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(54) Title: SKIN LIGHTENING METHODS, COMPOSITIONS AND PRODUCTS

(57) Abstract: The invention relates to methods of cosmetic lightening the human skin, compounds and perfume compositions that have a skin lightening effect and personal care products for application to the human skin comprising such skin lightening compounds and perfume compositions. A number of compounds not known before to have a skin lightening effect were identified. These skin lightening compounds provide the perfumer with a larger palette of fragrance notes and provide more possibilities to create desired fragrance accords in skin lightening perfume compositions and skin lightening personal care products. Skin lightening perfume compositions and skin lightening personal care products according to the invention comprise at least one of the identified fragrant skin lightening compounds.

SKIN LIGHTENING METHODS, COMPOSITIONS AND PRODUCTS

The present invention is directed to methods of providing a skin lightening effect by employing certain compounds, perfume compositions comprising said compounds to provide said effect, and personal care products formed by admixing said compounds or compositions.

Products that have a skin lightening, also called skin whitening, effect are available on the market for consumers who wish to prevent or reverse skin tanning, age spots and/or hyperpigmentation for aesthetic reasons. Skin tanning is caused by the accumulation of melanin in the skin. If melanin accumulates in isolated spots, age spots and hyperpigmentations result.

Melanin is formed from tyrosine, which reaction is catalysed by the enzyme Tyrosinase. Known skin lightening compounds are tyrosinase inhibitors that directly inhibit the enzyme, for example, Arbutin, and Kojic acid. Arbutin is a plant-derived hydroquinone derivative from the leaves of the bearberry, cranberry and blueberry shrubs, and most types of pears.

Other common ingredients of skin lightening personal care products are antioxidants such as ascorbic acid and its derivatives, such as palmitoyl – ascorbic acid, glucosides of ascorbic acid and particularly ascorbic acid 2 – phosphate, and the natural polyphenolic compounds Emblicanin A and Emblicanin B.

Another potential mechanism of action for achieving reduction of melanin formation and therefore a skin lightening effect is the suppression of tyrosinase formation at the transcription or translation level. Such an effect may be achieved with octadecendioic acid.

The use of certain perfume ingredients to reduce melanin formation in melanocyte cultures is known, for example, the use of eugenol, the use of certain trimethylcyclohexane derivatives, and the use of sandalwood oil as a skin lightening agent.

Certain perfume ingredients are known as inhibitors of melanine formation, for example, beta-ionone, tetrahydro-ionone, and both forms of di-hydro-beta-ionone, the fragrant macrocyclic ketones described in EP 1264594 A2, and the fragrance terpene alcohols and their esters described in US 5466718.

In the case of personal care products (in particular those applied to the human skin in form of a cream, lotion, gel or spray), the skin lightening agents should have a sufficient skin lightening activity, in particular when used at a concentration of maximally 0.2 to 2%, in the personal care product.

Many known skin lightening ingredients have undesirable characteristics that hamper their efficiency or usefulness in personal care products, especially those applied to the skin. For example, a compound may have a strong unpleasant odor, a high volatility so that it does not stay on the skin for long, it may be too hydrophilic so that it cannot penetrate the skin sufficiently to have an effect, or it may lack stability either in the composition or on the skin when exposed to oxygen and UV.

While several skin lightening agents are known, there remains a need for additional or alternative skin lightening compounds, in particular ones that have one or more of the following desirable characteristics: a high skin lightening activity at a low concentration, the ability to penetrate the skin at least partially, a low volatility in order to stay on the skin for a sufficient time to have an effect, good stability in a perfume composition, in a formulation for a personal care product as well as on the skin. Further, there remains a need for skin lightening compounds which at the concentration of use in a personal care product enhance the activity of existing skin lightening compounds, so that either the activity can be improved at a given concentration, or the concentration of a particular skin lightener and accordingly its undesired characteristics, such as a detrimental effect on the skin and/or an unpleasant smell, can be reduced.

With the few currently known fragrant skin lightening compounds, it is difficult for perfumers to achieve perfume compositions with sufficient activity and an acceptable odour. This is made even more difficult for skin lightening ingredients that need to be integrated into a perfume composition in a high concentration to have a skin lightening effect in the product. The odor is crucial for consumer acceptance of a product. Using only one fragrant skin lightening compound (or a skin lightening perfume ingredient comprising a mixture of compounds with one skin lightening ingredient being dominant), an overpowering fragrance note may result. This is in particular true for such compounds or ingredients that require a high concentration for activity so that the resulting skin lightening product will be perceived as unpleasant by the consumer. The availability of a larger variety of skin lightening compounds, in particular fragrant ones of particular fragrance notes, would provide the perfumer with more possibilities to create a desired fragrance accord while providing skin lightening activity at the same time.

Among a large number of compounds, there have been identified certain compounds of different fragrance classes that have a skin lightening activity.

The use of such compounds in perfumes in general is known, this includes e.g. perfumes that may comprise, among others, iso E super and Galaxolide (WO 96/12467). Products according to WO 96/12467 include such perfumes and optionally, for skin bleaching, bleaching agents (hydrochinone, ascorbic acid, kojic acid, sodium bisulfite). However, these perfumes do not contain the identified skin lighteners in a high concentration and in combination of at least two skin lightening compounds according to the invention. If only one skin lightening compound is used in sufficiently high concentration, it will be difficult to formulate a perfume composition that is both active as skin lightener in a product and has a fragrance acceptable for the consumer.
Some compounds may be known not only as perfume but also as actives that are used in specialist personal care products, for example deodorants, antiperspirants, antibacterials, anti-acne products, and shampoos. This is the case for Sandela which has an antibacterial and thereby anti-malodorant effect (EP 1181866). Such specialised formulations are not normally used on parts of the body where skin lightening is of interest and may be unsuitable for achieving a skin lightening effect. In particular, products against acne and antibacterials are usually not evenly applied, and deodorants, anti-perspirants or shampoos are applied to the human skin in regions that are not exposed to sun (axilla, hair) and where the skin will not need lightening.

The identified skin lightening compounds can be admixed to personal care products to lighten the human skin. Because of their pleasant fragrance characteristics and their high skin lightening activity even at low concentrations, they are easily integrated into perfume compositions for skin lightening personal care products. Because of their lipophilic nature, they are able to penetrate the skin, and they have a low volatility so they will stay on the skin for a longer time. Skin lightening compounds for use in compositions and methods according to the invention as defined hereinabove have a high degree of lipophilic nature, preferably a clogP of higher than 3.6. ClogP is calculated using the ACD program ACD/LogP, version 4.0, Advanced Chemistry Development, Inc., Toronto ON, Canada. Further, skin lightening compounds have a low volatility, in particular a vapour pressure of below 250 µ(micro)g/L, as measured by the saturated concentration in air at 25°C.

Skin lightening compounds for use in compositions and methods according to the invention can be used to form stable skin lightening perfume compositions and skin lightening personal care products.

Further, skin lightening compounds for use in compositions and methods according to the invention can be combined with other known skin lightening compounds, in particular one or more compounds selected from the group consisting of arbutin, and octadecendioic acid (CAS 70445-23-7, commercially available as Arlatone dioic DCA™ from Seppic, Netherlands), and have an enhancing effect. Therefore, they can be used to reduce the concentration of the skin lightener used in combination while keeping the effectiveness, or enhance the effect at a

given concentration. A similar advantageous combination of skin lightening compounds as defined hereinabove with deoxyarbutin (4-[(tetrahydro-2H-pyran-2-yl)oxy]phenol) also has said enhancing effect and can be used accordingly.

In a first aspect, the invention is directed to the use of skin lightening compounds as defined hereinbelow for the cosmetic lightening of the skin, and in particular, to a cosmetic method employing one or more such skin lightening compounds for the lightening of the human skin. This method involves applying at least one skin lightening compound, preferably at least two skin lightening compounds, to the skin in regular intervals to achieve a lightening of the skin. The application may be in form of a skin lightening personal care product.

