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(71) Applicant: **HENKEL AG & CO. KGAA** [DE/DE]; Henkelstrasse 67, 40589 Düsseldorf (DE).(72) Inventor: **CHANG, Xiaowei**; B1 Building No. 8, Knowledge & Innovation Community (KIC), 398 Songhu Road, Yangpu District, Shanghai 200433 (CN).(74) Agent: **NTD UNIVATION INTELLECTUAL PROPERTY AGENCY LTD.**; Room 1802, 18th Floor, Block A, Investment Plaza, 27 Jinrongdajie, Xicheng District, Beijing 100033 (CN).

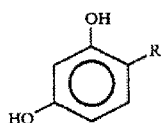
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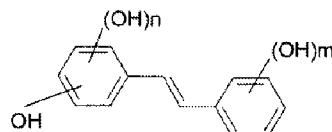
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(54) Title: A COSMETIC COMPOSITION FOR SKIN BRIGHTENING



(I)



(II)

(57) Abstract: A cosmetic composition for skin brightening comprises: (a) 0.01 to 3.0% by weight of a saturated resorcinol derivative of formula (I), wherein R represents a (C₂-C₈) alkyl, (C₃-C₈) cycloalkyl or aryl (C₁-C₆) alkyl, (b) 0.001 to 0.5% by weight of a hydroxystilbene compound of formula (II), wherein n is an integer from 0 to 4, and m is an integer from 0 to 5, (c) 0.001 to 5% by weight of a stabilizer, and (d) 70 to 99.9% by weight of a cosmetically acceptably carrier, in which the weight percentages are based on the total weight of all components of the cosmetic composition. The composition is useful at inhibiting melanogenesis and reducing skin pigmentation.



A cosmetic composition for skin brightening

Technical Field

The present invention relates to a cosmetic composition for skin brightening and the use thereof.

Background

Consumers worldwide, particularly in Asia are looking for white and bright skin complexion. In humans, skin color arises from a complex series of cellular processes that are carried out within a group of cells known as melanocytes. Melanocytes are located in the lower part of the epidermis and their function is to synthesize the skin pigment, melanin, which helps protect the body from the damaging effects of ultraviolet radiation. Melanin is a biopolymer originating from conversions of the amino acids phenylalanine or tyrosine.

A variety of methods have been proposed to achieve depigmentation, i.e., reduction or inhibition of skin pigmentation or skin color. For example, arbutin, kojic acid, hydroquinone, retinoids, etc. have been used for skin depigmentation. However, these compounds have been found to be irritating to the skin and, therefore, undesirable for use. In addition, resorcinol derivatives have been proposed to be used in skin lightening products.

For example, US 4,959,393 A discloses a skin depigmental agent, comprising a resorcinol derivative having a linear alkyl group, especially 4-isoamyl resorcinol, 4-hexyl resorcinol.

US 2008/0305059 A1 discloses a skin lightening composition comprising highly purified hexylresorcinol.

US 6,863,897 B2 discloses a cosmetic composition for skin brightening containing a micronized metal oxide along with a 4-substituted cyclic resorcinol derivatives, especially 4-cyclopentyl, 4-cyclohexyl, 4-cycloheptyl and 4-cyclooctyl resorcinols.

US 2012/0128605 A1 discloses a composition comprising a skin-lightening resorcinol, such as 4-hexyl resorcinol and 4-octyl resorcinol and a skin darkening agent for treating signs of aging.

However, these resorcinols used for skin lightening are described as inhibitors of tyrosinase. Tyrosinase (Tyr) is the initial and essential enzyme that catalyzes the first step of the conversion of tyrosine to melanin. Although tyrosinase production and activity is a key factor in melanin formation, skin pigmentation is the result of a multi-step process and involves other important and rate-limiting steps than tyrosinase catalyzed conversion of L-tyrosine, L-Dopa and Dopa-quinone. These factors also involved along the melanogenesis pathway include MCR1, gp100, TRPs, ckit, etc. Ckit is the receptor for the growth factor SCF. SCF supports cell division of the melanocytes by coupling to the receptor. If the receptor expression is reduced the stimulatory effect of SCF can be inhibited. Gp100 encodes a protein of the melanosomal membrane in which the melanin (produced by the melanocytes) is transferred to the keratinocytes. By inhibition of the gene transfer melanin can be reduced. The enzymes TRPs play an important role in the enzymatic conversion of tyrosine to melanin during melanin synthesis.

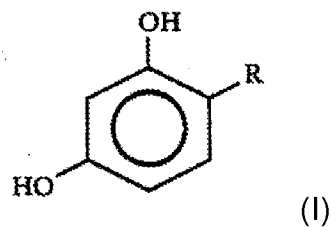
Since these steps are also of essential importance in the skin pigmentation, it will be advantageous to influence these molecular signals, if the synthesis of melanin in the human skin maintained, reactivated or inhibited in a long term through the application of a cosmetic composition.

There is a desire therefore of providing a cosmetic composition which can improve the skin brightening effect by modulating one or more of the multiple steps involved in melanogenesis in a long term.

Summary of the Invention

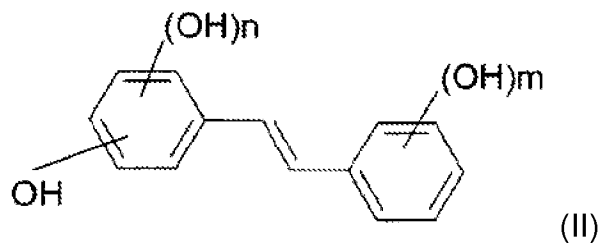
Based on the foregoing discussion, an object of the present invention is to provide a cosmetic composition for skin brightening according to the present invention, comprising:

(a) 0.01 to 3.0% by weight of a saturated resorcinol derivative of formula (I)



wherein R represents (C₂-C₈)alkyl, (C₃-C₈)cycloalkyl or aryl (C₁-C₆)alkyl,

(b) 0.001 to 0.5% by weight of a hydroxystilbene compound of formula (II)



wherein n is an integer from 0 to 4, and m is an integer from 0 to 5,

(c) 0.001 to 5% by weight of a stabilizer, and

(d) 70 to 99.9% by weight of a cosmetically acceptable carrier,

in which the weight percentages are based on the total weight of all components of the cosmetic composition.

Also provided is the use of the cosmetic composition for skin brightening in inhibiting melanogenesis and reducing skin pigmentation.

The inventor has surprisingly found that, the combined use of a saturated resorcinol derivative represented by formula (I) and a hydroxystilbene compound represented formula (II) allows to exert a remarkable inhibitory performance on melanin biosynthesis which is considerably more effective than that of either of said two active ingredients and other actives known in the art.

