-dispersible hair polymer
5. 0 to 0.3 % by weight of at least one water-insoluble silicone;
6. 0 to 0.5 wt.-% of at least one wax, preferably at least one fatty acid amide;
7. customary additives.

30

Another hair care composition with the compound of the present invention may comprise:

1. 0.05 to 20 wt.-% of at least one hair polymer;
2. 20 to 99.95 wt % of water and/or alcohol;

3. 0 to 79.5 wt.-% of customary additives;
 4. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention.
- 5 An exemplary composition for aerosol foams with the compound of the present invention may comprise:
1. 0.1 to 10 wt.-% of at least one hair polymer;
 2. 55 to 99.8 wt.-% water and/or alcohol;
 3. 5 to 20 wt.-% of a propellant;
 - 10 4. 0.1 to 5 wt.-% of an emulsifier;
 5. 0 to 10 wt.-% of customary additives.
 6. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention.
- 15 An exemplary shampoo preparation with the compound of the present invention may comprise:
1. 0.05 to 10 wt.-% of a hair polymer;
 2. 25 to 94.95 wt.-% of water;
 3. 5 to 50 wt.-% of surfactant;
 - 20 4. 0 to 5 wt.-% of an additional conditioning agent;
 5. 0 to 10 wt.-% other customary additives.
 6. 0.005 to 5 wt.-% of a compound of formula (I) according to the present invention,
 7. 0 to 5 wt.-% opacifiers and/or pearly gloss-imparting substances

25

The hair care composition according to the invention can comprise at least a water-soluble or water-dispersible hair polymer. Typical hair polymers for use in the present invention are commercially available polymers for hair care such as hair styling or conditioning polymers such as e.g. copolymers of vinyl acetate and cro-

30 tonic acid, copolymers of methyl vinyl ether and maleic anhydride, copolymers of acrylic acid or methacrylic acid with other monomers, polyurethanes, N-vinylpyrrolidone and silicone polymers.

The content of the hair polymer is generally from about 0.1 to 10 % by weight, based on the total weight of the composition. Here, it is preferable to use water-soluble or water-dispersible polyurethanes which, if desired, additionally comprise siloxane groups in copolymerized form.

5

The composition according to the invention can further comprise, at least one water-insoluble silicone, in particular a polydimethylsiloxane, e.g. the Abil® grades from Goldschmidt. The content of the silicone is then generally from about 0.0001 to about 2 % by weight, preferably from about 0.001 to about 1 % by weight, based on the total weight of the composition. Preferred waxes according to the present invention are fatty acid amides, such as, for example, erucamide.

The hair care compositions according to the present invention can, where appropriate, additionally comprise an antifoaming agent, e.g. based on silicone. The amount of antifoaming agent is generally up to 0.001 % by weight, based on the total amount of the composition. The compositions according to the invention have the advantage that, on the one hand, they impart the desired hold to the hair and, on the other hand, the polymers are easy to wash out (redispersible). Generally, a natural appearance and shine is imparted to the hair, even when the hair is by its very nature especially thick and/or dark.

The term alcohol refers to all alcohols usually used in cosmetic compositions such as ethanol, n-propanol, isopropanol.

Other ingredients are cosmetic adjuvants and additives such as propellants, anti-foaming agents, surface active ingredients e.g. tensides, emulsifiers, foam former and solubilisators. The used surface active ingredients may be anionic, cationic, amphoteric or neutral. Further ingredients may be preservatives, antioxidants, perfume oils, lipidic refatters, active and/or caring ingredients such as panthenol, collagen, vitamins, protein hydrolysates, alpha- and beta hydroxyl carbonic acids, stabilisators, pH regulators, opacifiers, colorants, dyes, gel formers, salts, moisturizers, complex formers, viscosity regulators or light screening agents without being limited thereto.

In order to obtain certain properties the hair care compositions may additionally comprise conditioning compounds based on silicone such as polyalkylsiloxane, polyarylsiloxane, polyarylsiloxane, polyarylsiloxane, silicone resins, polyethersiloxane or dimethicone copolyole (CTFA) and amino functionalized silicone compounds such as amodimethicone (CTFA), GP 4 Silicone fluid[®] and GP 7100[®] (Genesee), Q2 8220[®] (Dow Corning), AFL 40[®] (Union Carbide) or polymers as disclosed in EP 0 852 488. Other suitable ingredients comprise silicone propfpolymers having a polymeric silicone backbone and non-silicone containing side chains or a non silicone containing polymeric backbone and silicone side chains such as Luviflex[®] Silk or polymers disclosed in EP 0 852 488.

Typical propellants for hair sprays or aerosol foams may be used. Preferred are mixtures of propane/ butane, pentane, dimethylether, 1,1-difluoroethane (HFC-152a), carbon dioxide, nitrogen or compressed air.

All emulsifiers for aerosol foams or surfactants for shampoo preparations may be conventionally used non-ionic, cationic, anionic or amphoteric emulsifiers/surfactants.

Examples of non-ionic emulsifiers are (INCI-nomenclature) Laureths, e.g. Laureth-4; Ceteths, e.g. Ceteth-1, polyethyleneglycolcetylether; cetareths, e.g. cetareth-25, polyglycol fatty acid glycerides, hydroxylated lecithins, lactyl esters of fatty acids, alkylpolyglycosides. Examples of non-ionic surfactants are e.g. reaction products of aliphatic alcohols or alkylphenols with 6 to 20 C-Atoms of a linear or branched alkyl chain with ethyleneoxide and/or propyleneoxide. The amount of alkyleneoxide is about 6 to 60 mol to one mol alcohol. Furthermore alkylaminoxide, mono- or dialkylalkanolamide, fatty esters of polyethylene glycols, alkylpolyglycosides or sorbitan ester are suitable for the incorporation of hair care compositions according to the invention.

