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(54) Title: HYDROXYCINNAMIC ACID DERIVATIVES AND PREPARATION METHOD THEREOF AND COSMETIC COMPOSITION CONTAINING IT

(57) Abstract: The present invention relates to hydroxycinnamic acid derivatives conjugated with adamantylamide, a preparation method thereof and cosmetic compositions containing the same. The hydroxycinnamic acid derivatives of the present invention have activities of inhibiting melanin generation by anti-oxidation and promoting collagen synthesis. Therefore, compositions containing the derivatives of the invention can be effectively used as cosmetic compositions with anti-oxidation effect, skin pigmentation improving effect and anti-wrinkle effect by promoting collagen synthesis.



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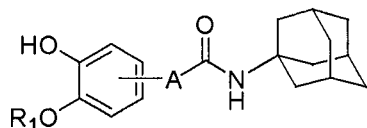
【DESCRIPTION】**【Invention Title】**

HYDROXYCINNAMIC ACID DERIVATIVES AND PREPARATION METHOD
THEREOF AND COSMETIC COMPOSITION CONTAINING IT

5

【Technical Field】

The present invention relates to hydroxycinnamic acid derivatives conjugated with adamantylamide represented by the following formula 1 and a preparation method thereof and a
10 cosmetic composition containing the same as an active ingredient.

【Formula I】

[Wherein, R₁ is H or C1~C7 alkyl; A is -CH=CH- or -CH₂-
15 CH₂-.]

【Background Art】

UV irradiation causes skin troubles such as pigmentation or wrinkles. Recent studies report that the active oxygen
20 acts as a key factor to cause such skin troubles.

Human skin color is determined by many factors such as erythrocytes in blood, carotene and melanin. But, it is melanin that makes difference in skin tone among races and

brings hyperchromasia represented by skin stain and freckle. Melanin existing in the outer skin layer plays a role in blocking UV to protect skin organ under the corium and at the same time in scavenging free radical generated in skin system
5 to protect proteins and genes therein.

However, melanin is a very stable substance that is not easily gotten rid of until keratinization once it is generated by internal or outer stress stimulus. Endogenous melanin is produced by polymerizing oxidation using tyrosine or DOPA as a
10 substrate and tyrosinase as a catalyst and this melanin is increased with the increase of free radical, inflammation or UV. UV increases the generation of endogenous active oxygen and this active oxygen increases melanin generation. And then, the increased local melanin becomes skin stain which might
15 spoil the beauty and further cause serious problems such as wrinkles and skin cancer with threatening our lives.

To overcome those problems, active oxygen inhibitors such as ascorbic acid and its derivatives, *Mori Cotex Radicis* extract, green tea extract, aloe extract, *Scutellariae Radix*
20 extract, which are so called natural polyphenol extracts, have been tried. But, these natural polyphenol extracts are so unstable that their effects cannot be constant during mixing procedure and percutaneous absorption is difficult, resulting in doubt in whitening and anti-wrinkle effects.

【Disclosure】**【Technical Problem】**

The present inventors studied to overcome the
5 disadvantages of the natural polyphenol and aftermath the
inventors succeeded in increasing anti-oxidation activity by
using hydroxycinnamic acid of natural polyphenol and prepared
hydroxycinnamic acid derivatives conjugated with
adamantylamide by reacting thereof with adamantaneamine having
10 hydrophobic group to improve percutaneous absorption. Most of
hydroxycinnamic acid derivatives conjugated with
adamantylamide exhibit active oxygen inhibitory effect and
melanin generation inhibitory effect as well as procollagen
synthesis inducing effect. The present inventors completed
15 this invention by confirming that hydroxycinnamic acid
derivatives conjugated with adamantylamide had melanin
generation inhibitory activity or procollagen synthesis
inducing effect, and therefore it can be an excellent cosmetic
composition to bring whitening effect or anti-wrinkle effect.

20 It is an object of the present invention to provide
hydroxycinnamic acid derivatives conjugated with
adamantylamide having a novel chemical structure and a
preparation method thereof.

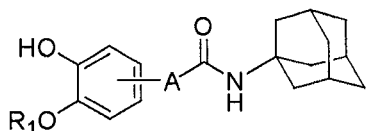
It is another object of the present invention to provide

an anti-oxidative cosmetic composition, a whitening cosmetic composition or an anti-wrinkle cosmetic composition containing the hydroxycinnamic acid derivatives conjugated with adamantylamide as an active ingredient in an amount of 0.01 -
 5 20 weight%.