These and other objects, features and advantages of the present invention will become better understood upon having reference to the following description of the invention.

Brief Description of the Drawings

Figure 1 shows the electron micrograph of the Fontana-Masson (FM) staining of skin model treated by base cream by RHPE test on day 8.

Figure 2 shows the electron micrograph of the FM staining of skin model treated by 0.5% by weight of Mg ascorbyl phosphate in base cream by RHPE test on day 8.

Figure 3 shows the electron micrograph of the FM staining of skin model treated by the composition having 0.5% by weight of phenylethyl resorcinol and 0.1% by weight of resveratrol in cream base by RHPE test on day 8.

Figure 4 shows the electron micrograph of the FM staining of skin model treated by the composition having 0.5% by weight of phenylethyl resorcinol and 0.01% by weight of resveratrol in cream base by RHPE test on day 8.

Figure 5 shows the electron micrograph of the FM staining of skin model treated by the composition having 0.5% by weight of phenylethyl resorcinol and 0.5% by weight of Mg ascorbyl phosphate in cream base by RHPE test on day 8.

Detailed Description

It is to be understood by one of ordinary skill in the art that the present application is a description of exemplary embodiments only, and is not intended as limiting the broader aspects of the present invention.

All percentages listed in this specification are percentages of components by weight, unless otherwise specifically mentioned.

As used herein, the term "skin lightening" refers generally to lightening, brightening, whitening, and/or evening of the skin tone, skin color, and/or shade of skin, and/or to the reduction in sallowness, and/or to the lightening and/or fading of hyperpigmented marks and/or lesions including, but not limited to, pigmented spots, melanin spots, age spots, sun spots, senile lentigos, freckles, lentigos simplex, pigmented solar keratosis, seborrhoeic keratosis, melasma, acne marks, post-inflammatory hyperpigmentation, lentigines, ephelides, combinations of two or

more thereof and the like.

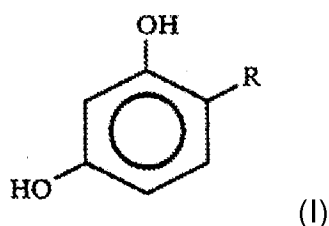
As used herein, "cosmetic" refers to a beautifying substance or preparation which preserves, restores, bestows, simulates, or enhances the appearance of bodily beauty or appears to enhance the beauty or youthfulness, specifically as it relates to the appearance of tissue or skin. The term "cosmetically acceptable carrier" refers to a vehicle, for cosmetic use, which vehicle delivers the active components to the intended target and which will not cause harm to humans or other recipient organisms.

The term "alkyl", as used herein, unless otherwise indicated, includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof.

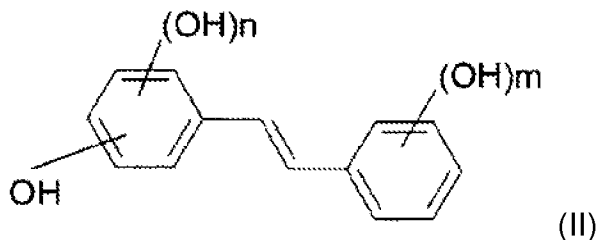
The term "aryl" refers to an unsaturated aromatic carbocyclic group of from 6 to 20 carbon atoms having a single ring (e.g., phenyl) or multiple condensed (fused) rings, wherein at least one ring is aromatic (e.g., naphthyl, dihydrophenanthrenyl, fluorenyl, or anthryl). Preferred aryls include phenyl, naphthyl and the like.

The present invention is directed to a cosmetic composition for skin brightening, by inhibiting melanogenesis and reducing skin pigmentation, comprising:

(a) 0.01 to 3.0% by weight of a saturated resorcinol derivative of formula (I)



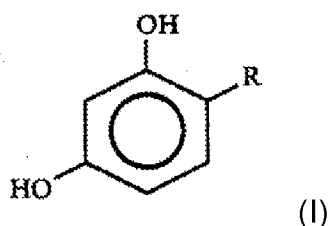
wherein R represents (C₂-C₈)alkyl, (C₃-C₈)cycloalkyl or aryl (C₁-C₆)alkyl,
(b) 0.001 to 0.5% by weight of a hydroxystilbene compound of formula (II)



wherein n is an integer from 0 to 4, and m is an integer from 0 to 5,
(c) 0.001 to 5% by weight of a stabilizer, and
(d) 70 to 99.9% by weight of a cosmetically acceptable carrier,
in which the weight percentages are based on the total weight of all components of the cosmetic composition.

Saturated resorcinol derivative

Resorcinol derivatives are known as a melanogenesis inhibitor in the art. Provided herein is a saturated resorcinol derivative of formula (I)



wherein R represents (C₂-C₈)alkyl, (C₃-C₈)cycloalkyl or aryl (C₁-C₆)alkyl.

Preferably, R represents (C₂-C₄)alkyl, (C₃-C₆)cycloalkyl or phenyl (C₁-C₄)alkyl. More preferably, R represents ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, n-hexyl, n-octyl, n-dodecyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, benzyl, phenyl ethyl, or phenyl propyl. Most preferably, R represents ethyl, n-propyl, iso-butyl, n-hexyl, n-octyl, n-dodecyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, or phenyl ethyl. Examples of the saturated resorcinol derivative of formula (I) useful in the present invention are e.g. 4-isoamyl resorcinol, 4-hexyl resorcinol, 4-octyl resorcinol, 4-cyclohexyl resorcinol and 4-phenyl ethyl resorcinol. These resorcinols are disclosed for example in U.S. Pat. No. 4,959,393 (Tori-hara, et al.), U.S. Pat. No. 6,863,897 (Love et al.) and US Published Patent Application No. 2008/0305059 (Chaudhari et al.), the disclosures of which are incorporated herein by reference.

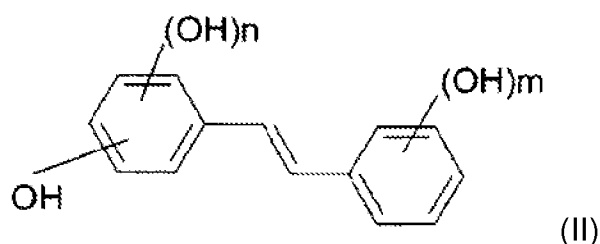
These saturated resorcinol derivatives can be synthesized according to the methods known in the art, or commercially available. For example, 4-hexyl resorcinol is commercially available as "SYNOVEA HR" from Sytheon of Lincoln Park, N.J. 4-octylresorcinol is commercially available from City Chemical LLC of West Haven, Conn. 4-phenyl ethyl resorcinol (hereinafter referred as phenylethyl

resorcinol) is sold under the name SymWhite 377® or Bio 377 by Symrise.