Examples of cationic emulsifiers/surfactants are quaternised ammonium compounds e.g. cetyltrimethylammoniumchloride or bromide (INCI: cetrimoniumchloride or bromide), stearyl benzyl dimethyl ammonium chloride, distearyldimethylammonium chloride, stearamidopropyldimethylamine, hydroxyethylcetyldimonium

phosphate (INCI: Quaternium-44), Luviquat[®] Mono LS (INCI: Cocotrimoniummethosulfate), poly(oxy-1,2-ethandiyl), (octadecylnitrilio) tri-2, 1-Ethandiyl) tris-(hydroxy)-phosphate (INCI Quaternium-52). Furthermore, cationic guar derivatives such as guarhydroxypropyltrimoniumchloride (INCI) may be used in conditioner/shampoo preparations.

Anionic emulsifiers/surfactants can be selected from alkylsulfate, alkylethersulfate, alkylsulfonate, alkylarylsulfonate, alkylsuccinate, alkylsulfosuccinate, N-alkylsarkosinate, acyltaurate, acylisethionate, alkylphosphate, alkyletherphosphate, alkylethercarboxylate, alpha-olefinsulfonate, especially the alkali- and earth alkali salts, e.g. sodium, potassium, magnesium, calcium, as well as ammonium- and triethanol amine-salts. The alkylethersulfate, alkyletherphosphate and alkylethercarboxylate may comprise between 1 to 10 ethyleneoxide or propyleneoxide units, preferably 1 to 3 ethyleneoxide-units per molecule.

Suitable anionic surfactants are e.g. sodium laurylsulfate, ammonium laury sulfate, sodium laurylethersulfate, ammonium laurylethersulfate, sodium lauroylsarkonisate, sodiummoleylsuccinate, ammonium laurylsulfosuccinate, sodium dodecylbenzolsulfonate, triethanolamidodecylbenzolsulfonate.

Suitable amphoteric surfactants are e.g. alkylbetaine, alkylamidopropylbetaine, alkylsulfobetaine, alkylglycinate, alkylcarboxyglycinate, alkylamphoacetate or propionate, alkylamphodiacetate or dipropionate such as cocodimethylsulfopropylbetaine, laurylbetaine, cocamidopropylbetaine or sodium cocamphopropionate.

As gel formers, all typical cosmetic gel formers can be used such as slightly cross linked polyacrylic acid e.g. Carbomer (INCI), cellulose derivatives, polysaccharides e.g. xanthan gum, caprylic/ capric triglyceride (INCI), sodiumacrylate-copolymers, polyquaternium-32 (and) paraffinum liquidum (INCI), sodiumacrylate-copolymers (and) paraffinum liquidum (INCI) (and) PPG-1 trideceth-6, polyquaternium-37 (and) propyleneglycoldicapratdicarylate (and) PPG-1 trideceth-6, polyquaternium-7, polyquaternium-44.

In order to provide the formulation a pearlescent appearance or to give the impression of a richer or creamier product, the hair care composition may additionally comprise opacifiers and/or pearly gloss-imparting substances, such as soaps or salts of carboxylic acids, cationics including cationic polymers, dimethicone (INCI) or amodimethicone (INCI).

Other customary additives are for example long chain fatty alcohols such as cetyl alcohol, stearyl alcohol, cetylstearyl alcohol, dimethylstearamine. Furthermore the hair care composition may contain lipids such as dimethicone, amodimethicone, mineral oil, or silicon derivatives such as Dimethicone Copolyol.

In another embodiment, the present invention also relates to a dual-vial packaging system as described in WO2008049443 containing the compound of formula (I) as a dried powder in a compartment, and a cosmetically acceptable carrier in the other compartment.

The invention is further illustrated by the Examples which follow without being limited thereto.

EXAMPLES

Example 1: Growth of Human Hair Follicle

Human hair follicles were obtained from human skin fragments (obtained by plastic surgery) and grown in supplemented William's E medium supplemented with penicillin/streptomycin, L-glutamine (2 mM), insulin (10 µg/ml and hydrocortisone (8 nM). Hair follicle growth was assessed via length measurements (day 0, 4, 7). Triiodothyronine (T3, 30 µM) was used as positive control. The effect of steviol (at 0.625 to 5 µg/ml) was tested in parallel. At day 7, RNA was extracted from hair follicles that had been subjected to different treatments (control, T3, steviol). RNA was processed for Affymetrix® DNA microarray analysis in order to identify effects of compounds on gene expression. Where appropriate, RNA expression levels were further quantified by RT-PCR using the ABI 7900 Taqman instrumentation.

In all procedures the protocols suggested by the manufacturers were strictly followed.

Results

5

Effects on hair follicle growth:

Steviol dose-dependently favoured the elongation of hair follicles. At low concentrations the effect was significant, whereas at higher concentrations the compound

10

Table 1

Treatment	Concentration	Growth (% of control)	p-value
Control	-	100	-
Triiodothyronine	30 μ M	133	< 0.01
Steviol	0.625 μ g/mL	122	< 0.1
	1.25 μ g/mL	121	< 0.1
	2.5 μ g/mL	113	Not significant
	5 μ g/mL	117	Not significant

Effect on gene expression:

15

Global effects of steviol on gene expression were determined by transcriptomics *i.e.* DNA microarray analysis. The obtained data were processed with Genedata software tools. This resulted in a list of genes that had significantly different expression levels in steviol-treated hair follicles (compared to untreated hair follicles).