【Technical Solution】

The present invention relates to hydroxycinnamic acid derivatives conjugated with adamantylamide represented by
 10 formula 1 and a preparation method thereof as well as an antioxidant, a whitening or an anti-wrinkle cosmetic composition containing the same as an active ingredient.

[Formula I]



15 [Wherein, R₁ is H or C1~C7 alkyl; A is -CH=CH- or -CH₂-CH₂-.]

Hereinafter, the present invention is described in detail.

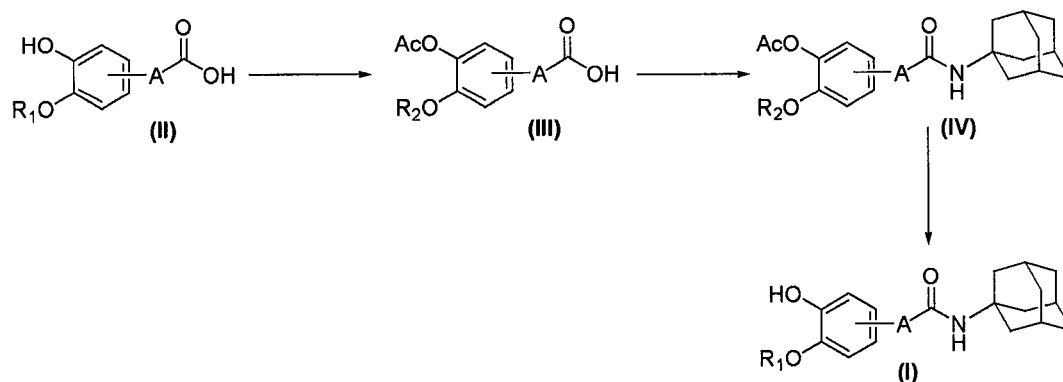
20 The hydroxycinnamic acid derivatives conjugated with adamantylamide of the present invention represented by formula 1 are generated by the following reaction formula, in which the following steps are included,

1) preparing the acetylated compound of formula III by converting H of hydroxyl group to acetyl group by using hydroxycinnamic acid of formula II, acetic anhydride, base and a catalyst;

2) preparing the amide compound of formula IV by reacting the acetylated compound of formula III prepared in the above step 1) with adamantaneamine having hydrophobic group and ethylchloroformate; and

3) obtaining hydroxycinnamic acid derivatives conjugated with adamantylamide of formula I by hydrolyzing the acetyl group of the amide compound of formula IV prepared in the above step 2).

[Reaction Formula 1]



[Wherein, R₁ is H or C1~C7 alkyl; A is -CH=CH- or -CH₂-CH₂-; and When R₁ is C1~C7 alkyl, R₁ is the same as R₂ but when R₁ is H, R₂ is acetyl.]

The method of preparing hydroxycinnamic acid derivatives conjugated with adamantylamide, as explained in the above

reaction formula 1, is described in more detail hereinafter.

In step 1), hydrogen atom of hydroxyl group is converted to acetyl group by the reaction of hydroxycinnamic acid, acetic anhydride and base in the presence of a catalyst. In
5 this reaction, base is pyridine or triethylamine, and a reaction solvent is selected from the group consisting of dichloromethane, chloroform and tetrahydrofuran. For smooth reaction, dimethylaminopyridine is used as a catalyst, and if not, the reaction is not smoothly carried out and yield is not
10 high. The reaction temperature is preferably 10 - 80°C and more preferably 40°C.

In step 2), the reaction of the acetylated compound (III) with adamantylamine having hydrophobic group and ethylchloroformate is induced to give an adamantylamide
15 compound (IV). This reaction can be induced by acid halogenation, active ester method, or acid anhydride method, but it is preferred to convert the compound to adamantylamine having hydrophobic group under anhydrous condition to produce adamantylamide compound (IV). The equivalence ratio of
20 adamantylamine having hydrophobic group to be reacted with the acetylated compound (III) is preferably 1.1 - 1.3. If the equivalence ratio is under 1:1, the level of adamantylamide compound (IV) is reduced.

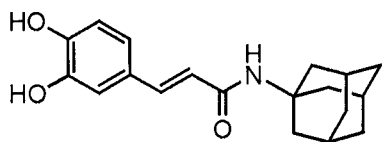
The base herein is pyridine or triethylamine but

preferably triethylamine. A reaction solvent is selected from the group consisting of dichloromethane, acetone, N,N-dimethylformamide, acetonitrile and tetrahydrofuran, but N,N-dimethylformamide and tetrahydrofuran are preferred. The
5 preferable reaction temperature is 10 - 60°C and 30°C is more preferred.