In one embodiment, the saturated resorcinol derivative is present in the composition in an amount of from 0.01 to 3.0% by weight, preferably from 0.05 to 2.0%, and more preferably from 0.25 to 1.0% by weight based on the total weight of all components of the cosmetic composition.

Hydroxystilbene compound

The cosmetic composition for skin brightening of the present invention also comprises a hydroxystilbene compound represented by formula (II)



wherein n is an integer from 0 to 4, and m is an integer from 0 to 5. Preferably, n is an integer from 0 to 2, and m is an integer from 0 to 3. More preferably, n is 1 and m is 1. These compounds may be in a cis or trans form. According to the present invention, the term hydroxystilbene covers both the compounds of formula (II) and their hydroxyalkyl derivatives.

Hydroxystilbenes useful in the invention may be of natural or synthetic origin, and are selected from the group consisting of: 4'-hydroxystilbene, 2',4'-dihydroxystilbene, 3',4'-dihydroxystilbene, 4,4'-dihydroxystilbene, 2',4',4-trihydroxystilbene, 3',4',4-trihydroxystilbene, 2,4,4'-trihydroxystilbene, 3,4,4'-trihydroxystilbene, 3,4',5-trihydroxystilbene, 2',3,4-trihydroxystilbene, 2,3',4-trihydroxystilbene, 2',2,4'-trihydroxystilbene, 2,4,4',5-tetrahydroxystilbene, 2',3,4',5-tetrahydroxystilbene, 2,2',4,4'-tetrahydroxystilbene, 3,3',4',5-tetrahydroxystilbene, 2,3',4,4'-tetrahydroxystilbene, 3,3',4,4'-tetrahydroxystilbene, 3,3',4',5,5'-pentahydroxystilbene, 2,2',4,4',6-pentahydroxystilbene, 2,3',4,4',6-pentahydroxystilbene, 2,2',4,4',6,6'-hexahydroxystilbene, and the combination thereof.

Among these compounds, resveratrol, 3,5,4'-trihydroxy-*trans*-stilbene is preferred

to be used in the cosmetic composition, together with the saturated resorcinol derivative as active components against melanogenesis. Resveratrol is a widely distributed natural stilbenoid in nature such as in grapes. It is currently the subject of many research investigations due to its health beneficial effects including antioxidative, antifungal, anticarcinogenic, cardioprotective, and anti-aging actions.

In one embodiment, the hydroxystilbene compound is comprised in the cosmetic composition for skin brightening in an amount of from 0.001 to 0.5% by weight, preferably from 0.01 to 0.2%, more preferably from 0.05 to 0.1% by weight based on the total weight of all components of the cosmetic composition.

Stabilizer

The cosmetic composition for skin brightening of the present invention also comprises a stabilizer. Any compounds that facilitate to chemically stabilize the active components in the cosmetic composition can be used, including, but not limited to, sodium metabisulfite, sodium bisulfate, BHT, BHA, propyl gallate, disodium EDTA, lemon extract, and tocopherol and derivatives of tocopherol such as, sodium vitamin E phosphate (VEP), lauryl imino dipropionic acid tocopheryl phosphate, tocopheryl glucoside, tocopheryl succinate, tocophersolan (tocopheryl polyethylene glycol 1000 succinate), disodium lauriminodipropionate tocopheryl phosphates, tocophereth-5, 10, 12, 18, and 50 (polyethylene glycol (PEG) tocopheryl ethers. Sulfites such as sodium hyposulphite, sodium sulfite, sodium metabisulfite, and/or sodium bisulfate are particularly useful to stabilize the saturated resorcinol derivative and the hydroxystilbene compound present in the cosmetic composition.

In one preferred embodiment, the cosmetic composition contains a stabilizer selected from the group consisting of sodium hyposulphite, sodium sulfite, and combination thereof. More preferably, the stabilizer comprised in the inventive composition is sodium hyposulphite.

In another preferred embodiment, the cosmetic composition for skin brightening does not comprise ascorbic acid (vitamin C) and its derivatives such as phosphate

derivatives of ascorbic acid including sodium or magnesium ascorbyl phosphate, aminopropyl ascorbyl phosphate, and other known phosphate derivatives of ascorbic acid having antioxidant properties.

In one embodiment, the stabilizer is present in an amount of from 0.001 to 5% by weight, preferably from 0.05 to 1% by weight, and more preferably from 0.1 to 0.5% by weight based on the total weight of all components of the cosmetic composition.

Cosmetically acceptable carrier

The compositions of the present invention also include at least one cosmetically acceptable carrier. A cosmetically acceptable carrier refers to any organic or aqueous solvent or solvent system that is compatible with the other components of the invention and suitable for human use. However, persons skilled in the art would appreciate that not every carrier for the polymer and metal is "cosmetically acceptable". Examples of non-cosmetically acceptable carriers include tetrahydrofuran, dimethyl sulfoxide, benzene, benzene derivatives, and dimethylformamide. In addition, carriers that are toxic, abrasive, or in any way damaging to keratinous substrates should not be utilized.

Generally, cosmetically acceptable carriers may be selected from volatile organic solvents, non-volatile organic solvents, water, and mixtures thereof. Alcohols that may be utilized as carriers include C₁ to C₂₀ straight chain, branched, or cyclic mono-alcohols, including ethanol, propanol, butanol, tert-butanol, isopropanol and mixtures thereof, polyalcohols (e.g., diethylene glycol), glycol ethers and alkyl ethers of glycol or of diethylene glycol. Other cosmetically acceptable carriers such as triglycerides (e.g., glycerin), fatty alcohols derived from natural fats and/or oils (e.g., 1-dodecanol and 1-octadecanol), hydrocarbons (e.g., mineral oils, mineral solvents, mineral spirits, petroleum, waxes, synthetic hydrocarbons, animal oils, vegetable oils, and volatile hydrocarbons (e.g., isododecane)), light paraffinic solvents, and non-hydrocarbon solvents (e.g., amyl acetate, butyl acetate, isobutyl acetate, ethyl acetate, propyl acetate and isopropyl acetate) may also be useful.

In one preferred embodiment, the cosmetically acceptable carrier is selected from mono-alcohols, water, and mixture thereof.