20

Examples of genes that were differentially up-regulated by steviol and which are involved in epidermal physiology are given in Table 2. Only genes directly or indirectly involved in epidermal proliferation or differentiation and which were at least 2-fold up-regulated are listed.

Table 2

Gene	Ratio of steviol-treated/untreated	p - value
Transmembrane protein with EGF-like and two follistatin-like domains 2	3.10	0.0001
Fibroblast growth factor 7 (keratinocyte growth factor)	2.91	0.0006
CASP8 and FADD-like apoptosis regulator	2.58	0.0004
Topoisomerase (DNA) II alpha 170kDa	2.45	0.0004
TIMP metalloproteinase inhibitor 3	2.32	0.0001
Chemokine (C-X-C motif) ligand 12 (stromal cell-derived factor 1)	2.22	0.0005
Integrin, alpha 6	2.15	0.0004
Collagen, type IV, alpha 6	2.04	0.0008
Insulin-like growth factor 1 receptor	2.00	0.001

The genes regulated by steviol were further mapped to biological pathways using statistical tools provided with the Genedata software package. Steviol modulated gene expression of the pathways of the epidermal development, ectoderm development and keratinocyte differentiation with a high statistical significance (indicated by p- value in Table 2); other pathways were not significantly affected. This data is in line with the observed effect of steviol on hair follicle elongation (see Table 1) and corroborate that steviol modulates molecular pathways that lead to changes in hair growth.

The mRNA level of some marker genes involved in growth and/or differentiation of cells in the skin and in hair follicle was further determined by RT-PCR and is shown in Table 3.

Table 3

Gene	Treatment of human hair follicle (concentration)	Fold changes (versus control)
All genes	Control (untreated)	1
Keratin 6	Steviol (10 µg/mL)	1.33 ± 0.11
COX-2	Steviol (1.25 µg/mL)	0.46 ± 0.17
Integrin alpha-6	Steviol (0.625 µg/mL)	1.62 ± 0.06
HO-1	Steviol (1.25 µg/mL)	0.64 ± 0.08
Involucrin	Steviol (1.25 µg/mL)	0.51 ± 0.22

The importance of these genes in epidermal and therefore also hair development is described and discussed in detail e.g. by Adriani et al. *J. Invest Dermatol* 120: 923-931 (2003); Grochot-Preczek et al. *Thromb Haemost* 104 (on-line 10-June 2010); Li et al. *Exp Dermat* 9: 431-438 (2000); Ma et al. *Ann Acad Med Singapore* 33: 784-8 (2004); Neufang et al. *Proc Nat Acad Sci (USA)* 98: 7629-7634 (2001).

Example 2: Anti Dandruff Shampoo

INCI NOMENCLATURE	wt.-%
Aqua	Ad 100
Ammonium Laureth Sulphate (28 %)	35.00
Ammonium Lauryl Sulphate (25 %)	15.00
Glycol Distearate	1.00
Dimethicone	1.00
Cetyl Alcohol	0.50
Cocamide MEA	3.00
Zinc Pyrithione	1.00
Guar Hydroxypropyltrimonium Chloride	0.20
Hydrogenated Polydecene	1.00
Polyquaternium-10	0.10
PEG 7m	0.50
Trimethylpropane Tricaprylate/Tricaprate	1.00
Preservative	q.s.
Fragrance	0.30
E 104,E 110,E 132	0.02

INCI NOMENCLATURE	wt.-%
Compound of formula (I), in particular steviol	0.01

Combine all ingredients and mix intensively until a homogeneous solution is obtained. At the end, add the water under slow agitation and wait until the foam has disappeared.

5

Example 3: Conditioning Shampoo

INCI NOMENCLATURE	wt.-%
Aqua	Ad 100
Sodium Laureth Sulphate (28 %)	25.00
Cocamidopropyl Betaine (40 %)	5.00
Sodium Chloride	2.50
Glycol Distearate	1.00
Glycerin	2.00
Dimethiconol	0.50
Parfum	0.50
Coco-Glucoside (40%)	3.00
Carbomer	0.10
Arginine	0.05
Glyceryl Oleate	0.05
Glyceryl Stearate	1.00
Guar Hydroxypropyltrimonium Chloride	0.10
Panthenol	1.00
Disodium EDTA	0.05
Preservative	q.s.
Hydrolyzed Keratin	0.10
Citric Acid/ Sodium Hydroxide	q.s
Compound of formula (I) according to the present invention such as in particular steviol	0.005
E 102, E 110, FD&C blue	0.01

Combine all ingredients and mix intensively until a homogeneous solution is obtained. At the end, add the water under slow agitation and wait until the foam has disappeared. Then carefully add the thickening agent (sodium chloride).

5 **Example 4: Shine Shampoo**

INCI NOMENCLATURE	wt.-%
Aqua	Ad 100
Sodium Laureth Sulfate (28%)	15.00
Disodium Cocoamphodiacetate (40%)	15.00
Sodium Chloride	2.00
Glycol Distearate	1.00
Cocamidopropyl Betaine (40%)	2.00
Laurdimonium Hydroxypropyl Hydrolyzed Wheat Protein	1.00
PEG-12 Dimethicone	1.00
Guar Hydroxypropyltrimonium Chloride	0.05
Hydrolyzed Wheat Protein	0.20
Laureth-4	1.00
PEG-7 Glyceryl Cocoate	2.00
Hydrogenated Castor Oil	1.00
Laureth-2	0.50
PEG-55 Propylene Glycol Oleate,	2.00
Propylene Glycol	2.00
Mica	0.20
Citric Acid	0.01
Parfum	1.00
E 110, E 104, E 122	0.05
Compound of formula (I) according to the present invention such as in particular steviol	0.05

Combine all ingredients and mix intensively until a homogeneous solution is obtained. At the end, add the water under slow agitation and wait until the foam has disappeared. Than add carefully the thickening agent (sodium chloride).

