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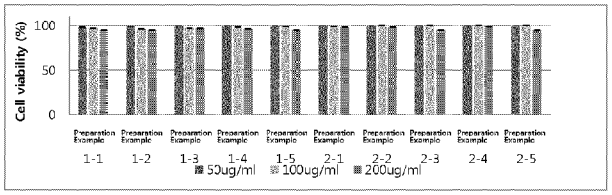
(54) **Title:** PHARMACEUTICAL OR COSMETIC COMPOSITION FOR PREVENTING OR TREATING HAIR LOSS OR PROMOTING HAIR GROWTH

[Fig. 1]



(57) **Abstract:** The present invention relates to a pharmaceutical composition or a cosmetic composition for preventing or treating hair loss, or promoting hair growth. The composition according to the present invention exhibits an excellent effect of preventing or treating hair loss and promoting hair growth, and can be safely used regardless of sex and age.

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Description

Title of Invention: PHARMACEUTICAL OR COSMETIC COMPOSITION FOR PREVENTING OR TREATING HAIR LOSS OR PROMOTING HAIR GROWTH

Technical Field

[1] The present invention relates to a pharmaceutical composition or a cosmetic composition for preventing or treating hair loss, or promoting hair growth. More particularly, the present invention relates to a pharmaceutical composition or a cosmetic composition for preventing or treating hair loss, or promoting hair growth, comprising nicotinic acid adenine dinucleotide phosphate(NAADP), and at least one selected from the group comprising one or more nature-derived amino acid or salt thereof, one or more growth factor, noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor and one or more water-soluble vitamin or salt thereof.

Background Art

[2] It has been known that hair loss is caused by local infections, endocrine disorders, genetic factors and autoimmunity as well as already known genetic causes. Recently, hair loss has been shown not only in middle-aged and elderly men but also in women or younger generation. Thus, as the need for prevention and treatment of such hair loss has increased, researches have been made on substances having various efficacy to overcome hair loss.

[3] Drugs currently used to prevent or treat hair loss and promote hair growth include vasodilators to circulate enough blood in the scalp, an activity inhibitor inhibiting an activity of 5α-reductase that converts testosterone into 5-DHT(5-dihydrotestosterone), and the like. Examples of the vasodilator include minoxidil and the like, and examples of the 5-DHT activity inhibitor include finasteride, dutasteride, and the like. On the other hand, natural derivatives such as various plant extracts are also used in addition to the organic synthetic materials as described above, but the mechanism and effect thereof are not clearly revealed.

[4] However, since the currently used preparations for preventing and treating hair loss and promoting hair growth are insufficient in their effects or have various problems such as side effects, it is necessary to develop a more effective and safe preparation for preventing or treating hair loss, or for promoting hair growth.

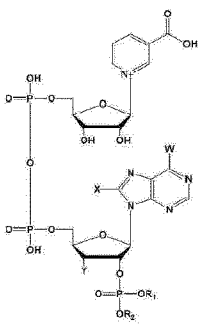
Disclosure of Invention

Technical Problem

[5] The purpose of the present invention is to provide a safe pharmaceutical composition and a safe cosmetic composition that have an excellent effect in prevention or treatment of hair loss or promotion of hair growth and are applicable irrespective of age and sex.

Solution to Problem

[6] In order to achieve the purpose above, the present invention provides a pharmaceutical composition and a cosmetic composition for preventing or treating hair loss, or promoting hair growth, comprising a compound having the structure represented by the following Formula (I) or salt thereof; and at least one selected from the group comprising one or more nature-derived amino acid or salt thereof, one or more growth factor, noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor and one or more water-soluble vitamin or salt thereof:

[7]  (I)

[8] wherein,

[9] R_1 and R_2 are each independently H, C_{1-4} alkyl which is unsubstituted or substituted with halogen, or $-CH_2-CO-CH_3$;

[10] W is selected from the group consisting of NH_2, OH and SH;

[11] X is selected from the group consisting of H, OH, SH, NH_2 and halogen; and

[12] Y is selected from the group consisting of OH, H, NH_2 and halogen.

Advantageous Effects of Invention

[13] The composition according to the present invention exhibits an excellent effect of preventing or treating hair loss and promoting hair growth, and can be safely used regardless of sex and age.

Brief Description of Drawings

[14] Fig. 1 is a graph showing the results of cytotoxicity test in human hair dermal papilla cells according to Experimental Example 1.

[15] Fig. 2 is a graph showing the test results for promotion of proliferation of human hair dermal papilla cells according to Experimental Example 2.

[16] Fig. 3 is a graph showing the test results for the hair root production rate in the hair dermal papilla cells according to Experimental Example 3.

[17] Fig. 4 is a graph showing the test results for the hair density according to Experimental Example 4.

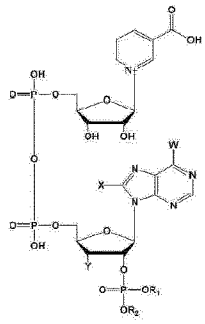
[18] Fig. 5 is a graph showing the measurement results of hair enlongation rate according to Experimental Example 5.

Best Mode for Carrying out the Invention

[19] The present invention is described in detail below.

[20] The present invention is related to a pharmaceutical composition for preventing or treating hair loss, or promoting hair growth and a cosmetic composition for preventing or improving hair loss, or promoting hair growth, comprising a compound having the structure represented by the following Formula (I) or salt thereof; and at least one selected from the group comprising one or more nature-derived amino acid or salt thereof, one or more growth factor, noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor and one or more water-soluble vitamin or salt thereof:

[21] (I)



[22] wherein,

[23] R_1 and R_2 are each independently H, C_{1-4} alkyl which is unsubstituted or substituted with halogen, or $-CH_2-CO-CH_3$;

[24] W is selected from the group consisting of NH_2, OH and SH;

[25] X is selected from the group consisting of H, OH, SH, NH_2 and halogen; and

[26] Y is selected from the group consisting of OH, H, NH_2 and halogen.