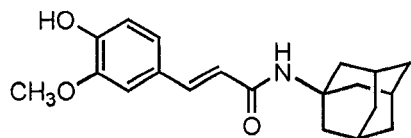
In step 3), hydroxycinnamic acid derivatives conjugated with adamantylamide represented by formula I is obtained. The hydrolysis of acetyl group of adamantylamide compound (IV) is
10 induced in the presence of a base selected among alkali metal hydroxides such as sodium hydroxide and potassium hydroxide. In this reaction, a reaction solvent is selected from the group consisting of water, methanol, ethanol, propanol, tetrahydrofuran and dichloromethane. It is preferred to mix
15 tetrahydrofuran and methanol at the volume ratio of 1 : 1 - 1 : 5, and more preferably 1 : 1 for desirable reaction in a short period of time.

The preferable embodiments of hydroxycinnamic acid derivatives conjugated with adamantylamide represented by
20 formula I which can be generated by the above preparation method are as follows.

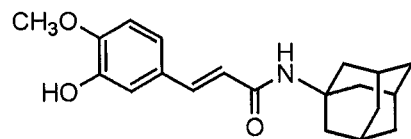
[Formula I-a] 3-(3,4-dihydroxyphenyl)-N-adamantyl-propeneamide



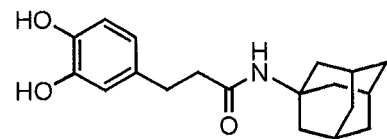
[Formula I-b] 3-(4-hydroxy-3-methoxyphenyl)-N-adamantyl-propeneamide



5 [Formula I-c] 3-(3-hydroxy-4-methoxyphenyl)-N-adamantyl-propeneamide



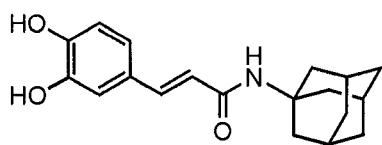
[Formula I-d] 3-(3,4-dihydroxyphenyl)-N-adamantyl-propaneamide



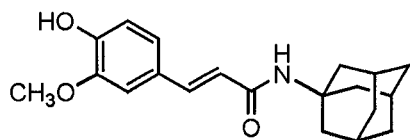
10 The hydroxycinnamic acid derivatives conjugated with adamantylamide (I) prepared by the method of the present invention can be included in an anti-oxidant, a whitening or an anti-wrinkle cosmetic composition as an active ingredient, and at this time, the concentration can be determined considering the maximum effect of anti-oxidant, whitening or anti-wrinkle activity. For example, the compound can be contained in an amount of 0.01 - 20.0 weight%, based on the total cosmetic composition and formulation form can be cream, lotion, toner, massage cream or essence but not always limited

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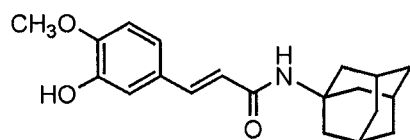
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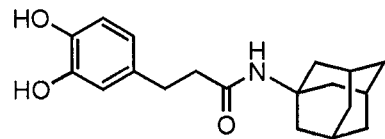
[Formula I-b] 3-(4-hydroxy-3-methoxyphenyl)-N-adamantyl-propeneamide



5 [Formula I-c] 3-(3-hydroxy-4-methoxyphenyl)-N-adamantyl-propeneamide



[Formula I-d] 3-(3,4-dihydroxyphenyl)-N-adamantyl-propaneamide



10 The hydroxycinnamic acid derivatives conjugated with adamantylamide (I) prepared by the method of the present invention can be included in an anti-oxidant, a whitening or an anti-wrinkle cosmetic composition as an active ingredient, and at this time, the concentration can be determined considering the maximum effect of anti-oxidant, whitening or anti-wrinkle activity. For example, the compound can be contained in an amount of 0.01 - 20.0 weight%, based on the total cosmetic composition and formulation form can be cream, lotion, toner, massage cream or essence but not always limited

15

20

thereto.

The composition of the present invention can include other general ingredients according to its formulation and the kinds, and contents of such ingredients can be generally determined by those in the art. The composition of the present invention can include any other anti-oxidant, whitening or anti-wrinkle agent in addition to the hydroxycinnamic acid derivatives conjugated with adamantylamide (I) of the present invention in order to increase the anti-oxidative, whitening or anti-wrinkle effect. At this time, the kind and concentration of an acceptable conventional anti-oxidant, whitening or anti-wrinkle agents are well informed to those in the art.

【Best Mode】

Practical and presently preferred embodiments of the present invention are illustrative as shown in the following Examples.