Example 5: Extra Shine Revitalizing Hair Cream

	INCI Nomenclature	wt.-%
A	Simmondsia Chinensis (Jojoba) Seed Oil	3.00
	Prunus Armeniaca (Apricot) Kernel Oil	3.00
	Phenyl Trimethicone	2.00
	C12-15 Alkyl Benzoate	2.00
	Glyceryl Stearate SE	2.00
	Polysilicone-15	0.50
	Tocopheryl Acetate	0.50
	Cetearyl Alcohol	1.60
B	Aqua	Ad 100
	Compound of formula (I) according to the present invention such as in particular steviol	0.005
C	Behentrimonium Chloride	1.00
	Cocodimonium Hydroxypropyl Hydrolyzed Wheat Protein	0.30
	Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben	1.00

Heat part A and part B separately to 65 °C under moderate agitation. When both
5 have the same temperature, add part B into part A under agitation. Let cool to 40 °C and add part C under agitation, homogenize. Cool to ambient temperature.

Example 6: Hair Repair Treatment

	INCI NOMENCLATURE	wt.-%
A	Cetearyl Octanoate	0.20
	Phytantriol	0.10
	PEG-40 Hydrogenated Castor Oil	2.00
B	Parfum	q.s.
	Cocotrimonium Methosulfate	2.00
C	Aqua	Ad 100
D	Polyquaternium-16	2.00
	Dimethicone Copolyol	1.00

	Compound of formula (I) according to the present invention such as in particular steviol	0.5
	Parfum	q.s.
	Alcohol denat.	10.00
	Citric Acid	q.s.

Heat Part A to 70 °C. Add part B to part A under stirring. Add the mixture to part C and homogenize. Add part D and let cool down under moderate agitation.

5 **Example 7: Color Balm**

	INCI NOMENCLATURE	wt.-%
A	Ceteareth-6, Stearyl Alcohol	1.50
	Ceteareth-25	1.50
	Cetearyl Alcohol	3.00
	Cetearyl Octanoate	6.00
	Phytantriol	0.30
B	Polyquaternium-44 (13% in water)	7.70
	Compound of formula (I) according to the present invention such as in particular steviol	0.005
	Propylene Glycol	2.00
	Panthenol	1.00
	Parfum	q.s.
	Aqua	Ad 100
C	C.I. 42510, Basic Violet 14	0.05
	C.I. 12245, Basic Red 76	0.08
	Preservative	q.s.
	Citric Acid	q.s.

Heat parts A and B separately to 70°C. Add part A to B and homogenize. Add part C under stirring.

Example 8: Silky Hair Cocktail

	INCI NOMENCLATURE	wt.-%
A	Caprylic/Capric Triglyceride (and) Acrylates Copolymer	3.00
	Dimethicone Copolyol	0.50
	Dimethicone Copolyol	2.00
	Cyclomethicone (and) Dimethiconol	3.00
	Amodimethicone (and) Cetrimonium Chloride (and) Trideceth-10	2.00
	Phenyl Trimethicone	2.00
	Macadamia (Ternifloria) Nut Oil	1.00
	Tocopheryl Acetate	0.50
	PEG-40 Hydrogenated Castor Oil	1.00
	Parfum	q.s.
B	Aqua	Ad 100
	Aminomethyl Propanol	0.46
	Compound of formula (I) according to the present invention such as in particular steviol	0.01
	PEG/PPG-25/25 Dimethicone/ Acrylates Copolymer (50%)	4.00
	Preservative	q.s.

Heat parts A and B separately to 70°C. Add part A to B and homogenize. Let cool
 5 down under stirring.

Example 9: Oil Sheen Moisturizer

	INCI NOMENCLATURE	wt.-%
A	Cetyl Alcohol	2.00
	PEG-75 Lanolin	1.00
	Glyceryl Stearate	4.00
	Ceteareth-25	1.00
	Cetearyl Octanoate	4
B	Glycerin	10.00

	Compound of formula (I) according to the present invention such as in particular steviol	0.05
	Propylene Glycol	2.00
	Cocotrimonium Methosulfate	1.00
	Trimethylsilylamodimethicone, SM 2115 Octoxynol-40, Isolaureth-6, Glycerin	1.50
	Polysorbate 20	1.00
	Aqua	Ad 100
C	Panthenol	0.50
	Preservative	q.s.
	Parfum	q.s.
	Citric Acid	q.s.

Heat parts A and B separately to 70°C. Add part A to B and homogenize. Add part C under stirring.

5 **Example 10: Setting Cream High Gloss**

	INCI NOMENCLATURE	wt.-%
A	Cetyl Alcohol	5.00
	Glyceryl Stearate SE	10.00
	Isopropyl Myristate	5.00
	Preservative	q.s.
	Dimethicone	1.00
B	Glycerin	5.00
	Compound of formula (I) according to the present invention such as in particular steviol	0.05
	Disodium EDTA	0.20
	PVP	2.00
	Aqua	Ad 100
C	Parfum	q.s.

Heat parts A and B separately to 70°C. Add part A to B and homogenize. Add part C under stirring.