[27] In one embodiment of the present invention, the compound of Formula (I) may be nicotinic acid adenine dinucleotide phosphate(NAADP), or a salt or derivative thereof. The NAADP used in the present invention is the one synthesized by CD38, i.e. ADP-ribosyl cyclase in a cell (Chini EN. et al., Biochem J 362:125-130, 2002; BERRIDGE G. et al., Biochem. J., 365: 295-301, 2002; Aarhus R. et al., J Biol Chem., 270(51): 30327-30333, 1995).

[28] Further, the compound having the structure of Formula (I) used in the present invention may be provided as a free substance, as well as a pharmaceutically acceptable salt, solvate, polymorph, or prodrug thereof. Moreover, the salt of the compound having the structure of Formula (I) is not particularly limited as long as it is

in a form that can be compounded in a medicine or cosmetics, and may include an inorganic salt or an organic salt and be an acidic salt or an alkaline salt. In particular, when the salt is formed by a cation, it may be alkali metal salts such as sodium salts or potassium salts; alkaline earth metal salts such as calcium salts, magnesium salts or barium salts; basic amino acid salts such as arginine and lysine; ammonium salts such as ammonium salts or tricyclohexylammonium salts; and various alkanolamine salts such as monoethanolamine salts, diethanolamine salts, triethanolamine salts, monoisopropanolamine salts, diisopropanolamine salts, and triisopropanolamine salts and the like. Preferably, the salt is an alkali metal salt, and more preferably, may be tetrasodium salt.

[29] In one embodiment of the present invention, the amino acid may be selected from the group comprising alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine, and the salt of the amino acid is not limited as long as it is a pharmaceutically acceptable salt.

[30] As used herein, the term "growth factor" refers to a polypeptide having a function of promoting division, growth and differentiation of various cells in a human body, and includes those obtained through gene recombination or extraction.

[31] In one embodiment of the present invention, the growth factor may be selected from the group comprising an epithelial growth factor (EGF), an acidic fibroblast growth factor (FGF (a)), a basic fibroblast growth factor (FGF (b)), a vascular endothelial growth factor (VEGF), a platelet-derived growth factor (PDGF) and a keratinocyte growth factor (KGF).

[32] As used herein, the term "noggin" refers to a protein that is involved in the development of nerve tissues, muscles, and bones among human tissues.

[33] In one embodiment of the present invention, noggin may be obtained through a method known in the art.

[34] In one embodiment of the present invention, although the long-chain fatty acid is not particularly limited as long as it is a saturated or unsaturated C8 to C18 long chain fatty acid, the long-chain fatty acid may be selected from the group comprising linolenic acid, myristic acid, oleic acid and palmitic acid, and the salt of the long-chain fatty acid is not particularly limited as long as it is pharmaceutically acceptable.

[35] In one embodiment of the present invention, the active factor may be selected from the group comprising inositol, adenine, glutathione and cholesterol.

[36] In one embodiment of the present invention, the water-soluble vitamins may be selected from the group comprising thiamine (B1), riboflavin (B2), niacinamide (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9), cyanocobalamin (B12) and ascorbic acid (C), and the salt of the water-soluble vitamin is not par-

ticularly limited as long as it is pharmaceutically acceptable.

[37] In one embodiment of the present invention, the pharmaceutical or cosmetic composition promotes proliferation of hair dermal papilla cells, prolongs the life of hair dermal papilla cells, produces hair roots of hair dermal papilla cells, and increases density, thickness, or length of hair, or combination thereof, resulting in effects of prevention or treatment of hair loss, promotion of hair growth, and prevention or improvement of hair loss, which are demonstrated by the experimental examples disclosed herein.

[38] In one embodiment of the present invention, the pharmaceutical or cosmetic composition may comprise the compound having the structure of Formula (I) above or salt thereof, one or more nature-derived amino acid or salt thereof, a mixture comprising one or more growth factor and noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor selected from the group comprising inositol, adenine, glutathione and cholesterole, and one or more water-soluble vitamin or salt thereof.

[39] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the compound having the structure of Formula (I) above or salt thereof in an amount of 0.001 to 1% by weight based on the total weight of the composition.

[40] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the amino acid or salt thereof in an amount of 0.001 to 20% by weight based on the total weight of the composition, and this amount may be properly adjusted depending on a formulation and the conditions of production.

[41] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise a mixture comprising the growth factor and noggin in an amount of 0.001 to 5% by weight, preferably 0.5 to 4% by weight, based on the total weight of the composition.

[42] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the long chain fatty acid or salt thereof in an amount of 0.001 to 5% by weight, preferably 0.2 to 1% by weight, based on the total weight of the composition.

[43] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the active factor in an amount of 0.001 to 5% by weight, preferably 0.1 to 0.5% by weight, based on the total weight of the composition.

[44] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the water-soluble vitamin or salt thereof in an amount of 0.001 to 5% by weight, preferably 0.2 to 1.2% by weight, based on the total weight of the composition.

[45] In one embodiment of the present invention, the pharmaceutical composition or cosmetic composition may comprise the amino acid in an amount of 4000 parts by weight to 40000 parts by weight, preferably 16000 parts by weight to 40000 parts by weight, based on 100 parts by weight of the growth factor and noggin,

[46] the water-soluble vitamin or salt thereof in an amount of 240 parts by weight to 4000 parts by weight, preferably 1000 parts by weight to 4000 parts by weight, based on 100 parts by weight of the growth factor and noggin,

[47] the active factor in an amount of 80 parts by weight to 1600 parts by weight, preferably 160 parts by weight to 800 parts by weight, based on 100 parts by weight of the growth factor and noggin,

[48] the long chain fatty acid or salt thereof in an amount of 200 parts by weight to 3200 parts by weight, preferably 400 parts by weight to 1600 parts by weight, based on 100 parts by weight of the growth factor and noggoin, and

[49] the growth factor and noggin in an amount of 6.25 parts by weight to 125 parts by weight, preferably 12.5 parts by weight to 50 parts by weight, based on 100 parts by weight of the active factor.

[50] In one embodiment of the present invention, the growth factor comprises an epithelial growth factor (EGF), an acidic fibroblast growth factor (FGF (a)), a basic fibroblast growth factor (FGF (b)), a vascular endothelial growth factor (VEGF), a platelet-derived growth factor (PDGF) and a keratinocyte growth factor (KGF). Further, the weight ratio of epithelial growth factor (EGF): acidic fibroblast growth factor (FGF (a)): basic fibroblast growth factor (FGF (b)): vascular endothelial growth factor (VEGF): platelet-derived growth factor (PDGF): keratinocyte growth factor (KGF): noggin in the pharmaceutical or cosmetic composition may be 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10, preferably 2 to 6 : 4 to 8 : 4 to 8 : 1 to 2 : 1 to 2 : 1 to 2 : 1 to 2, and more perferably 2 to 4 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6.