Skin lightening compounds for use in compositions and methods according to the invention are selected from the group consisting of 2-[2-(4-methyl-3-cyclohexen-1-yl)-propyl]-cyclopentanone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one, 1-(2,6,6-trimethylcyclohex-1-en-1-yl)-but-2-ene-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-but-2-ene-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-but-2-ene-1-one, alpha ionone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-penten-3-one, 6-isopropyl-octahydro-naphthalen-2-one, 4,7,7-trimethyl-2-(3-methyl-but-2-enyl)-bicyclo[4.1.0]heptan-3-one, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl)-ethanone, 1,1,2,3,3,8-hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[b]naphthalene, 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene, 1,1,2,3,3-pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one, 1-(2,3,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone, 2,2,3',7',7'-PENTAMETHYLSPIRO(1,3-dioxan-5,2'-norcarane), methyl-n-3,7-dimethyl-7-hydroxyoctylidene anthranilate, 2-[3-(4-tert-butyl-phenyl)-2-methyl-propenylamino]-benzoic acid methyl ester, 2-[(2,4-dimethyl-cyclohex-3-enylmethylene)-amino]-benzoic acid methyl ester, 2-methyl-4-(2,6,6-trimethyl-cyclohex-2-enyl)-butyraldehyde, 3-(3-isopropyl-phenyl)-butyraldehyde, 3-(4-isobutyl-phenyl)-2-methyl-propionaldehyde, [1-methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol, 2-ethyl-4-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-but-2-en-1-ol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, the product of the sandela-process comprising 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol (commercially available as "sandela™", 3-methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, (e)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on, and oxacyclohexadec-12-en-2-one (compare table 1 for structures and tradenames of commercially available compounds or mixtures of compounds).

In another aspect, the invention is directed to skin lightening perfume compositions.

Said skin lightening perfume composition comprises
(a) at least 30% (w/w) of at least two skin lightening compounds as defined hereinabove

(b) up to 70% (w/w) of optional ingredients selected from one or more of additional perfume ingredients including additives, excipients, and solvents used in perfumes.

In another aspect, the invention is directed to a method of preparing a skin lightening personal care product wherein at least one skin lightening compound or composition, as hereinabove defined, is admixed to a personal care product formulation.

In another aspect, the invention is directed to skin lightening personal care products comprising skin lightening compounds or compositions as herein defined.

In another aspect, the invention is directed to the cosmetic use of at least one skin lightening compounds as defined hereinabove as skin lightening actives in skin lightening personal care products.

In yet another aspect, the invention is directed to a method of preparing a skin lightening personal care product comprising the steps of
a) providing a personal care product prepared by admixing at least one skin lightening compound, as hereinabove defined, to a personal care product formulation and forming a personal care product
b) packaging the personal care product
c) providing instructions for the use for cosmetic lightening of the skin to the packaged personal care product.

In another aspect, the invention is directed to a method of cosmetic lightening of the skin by applying at least one skin lightening compound, as hereinabove defined, to pigmented or hyperpigmented human skin regularly and in a sufficient amount.

The skin lightening personal care product is formed by admixing at least one skin lightening compound, preferably at least 2, 3, 4 or 5 skin lightening compounds, as hereinabove defined, to a personal care product formulation in a sufficient concentration to provide a skin lightening effect. A skin lightening personal care product may by formulated by first preparing a skin lightening perfume composition and then combining this perfume composition with the rest of the formulation. Such a perfume composition is made up of skin lightening ingredients as hereinabove described and other optional ingredients, such as perfume ingredients and excipients.

The concentration of a skin lightening compound suitable in a personal care product applied to the skin depends on the particular compound. Because of skin penetration and dilution in the underlying tissue, the concentration

needed in a personal care product generally is considerably higher than the active concentration in a cell culture system (compare example 1 and 2). A useful concentration in a personal care product usually is about 100 – 1000 times that of the concentration active in a cell culture assay system as described herein and may be easily tested.

A preferred sufficient concentration is 0.1% to 2%, preferably to 0.2% to 1.5%, most preferably 0.6% to 1.2%. The concentration also depends on the type of personal care product, and in particular how the product is applied to the skin and how long it stays on the skin, as will be apparent to the skilled person. For rinse-off products, i.e. products applied to the skin only for a short time, e.g. a few seconds up to a few minutes (soap, shower gel etc.), a higher concentration should be used, for example 0.6% to 2%, preferably 0.8 to 2%, more preferably 1 to 2%. For personal care products that stay on the skin for a longer period, e.g. of several hours (creams, lotions and similar), a concentration of 0.1% to 1.5%, preferably 0.4% to 1.2%, more preferably 0.5% to 1 % is preferred.

Skin lightening personal care products are formed by admixing skin lightening compounds or perfume compositions with ingredients for personal care products, as is well-known in the art. Such products may be formed, for example, as described in *Kosmetik,* ed. W. Umbach, 1988, Georg Thieme Verlag, Stuttgard, New York. In particular, the products include personal care products for application to the human skin, such as creams, lotions, gels, talcum powders, sprays, sunscreen and after-sun preparations in any suitable form, such as creams, lotions, gels and sprays, wash formulations for the human skin including hand wash formulations, soap bars, aqueous soap formulations, syndet solutions (synthetic detergents), and shower gels. These products contain excipients including, for example, surfactants, emulsifiers, soap acids, solvents, colorants, preservatives, antioxidants, antifoaming agents, antimicrobial agents, antiredeposition agents, enzymes, vegetal or mineral oils, fats, fluorescent materials, fungicides, hydrotropes, moisturizers, perfume carriers, perfume, preservatives, proteins, silicones, solubilizers, sugar derivatives, sun screens, vitamins, plant extracts and waxes. Excipients generally used in such products may be found in the "International cosmetic ingredient dictionary",6th ed., The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, 1995.

Perfume compositions according to the present invention comprise at least one skin lightening compound as defined hereinabove, preferably at least 2, 3, 4 or 5, in a concentration (v/v) of at least 30%, preferably at least 50%, more preferably at least 70% based on volume per total volume of perfume ingredients.

Optionally, the inventive perfume compositions may contain further perfume ingredients (single compounds or complex mixtures such as natural oils) of up to 30%, up to 50%, or up to 70%, respectively.

Preferably, inventive perfume compositions contain skin lightening compounds as defined hereinabove selected from more than one of the fragrance note classes, preferably 2, 3, 4, or 5 of these classes detailed hereinunder.

The variety of skin lightening perfume compounds of the present invention allows the perfumer to compose perfume compositions that are skin lightening as well as pleasing to the senses, which has not been possible to the same extent before.

Skin lightening perfume compounds of the present invention are classified into 5 classes according to their chemical structure and their fragrance notes. These classes and the skin lightening compounds of said classes are detailed below.

Class 1: fruity-woody ketones, Class 2: polycyclic woody-musky compounds, Class 3: Floral Schiff bases of anthranilate and aldehydes, Class 4: Sandalwood alcohols, Class 5: macrocyclic musky lactones and ketones.

Class 1 skin lightening compounds are selected from the group consisting of 2-[2-(4-methyl-3-cyclohexen-1-yl)-propyl]-cyclopentanone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-2-buten-1-one, 1-(2,6,6-trimethylcyclohex-1-en-1-yl)-but-2-ene-1-one, 1-(2,6,6-trimethyl-3-cyclohexen-1-yl)-but-2-ene-1-one, 1-(2,6,6-trimethyl-1,3-cyclohexadien-1-yl)-but-2-ene-1-one, alpha ionone, 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-penten-3-one, 6-isopropyl-octahydro-naphthalen-2-one, 4,7,7-trimethyl-2-(3-methyl-but-2-enyl)-bicyclo[4.1.0]heptan-3-one.