Example 11: Hair Gel

INCI NOMENCLATURE	wt.-%
Carbomer	0.50
Aqua	Ad 100
AMP-95	0.52
Compound of formula (I) according to the present invention such as in particular steviol	0.01
PVP	5.00
Parfum	q.s.
PEG-40 Hydrogenated Castor Oil	q.s.
Phenoxyethanol (and) Methylparaben (and) Butylparaben (and) Ethylparaben (and) Propylparaben	0.10
Tocopheryl Actetate	0.10

Disperse carbomer in about 50% of the water amount and add AMP under stirring
 5 till a clear gel is formed. Dissolve PVP in the rest of the water. Premix the perfume with PEG-40 hydrogenated castor oil. Mix all parts, and finally add preservative and tocopheryl acetate.

Example 12: Hair Gel

10

INCI NOMENCLATURE	wt.-%
Compound of formula (I) according to the present invention such as in particular steviol	0.1
Polyquaternium-46 (20%)	2.50
Alcohol denat.	15.00
Aqua	Ad 100
Parfum	0.10
Glycerin	0.10
Hydroxyethylcellulose	2.00

Combine all ingredients of part 1 and mix intensively until a homogeneous gel is obtained.

Example 13: Permanent hair tinting formulationPart I

	INCI Nomenclature	wt.-%
A	Cetearyl Alcohol	9.00
	Sodium Cetearyl Sulfate	3.00
	Glyceryl Stearate	2.50
	Laureth-2	2.00
	Stearamide MEA-Stearate	0.75
	PEG-5 Cocamide	0.50
	Oleic Acid	0.50
	Hair Dye	0.30
B	Aqua	Ad 100
	Ammonium Sulfate	2.00
	Sodium Sulfite	0.50
	Disodium EDTA	0.05
	Compound of formula (I) according to the present invention such as in particular steviol	0.1
	Ascorbic Acid	0.50
	Ammonium Hydroxide	2.50

5 Part II

	INCI Nomenclature	wt.-%
A	Cetearyl Alcohol	6.00
B	Aqua	Ad 100
	Hydrogen Peroxide (30%)	9.00
	Sodium Lauryl Sulfate (28%)	3.00
	Disodium Phosphate	0.15
	Phosphoric Acid (85%)	pH 2.0

Heat phase A and B of Part I separately to 70 °C. Add phase A to phase B under stirring. Adjust the pH to 11.2.

Heat phase A and B of Part II separately to 70 °C. Add phase A to phase B under stirring. Adjust the pH. Combine Parts I and II shortly before use.

Example 14: *Pharmaceutical Shampoo*

5

Part I

	INCI Nomenclature	wt.-%
A	Aqua	50.00
	Compound of formula (I) according to the present invention such as in particular steviol	5.00
	Methylcellulose	0.30

Part II

	INCI Nomenclature	wt.-%
A	Sodium Laureth Sulfate (28%)	44.50
	Ethylparaben	0.20

- 10 Dissolve compound of formula (I) according to the present invention (in particular steviol) in water, add Methylcellulose and stir until dissolved; mix Ethylparaben with Sodium Laureth Sulfate.

Mix part 1 with part 2.

15

Example 15: *Induction of melanin synthesis by Steviol:*

Quantification of melanin synthesis in cell culture:

- 20 Normal human melanocytes NHM (HEMn-MP, Clonetics) were seeded in 96 well cell culture plates and grown to sub-confluence for two days in a mixture of M2-Medium (Clonetics) and Medium (Promocell). Culture medium was exchanged with Culture Medium containing Steviol and melanogenesis progressed for another three days at 37 °C with another medium exchange on day two. Including cell
25 layer and culture supernatant the total melanin was extracted using 1.7M KOH with vigorous shaking at RT. We measured melanin content at 405 nm in an ab-

sorbance plate reader. The data is normalized to 100 % for the un-treated control sample, and expressed as percentage of the control.

The results are summarized in the table below:

Control	Glycyrrhizin 1.5 mM	Steviol 0.25 microM	Steviol 0.5 micro M	Steviol 1 mic- ro M
100 %	132 %	109 %	124 %	130 %

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Glycyrrhizin is used as a positive control since it is a known inducer of melanogenesis. Steviol shows a clear dose dependent positive effect on the production of melanin in human melanocytes.

10 **Example 16:** *Silk & Shine Conditioning Fluid:*

Phase	INCI Name	% w / w
A	Aqua	51.45
	Stearamidopropyl Dimethylamine	2.40
	Polyquaternium-67	0.15
B	Cetearyl Alcohol	2.40
	Behenyl Alcohol	1.80
C	Water , Dimethicone , Polyquaternium- 74, Laureth-7, Sodium Benzoate, Phenoxyethanol	2.80
	Cyclopentasiloxane & Dimethiconol	1.00
	Argania Spinosa Kernel Oil	0.50
D	Aqua	Ad 100.00
	Glutamic Acid	0.15
	Steviol	0.50
	Panthenyl Ethyl Ether	0.75
	Hydrolyzed Sericin	0.20
	Citric acid	q.s.
E	Parfum	0.60
	Phenoxyethanol & Ethylhexylglycerin	0.30

Procedure:

- A/B Heat part A and part B separately to 70°C.
When both have reached the same temperature, add part B to part A.
- C Add. Ingredients of part C and homogenize balanced.
- D Water phase II cold: Add. all ingredients of part D in water. Add. the cold solution under stirring into the product.
- E Add. Preservative and Parfum. Homogenize thoroughly and then with continued mixing cool down to ambient temperature.