The amount of cosmetically acceptable carrier is present in an amount of from 70 to 99.9% by weight, preferably from 75 to 99.5% by weight, and more preferably from 80 to 99% by weight based on the total weight of all components of the cosmetic composition.

The cosmetic compositions of the present invention may be formulated in a variety of products, such as foundation, rouge, skin cream, lotion, mascara, spray, etc.

Optional components

In the cosmetic composition for skin brightening of the present invention, there may be added various cosmetic adjuvants selected from the group consisting of emollients, emulsifiers, vitamins, hormones, amino acids, surfactants, colorants, dyes, pigments, fragrances, odor absorbers, antiseptics, preservatives, bactericides, humectants, thickeners, solvents, fillers, antioxidants, sequestering agents, sunscreens, or any other known components and additives as long as the effects of the present invention are not impaired.

Examples of suitable emollients nonexclusively include mineral oil, lanolin, plant-derived oils including but not limited to cocoglycerides, coconut oil, palm kernel oil, babssu oil, sunflower seed oil, japan wax, palm oil, apricot kernel oil, tallow, argan oil, baobab oil, cocoa butter, andiroba seed oil, mango butter, avocado oil, cottonseed oil, rice bran oil, shea butter, marula oil, papaya seed oil, pumpkin seed oil, wheat germ oil, illipe butter, corn oil, olive oil, poppy seed oil, grapeseed oil, sesam oil, yangu seed oil, sweet almond oil, hazelnut oil, soybean oil, acai oil, safflower oil, hydbrid safflower oil, walnut oil, canola oil, black currant seed oil, hazel seed oil, peanut oil, cranberry seed oil, tall oil, kokum butter, manketti nut oil, moringa oil, raspberry seed oil, cupuacu butter, linseed oil, tung oil, jojoba oil, borage seed oil, evening primrose oil, veronica oil, ongokea oil], vegetable oils, isostearyl isostearate, glyceryl laurate, methyl gluceth-10, methyl gluceth-20 chitosan, and mixtures thereof.

Emulsifiers and co-emulsifiers that may be used include, for example, carboxyvinyl polymers of high molecular weight (for example Carbopol[®]), polysorbates (for example Tween 20[®] or Tween 60), sorbitan esters and in particular a sorbitan monostearate, tristearate, monopalmitate or laurate. Other emulsifiers such as various stearic acid or palmitic acid derivatives, for example PEG-100 stearate, stearic acid or palmitic acid mono- or diglycerides, a self-emulsifying propylene glycol stearate, or polyglyceryl 2-sesquioleate, polyoxyethylene cetyl ether, a siloxane polyglucoside or an emulsifiable silicone may also be used.

Examples of UV screening agent nonexclusively include benzophenones, bornelone, butyl paba, cinnamidopropyl trimethyl ammonium chloride, disodium distyrylbiphenyl disulfonate, paba, potassium methoxycinnamate, butyl methoxydibenzoylmethane, octyl methoxycinnamate, oxybenzone, octocrylene, octyl salicylate, phenylbenzimidazole sulfonic acid, ethyl hydroxypropyl aminobenzoate, menthyl anthranilate, aminobenzoic acid, cinoxate, diethanolamine methoxycinnamate, glyceryl aminobenzoate, titanium dioxide, zinc oxide, oxybenzone, Padimate O, red petrolatum, and mixtures thereof.

Fragrance components and mixtures thereof may be obtained from natural products such as essential oils, absolutes, resinoids, resins and concretes, as well as synthetic products such as hydrocarbons, alcohols, aldehydes, ketones, ethers, carboxylic acids, esters, acetals, ketals, nitriles and the like, including saturated and unsaturated compounds, aliphatic, carbocyclic and heterocyclic compounds.

The surfactant may be selected from the group consisting of anionic, nonionic, cationic and amphoteric actives. Particularly preferred nonionic surfactants are those with a C₁₀-C₂₀ fatty alcohol or acid hydrophobe condensed with from 2 to 100 moles of ethylene oxide or propylene oxide per mole of hydrophobe; C₂-C₁₀ alkyl phenols condensed with from 2 to 20 moles of alkylene oxide; mono- and di-fatty acid esters of ethylene glycol; fatty acid monoglyceride; sorbitan, mono- and di-C₈-C₂₀ fatty acids; and polyoxyethylene sorbitan as well as combinations thereof.

Amounts of these cosmetic adjuvants may range from 0.001% to 20% by weight based on the total weight of all components of the cosmetic composition.

The cosmetic composition can be a care composition, in particular can be a product for caring for the skin, such as a care base for the skin, a care cream (day cream, night cream, antiwrinkle cream) or a makeup base, a care composition for the lips (lip balm), or a sun-protection or self-tanning composition.

The composition can also be a makeup composition, in particular a composition for making up the skin or lips. In particular, the makeup composition can be a foundation, a blusher, an eyeshadow, a concealer or a product for making up the body, such as a lotion.

The cosmetic composition for skin brightening according to the present invention can be prepared by means of methods or process known in the art. For example, an oil-in-water emulsion can be prepared according to the following general procedure: The constituents of the aqueous phase are mixed by heating at a temperature of approximately 70°C. The oils, the actives and the surfactants are furthermore mixed by heating at a temperature of approximately 80°C. The fatty phase is run into the aqueous phase at a temperature of approximately 70°C, and then the mixture is stirred for 10 minutes at high speed using a turbine mixer. The emulsion obtained is cooled to approximately 60°C. The thickeners are subsequently added and then the mixture is again stirred for 10 minutes. The other actives are subsequently optionally introduced.

Surprisingly, the cosmetic composition according to the present invention exhibited an excellent effect in melanogenesis inhibition and/or skin pigmentation reduction by downregulating various melanogenic markers especially in a long term.

The present invention may be better understood with reference to the following examples.

Examples**Example 1: Skin lightening cream**

A cream for skin brightening was prepared according to the formulation as shown in Table 1.

Table 1.