[51] In one embodiment of the present invention, the weight ratio of amino acid or salt thereof: long chain fatty acid or salt thereof: active factor: water-soluble vitamin or salt thereof in the pharmaceutical composition or cosmetic composition may be 100 to 2000: 10 to 200: 5 to 200: 10 to 200.

[52] In one embodiment of the present invention, the composition may further comprise suitable carriers, excipients and diluents conventionally used in the manufacture of pharmaceutical compositions or cosmetic compositions.

[53] In particular, the composition is formulated using excipients or diluents such as pharmaceutically acceptable fillers, extenders, binders, humectants, disintegrants, surfactants and the like which are generally used. In addition, anticoagulants, lubricants, fragrances, emulsifiers, preservatives, and the like may be added, and the composition

may be formulated using methods well known in the art to provide rapid, sustained, or delayed release of the active ingredient after administration to the mammal.

[54] The pharmaceutical composition according to the present invention may be formulated into a conventional pharmaceutical formulation known in the art, and preferably it may be formulated into a transdermal preparation and an external preparation for skin for topical application.

[55] In one embodiment of the present invention, the pharmaceutical composition according to the present invention may be an external preparation for skin, and can be formulated into any possible formulations applicable to skin, especially, scalp, such as ointment, paste, gel, jelly, serum, aerosol spray, non-aerosol spray, foam, cream, lotion, solution or suspension.

[56] The composition according to the present invention can be administered by topical application once or twice a day to a site where prevention or treatment of hair loss, or promotion of hair growth is desired. The daily application amount of the composition is about 0.5 to 3 mg/cm^2 (skin surface area) based on 1 wt% of the active ingredient, and may be increased or decreased depending on the area of the application site. The dose and the frequency of administration can be appropriately increased or decreased according to the patient's age, sex, and degree of progress of hair loss.

[57] On the other hand, the cosmetic composition according to the present invention may be applied in any possible formulations applied to the skin, particularly scalp. More specifically, the composition may be prepared in a formulation such as a hair tonic, a hair conditioner, a hair essence, a hair lotion, a hair nutrition lotion, a hair shampoo, a hair rinse, a hair treatment, a hair cream, a hair nutrition cream, a hair moisturizing cream, a hair massage cream, a hair wax, a hair aerosol, a hair pack, a hair nutrition pack, a hair soap, a hair cleansing foam, a hair oil, a hair drying agent, an agent for preserving hair, a hair dye, a hair waving agent, a hair bleaching agent, a hair gel, a hair glaze, a hair dressinger, a hair lacquer, a hair moisturizer, a hair mousse or a hair spray. In addition, it can also be prepared as a skin-contacting substance that comes into contact with a skin, such as cosmetics, detergents, and fibers.

[58] In one embodiment of the present invention, the components of the cosmetic composition can be appropriately selected and blended by those skilled in the art within a range not to impair the purposes and effects of the present invention. Examples of the compounding ingredients that can be added include an oil and fat component, a moisturizer, an emollient, a surfactant, organic and inorganic pigments, an organic powder, an ultraviolet absorber, a preservative, a bactericide, an antioxidant, a plant extract, a pH adjuster, an alcohol, a dye, fragrances, a blood circulation promoter, a skin cooling agent, an anhydrotics, purified water and the like.

Mode for the Invention

[59] Hereinafter, the present invention will be described in more detail by way of examples. It will be apparent to those skilled in the art that the following examples are illustrative only and various changes and modifications may be made without departing from the spirit and scope of the invention, and such changes and modifications are also within the scope of the appended claims.

[60]

[61] **Exmaples**

[62] **Preparation Example 1. Preparation of a mixture comprising a growth factor and noggin**

[63] An ephithelial growth factor (EGF), an acidic fibroblast growth factor (FGF (a)), a basic fibroblast growth factor (FGF (b)), a vascular endothelial growth factor (VEGF), a platelet-derived growth factor (PDGF), a keratinocyte growth factor (KGF), and Noggin were mixed in a composition shown in Table 1 below and then prepared into liposomes using a high-speed homogenizer (Preparation Examples (1-1) to (1-5)). The growth factors and Noggin were synthesized by transforming E. coli with human-derived genes, and their contents were measured by SDS-PAGE and HPLC. The growth factors and proteins were prepared in accordance with the criteria for the use in cosmetics or pharmaceuticals of Korean Ministry of Food and Drug Safety and INCI [International nomenclature cosmetic ingredient] of US PCPC (Personal care products councils).

[64] [Table 1]

(Unit: mg)	EGF	FGF(a)	FGF(b)	VEGF	PDGF	KGF	Noggin
Preparation Example(1-1)	1	1.5	1.5	0.25	0.25	0.25	0.25
Preparation Example(1-2)	0.5	1	1	0.5	0.5	0.5	0.5
Preparation Example(1-3)	1	0.5	0.5	0.25	0.25	1	1
Preparation Example(1-4)	0.5	1	1	0.5	0.5	0.25	0.25
Preparation Example(1-5)	1	0.5	0.5	0.25	0.25	0.5	0.5

[65]

[66] **Preparation Example 2. Preparation of a mixture of nutrients**

[67] Amino acids, long chain fatty acids, active factors and water-soluble vitamins were

mixed in the compositions shown in Table 2 below, and then prepared into liposomes using a high-speed homogenizer. (Preparation Examples (2-1) to (2-5)). The amino acids, long chain fatty acids, active factors and water-soluble vitamins were prepared in accordance with the criteria for the use in cosmetics or pharmaceuticals of Korean Ministry of Food and Drug Safety. In the case of amino acids, 20 amino acids derived from nature were evenly blended on the basis of weight, and vitamins, active factors and fatty acids were also blended evenly on the basis of weight. Standard error for each component was less than 10%.