5 Technical Data:

pH: 4.8	Viscosity: 30.000 mPas (# 6/5 RPM)
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Example 17: Sulfate Free Shampoo:

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Phase	INCI Name	% w / w
A	Aqua	50.7299
	Acrylates/Beheneth-25 Methacrylate Copolymer (30 %)	6.00
B	Sodium Cocoyl Apple Amino Acids (40 %)	4.00
	Caprylyl/Capryl Glucoside (63 %)	3.00
	Sodium Lauroyl Glutamate (40 %)	5.00
	Sodium Cocoamphoacetate (32 %)	16.00
C	Polyquaternium-22 (40 %)	1.50
	Panthenol	0.67
	Calcium Pantothenate	0.20
	Silica & Titanium Dioxide (CI 77891) & Tin Oxide (CI 77861)	0.05
D	Parfum	0.80
	Argania Spinosa Kernel Oil	0.10
	PEG-90M	0.15
	PEG-18 Glyceryl Oleate/Cocoate	3.00
	PEG-40 Hydrogenated Castor Oil	1.40
E	Phenoxyethanol & Ethylhexylglycerin	0.80
	Coco-Betaine (30 %)	6.00
	Citric Acid	0.60

Procedure:

- 1 Mix part A under stirring.
- 2 Add ingredients of part B step by step to A under stirring until equal distribu-
- 5 tion is optioned.
- 3 Add ingredients of part C step by step to the first part under stirring.
- 6 Mixing separate: all ingredients of part D and add to the shampoo.
- 7 Addition ingredients of part E. The batch will thicken.

10 Technical Data:

pH: 5.9	Viscosity: 3500-5000 mPas	(Brookfield, #4 / 10 rpm)
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Example 18: Color Protection Shampoo:

Phase	INCI Name	% w / w
A	Aqua	Ad. 100
	Acrylates Copolymer (30 %)	4.50
B	Sodium Laureth Sulfate (28 %)	40.00
	Sodium Lauroyl Glutamate (40 %)	4.00
	Sodium Cocoamphoacetate (32 %)	5.00
	Sodium Hydroxide (30 %)	0.20
C	Polyquaternium-7	2.00
	Silica & Titanium Dioxide (EU:CI 77891) & Tin Oxide (EU:CI 77861)	0.10
	Peg-4 Distearyl Ether & Sodium Laureth Sulfate & Distearyl Ether & Dicaprylyl Ether	6.00
	Dimethicone	0.80
	Saccharide Isomerate	0.50
	Steviol	0.25
D	Polysilicone-15	0.10
	Phytantriol	0.20
	Octocrylene & Homosalate & Butyl Methoxydibenzoylmethane & Tocopherol & Glycine Soja (Soyabean) Oil	0.20
	Parfum	1.00
E	Coco-Betaine (30 %)	5.50
F	preservative	0.80
	Sodium Chloride	1.00

Procedure:

- A Mix part A under stirring.
- B Add. ingredients of part B step by step to part A, under stirring. Neutralize with NaOH.
- C Add. all ingredients of part C step by step to the mixture.
- D Mixing separate: ingredients of part D all in perfume and add. into the shampoo.
- E/F Then add. the thickening agent until desired viscosity is reached. Add preservative.

pH: 6.10	Viscosity: 8.000 mPas (S 4/ 10 Rpm)
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Example 19: 2-Phase leave-on Conditioner:

Phase	INCI Name	% w / w
A	Aqua	65.50
	Polyquaternium-6 (40 %)	1.45
	Lactic Acid (10 %)	0.10
B	Chitosan Glycolate	5.00
	PEG/PPG-18/18 Dimethicone	2.00
	Sericin	1.00
C	Niacinamide	0.50
	Panthenyl Ethyl Ether	0.75
	Sodium Benzoate	0.50
	Steviol	q.n.
D	Alcohol	6.00
	Polysilicone-15	1.50
	Octocrylene & Homosalate & Butyl Methoxydibenzoylmethane & Tocopherol & Glycine Soja (Soyabean) Oil	0.20
	Cyclopentasiloxane	8.00
	Parfum	0.50
	Trisiloxane & Dimethicone	7.00

Procedure:

- A Add the polymer in water and mix thoroughly until a homogeneous solution is obtained.
Add lactic acid
- B Add all ingredients of part B successively and mix until clear and uniform.
- C Add all ingredients of part C successively and mix with moderate propeller agitation.
- D Mixing separate : all ingredients of part D dissolve in ethanol.
Add the solution into the product.
Homogenize moderate!

5 Technical Data:

pH: 4.52	Viscosity: spray able 2-phases
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Example 20: Solid product which needs to be dissolved prior to the application:

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Product forms to treat the hair or the scalp consisting of

- a) a solid part
- b) a liquid part,

wherein the solid part and the liquid part are mixed prior to application.

15

The solid part contains Steviol, and the liquid part contains 0 to 100 % water or/and ethanol (0 to 100 %), and/or other compounds required to dissolve the solid part in a comfortable/convenient time (1-8 min), e.g. emulsifiers, glycerine, propylene glycol, butylene glycol, rheological modifier, e.g. Carbomers, Hydroxyethyl

20

cellulose, pH-regulators.

Composition:Solid parts:

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Nr	ingredient	Wt-%
1	Mannitol	30
2	Ascorbyl Glucoside	20
3	Sodium Citrate	10

	Ceratonia Siliqua Gum	25
5	Steviol	15

Liquid phase:

Nr	ingredient	Wt-%
1	Ethanol	45
2	Water	50
3	Sorbitol	3
	Polysorbate-40	0.4
5	frangrance	q.n.

- 5 Solid part (0.01 to 10g) are mixed with the liquid part (5 mL-30mL) prior to application in an appropriated system by shaking.