Material	Amount	Commercial Source
Group 1		
Phenylethyl resorcinol	0.5 g	Symrise
Squalane	2.0 g	Nikkol
Monoglycerol stearate	1.0 g	BASF
Caprylic/capric triglyceride	2.0 g	Croda
Shea butter oil	2.0 g	BASF
Cetyl glucoside	3.0 g	BASF
Group 2		
Sodium sulphite	0.2 g	Sinopharm
Water, demineralized	70 g	
Group 3		
Water, demineralized	10 g	
Resveratrol	0.1 g	DSM
Group 4		
Phenoxyethanol	0.5 g	Clariant
Methyl paraben	0.2 g	Clariant
Propyl paraben	0.1 g	Clariant
Group 5		
Carbopol	1.0 g	Lubrizol
Water, demineralized	added to 100 g	

The materials in group 1 were mixed at elevated temperature around 80°C. Then the mixture of group 1 was added into pre-heated mixture of group 2 at 80°C with stirring. The mixture of groups 1 and 2 was homogenized at 70~80°C for 5~10 min, followed by addition of the solution of group 3 at 60~70°C with gentle stirring. The

mixture was cooled down with slow agitation until 45~50°C, then the preservatives in group 4 were added as solution mixture. The pre-mixed group 5 as carbopol dispersion was added with stirring at last at 45~50°C. The whole mixture was cooled down to room temperature with stirring to obtain the white cream.

Example 2: Skin brightening lotion

A skin lotion for skin brightening was prepared according to the formulation as shown in Table 2.

Table 2.

Material	Amount	Commercial Source
Group 1		
Phenylethyl resorcinol	0.7 g	Symrise
Caprylic/capric triglyceride	0.5 g	Croda
Polydimethicone	0.5 g	Dow Corning
PEG-60 hydrogenated castor oil	2.0 g	BASF
Group 2		
Sodium hyposulphite	0.2 g	Sinopharm
Water, demineralized	70 g	
Group 3		
Water, demineralized	10 g	DSM
Resveratrol	0.01 g	
Group 4		
Xanthan gum	0.5 g	CP KELCO
Butylene glycol	2.0 g	Clariant
Phenoxyethanol	0.6 g	Clariant
Methyl paraben	0.2 g	Clariant
Propyl paraben	0.2 g	Clariant
Water, demineralized	added to 100 g	

The materials in group 1 were mixed at elevated temperature around 80°C. Then the mixture of group 1 was added into pre-heated mixture of group 2 at 80°C with stirring. The mixture of groups 1 and 2 was homogenized at 70~80°C for 5~10 min,

followed by addition of solution of group 3 at 60~70°C with gentle stirring. The mixture was cooled down with slow agitation until 45~50°C, then the preservatives in group 4 were added as solution mixture. The xanthan gum was pre-dispersed in butylene glycol then added with stirring at last at 45~50°C. The whole mixture was cooled down to room temperature with stirring to obtain the skin lotion.

Example 3:

The composition of Example 3 (E3) is the same as that of Example 1, except that in E3, resveratrol is present in an amount of 0.01% by weight. E3 was prepared in the same manner as in Example 1.

Comparative Examples 1 to 4:

The compositions of Comparative Examples 1 to 4 (CE1 to CE4) are the same as that of Example 1, except that in CE1, the composition contains no actives, in CE2, phenylethyl resorcinol and resveratrol both as active were replaced by 0.5% by weight of magnesium ascorbic phosphate, in CE3, the active was replaced by 0.5% by weight of phenylethyl resorcinol and 0.5% by weight of magnesium ascorbic phosphate. CE1 to CE3 were prepared in the same manner as in Example 1.

Example 4:

An aqueous solution for the melanin content test in Method 3 as below was prepared according to the formulation as shown in Table 3.

Table 3.

Material	Amount	Commercial Source
Phenylethyl resorcinol	1.0 g	Symrise
Resveratrol	0.05 g	DSM
Water, demineralized	added to 100 g	

Phenylethyl resorcinol and resveratrol were dissolved in demineralized water, with slightly heating if necessary.

Examples 5 and 6:

The compositions of E5 and E6 are the same as that of E4, except that in E5, phenyl ethyl resorcinol is present in an amount of 0.5% by weight, and resveratrol is present in an amount of 0.1% by weight, in E6, phenyl ethyl resorcinol is present in an amount of 0.25% by weight, and resveratrol is present in an amount of 0.1% by weight. E5 and E6 were prepared in the same manner as in E4.

Comparative Examples 5 to 9:

The compositions of CE5 to CE9 are the same as that of E4, except that in CE5, the composition contains no melanogenesis inhibiting actives, in CE6, the actives were replaced by ascorbic acid present in an amount of 0.05% by weight, in CE7, the actives were replaced by magnesium ascorbic phosphate present in an amount of 0.05% by weight, in CE8, the composition contains resveratrol in an amount of 0.05% by weight only, and in CE9, the composition contains phenyl ethyl resorcinol in an amount of 0.5% by weight only. CE5 to CE9 were prepared in the same manner as in E4.

Evaluation:

Gene expression analysis of melanogenic markers

Sample Preparation

The skin models were transferred into fresh medium. After incubation overnight all models were treated topically with 3 μ l of each cream having the composition shown in Table 3. The models were incubated for 24 hours (PCR) at 37°C and 5% CO₂. In addition to this, some skin models were cultured 8 days, treated every two days excepting weekend. At the end of the study models were prepared for histological sections and staining of melanin (Fontana-Masson staining).

Method 1. Gene expression analysis of melanogenic markers

For the analysis of different gene expression, RNA was isolated from the RHPE using the RNeasy MiniKit (Qiagen) according to the manufacturer's instructions. Spectrometric quantification of the isolated RNA has been performed with SPECTRAmax (from Molecular Devices). Following standard reverse transcription of each RNA sample quantitative PCR analysis was performed using a MX3000P Real Time PCR System (from Stratagene, La Jolla, California) with gene specific

primer sets for the melanogenic markers as well as for a reference house keeping gene. During the amplification of the DNA a fluorescent signal was recorded. The intensity of this signal increases with the amount of amplified DNA.

Arithmetic mean was calculated of each triplicate and delta Ct-values were formed by subtracting the value of the house keeping gene from values of the genes of interest. Normalization was based on untreated controls (having no actives). Relative gene expressions were calculated.

The gene expressions of melanogenic markers were analyzed using quantitative Real-Time-PCR. The following parameters were examined: ckit, gp100, TRP2 and Tyr.

Besides the key enzyme tyrosinase, TRP2 produces dihydroxyindol carboxylic acid (DHICA) and is therefore responsible for preserving carboxyl group in melanins. The product of TRP2, DHICA, serves as a substrate for another enzyme TRP1 for further production of eumelanin more than phaeomelanin in human melanoma cell lines. The melanocortin-1 receptor (MCR-1) and stem cell factor receptor (ckit) are other key regulators of human cutaneous pigmentation. In melanogenesis, melanoblasts migrate from the neural crest to their appropriate locations in the epidermis. Glycoprotein 100, gp100 is 661 amino acids long and is a type I transmembrane glycoprotein enriched in melanosomes, which are the melanin-producing organelles in melanocytes. This protein is involved in melanosome maturation.