[68] [Table 2]

component(unit: mg)	Preparation Example(2-1)	Preparation Example(2-2)	Preparation Example(2-3)	Preparation Example(2-4)	Preparation Example(2-5)
Alanine	400	600	800	1000	1200
Arginine HCl					
Asparagine					
Aspartic acid					
Cysteine HCl					
Glutamic acid					
Glutamine					
Glycine					
Histidine HCl					
Isoleucine					
Leucine					
Lysine HCl					
Methionine					
Phenylalanine					
Proline					
Serine					
Threonine					
Tryptophan					
Tyrosine					
Valine					
Biotin(B7)	20	30	40	50	60

Ascorbic acid(C)	5	6	7	8	9
Niacinamide(B3)					
Calcium pan-tothenate(B5)					
Pyridoxine HCl(B6)					
Riboflavin(B2)					
Thiamin HCl(B1)					
Cyanocobalamin(B12)					
Inositol	10	20	40	60	100
Adenine					
Glutathione					
Cholesterole					
Linolenic acid	20	40	60	80	100
Myristic acid					
Oleic acid					
Palmitic acid					

[69]

[70] **Comparative Preparation Example 1. NAADP Liposome solution**

[71] NAADP was prepared according to the method described in "Acidic residues at the active sites of CD38 and ADP-ribosyl cyclase determine nicotinic acid adenine dinucleotide phosphate (NAADP) synthesis and hydrolysis activities". The Journal of Biological Chemistry. 281 (39): 28951-7, using NADP (nicotinamide adenine dinucleotide phosphate), nicotinic acid (NA) and ADP-ribosyl cyclase purchased from Sigma-Aldrich (USA).

[72] The prepared NAADP was prepared into liposomes using a medium prepared by mixing phospholipids, lecithin, oleic acid, and caprylyl glycol in a ratio of 1: 1: 0.05: 0.05, and a high-speed homogenizer.

[73]

[74] **Examples 1 to 9. Preparation of mixtures**

[75] A mixture comprising the mixture of Preparation Example 1 and the mixture of Preparation Example 2 in the composition shown in Table 3 below was prepared by a known method. Specifically, the mixture of Preparation Example 1 was added to 1 L of

purified water by the weight indicated in Table 1, and the mixture of Preparation Example 2 was added thereto by two times the weight indicated in Table 2 above.

[76] [Table 3]

	NAADP	Preparation Example(1-1)	Preparation Example(1-2)	Preparation Example(1-3)	Preparation Example(2-1)	Preparation Example(2-2)	Preparation Example(2-3)
Comparative Preparation Example 1	O	-	-	-	-	-	-
Example 1	O	O			O		
Example 2	O		O			O	
Example 3	O			O			O
Example 4	O	O				O	
Example 5	O	O					O
Example 6	O		O		O		
Example 7	O		O				O
Example 8	O			O	O		
Example 9	O			O		O	

[77]

[78] **Example 10. Preparation of a mixture**

[79] A mixture was prepared in the same manner as in Example 1, except that the amount of Preparation Example (1-1) was changed to 0.25 times.

[80]

[81] **Example 11. Preparation of a mixture**

[82] A mixture was prepared in the same manner as in Example 1, except that the amount of Preparation Example (1-1) was changed to 0.5 times.

[83]

[84] **Example 12. Preparation of a mixture**

[85] A mixture was prepared in the same manner as in Example 1, except that the amount of Preparation Example (1-1) was changed to 2 times.

[86]

[87] **Example 13. Preparation of a mixture**

[88] A mixture was prepared in the same manner as in Example 1, except that the amount of Preparation Example (1-1) was changed to 5 times.

[89]

[90] **Example 14. Preparation of a mixture**

[91] A mixture was prepared in the same manner as in Example 1, except that the added amount of the amino acid was changed to 200 mg.

[92]

[93] **Example 15. Preparation of a mixture**

[94] A mixture was prepared in the same manner as in Example 1, except that the added amount of the amino acid was changed to 400 mg.

[95]

[96] **Example 16. Preparation of a mixture**

[97] A mixture was prepared in the same manner as in Example 1, except that the added amount of the amino acid was changed to 1600 mg.

[98]

[99] **Example 17. Preparation of a mixture**

[100] A mixture was prepared in the same manner as in Example 1, except that the added amount of the amino acid was changed to 2000 mg.

[101]

[102] **Example 18. Preparation of a mixture**

[103] A mixture was prepared in the same manner as in Example 1, except that the added amount of the water-soluble vitamins including biotin was changed to 12 mg.

[104]

[105] **Example 19. Preparation of a mixture**

[106] A mixture was prepared in the same manner as in Example 1, except that the added amount of the water-soluble vitamins including biotin was changed to 24 mg.

[107]

[108] **Example 20. Preparation of a mixture**

[109] A mixture was prepared in the same manner as in Example 1, except that the added amount of the water-soluble vitamins including biotin was changed to 100 mg.

[110]

[111] **Example 21. Preparation of a mixture**

[112] A mixture was prepared in the same manner as in Example 1, except that the added amount of the water-soluble vitamins including biotin was changed to 200 mg.

[113]

[114] **Example 22. Preparation of a mixture**

[115] A mixture was prepared in the same manner as in Example 1, except that the added amount of the active factor was changed to 4 mg.

[116]

[117] **Example 23. Preparation of a mixture**

[118] A mixture was prepared in the same manner as in Example 1, except that the added amount of the active factor was changed to 8 mg.

[119]

[120] **Example 24. Preparation of a mixture**

[121] A mixture was prepared in the same manner as in Example 1, except that the added amount of the active factor was changed to 40 mg.

[122]

[123] **Example 25. Preparation of a mixture**

[124] A mixture was prepared in the same manner as in Example 1, except that the added amount of the active factor was changed to 80 mg.

[125]

[126] **Example 26. Preparation of a mixture**

[127] A mixture was prepared in the same manner as in Example 1, except that the added amount of the long chain fatty acid was changed to 10 mg.

[128]

[129] **Example 27. Preparation of a mixture**

[130] A mixture was prepared in the same manner as in Example 1, except that the added amount of the long chain fatty acid was changed to 20 mg.

[131]

[132] **Example 28. Preparation of a mixture**

[133] A mixture was prepared in the same manner as in Example 1, except that the added amount of the long chain fatty acid was changed to 80 mg.