Example 21: *Stabilization of steviol in acidic aqueous solution:*

- 10 Steviol was dissolved at 1 wt.-% in water and the pH adjusted at different values as shown below. At pH 9, the solution turns brown within 1 day demonstrating instability of Steviol. However, the more acidic the pH, the less discoloration was observed as reported by the patone color index.
- 15 Color index of 1% Steviol solution in water at different pH:

	pH 9	pH 7	pH 6.5	pH 6
Pantone index	160	158	155	155

Example 22: *Effect on Steviol on hair follicle melanogenesis:*

- 20 Material & Method:

For optimal quality of hair follicles with an intact pigmentary-unit, normal human scalp skin hair follicles in the anagen VI stage of the hair cycle were isolated from scalp skin biopsies obtained from elective plastic surgery after obtaining informed

consent from patients following the protocol published by Philpott and colleagues with slight modifications (Philpott et al. 1990, Philpott 1999). Briefly, after separation of epidermis and dermis from subcutaneous fat the dermis just above the dermis/subcutis border under a binocular dissecting microscope, the proximal two thirds of anagen hair follicles located in the subcutaneous fat were isolated using watchmakers forceps and subsequently collected in Petri dishes containing complete hair follicle culture medium (Williams E, Biochrom KG seromed, Berlin, Germany); 1 % Penicillin-Streptomycin; 1 % L-Glutamine 200mM; 0.02 % hydrocortisone; 0.1 % Insulin. Three hair follicles per well were then randomly distributed and cultured in 24 well plates (Costar, NY, USA) containing 500 µl of complete hair follicle culture medium per well.

Per experiment, a minimum of three wells (containing three hair follicles each) was assigned to each test group, and was supplemented with different concentrations of test substances pre-diluted in the respective dissolvent 100 x concentrated. An equal number of control follicles were cultured in complete hair follicle culture medium alone. Each experiment was repeated with hair follicles from at least three different age, pigmentation and sex matched donors.

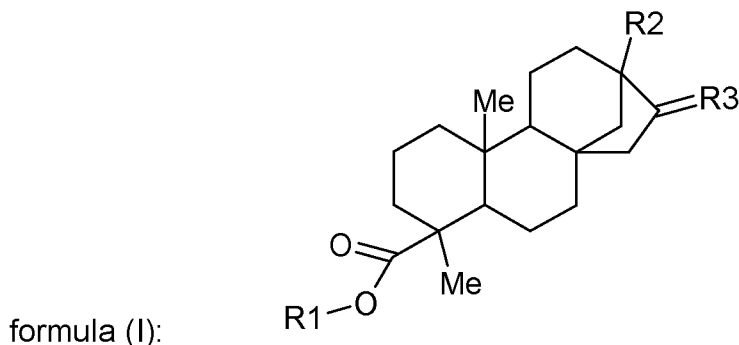
Every second day, each well was photo-documented, the pigmentation degree of each hair follicle determined, medium replaced and fresh supplements added. After 7 days hair follicles were snap frozen and stored at -80°C .

Steviol was tested at two different concentrations (0.625 and 1.25 μM). Macroscopic analysis of hair follicle pigmentation showed a slow loss of active pigmentation in the control group over the seven day culture period (in vitro graying) remaining pigmentation is scored minimal (+) in the table below. Sphingosyl phosphorylcholine at 1 μM was used as a positive control as it is known from previous work to reduce the speed of in vitro hair graying. Remaining pigmentation is scored (+++). As shown in the table below, a clear and significant improvement of hair follicle pigmentation was observed when steviol was used. This remaining pigmentation was superior when steviol was used at 0.625 μM (+++) when compared to steviol 1.25 μM (++) .

	Pigmentation	Dystrophy
Control	+	-
Sphingosylphosphorylcholine 1 microM	+++	-
Steviol 0.625 microM	+++	-
Steviol 1.25 microM	++	-

Claims

1. Topical use of a compound of formula (I) or a salt thereof,



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wherein

- R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,
- 10 R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group, and
- R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),
- for enhancement of the appearance of hair in an animal including human, wherein
- 15 the enhancement of the appearance of hair is selected from the group consisting of: restoring hair color and delaying the onset of greyness in hair, lessening hair loss, restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and
- 20 thinning, maintaining of the natural hair color, increasing hair shininess, glossiness or volume.

2. The use according to claim 1, wherein

- R1 is hydrogen (H) or a saturated, straight or branched C₁-C₅ alkyl group,
- 25 R2 is independently a saturated, straight or branched C₁-C₃ alkyl group, -O-C₁-C₃ alkyl group, -OH group, a -O-C(O)-C₁-C₃ alkyl group, and
- R3 is independently CH₂, O, or CHCH₃.

3. The use according to any of claims 1 or 2, wherein
 R1 is hydrogen (H) or a saturated, straight or branched C₁-C₃ alkyl group,
 R2 is independently a -OH group or a methyl group, and
 R3 is independently CH₂ or O.

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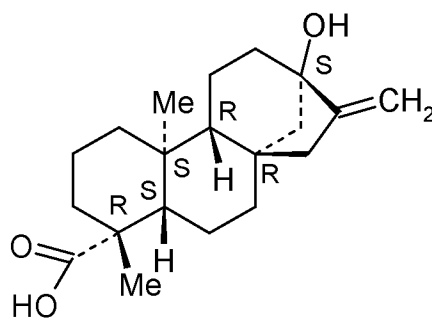
4. The use according to any of claims 1 to 3, wherein
 R1 is hydrogen (H),
 R2 is hydroxyl (OH), and
 R3 is CH₂.