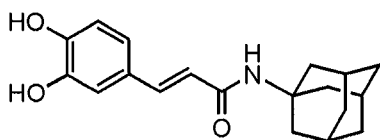
However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modifications and improvements within the spirit and scope of the present invention.

[Example 1] 3-(3,4-dihydroxyphenyl)-N-adamantyl-propeneamide
(Formula I-a)

3,4-dihydroxycinnamic acid (100 g, 0.56 mol) was dissolved in 1000 ml of dichloromethane, to which
5 dimethylaminopyridine (4 g, 0.03 mol) was added as a catalyst, followed by reflux for 5 minutes. Triethylamine (199 ml, 1.43 mol) was added thereto. To the reaction solution, acetic anhydride (135 ml, 1.43 mol) was added slowly, followed by reflux for 2 hours at 40°C. Upon completion of the reaction,
10 dichloromethane (1000 ml) was added to the reaction solution for dilution, which was then washed with 1000 ml of water and 500 ml of 1 M HCl solution. The mixture was dried over manganese anhydride (100 g), filtered and concentrated, and crystallized with hexane. The product was filtered again and
15 hydrogen atom of 3,4-dihydroxy group of 3,4-dihydroxycinnamic acid was converted to acetyl group to give 123 g of an acetyl compound (yield = 83%). The resulted compound (100 g, 0.38 mol) was dissolved in tetrahydrofuran (1500 ml), to which triethylamine (76.1 ml, 0.55 mol) was slowly added. 1.3
20 equivalence ratio of ethylchloroformate (56.9 ml, 0.49 mol) was slowly added to the mixture, followed by stirring for 30 minutes. Upon completion of the stirring, adamantaneamine hydrochloric acid (78.8 g, 0.42 mol) and triethylamine (68.3 ml, 0.49 mol) dissolved in 1500 ml of N,N-dimethylformamide by heat

were slowly loaded to the reaction solution, followed by further stirring for 3 hours. Upon completion of the reaction, the reaction mixture was filtered and concentrated. The concentrated reaction mixture was dissolved in 1500 ml of dichloromethane and then washed with distilled water (500 ml) and secondly washed with 500 ml of saturated sodium hydrogen carbonate. The mixture was dried over manganese anhydride (100 g), filtered, concentrated and crystallized using hexane. The crystallized product was filtered again to give 133 g of an adamantylamide compound (yield = 88%). The obtained compound (100 g, 0.25 mol) was dissolved in 1500 ml of solvent in which tetrahydrofuran and methanol were mixed at 1:1, followed by stirring in 100 ml of 15% potassium hydroxide for 30 minutes. Upon completion of the reaction, acid was added to neutralize the mixture. The reaction solution was then concentrated, to which 1500 ml of ethyl acetate was added to dissolve the mixture. The reaction mixture was then washed with 1000 ml of water, concentrated, crystallized using hexane and filtered to give 69 g of the target compound 3-(3,4-dihydroxyphenyl)-N-adamantyl-propeneamide (Formula I-a) as a light yellow solid (yield = 89%).

[Formula I-a]



TLC (ethyl acetate : hexane = 1 : 1) R_f = 0.78

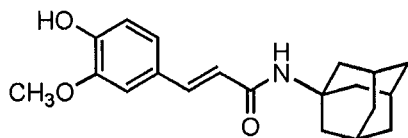
^1H NMR(DMSO- d_6 , δ) : 9.05(m, 2H), 7.46(d, 1H), 7.25(s, 1H), 7.01(s, 1H), 6.92(d, 1H), 6.78(d, 1H), 6.16(d, 1H), 1.96(m, 9H), 1.52(m, 6H).

5

[Example 2] 3-(4-hydroxy-3-methoxyphenyl)-N-adamantyl-propeneamide (Formula I-b)

The target compound 3-(4-hydroxy-3-methoxyphenyl)-N-adamantyl-propeneamide (Formula I-b) was prepared as 72g of a light yellow solid (yield = 82%) by the same manner as described in Example 1 except that 4-hydroxy-3-methoxycinnamic acid was used instead of 3,4-dihydroxycinnamic acid.

[Formula I-b]



15 TLC (ethyl acetate : hexane = 1 : 1) R_f = 0.69

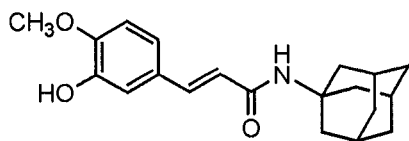
^1H NMR(DMSO- d_6 , δ) : 9.02(s, 1H), 7.52(d, 1H), 7.31(s, 1H), 7.28(s, 1H), 7.12(d, 1H), 6.82(d, 1H), 6.46(d, 1H), 3.82(s, 3H), 1.93(m, 9H), 1.49(m, 6H).