The gene expression analysis results in Table 3 as below shown the gene expressions of melanogenic markers (ckit, gp100, TRP2 and Tyr) after treating with the compositions of CE1 to CE3 and E1 and E3 in a short period (24 hours). It is clear that the compositions according to the present invention exhibited a better effect of downregulating the melanogenic markers. In addition, compared to the positive control having 0.5% by weight of Mg AscP (CE1) and 0.5% by weight of phenylethyl resorcinol and 0.5% by weight of Mg AscP (CE3), the compositions according to the present invention exhibited a comparable overall benefit and

possessed better expressions both in TRP2 and Tyr. It was further demonstrated that the modulation of one or more of the multiple steps involved in melanogenesis was surprisingly achieved by the combined use of phenylethyl resorcinol and resveratrol.

Tabel 3. Test samples and results of relative gene expressions of melanogenic markers

Example	Relative gene expressions			
	ckit	gp100	TRP2	Tyr
CE1	1.00	1.00	1.00	1.00
CE2	0.86	0.63	0.71	0.99
E1	0.82	0.61	0.53	0.78
E3	0.87	0.81	0.51	0.60
CE3	0.83	0.72	0.72	0.86

Method 2. Visualization of pigmentation by using Reconstructed Human Pigmented Epidermis (RHPE)

The RHPE model is described as three-dimensional skin model, consisting of a multilayered, stratified and pigmented epidermis.

Normal human keratinocytes cultured in the presence of melanocytes of phototype VI form an epidermal tissue with a tanning degree corresponding to the equivalent phototypes of human skin.

Melanin detection method: Fontana-Masson staining

Fontana-Masson (FM) technique is used in the histological visualization of melanin in paraffin or frozen sections. This method is based on the ability of melanin to reduce ammoniacal silver nitrate to a visible metallic state. The product is a brown-black precipitate, which enables melanin detection under light microscope as shown in Figs. 1 to 5. For visualisation of possible effects of the creams histological slices were prepared and stained with Fontana-Masson (FM).

The electronic micrograph pictures in Figs. 3 and 4 both shown an overall paler staining for E1 and E3 than those of CE1 to CE3, which surprisingly exhibited that the cosmetic compositions according to the present invention had a significantly higher inhibition effect of melanogenesis than the comparative examples in a long term (8 days).

Method 3. Quantification of the melanin produced in B16 mouse melanoma cells

To evaluate the efficiency of the active compositions of the present invention, the melanin contents treated by the aqueous solution containing phenylethyl resorcinol and/or other actives were also studied.

Melanocytes were cultivated in the DMEM culture containing 10% fetal bovine serum. Cultured cells were passaged twice to confirm the cell growth in stable condition, and a growth rate of about 80% of the fusion cell was prepared.

The melanoma cells were collected and transferred to the centrifuge tube and seeded in the 6 well plate as 1.5×10^5 cells / well. The testing solutions of CE5 to CE9 and E4 to E6 were added to the plate, respectively. The plate was then incubated for 72 hours.

Recover the cells and count the cell number. The cells were dissolved in 1 N NaOH and OD₄₇₅ was measured by a spectrophotometer. The negative control (blank sample, CE5) was set up to 100% of melanin content, and then the melanin contents of other examples were normalized.

Table 4. Results of melanin content quantification

Example	Melanin content (%)
CE5	100%
CE6	39.37%
CE7	94.97%
CE8	26.57%

CE9	22.38%
E4	13.57%
E5	16.08%
E6	20.49%

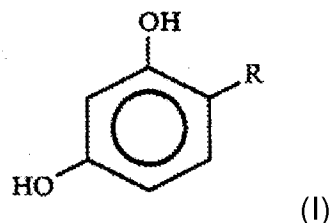
As can be seen in Table 4, the melanin contents after the treatment by various combinations of 4-phenyl ethyl resorcinol and resveratrol according to the present invention (E4 to E6) are significantly lower than the melanin contents obtained from the comparative examples. Compared to CE8 and CE9 containing either of 4-phenyl ethyl resorcinol and resveratrol, an excellent melanogenesis inhibition effect achieved by E4 to E6 demonstrated a positive synergistic effect in the presence of 4-phenyl ethyl resorcinol in combination with resveratrol.

These and other modifications and variations of the present invention may be practiced by those of ordinary skill in the art, without departing from the spirit and scope of the present invention. In addition, it should be understood that aspects of the various embodiments may be interchanged both in whole or in component. Furthermore, those of ordinary skill in the art will appreciate that the foregoing description is by way of example only, and is not intended to limit the invention so further described in such appended claims.

What is claimed is:

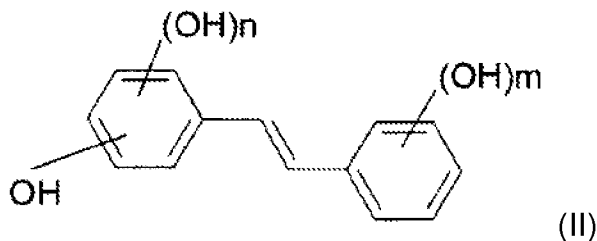
1. A cosmetic composition for skin brightening, comprising:

(a) 0.01 to 3.0% by weight of a saturated resorcinol derivative of formula (I)



wherein R represents (C₂-C₈)alkyl, (C₃-C₈)cycloalkyl or aryl (C₁-C₆)alkyl,

(b) 0.001 to 0.5% by weight of a hydroxystilbene compound of formula (II)



wherein n is an integer from 0 to 4, and m is an integer from 0 to 5,

(c) 0.001 to 5% by weight of a stabilizer, and

(d) 70 to 99.9% by weight of a cosmetically acceptable carrier,

in which the weight percentages are based on the total weight of all components of the cosmetic composition.

2. The cosmetic composition for skin brightening according to claim 1, wherein R represents (C₂-C₄)alkyl, (C₃-C₆)cycloalkyl or aryl (C₁-C₄)alkyl.

3. The cosmetic composition for skin brightening according to claim 1 or 2, wherein R is selected from the group consisting of ethyl, n-propyl, isopropyl, n-butyl, cyclopentyl, cyclohexyl, benzyl, phenyl ethyl, and phenyl n-propyl.

4. The cosmetic composition for skin brightening according to any of claims 1 to 3, wherein R is phenyl ethyl.

5. The cosmetic composition for skin brightening according to any of claims 1 to 4,

wherein the component (a) is present in an amount of from 0.05 to 2.0%, preferably from 0.25 to 1.0% by weight based on the total weight of all components of the cosmetic composition.

