

Skin-Lightening Active Ingredients in Japan

Subjects: Dermatology

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Japanese pharmaceutical cosmetics, often referred to as quasi-drugs, contain skin-lightening active ingredients formulated to prevent sun-induced pigment spots and freckles. Their mechanisms of action include suppressing melanin production in melanocytes and promoting epidermal growth to eliminate melanin more rapidly. For example, arbutin and rucinol are representative skin-lightening active ingredients that inhibit melanin production, and disodium adenosine monophosphate and dexpanthenol are skin-lightening active ingredients that inhibit melanin accumulation in the epidermis. In contrast, oral administration of vitamin C and tranexamic acid in pharmaceutical products can lighten freckles and melasma, and these products are more effective than quasi-drugs. On the basis of their clinical effectiveness, skin-lightening active ingredients can be divided into four categories according to their effectiveness and adverse effects.

Keywords: skin-lightening ; pharmaceutical cosmetics ; quasi-drug ; ingredient ; melasma: pigment spots

1. Development of Skin-Lightening Active Ingredients

Japanese pharmaceutical cosmetics are required to have one of the following purposes of use: (1) cleansing, (2) beautifying, (3) increasing attractiveness, (4) changing appearance, and (5) maintaining healthy skin or hair. Whether or not the product has the above purpose of use should be clarified by the efficacy or effectiveness, usage, and dosage of the product. If a product is determined not to meet the specified purpose of use on these bases of its efficacy or effectiveness, usage, and dosage, it is considered a “drug.” Examples of indications include “spots, freckles, pigmentation due to sunburn, etc.” (internal use), “spots, freckles, pigmentation due to sunburn/rash” (internal use), “skin pigmentation, senile pigmentation” (external use), “spots” (internal use), “Riehl melanosis, post-inflammatory hyperpigmentation” (for injection), and “melasma, freckles, post-inflammatory hyperpigmentation” (for internal use and injection). If the product has only the above efficacy or effectiveness, usage, and dosage, it cannot be considered a pharmaceutical cosmetic (quasi-drug).

In Japan, the efficacy for pharmaceutical cosmetics was changed in 2019 from “prevents sun spots and freckles” to “prevents sun spots and freckles by suppressing melanin production.” In 2004, the action of the ingredients in the formulation was changed to “prevents spots and freckles,” and, on the basis of the mechanism of action of the ingredients in the formula, the indication of “suppressing the accumulation of melanin and preventing spots and freckles” was approved. Thus, it is possible to apply for approval of pharmaceutical cosmetics for new efficacy within the scope of quasi-drug efficacy, on the basis of a clear scientific rationale.

The Japanese skincare market can be divided into the following functional categories: moisturizing, skin-lightening, anti-aging, sensitive skin, and pore and acne care. Lightening of the skin accounts for approximately 30% of the market and is the category with the most rapid growth over the past 35 years, particularly in terms of research and development ^[1]. Approximately twenty active ingredients have been developed for lightening-related quasi-drugs, including chemical substances and plant extracts with excellent inhibitory effects on tyrosinase activity and melanin production. A chronology of the development of skin-lightening active ingredients is presented in **Table 1**. The chemical structures of skin-lightening active ingredients in Japan are presented in **Figure 1**. Recent research on anti-aging skin-lightening has revealed new mechanisms and methods for the treatment of skin lightening. This section introduces the history of the skin-lightening ingredients developed in Japan.