20 [Example 3] 3-(3-hydroxy-4-methoxyphenyl)-N-adamantyl-propeneamide (Formula I-c)

The target compound 3-(3-hydroxy-4-methoxyphenyl)-N-adamantyl-propeneamide (Formula I-c) was prepared as 75g of a

light yellow solid (yield = 85%) by the same manner as described in Example 1 except that 3-hydroxy-4-methoxycinnamic acid was used instead of 3,4-dihydroxycinnamic acid.

[Formula I-c]



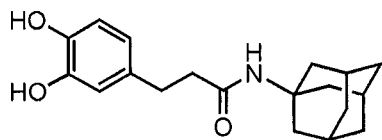
TLC (ethyl acetate : hexane = 1 : 1) R_f = 0.70

^1H NMR (DMSO- d_6 , δ) : 8.92 (s, 1H), 7.49 (d, 1H), 7.26 (s, 1H), 7.12 (m, 2H), 6.92 (d, 1H), 6.26 (d, 1H), 3.81 (s, 3H), 1.95 (m, 9H), 1.49 (m, 6H).

[Example 4] 3-(3,4-dihydroxyphenyl)-N-adamantyl-propaneamide (Formula I-d)

The target compound 3-(3,4-dihydroxyphenyl)-N-adamantyl-propaneamide (Formula I-d) was prepared as 72g of a light yellow solid (yield = 91%) by the same manner as described in Example 1 except that 3,4-dihydroxyhydrocinnamic acid was used instead of 3,4-dihydroxycinnamic acid.

[Formula I-d]



TLC (ethyl acetate : hexane = 1 : 1) R_f = 0.60

^1H NMR (DMSO- d_6 , δ) : 8.65 (m, 2H), 7.16 (s, 1H), 6.56 (m, 2H), 6.38 (d, 1H), 2.58 (t, 2H), 2.15 (t, 2H), 1.91 (m, 9H), 1.45 (m,

6H) .

[Experimental Example 1] Investigation of anti-oxidative effect using HaCat model

5 The anti-oxidative effect of hydroxycinnamic acid derivatives conjugated with adamantylamide prepared in Examples 1 - 4 was investigated. Human keratinocyte cell line HaCaT was distributed in 60 mm dish at the concentration of 1.0×10^6 cells per dish, which was cultured in DMEM (FBS 10%)
10 supplemented with penicillin/streptomycin in a 37°C, 5% CO₂ incubator for one day. The compounds of Examples 1 - 4, the most representative conventional anti-oxidant tocopherol (as a positive control), EGCG (Epigallocatechin Gallate) and BHT (t-butyl hydroperoxide) were treated thereto at the concentration
15 of 10^{-4} mol, followed by culture in a 37°C, 5% CO₂ incubator. Cells were obtained 4 hours later. The cells were lysed by freeze/thawing. The following experiments were performed according to the instructions of the assay kit.

20 To measure anti-oxidant effect, Calbiochem Lipid peroxidation assay kit (Cat. No.437634) was used. The level of lipid peroxidation was measured based on the principle that the reaction of long chain unsaturated fatty acid associated ester peroxide such as malondialdehyde (MDA) and 4-hydroxyalkenal (i.e. 4-hydroxy-2(E)-nonenal, 4-HNE) with the

above reagent produces a very stable compound at 586nm. The low number indicated the higher inhibition of lipid peroxidation.

[Table 1] Anti-oxidative effect of hydroxycinnamic acid

5 derivatives

Substance	MDA, HNE	Substance	MDA, HNE
Non-treated group	100	Example 1	223
t-BHP	320	Example 2	195
Tocopherol	250	Example 3	186
EGCG	230	Example 4	196

MDA and HNE shown in Table 1 are the products from the peroxidation of saturated fatty acid associated ester. So, measuring such aldehydes leads to the understanding of the level of lipid peroxidation. And the lower the value, the greater the lipid peroxidation inhibitory effect will be. From the results of investigation of anti-oxidation shown in Table 1, it was confirmed that hydroxycinnamic acid derivatives prepared in Examples 1 - 4 had excellent anti-oxidative effect, compared with the representative conventional anti-oxidants such as t-BHP, tocopherol and EGEG.

[Experimental Example 2] Melanin synthesis inhibitory effect in melanocytes

20 The effect on melanin generation of the compounds prepared in Examples 1 - 4 was investigated by Dooley's method.

Mel-Ab cell line derived from cutaneous pigment cells of C57BL/6 was used. Cell culture was carried out in DME supplemented with 10% FBS, 100 nM 12-OI-tetradecanoyl phorbol-13-acetate, 1 nM cholera toxin in a 37°C, 5% CO₂ incubator.