[134]

[135] **Example 29. Preparation of a mixture**

[136] A mixture was prepared in the same manner as in Example 1, except that the added amount of the long chain fatty acid was changed to 160 mg.

[137]

[138] **Formulation Example**

[139] Compositions according to Comparative Formulation Examples 1 and 2 and Formulation Examples 1 and 2 were prepared with the composition according to Table 4 below. However, the following formulation examples are intended to illustrate rather than limit the present invention.

[140] [Table 4]

(Weight%)	Comparative Formulation Example 1	Comparative Formulation Example 2	Formulation Example 1	Formulation Example 2
Purified water	52.9	51.9	41.9	40.9
Glycerine	3	3	3	3
EDTA-Na	0.05	0.05	0.05	0.05
Amisoft CS-22	30	30	30	30
Miconate LES	12	12	12	12
Citric acid	0.1	0.1	0.1	0.1
Phenoxyethanol	0.7	0.7	0.7	0.7
Ethylhexyl glycerin	0.05	0.05	0.05	0.05
Preparation Example 1-1	-	-	1	2
Preparation Example 2-1	-	-	10	10
NAADP	-	0.1	0.1	0.1
NaCl	1	1	1	1
Perfume	0.2	0.2	0.2	0.2
Total	100	100	100	100

[141]

[142] **Experimental Examples**

[143] **Experimental Examples 1.Cytotoxicity test in human hair dermal papilla cells**

[144] To confirm cytotoxicity in human hair dermal papilla cells (HHDPC), MTT assay which determines cytotoxicity by measuring mitochondrial reducing power by dehydrogenase action was conducted.

[145] Human hair dermal papilla cells were cultured in an HDP kit medium (Human hair dermal papilla cell media kit) at 37℃ in a 5% CO_2 incubator (manufactured by Thermo Fisher Scientific, USA).

[146] The cultured cells were dispensed into a 24-well plate at a concentration of 3×10^4

cells/well. After 18 hours, the mixtures according to Preparation Examples (1-1) to (1-5) and the mixtures according to Preparation Example (2-1) to (2-5) were added to each well at concentrations of 50 ㎍/ml, 100 ㎍/ml and 200 ㎍/ml, respectively. Then, the cells were cultured in the 5% CO_2 incubator at 37℃ for 48 hours. After 48 hours of incubation, each well was washed once with PBS (phosphate buffered saline) solution, and added with 50 ㎕ of 5 mg/mL MTT reagent (Sigma, USA) and 450 ㎕ of fresh medium. The wells were incubated for 2.5 hours and then supernatants were removed. As formazan crystals were observed in each well, DMSO (dimethylsulfoxide) was added and shaken for 30 minutes in the dark to dissolve the formazan crystal, and then the absorbance was measured at 750 nm using a spectrophotometer.

[147] The results of the measurement are shown in Table 5 and Fig. 1, and it was confirmed that no toxicity was observed regardless of the treatment concentration.

[148] [Table 5]

	50㎍/ml	100㎍/ml	200㎍/ml
Preparation Example 1-1	98	97	95
Preparation Example 1-2	99	96	95
Preparation Example 1-3	100	97	97
Preparation Example 1-4	100	98	96
Preparation Example 1-5	100	99	95
Preparation Example 2-1	100	99	98
Preparation Example 2-2	100	100	98
Preparation Example 2-3	100	100	95
Preparation Example 2-4	100	100	99
Preparation Example 2-5	100	100	95

[149]

[150] **Experimental Example 2. Comparison of cell proliferation efficacy in human hair dermal papilla cells**

[151] For comparison of cell proliferation efficacy, 100 ㎍/ml of each mixture according to Examples 1 to 9 and 1 μM NAADP solution according to Comparative Preparation Example 1 were tested in the same manner as in Experimental Example 1. The results are shown in Table 6 below and Fig. 2.

[152] Cell growth rate was better at the treatment of the mixtures according to Examples 1 to 9 than the treatment of the NAADP solution according to Comparative Preparation Example 1, and differentially increased cell proliferation was confirmed. In particular, Examples 1, 4, and 5, which include the mixture according to Preparation Example (1-1), exhibited more excellent efficacy for cell proliferation.

[153] [Table 6]

	Growth rate(%)
Comparative Preparation Example 1	20
Example 1	55
Example 2	47
Example 3	41
Example 4	51
Example 5	54
Example 6	45
Example 7	46
Example 8	41
Example 9	39

[154]

[155] **Experimental Example 3. Test of hair root production rate in human hair dermal papilla cells**

[156] The production rate of hair roots required for hair production was measured in human hair dermal papilla cells. The hair dermal papilla cells were cultured by the method described in Experimental Example 1 and then tested. The cultured hair dermal papilla cells were treated with the mixtures according to Examples 1, 4 and 5 and the NAADP solution according to Comparative Preparation Example 1 at concentrations of 50 ㎍/ml, 100 ㎍/ml and 200 ㎍/ml, respectively, and the numbers of hair roots were measured with a microscope. The results are shown in Table 7 below and Fig. 3. The yields of the hair roots were higher in the groups treated with mixtures according to Examples 1, 4 and 5 than the group treated with NAADP solution of Comparative

Example 1.

[157] [Table 7]

	50㎍/ml	100㎍/ml	200㎍/ml
untreated group	10	11	9
Comparative Preparation Example 1	13	21	23
Example 1	55	62	81
Example 4	51	53	78
Example 5	45	55	74
Unit: number of hair roots			

[158]

[159] **Experimental Example 4. Test of Hair density in human body**

[160] A test for the application of the composition of the present invention to human body was conducted, which was conducted according to a guideline provided by Korea Ministry of Food & Drug Safety. The test was conducted for 24 weeks, and men and women diagnosed with androgenetic alopecia aged 18 to 54 years were selected as test subjects. Twenty subjects were assigned to a test group and a control group, respectively. The compositions of Formulation Examples 1 and 2 and Comparative Formulation Example 2 were applied for 24 weeks for the test group. The composition of Comparative Formulation Example 1 was applied for 24 weeks for the control group. And then hair densities were measured. The hair density was evaluated as a score of 1 to 10, and the results are shown in Table 8 below and Fig. 4. The density score for the composition of Comparative Formulation Example 1 was 2 or less even at week 24. The density score for the composition of Comparative Formulation Example 2 was higher than the score for the composition of Comparative Formulation Example 1, but was lower than the scores for the compositions of Formulation Examples 1 and 2. The compositions of Formulation Examples 1 and 2 showed better evaluation scores than the compositions of Comparative Formulation Examples 1 and 2, with an average score of 8 or higher. From these results, it was found that Formulation Examples 1 and 2 improved hair densities more than Comparative Formulation Examples 1 and 2.