6. The cosmetic composition for skin brightening according to any of claims 1 to 5, wherein n is an integer from 0 to 2, preferably is 1 to 2, and m is an integer from 0 to 3, preferably is 1 to 2.
7. The cosmetic composition for skin brightening according to any of claims 1 to 6, wherein the hydroxystilbene compound is selected from the group consisting of 4'-hydroxystilbene, 2',4'-dihydroxystilbene, 3',4'-dihydroxystilbene, 4,4'-dihydroxystilbene, 2',4',4'-trihydroxystilbene, 3',4',4'-trihydroxystilbene, 2,4,4'-trihydroxystilbene, 3,4,4'-trihydroxystilbene, 3,4',5-trihydroxystilbene, 2',3,4-trihydroxystilbene, 2,3',4-trihydroxystilbene, 2',2,4'-trihydroxystilbene, 2,4,4',5-tetrahydroxystilbene, 2',3,4',5-tetrahydroxystilbene, 2,2',4,4'-tetrahydroxystilbene, 3,3',4',5-tetrahydroxystilbene, 2,3',4,4'-tetrahydroxystilbene, 3,3',4,4'-tetrahydroxystilbene, 3,3',4',5,5'-pentahydroxystilbene, 2,2',4,4',6-pentahydroxystilbene, 2,3',4,4',6-pentahydroxystilbene, 2,2',4,4',6,6'-hexahydroxystilbene and the combination thereof, and preferably is 3,4',5-trihydroxy-*trans*-stilbene.
8. The cosmetic composition for skin brightening according to any of claims 1 to 7, wherein the hydroxystilbene compound is present in an amount of from 0.01 to 0.2%, preferably from 0.05 to 0.1% by weight based on the total weight of all components of the cosmetic composition.
9. The cosmetic composition for skin brightening according to claims 1 to 8, wherein the stabilizer is selected from the group consisting of hyposulfite, bisulfite, sulfite, and the combination thereof, and preferably is sodium sulfite.
10. The cosmetic composition for skin brightening according to claims 1 to 9, wherein the stabilizer is present in an amount of from 0.05 to 1%, preferably from 0.1 to 0.5% by weight, based on the total weight of all components of the

cosmetic composition.

11. The cosmetic composition for skin brightening according to claims 1 to 10, further comprising a cosmetic adjuvant selected from the group consisting of an emollient, an emulsifier, a skin care active, a UV screening agent, a filler, a preservative, a fragrance, a bactericide, an odour absorber, a colouring material, a surfactant, a thickener, and combination thereof.
12. The use of the cosmetic composition for skin brightening according to any of claims 1 to 11 in inhibiting melanogenesis and reducing skin pigmentation.