5 Cultured Mel-Ab cells were recovered using 0.25% trypsin-EDTA and then re-distributed in a 24-well plate at the equal concentration (1×10^5 cells/well). For the three consecutive days from the second day of distribution, media each containing 10 ppm of sample were replaced. 5 days later, 1N NaOH was treated to take off melanin included in cells and the level of melanin was measured by measuring OD₄₀₀. The level of melanin was compared with that in the non-treated control group and the ratio (%) was calculated, which was shown in Table 2.

15 [Table 2] Inhibition of melanin generation by hydroxycinnamic acid derivatives

Sample	Melanin generation (% control)
Non-treated group	100
HQ	11.20
Kojic acid	89.1
Example 1	17.3
Example 2	28.5
Example 3	36.5
Example 4	18.3

Inhibitory effects on melanin generation of hydroquinone (HQ) and kojic acid, positive controls, were investigated and compared with those of the hydroxycinnamic acid derivatives

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conjugated with adamantylamide of Examples 1 - 4. As shown in Table 2, it was confirmed that the hydroxycinnamic acid derivatives conjugated with adamantylamide of Examples 1 - 4 had similar or greater inhibitory effect on melanin generation than the conventional whitening agents hydroquinone and kojic acid.

[Experimental Example 3] Whitening effect on human skin

12 healthy male volunteers were participated in this examination. An opaque tape with a hole of 1.5 cm in diameter was attached on the humeral region of the examinee. UVB was irradiated 1.5 - 2 times the minimal erythema dose to induce darkening of skin.

After irradiation, 2% of each compounds of Examples 1 - 4 (solvent: 1,3-butyleneglycol:ethanol=7:3), 2% of hydroquinone (control), 2% of lipoic acid and a vehicle were respectively applied for 10 weeks (one spot was just left without application). Skin color change was investigated by Colorimeter CR-300 (Minolta, Japan) every week. The change of color tone (ΔL) was measured, which is represented by the difference of 'L' value, and the results are shown in Table 3.

The improvement of pigmentation was investigated and used as basis for the evaluation of whitening effect and the results are shown in Table 3.

[Table 3] Whitening effect of hydroxycinnamic acid derivatives on human skin

Sample	Skin color tone (ΔL)
Vehicle	-6.1
HQ	-1.7
Lipoic acid	-3.1
Example 1	-1.5
Example 2	-1.8
Example 3	-1.9
Example 4	-1.6

As shown in Table 3, the hydroxycinnamic acid derivatives conjugated with adamantylamide of Examples 1 - 4 were confirmed to have excellent whitening effect, compared with lipoic acid that has been known as a whitening agent, which was also similar or even improved, compared with the whitening effect of hydroquinone (HQ).

[Experimental Example 4] Promotion of collagen biosynthesis

Collagen biosynthesis promoting effects of hydroxycinnamic acid derivatives conjugated with adamantylamide of Examples 1 - 4 were compared with those of retinol and retinoic acid.

Fibroblasts were seeded in a 24 well plate at the concentration of 10^5 cells per well and cultured until they grew 90%. After culturing in serum-free DMEM for 24 hours, the cells were treated with 10^{-4} mol of hydroxycinnamic acid derivatives of Examples 1 - 4, retinol and retinoic acid,

followed by further culture for 24 hours in a CO₂ incubator. The supernatant was tested for procollagen level by using procollagen type(I) ELISA kit. The results are shown in Table 4. Synthetic capacity was presented as the ratio to non-treated group (100).

[Table 4] Procollagen biosynthesis inducing effect of hydroxycinnamic acid derivatives

Sample	Synthetic capacity (%)
Non-treated group	100
Retinol	113
Retinoic acid	120
Example 1	134
Example 2	121
Example 3	122
Example 4	128

As shown in Table 4, hydroxycinnamic acid derivatives prepared in Examples 1 - 4 were confirmed to have similar or greater collagen biosynthesis inducing effect in skin, compared with retinol and retinoic acid.

[Experimental Example 5] Inhibitory effect on collagenase expression

The hydroxycinnamic acid derivatives prepared in Examples 1 - 4 were tested for the inhibitory effect on collagenase expression, by comparing those of retinol and retinoic acid.

Human fibroblasts were seeded in a 96 well microtiter plate containing DMEM (Dulbecco's Modified Eagle's Media)

supplemented with 2.5% FBS at the concentration of 5000 cells/well and cultured until they grew 90%. After culturing them in serum-free DMEM for 24 hours, the cells were treated with the hydroxycinnamic acid derivatives of Examples 1 - 4, retinol and retinoic acid by 10^{-4} mol each for 24 hours and then the cell culture medium was obtained.