10 or

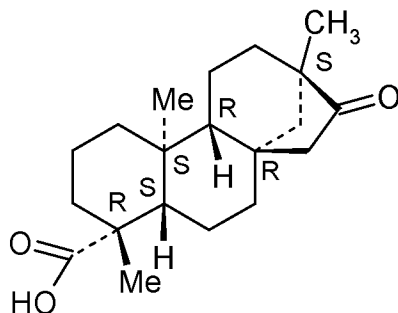
- R1 is hydrogen (H),
 R2 is methyl (CH₃), and
 R3 is oxygen (O).

- 15 5. The use according to any of claims 1 to 4, wherein the compound of formula (I) is steviol or isosteviol with the stereochemistry as depicted in of formula (IV) and formula (V).

formula (IV):



20 formula (V):



6. The use according to any of claims 1 to 5, wherein the enhancement of the appearance of hair is selected from the group consisting of: lessening hair loss,

restoring hair growth after the onset of baldness has occurred, increasing the thickness of hair, counteracting age-associated hair thinning, preventing premature hair loss, or delaying the onset or severity of age-associated hair loss and thinning.

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7. The use according to any of the claims 1 to 6, wherein the compound of formula (I) as defined by any of the claims 1 to 5 is combined with the use of at least one additional active substance selected from the group consisting of anti-oxidants, light screening agents, colorants and biological actives.

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8. The use according to any of the claims 1 to 7 wherein hair is a mammal's fur.

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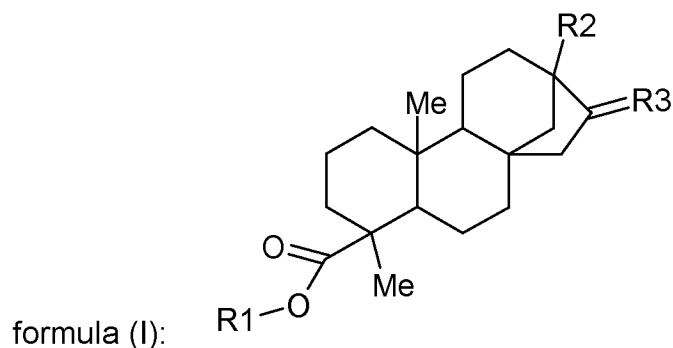
9. The use according to any of the claims 1 to 8, wherein the effective amount of compound of formula (I) is selected in the range of 0.00001 to 20 weight- %, based on the total weight of the topical composition.

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10. Use of a compound of formula (I) according to any of the claims 1 to 5 for increasing the total number of melanocytes in hair follicles, and/or for increasing the differentiation and migration of melanocytes from the hair sheath to the hair matrix and/or increasing proliferation of hair cells, and/or increasing the production of melanin, and/or for lengthening hair growth phase and/or shortening hair resting phase.

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11. Method for stimulating hair growth, and/or preventing the graying of hair or restoring or maintaining the natural hair color comprising the steps of applying to skin having hair, for a sufficient time, a topical composition comprising an effective amount of a compound of formula (I),



wherein

R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,

R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group,

R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),
and observing the result.

12. The method as in claim 11, wherein the compound of formula (I) is steviol and/or isoteviol of claims 4 or 5.

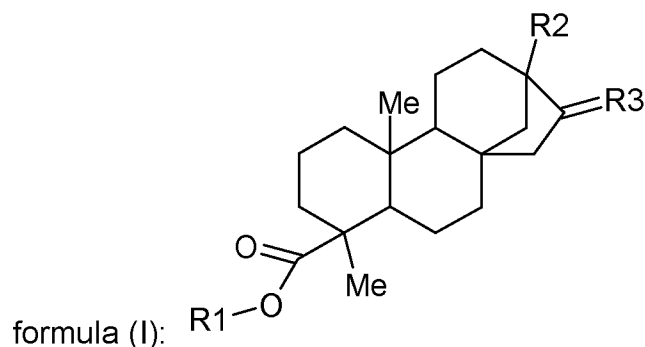
13. The method as in claims 11 or 12, wherein the effective amount of the compound of formula (I) is selected in the range of 0.00001 to 20 wt.-% based on the total weight of the topical composition.

14. The method according to any one of claims 11 to 13, wherein the topical composition is a hair care composition.

15. The method as in claim 14, wherein the hair care composition is a hair tonic, a conditioner, a shampoo, or a styling gel.

16. The method according to any one of claims 11 to 15, wherein the topical composition further comprises at least one additional active substance selected from the group consisting of antioxidants, light screening agents, colorants and biological actives.

17. Hair care composition comprising a compound of formula (I),



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wherein

R1 is hydrogen (H) or a saturated, straight or branched C₁-C₈ alkyl group non substituted or substituted with up to 3 hydroxyl-, alkoxy-, amino-, alkylamino- or dialkylamino- groups,

10 R2 is independently a saturated, straight or branched C₁-C₈ alkyl group, -O-C₁-C₈ saturated straight or branched alkyl group, -OH group, a -O-C(O) C₁-C₈ alkyl, or, -COO(C₁-C₈ alkyl) group,

R3 is independently CH₂, O, or CH-(C₁-C₇ alkyl),

and at least one conventional hair care carrier

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18. A hair care composition according to claim 17, wherein the pH of the composition is below 7.

19. Hair care composition as in any of the claims 17 or 18, further comprising
20 an antioxidant and/or a light screening agent selected from UV-A, UV-B and/or broadband UV filters.

20. A composition as in claim 17 to 19 which is a gel, a lotion, a tincture, a spray, a mousse, a cleansing composition, a shampoo, or a foam.

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