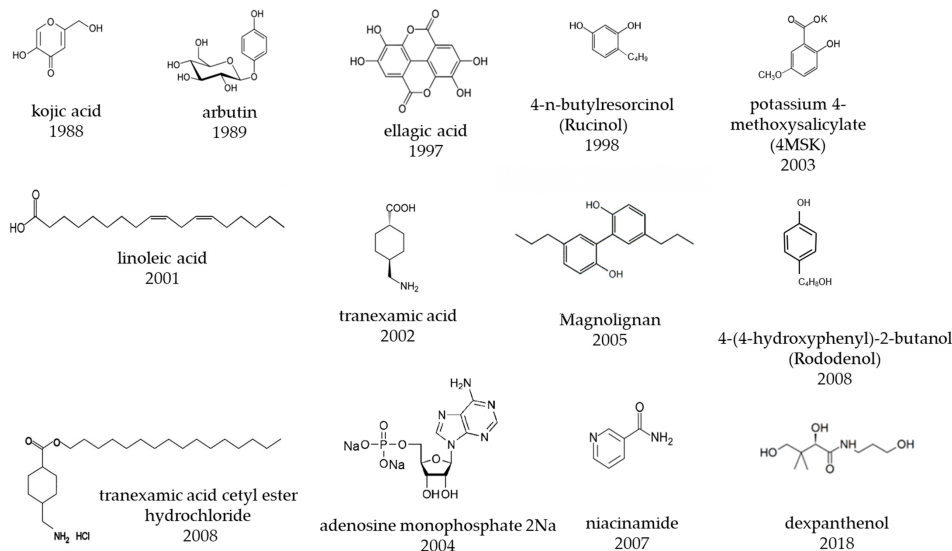


Figure 1. Chemical structure of skin-lightening active ingredients in Japan.

Table 1. List of skin-lightening active ingredients approved in Japan.

Approved Year	Generic Name	Development Company	Chemical Name/Substance Name	Main Mechanism of Action
	placenta extract			
1983	magnesium ascorbyl phosphate (APM)	Takeda Pharmaceutical Co., Ltd.	magnesium L-ascorbyl-2-phosphate	tyrosinase inhibition
1988	kojic acid	Sansho Seiyaku Co., Ltd.	kojic acid	tyrosinase inhibition
1989	arbutin	Shiseido Co., Ltd.	hydroquinone-β-D-glucopyranoside	tyrosinase inhibition
1994	ascorbyl glucoside (AA-2G)	Hayashibara Co., Ltd., Kaminomoto Co., Ltd., Shiseido Co., Ltd.	L- ascorbic acid 2-O-α-glucoside	tyrosinase inhibition
1997	ellagic acid	Lion Corporation	ellagic acid	tyrosinase inhibition
1998	Rucinol®	Kurarey Co., Ltd. POLA Chemical industries, Inc.	4-n-butylresorcinol	tyrosinase inhibition
1999	Chamomile ET	Kao Corporation	<i>Matricaria chamomilla</i> L Extract	endothelin blocker
2001	linoleic acid S	Sunstar Inc.	linoleic acid	tyrosinase degradation, stimulation of epidermal turn over
2002	tranexamic acid (t-AMCHA)	Shiseido Co., Ltd.	trans-4-aminocyclohexane carboxylic acid	inhibition of prostaglandin E ₂ production by anti-plasmin
2003	4MSK	Shiseido Co., Ltd.	potassium 4-methoxysalicylate	tyrosinase inhibition
2004	Vitamin C ethyl	Nippon Hypox Laboratories, Inc.	3-O-ethyl ascorbic acid	tyrosinase inhibition
2004	Energy signal AMP®	Otsuka Pharmaceutical Co., Ltd.	adenosine mono phosphate	stimulation of epidermal turnover
2005	Magnolignan®	Kanebo Cosmetics Inc.	5,5-dipropyl-biphenyl-2,2-diol	inhibition of tyrosinase maturation, cytotoxicity to melanocytes
2007	D-Melano (niacinamide W)	P&G Maxfactor	niacinamide	suppression of melanosome transfer
2008	Rhododenol®	Kanebo Cosmetics Inc.	4-(4-hydroxyphenyl)-2-butanol, Rhododendrol	tyrosinase inhibition, cytotoxicity of melanocytes

Approved Year	Generic Name	Development Company	Chemical Name/Substance Name	Main Mechanism of Action
2008	TXC	CHANEL	tranexamic acid cetyl ester hydrochloride	inhibition of prostaglandin E ₂ production
2009	ascorbyl tetraisopalmitate	Nikko Chemicals Co., Ltd.	ascorbyl tetra-2-hexyldecanoate	tyrosinase inhibition
2018	dexpantenol W (PCE-DP)	POLA ORBIS Holdings Inc.	dexpantenol	enhance energy production of epidermal cells

2. Report on the Effectiveness of a Formulation Containing a Lightening Agent and a Spot Remedy for Senile Pigmented Lesions