[161] [Table 8]

	Week 6	Week 12	Week 24
Comparative Formulation Example 1	1	2	2
Comparative Formulation Example 2	3	5	6
Formulation Example 1	5	8	9
Formulation Example 2	6	9	10
Unit: score			

[162]

[163] **Experimental Example 5. Test of hair elongation rate in human body**

[164] A test was conducted in the same manner as in Experimental Example 4 above. The elongation rate of hair was measured as the relative elongation rate for each week at weeks 6, 12, and 24. The results are shown in Table 9 below and Fig. 5. It was found that the compositions of Formulation Examples 1 and 2 improved the elongation rate by about 20 to 30% compared to the composition of Comparative Formulation Example 1. In addition, while the maximum enlongation rates of the compositions of Comparative Formulation Example 1 and Comparative Formulation Example 2 were limited to about 50% and about 70%, respectively, the compositions of Formulation Examples 1 and 2 exhibited an elongation rate of about 130%.

[165] [Table 9]

	Week 6	Week 12	Week 24
Comparative Formulation Example 1	25	39	47
Comparative Formulation Example 2	40	50	67
Formulation Example 1	81	120	130
Formulation Example 2	79	111	126

[166]

[167] **Experimental Example 6. Comparison of efficacies for cell proliferation in human hair dermal papilla cells**

[168] For comparison of efficacies for cell proliferation, a test was conducted in the same manner as in Experimental Example 1 for 100 μg/ml of each mixture according to Example 1 and Examples 10 to 25, and the results are shown in Table 10 below. The

degree of cell proliferation when hair dermal papilla cells were treated with the mixture of Example 1 was set as a reference(set at 100), and the degree of cell proliferation when the hair dermal papilla cells were treated with the mixtures of Examples 10 to 25 was expressed as a relative value compared to the reference.

[169] [Table 10]

	Values
Example 1	100
Example 10	22
Example 11	72
Example 12	81
Example 13	53
Example 14	17
Example 15	59
Example 16	87
Example 17	75
Example 18	11
Example 19	55
Example 20	91
Example 21	63
Example 22	52
Example 23	83
Example 24	98
Example 25	54
Example 26	8
Example 27	76
Example 28	78
Example 29	32

[170] As shown in the above results, the composition of the present invention improved the proliferation, activity and longevity of the hair dermal papilla cells at the experiment level of cells and also showed a high production rate of hair roots. In addition, clinical trials showed excellent increase in hair density and thickness and hair elongation efficacy. In particular, it was confirmed that the above effects were significantly higher

in quantity than that of the composition containing only NAADP.

[171] It was also confirmed that the composition of the present invention exhibits more excellent proliferation activity for hair dermal papilla cells when the content ratio of each component is within a specific value range.

[172] For example, it was confirmed that the effect was excellent when the content of the amino acids was 4,000 to 40,000 parts by weight, particularly 16,000 to 40,000 parts by weight based on 100 parts by weight of the growth factors and noggin.

[173] In addition, it was confirmed that the effect was excellent when the content of the water-soluble vitamins including biotin was 240 to 4,000 parts by weight, particularly 1,000 to 4,000 parts by weight based on 100 parts by weight of the growth factors and noggin.

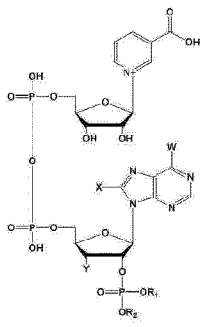
[174] In addition, it was confirmed that the effect was excellent when the content of the active factor was 80 to 1,600 parts by weight, particularly 160 to 800 parts by weight based on 100 parts by weight of the growth factors and noggin.

[175] In addition, it was confirmed that the effect was excellent when the content of the long chain fatty acid was 200 to 3,200 parts by weight, particularly 400 to 1,600 parts by weight based on 100 parts by weight of the growth factors and noggin.

[176] In addition, it was confirmed that the effect was excellent when the content of the growth factor and noggin were 6.25 to 125 parts by weight, particularly 12.5 to 50 parts by weight based on 100 parts by weight of the activating factor.

Claims

[Claim 1] A pharmaceutical composition for preventing or treating hair loss, or promoting hair growth, comprising
a compound having a structure represented by the following Formula (I) or salt thereof; and
at least one selected from a group comprising one or more nature-derived amino acid or salt thereof, one or more growth factor, noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor and one or more water-soluble vitamin or salt thereof:



(I)

wherein,
R_1 and R_2 are each independently H, C_{1-4} alkyl which is unsubstituted or substituted with halogen, or $-CH_2-CO-CH_3$;
W is selected from a group consisting of NH_2, OH and SH;
X is selected from a group consisting of H, OH, SH, NH_2 and halogen; and
Y is selected from a group consisting of OH, H, NH_2 and halogen.

[Claim 2] The pharmaceutical composition according to claim 1, wherein the compound of Formula (I) is nicotinic acid adenine dinucleotide phosphate(NAADP).

[Claim 3] The pharmaceutical composition according to claim 1, wherein the amino acid is selected from a group comprising alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine and valine.

[Claim 4] The pharmaceutical composition according to claim 1, wherein the one or more growth factor is selected from the group comprising an epithelial growth factor (EGF), an acidic fibroblast growth factor (FGF (a)), a basic fibroblast growth factor (FGF (b)), a vascular endothelial growth factor (VEGF), a platelet-derived growth factor (PDGF) and a

keratinocyte growth factor (KGF).

[Claim 5] The pharmaceutical composition according to claim 1, wherein the long-chain fatty acid is selected from the group comprising linolenic acid, myristic acid, oleic acid and palmitic acid.