Collagenase generation in the cell culture medium was measured by collagenase measuring kit (Amersham Pharmacia, USA). First, the cell culture medium was loaded in a 96 well plate supplemented evenly with the primary collagenase antibody to induce antigen-antibody reaction for 3 hours.

Three hours later, the chromophore-conjugated secondary collagen antibody was loaded in the 96 well plate again and reaction was induced for 15 minutes. A coloring material was added 15 minutes later to induce color development for 15 minutes and then 1 M sulfuric acid was added to terminate color development. The color of the reaction solution was yellow and the degree of yellow varied from the degree of reaction.

OD₄₀₅ of the yellow 96-well plate was measured and collagenase synthesis was calculated by the following mathematical formula 1. The optical density of the cell culture medium that had not been treated with any composition was considered as the control.

[Mathematical Formula 1]

Expression rate of collagenase (%) = OD of the
composition-treated cell group / OD of the control group x 100

The results of the examination of the inhibitory effect
5 on intracellular collagenase expression are shown in Table 5
and the expression inhibitory capacity was calculated by
considering the synthesis ability of non-treated group as 100.

[Table 5]

Sample	Expression level of collagenase (%)
Non-treated group	100
Retinol	85
Retinoic acid	60
Example 1	67
Example 2	69
Example 3	71
Example 4	66

10 As shown in Table 5, the hydroxycinnamic acid derivatives
of Examples 1 - 4 were confirmed to have similar or greater
collagenase expression inhibitory effect *in vitro*, compared
with retinol and retinoic acid.

15 Hereinafter, formulation examples of the hydroxycinnamic
acid derivatives of the present invention are described, but
it is well understood by those in the art that these cannot
limit the spirit or scope of the present invention.

Cosmetic compositions for whitening and anti-wrinkles
20 were prepared with the hydroxycinnamic acid derivatives of

Examples 1 - 4 having excellent melanin generation inhibitory effect and collagen biosynthesis promoting effect by the conventional cosmetic composition preparation method according to the following constitution and ratio.

5

[Formulation Example 1]

Anti-wrinkle cream formulation containing the compounds of Examples 1 - 4

	Stearic acid	10%
10	Palmitic acid	5%
	Myristic acid	15%
	Lauric acid	6%
	Potassium hydroxide	6%
	Glycerin	15%
15	Compounds of Examples 1 - 4	0.5%

Proper amounts of antiseptic, non-ionic surfactant, pigment, flavor, etc were added thereto, and then distilled water was added until the total volume reached 100%.

20 [Formulation Example 2]

Whitening cream formulation containing the compounds of Examples 1 - 4

	Stearic acid	2%
	Glyceryl mono stearate	3%

	Cetostearyl alcohol	3%
	Squalene	20%
	Macadamia nut	10%
	Silicon oil	3%
5	Polysorbate-60	2.5%
	Glycerin	10%
	Compounds of Examples 1 - 4	0.5%

Proper amounts of flavor, pigment, antiseptic, antioxidant, etc were added thereto, and then distilled water
10 was added until the total volume reached 100%.

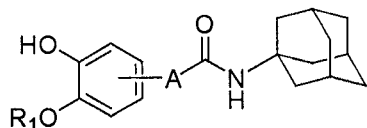
【Industrial Applicability】

As explained hereinbefore, hydroxycinnamic acid derivatives conjugated with adamantylamide of the present
15 invention have the activities of inhibiting active oxygen and melanin generation, promoting procollagen biosynthesis and inhibiting collagenase expression. So, the compositions containing the hydroxycinnamic acid derivatives as an active ingredient can be effectively used as an anti-oxidative
20 cosmetic composition with inhibiting effect of active oxygen, a cosmetic composition for whitening with improvement of skin pigmentation, or an anti-wrinkle cosmetic composition.

【CLAIMS】**【Claim 1】**

Hydroxycinnamic acid derivatives conjugated with
adamantylamide having the following formula 1.

[Formula I]

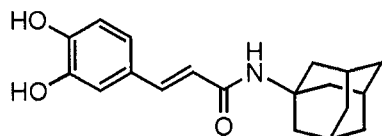


[Wherein, R₁ is H or C1~C7 alkyl; A is -CH=CH- or -CH₂-CH₂-.]