Class 2 skin lightening compounds are selected from the group consisting of 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl)-ethanone , 1,1,2,3,3,8-hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[b]naphthalene, 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene, 1,1,2,3,3-pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one, 1-(2,3,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone, and 2,2,3',7',7'-pentamethylspiro-(1,3-dioxan-5,2'-norcarane).

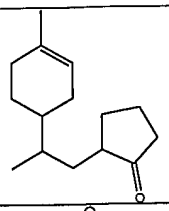
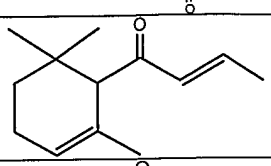
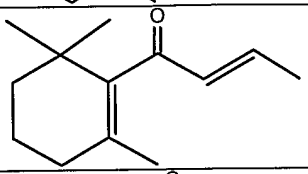
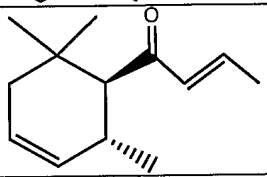
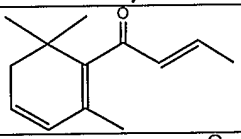
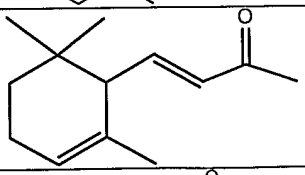
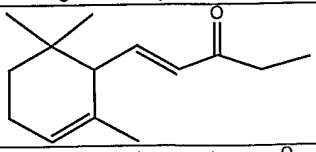
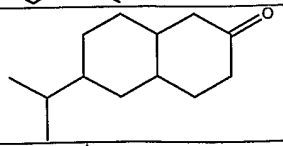
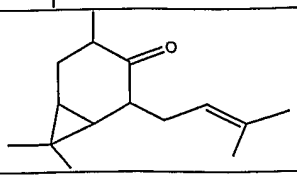
Class 3 skin lightening compounds are selected from the group consisting of methyl-n-3,7-dimethyl-7-hydroxyoctylidene anthranilate, 2-[3-(4-tert-butyl-phenyl)-2-methyl-propenylamino]-benzoic acid methyl ester, 2-[(2,4-dimethyl-cyclohex-3-enylmethylene)-amino]-benzoic acid methyl ester, 2-methyl-4-(2,6,6-trimethyl-cyclohex-2-enyl)-butyraldehyde, 3-(3-isopropyl-phenyl)-butyraldehyde, 3-(4-isobutyl-phenyl)-2-methyl-propionaldehyde.

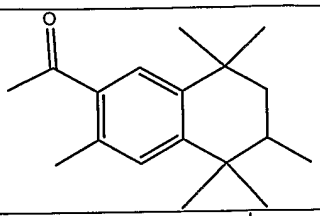
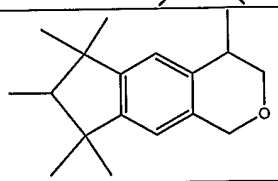
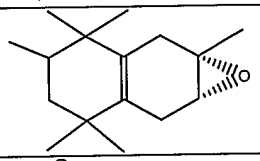
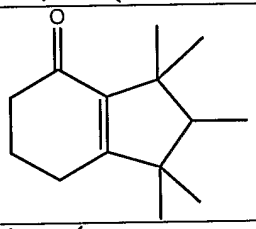
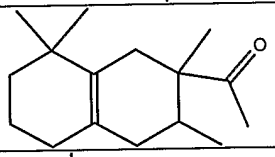
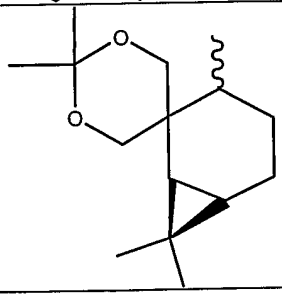
Class 4 skin lightening compounds are selected from the group consisting of [1-methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol, 2-ethyl-4-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-but-2-en-1-ol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexanol, the product of the sandela-process comprising 3-(5,5,6-

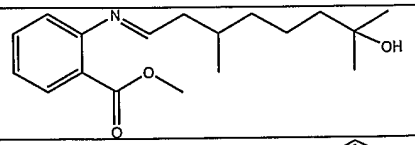
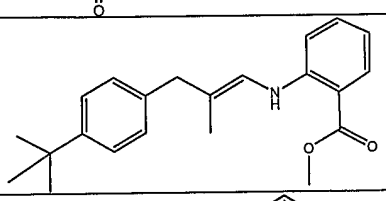
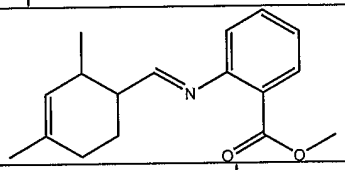
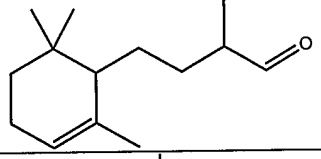
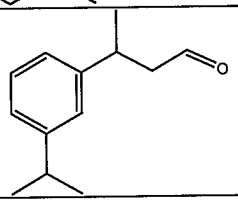
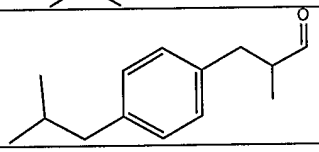
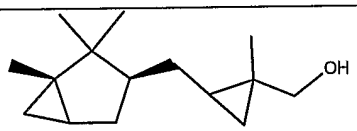
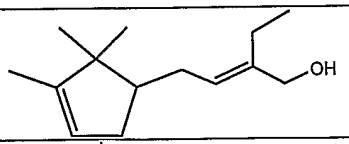
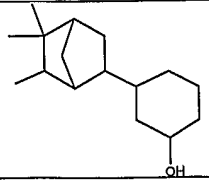
trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol (commercially available as "sandela™), 3-methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol,

Class 5 skin lightening compounds are selected from the group consisting of (e)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on, and oxacyclohexadec-12-en-2-one.

For the chemical structures of the skin lightening compounds, see the table below.

Class 1: Fruity- woody ketones	
Nectaryl™ 2-[2-(4-methyl-3-cyclohexen-1-yl)-propyl]-cyclopentanone	
Alpha Damascone™ 1-(2,6,6-trimethyl-2- cyclohexen -1-yl)-2-BUTEN-1-ONE	
Beta Damascone™ 1-(2,6,6- trimethyl cyclohex-1-en-1-yl)-but-2-ene-1-one	
Delta Damascone™ 1-(2,6,6- trimethyl -3- cyclohex -1-yl)-but-2-ene-1-one	
Damascenone™ 1-(2,6,6- trimethyl -1,3-cyclohexadien-1-yl)-but-2-ene-1-one	
Alpha ionone	
n-methyl-alpha ionone 1-(2,6,6-trimethyl-2-cyclohexen-1-yl)-1-penten-3-one	
Decatone™ 6-Isopropyl-octahydro-naphthalen-2-one	
Precarone™ 4,7,7-Trimethyl-2-(3-methyl-but-2-enyl)-bicyclo[4.1.0]heptan-3-one	

Class 2: Polycyclic woody-musky compounds	
Fixolide™ 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl) ethanone	
Galaxolide™ 1,1,2,3,3,8-Hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[b]naphthalene	
Moxalone™ 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene	
Cashmeran™ 1,1,2,3,3-Pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one	
Iso E Super™ 1-(2,3,8,8-Tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone	
Spirambrene™ 2,2,3',7',7'-pentamethylspiro(1,3-dioxan-5,2'-norcarane	