Clinical studies on senile pigmentation have investigated a formulation containing magnesium ascorbate phosphate salt, arbutin, and ellagic acid, which are active ingredients in quasi-drugs that prevent melanin production and freckles; a formulation containing kojic acid, which is no longer used in quasi-drugs because of concerns over its carcinogenic properties; a formulation containing vitamin A acid ^{[2][3][4]}, which is involved in regulating epidermal turnover and is used in the United States to treat diseases such as acne vulgaris and psoriasis, and is effective in treating wrinkles and pigmentation caused by sun damage; and a formulation containing 2% 4-hydroxyanisole and 0.01% vitamin A acid, which is marketed in the United States as a treatment for senile pigmentation ^{[5][6]}. The effectiveness of these compounds is summarized in **Table 2**.

In an open study of 34 patients, including 17 with senile pigmentation, patients were given a formulation containing 10% magnesium L-ascorbyl-2-phosphate—a content exceeding the 3% in most quasi-drugs. A total of 88.3% of patients with senile pigmentation showed slight or even higher effectiveness, as assessed by skin color measurement ^[7]. A 7% arbutin formulation demonstrated an effectiveness rate of 81.3% on senile pigmentation after 3 months in an open test, and effectiveness was observed for all patients when the treatment period was extended to 6 months and 1 year ^[8]. An open study in 13 women treated with a 0.5% formulation of ellagic acid for 1–3 months found improved effectiveness on senile pigmentation in 69.2% of participants ^[9]. In a study in 18 patients (5 men and 13 women) with senile pigmentation who received topical application of 1% kojic acid and 0.1% oil-soluble licorice extract over a 16-week period, 77.8% of participants showed an improved effectiveness rate ^[10]. Additionally, 2% 4-hydroxyanisole and 0.01% vitamin A acid have been found to be more effective than 3% hydroquinone in treating senile pigmentation ^[5]. In a double-blind study investigating the topical effectiveness of 2% 4-hydroxyanisole for 6 months in 421 patients, the improved effectiveness was 84.1%. Complete disappearance of pigmented lesions was observed in some cases, thus indicating high effectiveness, but some adverse effects including erythema and irritation were also observed ^[6].

Reported effectiveness rates differ depending on whether the effectiveness criteria were “effective”, “somewhat effective”, higher. In each study, different criteria are used to determine the level of improvement as “effective” or “somewhat effective”. In some studies, the criteria for determining effectiveness are unclear, and placebos may or may not be used to control effectiveness. Therefore, caution should be exercised in comparing effectiveness rates across studies in which the criteria for determining effectiveness are unclear or in open studies lacking placebo controls.

Table 2. Comparison of clinical trials of skin-lightening agents and drugs for the treatment of age spots.

	10% Magnesium Ascorbyl Phosphate Formulation	7% Arbutin Formulation	0.5% Ellagic Acid Formulation	1% Kojic Acid and 0.1% Oil-Soluble Licorice Extract Formulation	2% 4-Hydroxyanisole and 0.01% Vitamin A Acid Formulation	
Test design	Open study	Open study	Open study	Open study	Double-blind controlled study	
Number of cases	17	16	13	18	420	421
Sex	–	–	Women	5 men, 13 women	Men and women	
Age	–	–	Unknown	28–50 years old (average 39 years old)	34–85 years old (average 62.6 years old)	
Location	–	–	Unknown	Face	Forearm	Face

		10% Magnesium Ascorbyl Phosphate Formulation	7% Arbutin Formulation	0.5% Ellagic Acid Formulation	1% Kojic Acid and 0.1% Oil-Soluble Licorice Extract Formulation	2% 4-Hydroxyanisole and 0.01% Vitamin A Acid Formulation	
Period		–	3 months to 1 year	1 to 3 months	8 and 16 weeks	24 weeks	Observation up to 48 weeks after 24 weeks of application
Effectiveness judgment		Skin color value (color difference meter)	Visual observation	Visual observation	Close-up photograph determination and skin color value (image analysis)	Visual observation	Visual observation
Effectiveness ratio	Effective (improved or much improved) or higher	58.80%	3 months 0%, 6 months 15.4%, 1 year 66.7%	30.80%	8 weeks 5.6%, 16 weeks 22.2%	52.60%	56.30%
	Slightly effective (slightly improved) or more	88.20%	3 months 81.2%, 6 months 100%, 1 year 100%	69.20%	8 weeks 66.7%, 16 weeks 77.8%	79.30%	84.10%
Adverse effects		–	None	None	Irritation in a few cases, but no serious adverse effects	Redness 56%, burning 34%, desquamation 24%, itching 16%, irritation 7%, decoloration 9%.	–
References		[7]	[8]	[9]	[10]	[6]	[6]