[Claim 6] The pharmaceutical composition according to claim 1, wherein the active factor is selected from the group comprising inositol, adenine, glutathione and cholesterol.

[Claim 7] The pharmaceutical composition according to claim 1, wherein the water-soluble vitamin is selected from the group comprising thiamine (B1), riboflavin (B2), niacinamide (B3), pantothenic acid or salt thereof (B5), pyridoxine (B6), biotin (B7), folic acid (B9), cyanocobalamin (B12) and ascorbic acid (C).

[Claim 8] The pharmaceutical composition according to claim 1, wherein the composition promotes proliferation of hair dermal papilla cells.

[Claim 9] The pharmaceutical composition according to claim 1, wherein the composition prolongs the life of hair dermal papilla cells.

[Claim 10] The pharmaceutical composition according to claim 1, wherein the composition produces hair roots of hair dermal papilla cells.

[Claim 11] The pharmaceutical composition according to claim 1, wherein the composition increases density, thickness, or length of hair, or combination thereof.

[Claim 12] The pharmaceutical composition according to claim 1, wherein the composition comprises
the compound having the structure of Formula (I) or salt thereof;
one or more nature-derived amino acid or salt thereof;
a mixture comprising one or more growth factor and noggin;
one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof;
one or more active factor selected from the group comprising inositol, adenine, glutathione and cholesterole; and
one or more water-soluble vitamin or salt thereof.

[Claim 13] The pharmaceutical composition according to claim 12, wherein the composition comprises the compound having the structure of Formula (I) or salt thereof in an amount of 0.001 to 1% by weight, the amino acid or salt thereof in an amount of 0.001 to 20% by weight, the mixture comprising the growth factor and noggin in an amount of 0.001 to 5% by weight, the long chain fatty acid or salt thereof in an amount of 0.001 to 5% by weight, the active factor in an amount of 0.001 to 5%

by weight, and the water-soluble vitamin or salt thereof in an amount of 0.001 to 5% by weight, based on the total weight of the composition.

[Claim 14] The pharmaceutical composition according to claim 12, wherein the growth factor comprises an epithelial growth factor (EGF), an acidic fibroblast growth factor (FGF (a)), a basic fibroblast growth factor (FGF (b)), a vascular endothelial growth factor (VEGF), a platelet-derived growth factor (PDGF) and a keratinocyte growth factor (KGF), and the weight ratio of epithelial growth factor (EGF): acidic fibroblast growth factor (FGF (a)): basic fibroblast growth factor (FGF (b)): vascular endothelial growth factor (VEGF): platelet-derived growth factor (PDGF): keratinocyte growth factor (KGF): noggin in the composition is 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10: 0.1 to 10.

[Claim 15] The pharmaceutical composition according to claim 14, wherein the growth factors and noggin are comprised in the composition so that the weight ratio of epithelial growth factor (EGF): acidic fibroblast growth factor (FGF (a)): basic fibroblast growth factor (FGF (b)): vascular endothelial growth factor (VEGF): platelet-derived growth factor (PDGF): keratinocyte growth factor (KGF): noggin is 2 to 6 : 4 to 8 : 4 to 8 : 1 to 2 : 1 to 2 : 1 to 2 : 1 to 2.

[Claim 16] The pharmaceutical composition according to claim 15, wherein the growth factors and noggin are comprised in the composition so that the weight ratio of epithelial growth factor (EGF): acidic fibroblast growth factor (FGF (a)): basic fibroblast growth factor (FGF (b)): vascular endothelial growth factor (VEGF): platelet-derived growth factor (PDGF): keratinocyte growth factor (KGF): noggin is 2 to 4 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6 : 2 to 6.

[Claim 17] The pharmaceutical composition according to claim 12, wherein the weight ratio of amino acid or salt thereof: long chain fatty acid or salt thereof: active factor: water-soluble vitamin or salt thereof in the composition is 100 to 2000: 10 to 200: 5 to 200: 10 to 200.

[Claim 18] The pharmaceutical composition according to claim 12, wherein the composition comprises

the amino acid in an amount of 4000 parts by weight to 40000 parts by weight based on 100 parts by weight of the growth factor and noggin, the water-soluble vitamin or salt thereof in an amount of 240 parts by weight to 4000 parts by weight based on 100 parts by weight of the growth factor and noggin,

the active factor in an amount of 80 parts by weight to 1600 parts by weight based on 100 parts by weight of the growth factor and noggin, the long chain fatty acid or salt thereof in an amount of 200 parts by weight to 3200 parts by weight based on 100 parts by weight of the growth factor and noggoin, and

the growth factor and noggin in an amount of 6.25 parts by weight to 125 parts by weight based on 100 parts by weight of the active factor.

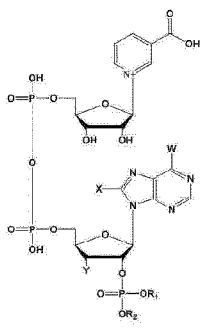
[Claim 19] The pharmaceutical composition according to any one of claims 1 to 18, wherein the composition is in the form selected from the formulations comprising ointment, paste, gel, jelly, serum, aerosol spray, non-aerosol spray, foam, cream, lotion, solution and suspension.

[Claim 20] A cosmetic composition for preventing or improving hair loss, or promoting hair growth, comprising

a compound having the structure represented by the following Formula (I) or salt thereof; and

at least one selected from the group comprising one or more nature-derived amino acid or salt thereof, one or more growth factor, noggin, one or more saturated or unsaturated C8 to C18 long chain fatty acid or salt thereof, one or more active factor and one or more water-soluble vitamin or salt thereof:

(I)



wherein,

R_1 and R_2 are each independently H, C_{1-4} alkyl which is unsubstituted or substituted with halogen, or $-CH_2-CO-CH_3$;

W is selected from the group consisting of NH_2, OH and SH;

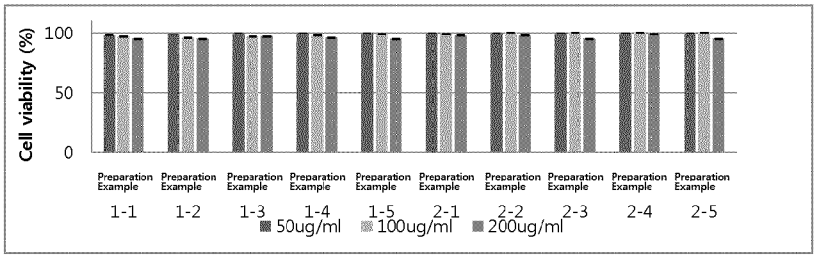
X is selected from the group consisting of H, OH, SH, NH_2 and halogen; and

Y is selected from the group consisting of OH, H, NH_2 and halogen.