Class 3: Floral Schiff bases of anthranilate and aldehydes	
Aurantiol™ methyl-N-3,7-dimethyl-7-hydroxyoctylidene anthranilate	
Verdantiol™ 2-[3-(4-tert-Butyl-phenyl)-2-methyl-propenylamino]-benzoic acid methyl ester	
Agrumea™ 2-[(2,4-Dimethyl-cyclohex-3-enylmethylene)-amino]-benzoic acid methyl ester	
Cetonal 2-Methyl-4-(2,6,6-trimethyl-cyclohex-2-enyl)-butyraldehyde	
Florhydral™ 3-(3-Isopropyl-phenyl)-butyraldehyde	
Silvial™ 3-(4-Isobutyl-phenyl)-2-methyl-propionaldehyde	
Class 4: Sandalwood alcohols	
Javanol™ [1-Methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol	
Radjanol™ 2-ETHYL-4-(2,2,3- trimethyl -cyclopent-3-en-1-yl)-but-2-en-1-ol	
3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol	

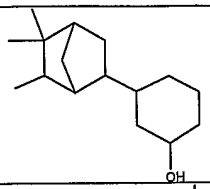
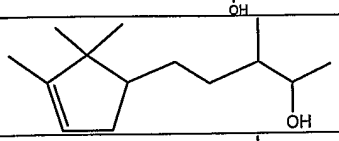
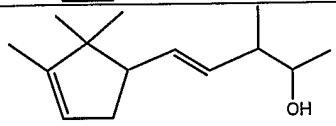
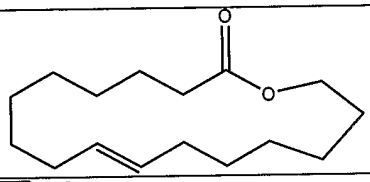
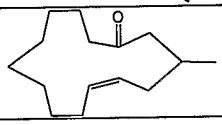
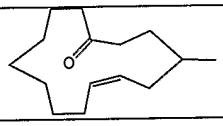
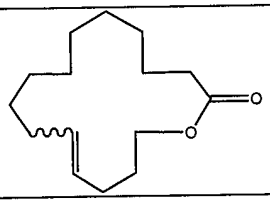
Sandela™ Mixture provided by the process as described herein-below, containing as a main component 3-(5,5,6-trimethyl-bicyclo-[2.2.1]hept-2-yl) cyclohexanol	
Sandalore™ 3-Methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol	
Ebanol™ 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-YL)-4-penten-2-ol	
Class 5: Macrocyclic musky ketones and lactones	
Ambrettolide™ (E)-oxacycloheptadec-10-en-2-one	
3-Methylcyclotetradec-5-en-1-on	
4-Methylcyclotetradec-6-en-1-on	
Habanolide Oxacyclohexadec-12-en-2-one	

Table 1 Skin lightening compounds of the present invention and their classes

The compounds or mixtures of compounds are available commercially under the tradenames as indicated in the table above, except for 3-methylcyclotetradec-5-en-1-on and 4-methylcyclotetradec-6-en-1-on. The latter compounds may be prepared by various known methods, for example as described in US6,326,349.
For example, 4-carboxy-3-methylbutyl)triphenylphosphonium bromide is subjected to a Wittig reaction, for example by treatment with potassium t-butoxide in tetrahydrofuran and subsequent addition of methyl 9-oxononanoate. The resulting product, dimethyl 3-methyltetradec-5-enedioate is subjected to an acyloin condensation and then treated with acetic anhydride/pyridine. The resulting mixture of mainly Z-4-methyl-2-

oxocyclotetradec-6-enyl acetate and Z-3-methyl-14-oxocyclotetradec-5-enyl acetate is treated with calcium in ammonia at a low temperature (e.g., between about -30° C to about -70° C.). The excess calcium is destroyed using bromobenzene. This method produces a mixture of the following compounds: E-3-methyl-cyclotetradec-5-enone, Z-3-methyl-cyclotetradec-5-enone, and Z-4-methyl-cyclotetradec-6-enone; the ratio of compounds may vary. A possible ratio is for example about 11%, 35%, and 49% of the above compounds. The compounds may be used as a mixture or may be separated by a suitable separation method as is well known in the art. Alternatively, 3-methylcyclotetradec-5-en-1-one (E- and Z-3-methylcyclotetradec-5-en-1-one isomers) may be obtained by pyrolysis of the silyl ether of cis/trans propenylcyclododec-3-en-1-ol, in analogy to the method described in WO02068372, as will be apparent to the skilled person.

Sandela™ is the reaction product which is formed from Camphene and Guaiacol with an acidic catalyst followed by hydrogenation (US 3'499'937). It is a mixture of isomers with 3-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexan-1-ol as the main constituent, but further comprising 2-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexan-1-ol and 4-(5,5,6-Trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexan-1-ol. It also contains low levels of 2-methoxy-4-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexanol and 2-methoxy-5- (5,5,6-trimethylbicyclo[2.2.1]hept-2-yl)-cyclohexanol.

Some compounds, in particulr many class 1 compounds (damascones, ionones and their derivates), all class 3 compounds, Javanol and Radjanol have a strong characteristic odour that makes their use as single skin lightening component in a perfume composition for personal care products or in the personal care end products in high concentration not feasible due to the resulting odour which will be perceived as unpleasant by the consumer.

The following perfume mixtures of skin lightening compounds as defined hereinabove are particularly preferred for their pleasant fragrance as well as good skin lightening activity:
The skin lightening compounds as defined hereinabove should together total to at least 30%, preferably at least 50%, most preferably at least 70% of the perfume composition, which may contain optional ingredients including other perfume ingredients.

A) Perfume mixture comprising
   - 10 – 40 % polycyclic woody – musky compounds
   - 5 -20 % sandalwood alcohols
   - 5 – 20% fruity - woody ketones

B) Perfume mixture comprising

- 2.5 – 10 % macrocyclic musky lactones and ketones
- 5 – 20 % sandalwood alcohols
- 5 – 40 % polycyclic woody – musky compounds
- 5 – 20% fruity - woody ketones

C) Perfume mixture comprising
- 10 – 40 % polycyclic woody – musky compounds
- 5 - 20 % sandalwood alcohols
- 2.5 – 20% Floral Schiff bases of anthranilate and aldehydes

D) Perfume mixture comprising
- 2.5 – 10 % macrocyclic musky lactones and ketones
- 10 – 40 % polycyclic woody – musky compounds
- 5 -20 % sandalwood alcohols
- 2.5 – 20% Floral Schiff bases of anthranilate and aldehydes

E) Perfume mixture comprising
- 2.5 – 10 % macrocyclic musky lactones and ketones
- 5 – 30 % polycyclic woody – musky compounds
- 5 -20 % sandalwood alcohols
- 2.5 - 10% Floral Schiff bases of anthranilate and aldehydes
- 5 – 20% fruity - woody ketones

F) Perfume mixture comprising
- 10 – 40 % polycyclic woody – musky compounds
- 5 – 20% fruity ketones
- 2.5 – 20% Floral Schiff bases of anthranilate and aldehydes

G) Perfume mixture comprising
- 2.5 – 10 % macrocyclic musky lactones and ketones
- 10 – 40 % polycyclic woody – musky compounds
- 5 – 20% fruity ketones
- 2.5 – 20% Floral Schiff bases of anthranilate and aldehydes

Particularly preferred skin-lightening compounds are selected from the group consisting of (E)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, and 4-methylcyclotetradec-6-en-1-one and Oxacyclohexadec-12-en-2-one. These compounds are particularly beneficial when combined with other skin lightening compounds. Without wishing to be bound by theory, it is believed that these compounds, in addition to their own intrinsic skin lightening potential, have a chemical structure that allows them to interact with other skin lightening compounds of a more hydrophilic nature, and therefore enhance the skin lightening effect by increasing the penetration into the skin.

Particularly the known skin lightening compounds arbutin, deoxyarbutin, octadecendioic acid, kojic acid, emblicanin A, emblicanin B, ascorbic acid, and ascorbic acid derivatives may be enhanced in their skin lightening activity by the combination with at least one skin lightening compound selected from the group consisting of (E)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-one, 4-methylcyclotetradec-6-en-1-one, and oxacyclohexadec-12-en-2-one (Habanolide™).