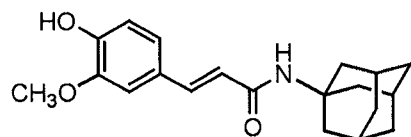
【Claim 2】

The hydroxycinnamic acid derivatives according to claim
1, wherein the derivatives have a structure selected from
those represented by formulas I-a - I-d.

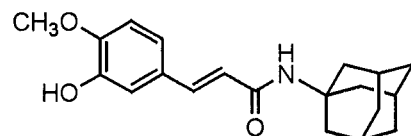
[Formula I-a]



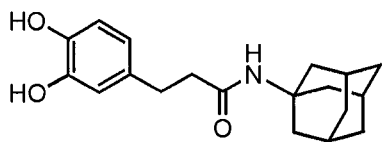
[Formula I-b]



[Formula I-c]



[Formula I-d]



【Claim 3】

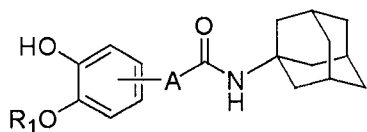
A method for producing hydroxycinnamic acid derivatives
5 conjugated with adamantylamide comprising the following steps:

1) preparing an acetylated compound of formula III by
converting H of hydroxyl group of hydroxycinnamic acid of
formula II to acetyl group;

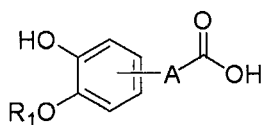
2) preparing an amide compound of formula IV by reacting
10 the acetylated compound of formula III prepared in the above
step 1) with ethylchloroformate and adamantaneamine having
hydrophobic group; and

3) obtaining hydroxycinnamic acid derivatives conjugated
with adamantylamide of formula I by hydrolyzing the acetyl
15 group of the amide compound of formula IV prepared in the
above step 2).

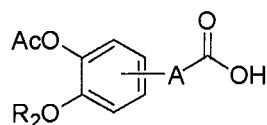
[Formula I]



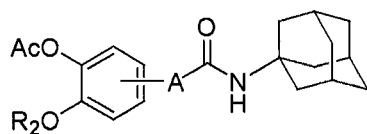
[Formula II]



[Formula III]



[Formula IV]



[Wherein, R_1 is H or C1~C7 alkyl; A is $-\text{CH}=\text{CH}-$ or $-\text{CH}_2-$
 5 CH_2- ; and When R_1 is C1~C7 alkyl, R_1 is the same as R_2 but when
 R_1 is H, R_2 is acetyl.]

【Claim 4】

The preparation method for the hydroxycinnamic acid
 10 derivatives according to claim 3, wherein the reagent of step
 1) is acetic anhydride, base and dimethylaminopyridine as a
 catalyst.

【Claim 5】

15 The preparation method for the hydroxycinnamic acid
 derivatives according to claim 3, wherein the reaction solvent
 of step 3) is the mixture of methanol and tetrahydrofuran at
 the volume ratio of 1:1 - 1:5.

20 【Claim 6】

A cosmetic composition containing the hydroxycinnamic
 acid derivatives conjugated with adamantylamide of claim 1 or

claim 2.

【Claim 7】

The cosmetic composition according to claim 6, wherein
5 the composition is for anti-oxidation.

【Claim 8】

The cosmetic composition according to claim 6, wherein
the composition is for whitening.

10

【Claim 9】

The cosmetic composition according to claim 6, wherein
the composition is for anti-wrinkle.

15 **【Claim 10】**

The cosmetic composition according to claim 6, wherein
the hydroxycinnamic acid derivative is contained in an amount
of 0.01 ~20 wt%, based on the total weight of the cosmetic
composition.

20

A. CLASSIFICATION OF SUBJECT MATTER*C07C 233/10(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)

IPC 8 C07C 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 practicable, search terms used)

STN(REGISTRY, CAPLUS), eKIPASS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	EP 0399814 A2 (SANKYO COMPANY LTD.) 28 November 1990 See example 83 and the general formula Ia of claim 1	1, 2 3-10
X A	EP0333522A2(MITSUI TOATSU CHEMICALS INC.) 20 September 1989 See compound 96 and claim 3	1, 2 3-10
A	US5426210A(SHISEIDO CO. LTD.) 20 June 1995 See claims 1-4	1-10
A	JP05105643A2(KAO CORP.) 27 April 1993 See general formula (1)	1-10
A	JP05246949A2(KAO CORP.) 24 September 1993 See general formula (1)	1-10
A	JP04009355A2(SHISEIDO CO. LTD.) 14 January 1992 See claims 1-2	1-10



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 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

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17 SEPTEMBER 2007 (17.09.2007)

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Telephone No. 82-42-481-8391



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2007/002847

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