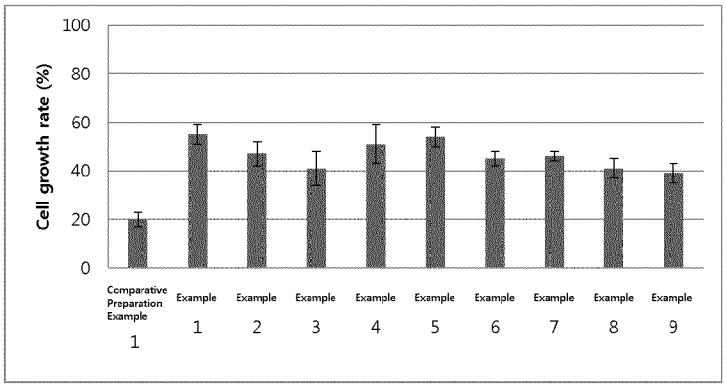
[Claim 21] The cosmetic composition according to claim 20, wherein the composition is in the form selected from the formulations comprising a hair tonic, a hair conditioner, a hair essence, a hair lotion, a hair nutrition lotion, a hair shampoo, a hair rinse, a hair treatment, a hair cream, a

hair nutrition cream, a hair moisturizing cream, a hair massage cream, a hair wax, a hair aerosol, a hair pack, a hair nutrition pack, a hair soap, a hair cleansing foam, a hair oil, a hair drying agent, an agent for preserving hair, a hair dye, a hair waving agent, a hair bleaching agent, a hair gel, a hair glaze, a hair dressinger, a hair lacquer, a hair moisturizer, a hair mousse or a hair spray.

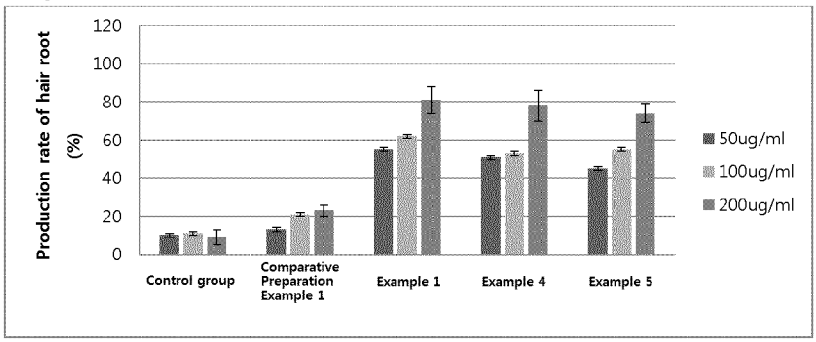
[Fig. 1]



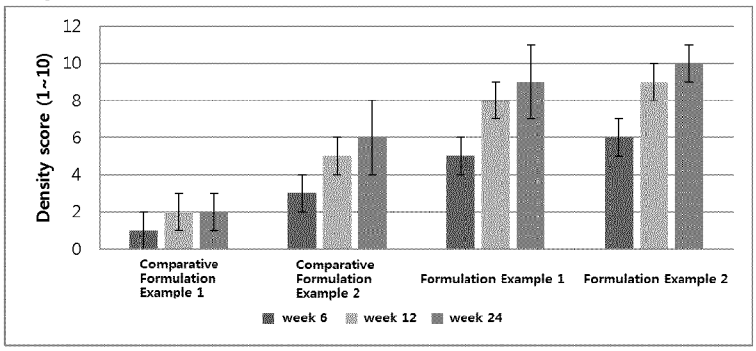
[Fig. 2]



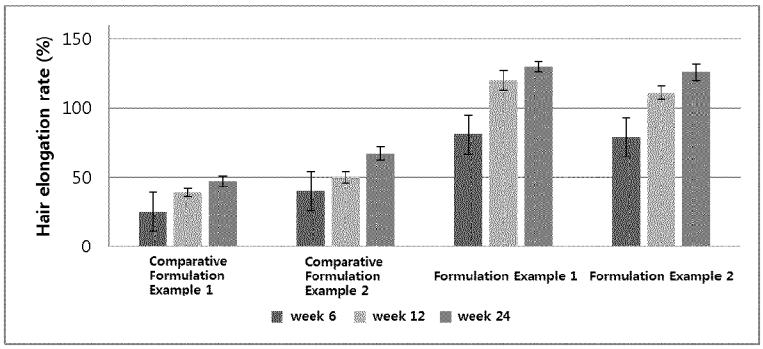
[Fig. 3]



[Fig. 4]



[Fig. 5]



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2018/006140

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/7084(2006.01)i, A61K 38/18(2006.01)i, A61K 31/202(2006.01)i, A61K 31/51(2006.01)i, A61K 8/60(2006.01)i, A61K 8/64(2006.01)i, A61K 8/67(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 31/7084; C12N 5/071; C12N 5/02; A61Q 7/00; A61K 8/60; A61K 8/97; A61K 31/7076; A61K 38/18; A61K 31/202; A61K 31/51; A61K 8/64; A61K 8/67

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), STN Express(Registry, Caplus), Google & Keywords: hair loss, hair growth, nicotinic acid adenine dinucleotide phosphate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	DIPPEL, E. et al., "Distribution of constitutive nitric oxide synthase immunoreactivity and NADPH-diaphorase activity in murine telogen and anagen skin", Journal of Investigative Dermatology, 1994, Vol. 103, No. 1, pages 112-115 See abstract; page 114, Table I.	1-21
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A	KR 10-2012-0014788 A (DAMY CHEMICAL CO., LTD.) 20 February 2012 See the whole document.	1-21

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

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
05 September 2018 (05.09.2018)	**05 September 2018 (05.09.2018)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2018/006140

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