Therefore, a particularly preferred skin lightening perfume composition, or skin lightening personal care product, comprises one or more compounds selected from the group consisting of (E)-oxacycloheptadec-10-en-2-one or 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on and oxacyclohexadec-12-en-2-one (Habanolide™); in combination with one or more other skin lightening compounds as defined hereinabove selected from the group consisting of arbutin, octadecendioic acid, deoxyarbutin, kojic acid, emblicanin A, emblicanin B, ascorbic acid, and ascorbic acid derivatives.

Skin lightening perfume compositions according to the invention are obtained by admixing one or more of skin lightening compounds as defined hereinabove in a concentration of at least 30%, at least 50%, or at least 70%, and one or more optional ingredients in a concentration of up to 70%, up to 50% or up to 30%.

The optional ingredients in skin lightening perfume compositions comprise solvents, non-skin lightening perfume ingredients for aesthetic reasons, known skin lightening actives for an additive effect, and other known additives and excipients. Additional perfume ingredients may be added to provide or change a particular desired perfume note. Such additives or excipients are, for example, described in "Perfume and Flavor Materials of Natural Origin", S. Arctander, Ed., Elizabeth, N.J., 1960; in "Perfume and Flavor Chemicals", S. Arctander, Ed., Vol. I & II, Allured Publishing Corporation, Carol Stream, USA, 1994; and "International cosmetic ingredient dictionary",,6th ed., The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, 1995.

A skin lightening activity of a skin lightening compound as defined hereinabove is determined by employing the classical test using the mouse melanoma cell line B16V, which has a high intrinsic ability to form melanin *in vitro*. In this test, skin lightening compounds as defined hereinabove are compared with known skin lightening compounds such as arbutin, deoxyarbutin, octadecendioic acid, or kojic acid. It has been found that skin lightening compounds as defined hereinabove inhibit melanin formation in the mouse melanoma cell line B16V at concentrations where they do not affect cell viability or cell growth and are thus identified to have a specific suppressive effect on melanin formation.
Skin lightening compounds as defined hereinabove have therefore a comparable or improved skin lightening effect when compared to the known skin lighteners arbutin and kojic acid, as shown in example 2. The effect of skin lightening compounds as defined hereinabove is, for example, an inhibition of melanine formation in the B16V test of at least 25% at a test concentration of 6.3 parts per million (ppm) or by an inhibition of at least 30% at a concentration of 12.5 ppm. Preferred skin lightening compounds have an inhibition of at least 30% at a test concentration of 6.3 parts per million (ppm) or by an inhibition of at least 35% at a concentration of 12.5 ppm.

Perfume compositions according to the invention inhibit the melanine formation in the B16V cell line test by at least 30% at 12.5 ppm, or by at least 20% at 6.25 ppm, or at least 20% at 3.125 ppm.
Preferred perfume compositions according to the invention inhibit the melanine formation in the B16V cell line test by at least 50% at 12.5 ppm, or by at least 30% at 6.25 ppm or by at least 30% at 3.125 ppm without affecting cell viability at any of these test concentrations.
These perfume compositions have a skin lightening effect in the human skin when used at a final concentration of 0.1 to 2%.

Further it has been found that most skin lightening perfume compounds as defined herein-above are compatible with arbutin, deoxyarbutin, and with octadecendioic acid, and, when used together with arbutin, or octadecendioic acid or a combination of these, provide an enhanced skin lightening effect. Deoxyarbutin may also provide said enhancing effect.

Skin lightening compounds or perfume compositions as defined herein- above may be admixed to personal care products in addition to known skin lightening compounds to form a perfumed skin lightening personal care product. Such a personal care product may, for example, comprise as a known skin lightening ingredient, for example arbutin, deoxyarbutin, or octadecendioic acid, or a combination thereof, in a concentration from 0.05 to 1 %.

Skin lightening compounds as defined hereinabove are compatible with a wide variety of compounds and instead of arbutin, deoxyarbutin, or octadecendioic acid, other compatible ingredients with skin lightening activity may be added. For example, ascorbic acid, derivatives of ascorbic acid such as ascorbic acid 2 –phosphate, kojic acid, eugenol, beta-ionone, tetrahydro-ionone, both forms of di-hydro-beta-ionone, macrocyclic ketones described in EP 1264594 A2, especially Cyclohexadec-5-ene-1-one and 4-(4-hydroxyphenyl)-butan-2-one.

Skin lightening personal care products are products intended for the cosmetic lightening of the skin. The directed use for skin lightening may be determined from the statements made on or in a product's label or labelling, insert or flyer provided with the product. Such use involves the regular application of a sufficient amount to the skin , in particular at least once daily, preferably twice daily , more peferably three times daily. A sufficient amount, when used at a concentration as defined herein above (for example from 0.1 to 2%), is an amount of 5-50 mg/cm^2 skin (equal to about 0.05 to 0.5 mm thickness of the product applied to the skin). The skin lightening personal care product, especially when left on the skin without rinsing off, should be applied evenly to the skin to ensure that the skin is lightened evenly.

Similarly, a skin lightening perfume composition is one intended for the cosmetic lightening of the skin. The directed use to perfume skin lightening personal care products, in particular by admixture of skin lightening compounds as defined hereinabove to personal care product formulations to form skin lightening personal care products, may be determined from the statements made on or in the perfume compositions label or labelling, insert or flyer provided with the skin lightening perfume composition.

Examples

Example 1

Determination of melanin formation in B16V cells

The cell line employed is mouse melanoma cell line B-16V, which may be obtained from the German collection of microorganisms and cell cultures (DSMZ, Braunschweig, Germany). It is maintained in medium RPMI 1640 (Invitrogen, Basel, Switzerland) supplemented with 5% heat inactivated fetal calf serum.

A confluent culture is diluted to a final cell density of 2 x 10^4 cells/ml and 2 ml of the cell suspension are added to each well of 6 well plate. Cells are cultivated for a period of 24 h at a humidity of 98% in a 5% carbon dioxide atmosphere. Test compounds are then added in dimethylsulfoxide (DMSO), with the maximal concentration in the culture medium not exceeding 0.5% DMSO. The cultures are further incubated for 72 h under the same conditions in presence of the test compounds. The supernatant is then removed, the cells are washed in phosphate buffered saline (PBS) and lysed by the addition of 0.5 ml per well of a solution containing 500 mM NaOH and incubation at 70°C for 30 min. The resulting solution is transferred to 96 well plates and the optical density is then measured at 405 nm to quantify the amount of formed melanin.

To confirm the specificity of results, parallel cultures containing the same inhibitory compounds at equal concentrations are used to determine potential cytotoxic effects of test compounds using the MTT assay as follows. Cells are treated as described above until washing in PBS. Then, a solution containing Thiazolyl blue tetrazolium bromide (MTT, 0.5 g / L in RPMI 1640) is added to the washed cells and they are incubated for 4 h at 37°C. Under these conditions, viable cells reduce MTT to a purple colored dye. A solution of sodium dodecyl sulfate (10%) is added to cells and they are left for 48 h at room temperature in order to lyse the cells and solubilise the reduced tetrazolium dye. The optical density of the resulting solution at 600 nm is then determined. The optical density of control cultures receiving DMSO only and no test compound is set as 100%, and the relative viability of treated cultures is assessed.

Results of these parallel assays show (a) the reduction in melanin formation at a given concentration of the test compound and (b) the relative viability of cultures at the same test concentration .

Example 2: Compounds with a skin lightening effect

For testing a skin lightening effect, mouse melanoma cell line B16V is used as described in example 1. A large number of commercially available materials including a collection of a large number of perfumery ingredients is tested.

The following perfume compounds are found to have a skin lightening effect at least comparable or better than known skin lightening compounds that were also tested (For chemical names of perfume compounds, see table in the description hereinabove.)