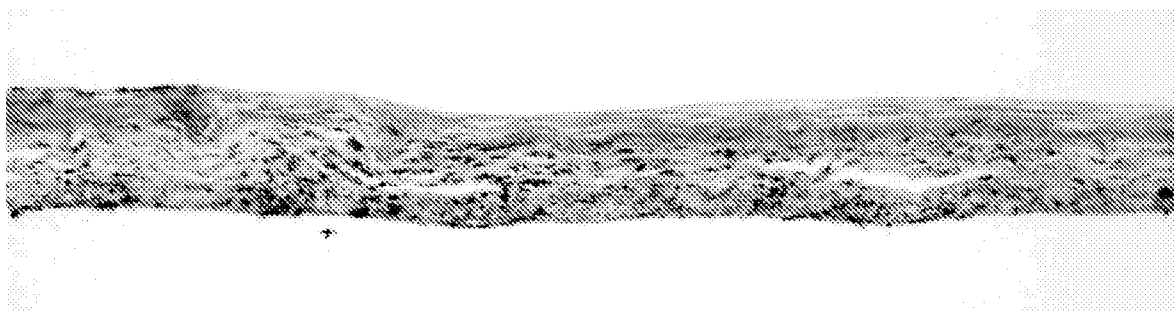


Fig. 1

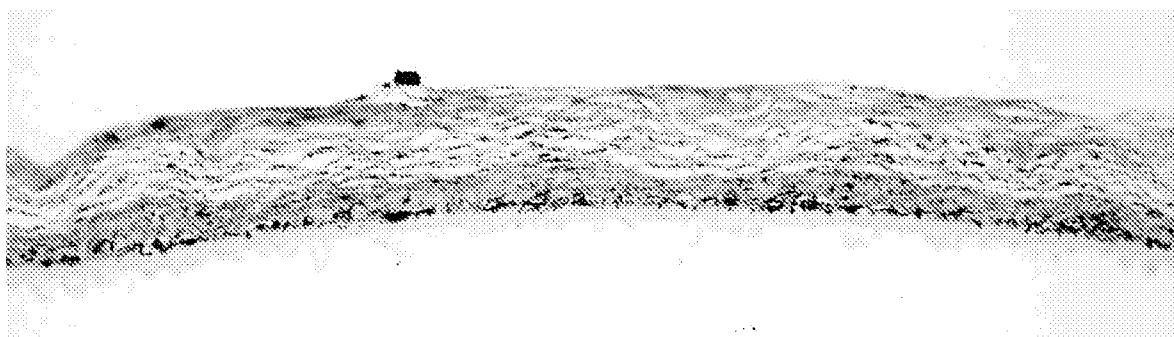


Fig. 2

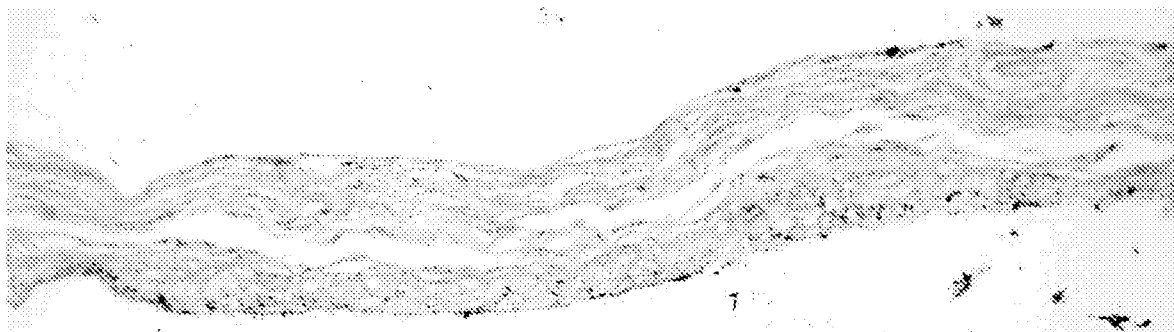


Fig. 3

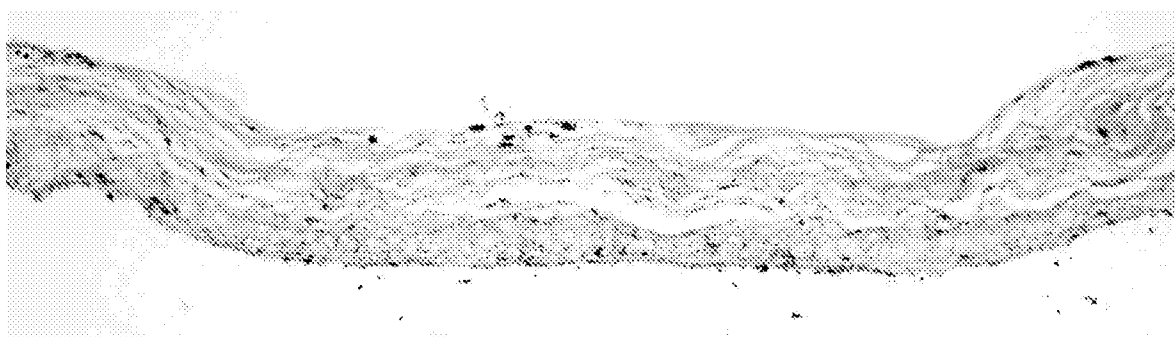


Fig. 4

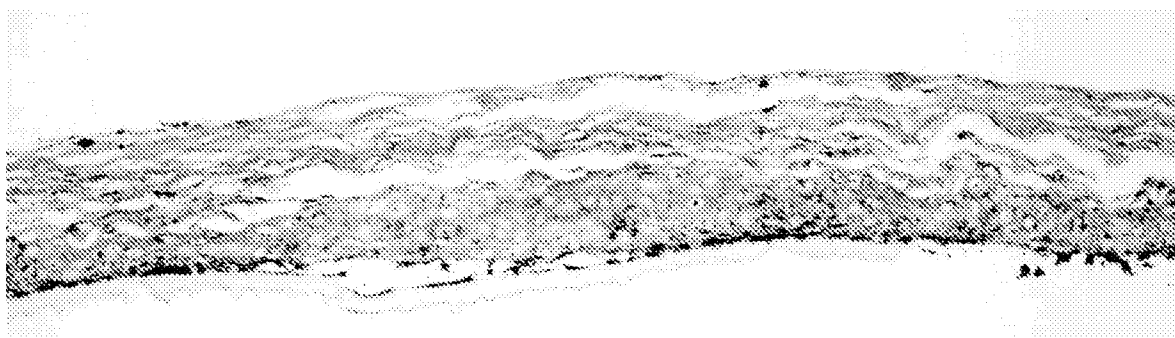


Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2015/094217

A. CLASSIFICATION OF SUBJECT MATTER

A61K 8/30(2006.01)i; A61K 8/33(2006.01)i; A61K 8/34(2006.01)i; A61K 8/46(2006.01)i; A61K 8/72(2006.01)i; A61Q 19/00(2006.01)i; A61Q 19/02(2006.01)i

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; A61Q

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

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

CNABS,CNKI,DWPI,EPODOC: white+, brighten+, lighten+, melanocyte+, pigment, resorcinol, hydroxystilbene, resveratrol, SYNOVEA HR, octylresorcinol, SymWhite 377, Bio 377

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 2004352628 A (KURARAY CO ET AL.) 16 December 2004 (2004-12-16) see example 1	1-12
X	WO 9915148 A1 (PFIZER PRODUCTS INC.) 01 April 1999 (1999-04-01) see claims 1, 2 and 20	1-12

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

“E” earlier application or patent but published on or after the international filing date

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

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

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

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

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

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

“&” document member of the same patent family

Date of the actual completion of the international search

04 August 2016

Date of mailing of the international search report

16 August 2016

Name and mailing address of the ISA/CN

STATE INTELLECTUAL PROPERTY OFFICE OF THE
P.R.CHINA
6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing
100088, China

Facsimile No. (86-10)62019451

Authorized officer

CHEN,Mao

Telephone No. (86-10)62412205

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.

PCT/CN2015/094217

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
JP	2004352628	A	16 December 2004	JP	4076477	B2	16 April 2008
WO	9915148	A1	01 April 1999	IL	134598	D0	30 April 2001
				HU	0003743	A2	28 April 2001
				UY	25550	A1	23 February 2000
				PA	8459901	A1	24 May 2000
				UY	25191	A1	27 August 2001
				PT	904774	E	29 August 2003
				HR	P20000168	B1	31 July 2006
				CA	2247748	A1	23 March 1999
				DE	69812519	T2	11 December 2003
				ID	24084	A	06 July 2000
				SK	284983	B6	02 March 2006
				GT	199800150	A	15 March 2000
				NO	20001473	A	22 March 2000
				CA	2247748	C	02 July 2002
				BR	9803596	A	25 April 2000
				TR	200000782	T2	21 September 2000
				JP	3591763	B2	24 November 2004
				EA	003576	B1	26 June 2003
				EP	0904774	A1	31 March 1999
				BG	104247	A	30 November 2000
				AT	235220	T	15 April 2003
				NO	20001473	D0	22 March 2000
				EG	23860	A	18 November 2007
				IL	170545	A	29 April 2010
				TW	585780	B	01 May 2004
				US	6132740	A	17 October 2000
				ZA	9808669	A	22 March 2000
				AR	012520	A1	18 October 2000
				MA	26548	A1	20 December 2004
				DE	69812519	D1	30 April 2003
				DZ	2614	A1	01 March 2003
				AU	735716	C	29 March 2007
				HR	P20000168	A2	31 August 2000
				SK	3782000	A3	11 June 2001
				JP	H11152203	A	08 June 1999
				PE	117299	A1	18 November 1999
				CZ	297669	B6	28 February 2007
				JP	2004210799	A	29 July 2004
				AP	9801349	D0	30 September 1998
				ES	2192301	T3	01 October 2003
				NZ	502797	A	26 April 2002
				EP	0904774	B1	26 March 2003
				BG	64524	B1	30 June 2005
				IS	5376	A	15 February 2000
				AP	857	A	11 July 2000
				CO	5070677	A1	28 August 2001
				CZ	20001037	A3	14 February 2001
				SI	0904774	T1	31 October 2003
				PT	904774	T	29 August 2003