These known skin lightening compounds are: Arbutin, Kojic acid, Emblicanin A / Emblicanin B extracted from *Phyllanthus emblica* fruit, sold under the trade name EMBLICA by Merck, Darmstadt, Germany and 4-(4-hydroxyphenyl)-butan-2-one..

	% inhibition of melanin formation in the cell line B16V after 3 days incubation with test agent			
	12.5 ppm	6.3 ppm	3.1 ppm	1.6 ppm
CONTROL: arbutin	59.1	45.3	35.5	n.d.
CONTROL: Kojic acid	9 [1)]	0	n.d.	n.d.
CONTROL: Emblica	15	0	n,d,	n.d.
Control: 4-(4-hydroxyphenyl)-butan-2-one	n.d.	62.8	54.4	n.d.
Nectaryl™	n.d.	48.3	33.5	n.d.
Alpha Damascone™	n.d.	78.0	70	60.0
Beta Damascone™	n.d.	87.3	84.9	n.d.
Delta Damascone™	n.d.	87.3	85.4	n.d.
Damascenone™	n.d.	83.3	72.1	n.d.
Alpha ionone	n.d.	58.5	35.8	n.d.
n-methyl-alpha ionone	n.d.	40.0	32.4	n.d.
Cetonal™	n.d.	40.5	41.8	n.d.
Fixolide™	n.d.	88.3	84.3	75.4

Galaxolide™	n.d.	n.d.	78.2	75.7
Moxalone™	28.4	32.8	35.8	n.d.
Iso E Super™	40.5	35.2	n.d.	n.d.
Cashmeran™	60.6	45.3	39.9	n.d.
Aurantiol™	n.d.	90.3	62.8	n.d.
Verdantiol™	75.0	52.6	n.d.	n.d.
Agrumea™	35	27.2	n.d.	n.d.
Javanol™	n.d.	91.4	43.1	33.6
Radjanol™	n.d.	68.1	58.3	n.d.
Sandela™	n.d.	92.0	86.7	63.2
Sandalore™	77.6	53.5	26.0	n.d.
Ebanol™	76.3	53.6	n.d.	n.d.
3-Methylcyclotetradec-5-en-1-on	78.3	56.3	53.6	n.d.
Ambrettolide™	40.3	34.3	44.2	n.d.
Habanolide™	36.9	26.35	n.d.	n.d.
Silvial™	56.5	23.3	n.d.	n.d.
Florhydral™	n.d.	n.d.	39.9	29.4

Decatone™	35.2	25.6	n.d.	n.d.
Precarone™	46.05	43.95	n.d.	n.d.
Spirambrene™	41.1	37.75	n.d.	n.d.

[1)] the control compound Kojic acid did significantly inhibit melanine formation only at higher concentrations: Thus Kojic acid gives 17% inhibition at 25 ppm and 37% inhibition at 50 ppm and 60% at 100 ppm. N.d. = not determined at a given concentration of test agent

3-Methylcyclotetradec-5-en-1-on may be replaced partly or compeltely with 4-Methylcyclotetradec-6-en-1-on to give similar results.

At the indicated test concentration, all compounds did not affect cellular viability.

Several hundred other compounds tested are found not to have the desired skin lightening effect.

Example 3: perfume compositions with skin lightening effect

The following perfume compositions were made:

Skin lightening perfume composition A:

Skin lightening compounds:	**Parts per 100**
Alpha Damascone™	0.13
Alpha ionone™	0.42
Ambrettolide™	0.42
Aurantiol™	1.67
Beta Damascone™	0.04
dipropyleneglycol	25.92
Fixolide™	8.33
Galaxolide™	25.00
Iso E Super™	15.00

Javanol™	0.04
Moxalone™	0.42
Nectaryl™	0.13
Radjanol™	2.50
Sandela™	4.17
Verdantiol™	1.67
Optional perfume ingredients:	
alpha-Cyclohexylidene benzeneacetonitrile	1.67
2-oxo-1-pentyl-cyclopentaneacetic acid-methyl ester	6.67
2-phenyl-ethanol	4.17
2-hydroxy-benzoic acid-benzyl ester	0.83
Acetic acid 2-tert-butyl-cyclohexyl ester	0.83

Skin lightening perfume composition B:

Skin lightening compounds:	Parts per 100
Ambrettolide™	10
Silvial™	5
Florhydral™	5
Iso E super™	5
Irisone alpha™	5
Alpha-Damascone™	5
Sandela™	10
Cashmeran™	5
Radjanol™	5
Aurantiol™	5
Fixolide™	10
Optional perfume ingredients:	
2-oxo-1-pentyl-cyclopentaneacetic acid-methyl ester	5
Linalool	10
Linalyl acetate	15

Skin lightening perfume composition C:

Skin lightening compounds:	Parts per 100
Ambrettolide™	10
Decatone™	10
Nectaryl™	10
Irisone alpha™	5
Alpha-Damascone™	5
Sandela™	15
Sandalore™	5
Galaxolide™	5
Optional perfume ingredients:	
Dipropyleneglycol	5
Citral	5
Linalool	10
Linalyl acetate	15

For comparison, perfume composition D containing a high concentration of monoterpenic alcohols is used. Monoterpenic alcohols are perfume compounds that have been reported to have skin lightening activity.

Comparative perfume composition D:

Perfume ingredient/compound:	**Parts per 1000**
Geraniol	100
3-methyl-5-phenyl-pentanol	100
dec-9-en-1-ol	10
2,2-dimethyl-3-(3-methyl phenyl)-propanol	50
4-(1-methylethyl)cyclohexyl-methanol	50
Nerol	30
3,7-dimethyl-7-octen-1-ol	20
2-methyl-5-phenyl-pentanol	60
Thymol	3
2-(1-methylpropyl)-cyclohexanone	30
Dihydromyrcenol	200
4-(1,1-dimethylethyl)-cyclohexanol	20
5-hexyl-furan-2(3H)-one	2

3,5-dimethyl-cyclohex-3-en-1-carboxaldehyde	15
Dihydroterpineol	150
1-(2-naphthalenyl)-ethanone	30
palmarosa oil	50
clove oil	40
Geranium oil	40

The skin lightening effect of perfume compositions A-C is compared to perfume composition D employing the test method as described in example 1:

	% inhibition of melanin formation in the cell line B16V after 3 days incubation with test perfume composition			
	12.5 ppm	6.25 ppm	3.125 ppm	1.6 ppm
Perfume composition A	90.5	88.1	55	49.9
Perfume composition B	91.4	86.5	57.1	46.5
Perfume composition C	89.8	88.1	42.1	44.2
Comparative Perfume composition D	29.8	14.5	11.1	0

As can be seen from the table above, the skin lightening effect of skin lightening perfume compositions of the present invention is much higher than the one of the comparative perfume composition.

The cell viability of perfume compositions A-C is compared to perfume composition D employing the test method as described in example 1; the results are shown in the table below.

	% MTT reduction vs. control cultures in the cell line B16V after 3 days incubation with test perfume composition			
	12.5 ppm	6.25 ppm	3.125 ppm	1.6 ppm
Perfume composition A	96.7	100.9	100	100
Perfume composition B	24.7	76.1	100	100
Perfume composition C	72.6	100	100	100
Comparative Perfume composition D	98.5	98.8	100	100

As shown in the table, perfume composition A and C have no or only a minor effect on cell growth at concentrations where they block the formation of melanine. Perfume composition B stops the cell growth at 12.5ppm but has no effect at lower concentrations.

Example 4: skin lightening perfume composition and arbutin

Inventive perfume composition E as described below is tested at various concentrations in combination with various concentrations of Arbutin. The effect of a low concentration of Arbutin is enhanced by the addition of a low concentration of perfume compositions E. The % inhibition of melanin formation in the cell line B16V after 3 days incubation with perfume composition and arbutin in various concentrations from 0 -3.2 ppm perfume composition and 0-3.2 ppm arbutin is shown.

Skin lightening perfume composition E:

Nectaryl™	10
Alpha-Damascone™	5
Sandela™	15
Aurantiol™	5
Fixolide™	5
Citral™	5
Linalool™	10
Linalyl acetate™	25
Optional perfume ingredients	30

The results are shown in the table below.

Concentration perfume composition	Concentration Arbutin	% inhibition of melanin formation in the cell line B16V after 3 days incubation with test mixtures
3.2	0	51.5
1.6	0	41.2
0	12.5	59.1
0	6.3	47.5
0	3.1	34.8
1.6	3.1	50.8
3.1	3.1	70.2
3.1	6.3	74.7
1.6	6.3	61.3

Example 5:

Evaluation of the effect of inventive perfume compositions on the skin tone of a reconstituted epidermis

Cocultures of normal human keratinocytes and melanocytes as a model of a pigmented human epidermis are purchased from MatTek (200 Homer Avenue, Ashland, MA 01721, USA). Skin lightening perfume compositions according to the invention are homogenized at a concentration of 0.02 to 0.1% in water by ultrasonification. The resulting solutions are applied every second day to the surface of the epidermal model for a period of 14 days. The epithelium is subsequently dissolved in 500mM NaOH and the melanin content is determined by measuring absorbance at 405 nm. Epithelium samples show a reduced melanine content after treatment with skin lightening perfume compositions.

Example 6:

Skin lightening cream with skin lightening perfume composition

INGREDIENTS	INCI name	%w/w
PHASE A		
EMULGADE F™	Cetearyl Alcohol (and) PEG-40 Castor oil (and) Sodium cetearyl Sulfate	8.00
CUTINA GMS™	Glyceryl Stearate	1.00
LANETTE 16™	Cetyl Alcohol	1.50
White VASELINE	Paraffin	2.00
Paraffine oil	Paraffinum Liquidum	5.00
EUTANOL G™	Octyldodecanol	2.00
DOWCORNING 200 FLUID™	Dimethicone	2.00
NIPAGIN M™	Methylparaben	0.15
NIPASOL M™	Propylparaben	0.10
PHASE B		
GLYCERINE	Glycerin	6.00
Water	---	71.05
PHASE C		
GERMALL 115™	Imidazolidinyl Urea	0.20
PHASE D		

Perfume composition A-C		1.00

A skin lightening cream is formed from the ingredients indicated in the table above as follows. The ingredients of phases A are admixed, for phase B the same applies. Phases A and B are each heated to 75-80°C, then B is added into A with slow stirring. The mixture is slowly cooled and as the cream thickens, stirring is increased. At 40°C, phase C is added and the mixture is homogenized. At a temperature of 35°C, one of the skin lightening perfume compositions A-C (compare examples hereinabove) is added. At room temperature (about 20-25°C), stirring is stopped.

Claims

1.Use of a skin lightening compound for the cosmetic lightening of the human skin, wherein the skin lightening compound is selected from the group consisting of 2-[2-(4-methyl-3-cyclohexen-1-yl)-propyl]-cyclopentanone, 6-isopropyl-octahydro-naphthalen-2-one, 4,7,7-trimethyl-2-(3-methyl-but-2-enyl)-bicyclo[4.1.0]heptan-3-one, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl)-ethanone, 1,1,2,3,3,8-hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[b]naphthalene, 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene, 1,1,2,3,3-pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one, 1-(2,3,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone, 2,2,3',7',7'-pentamethylspiro(1,3-dioxan-5,2'-norcarane), methyl-n-3,7-dimethyl-7-hydroxyoctylidene anthranilate, 2-[3-(4-tert-butyl-phenyl)-2-methyl-propenylamino]-benzoic acid methyl ester, 2-[(2,4-dimethyl-cyclohex-3-enylmethylene)-amino]-benzoic acid methyl ester, 2-methyl-4-(2,6,6-trimethyl-cyclohex-2-enyl)-butyraldehyde, 3-(3-isopropyl-phenyl)-butyraldehyde, 3-(4-isobutyl-phenyl)-2-methyl-propionaldehyde, [1-methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol, 2-ethyl-4-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-but-2-en-1-ol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, the product of the sandela-process comprising 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, 3-methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, (e)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on, and oxacyclohexadec-12-en-2-one.

2.Use according to claim 1, wherein the skin lightening compound is selected from the group consisting of 2-[2-(4-methyl-3-cyclohexen-1-yl)-propyl]-cyclopentanone, 6-isopropyl-octahydro-naphthalen-2-one, 4,7,7-trimethyl-2-(3-methyl-but-2-enyl)-bicyclo[4.1.0]heptan-3-one, 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl)-ethanone, 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene, 1,1,2,3,3-pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one, 2,2,3',7',7'-pentamethylspiro(1,3-dioxan-5,2'-norcarane), methyl-n-3,7-dimethyl-7-hydroxyoctylidene anthranilate, 2-[3-(4-tert-butyl-phenyl)-2-methyl-propenylamino]-benzoic acid methyl ester, 2-[(2,4-dimethyl-cyclohex-3-enylmethylene)-amino]-benzoic acid methyl ester, 2-methyl-4-(2,6,6-trimethyl-cyclohex-2-enyl)-butyraldehyde, 3-(3-isopropyl-phenyl)-butyraldehyde, 3-(4-isobutyl-phenyl)-2-methyl-propionaldehyde, [1-methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol, 2-ethyl-4-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-but-2-en-1-ol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, the product of the sandela-process comprising 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, 3-methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol, (e)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on, and oxacyclohexadec-12-en-2-one.

3. Use according to claim 1 wherein the skin lightening compound is selected from the group consisting of [1-methyl-2-(1,2,2-trimethyl-bicyclo[3.1.0]hex-3-ylmethyl)-cyclopropyl]-methanol, 2-ethyl-4-(2,2,3-trimethyl-cyclopent-3-en-1-yl)-but-2-en-1-ol, 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, the product of the sandela-process comprising 3-(5,5,6-trimethylbicyclo[2.2.1]hept-2-yl) cyclohexanol, 3-methyl-5-(2,2,3-trimethyl-cyclopent-3-enyl)-pentan-2-ol, 3-methyl-5-(2,2,3-trimethyl-3-cyclopenten-1-yl)-4-penten-2-ol.

4. Use according to claim 1 wherein the skin lightening compound is selected from the group consisting of 1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthal-enyl)-ethanone, 1,1,2,3,3-pentamethyl-1,2,3,5,6,7-hexahydro-inden-4-one, 1-(2,3,8,8-tetramethyl-1,2,3,4,5,6,7,8-octahydro-naphthalen-2-yl)-ethanone.

5. Use according to claim 1 wherein the skin lightening compound is selected from the group consisting of 1,1,2,3,3,8-hexamethyl-1,2,3,5,7,8-hexahydro-6-oxa-cyclopenta[b]naphthalene, 6,7-epoxy-1,1,2,4,4,7-hexamethyl-octahydro-naphthalene, 2,2,3',7',7'-pentamethylspiro(1,3-dioxan-5,2'-norcarane).

6. A method of lightening the human skin wherein a composition comprising at least one skin lightening compounds as defined in any one of claims 1 to 5 and optionally excipients is applied in a sufficient concentration to the human skin in regular intervals.

7. A method of forming a skin lightening personal care product wherein at least one skin lightening compound as defined in any one of claims 1 to 5 is admixed to a personal care product formulation in a concentration of 0.1 to 2% (w/v).

8. A method according to claim 7 wherein the concentration is 0.2% to 1.5%, preferably 0.6% to 1.2%.

9. A method according to claim 7 or 8 wherein as a first step, a composition is formed of at least one compound selected from a skin lightening compound as defined in any one of claims 1 to 5 and at least one ingredient selected from of the group consisting of arbutin, deoxyarbutin, octadecendioic acid, kojic acid, emblicanin A, emblicanin B, ascorbic acid, a derivative of ascorbic acid, perfume ingredients, solvents, additives, and excipients.

10. A skin lightening perfume composition comprising
(a) at least 30% (w/w) of at least two skin lightening compounds as defined in any one of claims 1 to 5
(b) up to 70% (w/w) of optional ingredients selected from one or more of additional perfume ingredients including additives, excipients, and solvents used in perfumes,

11. A skin lightening perfume composition according to claim 10, comprising at least one compound selected from the group consisting of (E)-oxacycloheptadec-10-en-2-one or 3-methylcyclotetradec-5-en-1-on, 4-methylcyclotetradec-6-en-1-on and oxacyclohexadec-12-en-2-one, and at least one skin lightening compound selected from the group consisting of arbutin, octadecendioic acid, deoxyarbutin, kojic acid, emblicanin A, emblicanin B, ascorbic acid, and a derivative of ascorbic acid.

12. A method of preparing a skin lightening personal care product wherein a composition as defined in claims 9, 10 or 11 is admixed to a personal care product formulation.

13. A skin lightening personal care product comprising at least 0.1% (w/v) of a composition according to claims 9, 10 or 11.

14. A skin lightening personal care product comprising at least two skin lightening compounds as defined in any one of claims 1 to 5 in a total concentration of 0.1% to 1%,

15. A skin lightening personal care product comprising at least one skin-lightening compound selected from the group consisting of (E)-oxacycloheptadec-10-en-2-one, 3-methylcyclotetradec-5-en-1-on, and 4-methylcyclotetradec-6-en-1-one, and oxacyclohexadec-12-en-2-one, and at least one compound selected from the group consisting of arbutin, deoxyarbutin, octadecendioic acid, kojic acid, emblicanin A, emblicanin B, ascorbic acid, and a derivative of ascorbic acid.

16. Use of at least one skin lightening compounds as defined in any one of claims 1 to 5 as skin lightening actives in skin lightening personal care products.

17. A method of preparing a skin lightening personal care product comprising the steps of
a) providing a personal care product prepared by admixing at least one skin lightening compounds as defined in any one of claims 1 to 5 to a personal care product formulation and forming a personal care product
b) packaging the personal care product
c) providing instructions for the use for cosmetic lightening of the skin to the packaged personal care product.

18. The method according to claim 17, wherein the instructions are to apply the personal care product to pigmented or hyperpigmented skin regularly and in a sufficient amount to achieve a skin lightening effect.

19. The method of claim 18, wherein the personal care product has a concentration of 0.1 to 2% of at least one of a skin lightening compound as defined in claim 1, and instructions are to apply the personal care product generously to pigmented or hyperpigmented skin at least once daily, preferably at least in an amount of 5-50 mg/cm2 skin, or in a thickness of 0.05 to 0.5 mm.

20. A method of lightening the skin by applying a compound as defined in any one of claims 1 to 5 to pigmented or hyperpigmented human skin regularly and in a sufficient amount.

21.The method of claim 20, wherein the personal care product has a concentration of 0.1 to 2% of at least one of a skin lightening compound as defined in any one of claims 1 to 5 and is applied at least once daily in an amount of 5-50 mg/cm2 skin, or in a thickness of 0.05 to 0.5 mm to the skin.

INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2006/000161

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61Q13/00 A61Q19/02 A61K8/35 A61K8/33 A61K8/34
A61K8/41 A61K8/37

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)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/08650 A (UNILEVER PLC; UNILEVER NV; HINDUSTAN LEVER LIMITED) 8 February 2001 (2001-02-08) claims 1,8,7 page 3, line 21 - page 4, line 14 tables 6a,6b page 45, line 3 - line 5	
A	DATABASE WPI Section Ch, Week 200432 Derwent Publications Ltd., London, GB; Class B05, AN 2004-344535 XP002381391 & JP 2004 123709 A (MIKADO KK) 22 April 2004 (2004-04-22) abstract	1,2, 6-10, 12-14, 16-21

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 May 2006	23. 08. 2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Krattinger, B

INTERNATIONAL SEARCH REPORT

International application No
PCT/CH2006/000161

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE WPI Section Ch, Week 199641 Derwent Publications Ltd., London, GB; Class A96, AN 1996-408308 XP002381392 & JP 08 198747 A (POLA CHEM IND INC) 6 August 1996 (1996-08-06) abstract	1,2, 6-10, 12-14, 16-21
X	EP 0 908 455 A (GIVAUDAN-ROURE S.A; GIVAUDAN SA) 14 April 1999 (1999-04-14) examples 40c,40f,40g	6-10, 12-14,16
X	US 6 242 413 B1 (FRATER GEORG ET AL) 5 June 2001 (2001-06-05) example 15	6-10, 12-14,16
X	EP 1 471 137 A (THE PROCTER & GAMBLE COMPANY) 27 October 2004 (2004-10-27) example 7a	6-10, 12-14,16
X	US 2004/223871 A1 (WOO RICKY AH-MAN ET AL) 11 November 2004 (2004-11-11) examples a,d,f,h	6-10, 12-14,16
X	US 6 184 419 B1 (BERG-SCHULTZ KATJA ET AL) 6 February 2001 (2001-02-06) examples 16,17	6-10, 12-14,16
X	US 2004/138078 A1 (CLARE JONATHAN RICHARD ET AL) 15 July 2004 (2004-07-15) paragraph [0126]	6-10, 12-14,16
X	US 2003/148906 A1 (ALAM ELIZABETH ANN ET AL) 7 August 2003 (2003-08-07) paragraph [0100]	6-10, 12-14,16
X	EP 1 216 691 A (GIVAUDAN SA) 26 June 2002 (2002-06-26) example 3	6-10, 12-14,16
X	WO 94/07887 A (GIVAUDAN-ROURE S.A) 14 April 1994 (1994-04-14) example 9	6-10, 12-14,16
X	WO 92/22518 A (GIVAUDAN-ROURE SA) 23 December 1992 (1992-12-23) example 9	6-10, 12-14,16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CH2006/000161

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / nectaryl

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2. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent, decatone

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3. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightning agent / precarone

---

4. claims: 1-2, 4, 6-10, 12-14, 16-21 (all partially), claim

skin lightning agent / filoxide

---

5. claims: 1-2, 6-10, 12-14, 16-21 (all partially), claim 5

skin lightening agent / galaxolide

---

6. claims: 1-2, 5-10, 12-14, 16-21 (all partially),

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7. claims: 1-2, 5-10, 12-14, 16-21 (all partially)

skin lightening agent / molaxone

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8. claims: 1-2, 4, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / cashmeran

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9. claims: 1-2, 4, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / Iso E super

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10. claims: 1-2, 5-10, 12-14, 16-21 (all partially)

skin lightening agent / spirambrene

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11. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

skin lightening agent / aurantiol

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12. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / verdantiol

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13. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / agrumea

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14. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / cetonal

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15. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / florhydral

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16. claims: 1-2, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / silvial

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17. claims: 1-3, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / javanol

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18. claims: 1-3, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / radjanol

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19. claims: 1-3, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / 3-(5,5,6-trimethylbicyclo hept-2-yl) cyclohexanol

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20. claims: 1-3, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / sandalore

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21. claims: 1-3, 6-10, 12-14, 16-21 (all partially)

skin lightening agent / ebanol

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22. claims: 1-2, 6-11, 12-21 (all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

skin lightening agent / ambrettolide

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23. claims: 1-2, 6-11, 12-21 (all partially)

skin lightening agent / 3-methylcyclotetradec-5-en-1-on

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24. claims: 1-2, 6-11, 12-21 (all partially)

skin lightening agent / 4-methylcyclotetradec-6-en-1-on

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25. claims: 1-2, 6-11, 12-21 (all partially)

skin lightening agent / habanolide

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