3. Effectiveness Indices of Lightening Ingredients Developed in Japan

Most Japanese tests of the effectiveness of pharmaceutical skin-lightening cosmetics have assessed the degree of prevention of skin darkening caused by artificial UVB irradiation. Skin-lightening effects are exclusively evaluated on skin that darkens when exposed to ultraviolet light in humans. There are two types of evaluation methods: the anti-pigmentation test and the accelerated pigmentation disappearance test. The former is a double-blind controlled study in which a test sample is applied before, during, or after the UV irradiation period and the degree of pigmentation formation is compared with a placebo. The latter is a double-blind controlled trial in which the test sample is applied to the pigmented area and the degree of fading of the pigmentation is compared with a placebo. Both are assessed by visual evaluation and instrumental measurement based on superiority or inferiority comparisons or score judgments.

Consumers expect that skin lightening products will “lighten spots and freckles”. Moreover, many consumers expect these products to “eliminate spots and freckles” [11] and want skin-lightening cosmetics to have an effect on spots that have already formed, rather than preventing formation, or promoting the fading, of pigmentation caused by ultraviolet rays. However, problems exist regarding the lightening effects of such cosmetics when actually used on spots and freckles: test results published in scientific journals are lacking, and a possibility exists that these cosmetics might cause skin problems.

Skin-lightening active ingredients can be divided into four categories according to their clinical effectiveness and adverse effects. This research discusses academic research and development regarding skin-lightening ingredients in Japan. The researchers have compiled a table of effectiveness indices for Japanese skin-lightening ingredients, on the basis of the published scientific literature (Table 3).

Category A: Effectiveness of the same concentration of cosmetic formulations on human pigment spots has been described in scientific journals and is highly recommended. Examples include tranexamic acid, arbutin, 3-O-ethyl ascorbic acid, magnesium ascorbyl phosphate (APM), ellagic acid, kojic acid, linoleic acid, 4-n-butylresorcinol, chamomile extract, and adenosine monophosphate.

Category B: Effectiveness of higher concentrations than those used in cosmetics on human pigment spots has been described in scientific journals and is recommended. Examples include oil-soluble licorice extract containing 50% glabridin, niacinamide, placenta extract, retinol, ascorbyl glucoside (AA-2G), and azelaic acid.

Category C: No effectiveness for human pigment spots has been described in scientific journals but may be considered; however, evidence is insufficient. Examples include potassium 4-methoxysalicylic acid and dexpantenol.

Category D: Not recommended, because of toxicity data described in scientific journals. Examples include Rhododenol, Magnolignan, and ascorbyl tetra-2-hexyldecanoate.

Table 3. Effectiveness indices of lightening ingredients developed in Japan.

Effectiveness Indices	Skin-Lightening Ingredients	Test Concentration (%)	General Purpose or Japanese Cosmetics Company	Scientific Articles Providing Evidence
A Effectiveness of same concentration of cosmetic formulations on human pigment spots has been published in scientific journals and is highly recommended.	tranexamic acid	2	General purpose	[12]
	arbutin	3	General purpose	[13]
	3-O-ethyl ascorbic acid (vitamin C ethyl)	1	General purpose	[14]
	magnesium L-ascorbyl-2-phosphate (APM)	3	General purpose	[15]
	ellagic acid	0.5	General purpose	[9]
	kojic acid	2.5, 0.5	General purpose	[16][17]
	linoleic acid	0.1	General purpose	[18]
	4-n-butyl resorcinol,	0.3	General purpose	[19]
	chamomile extract	0.5	Kao Corporation	[20]
	adenosine monophosphate	3	Otsuka Pharmaceutical Co., Ltd.	[21]
B Effectiveness of higher concentrations than those used in cosmetics on human pigment spots has been published in scientific journals and is recommended.	oil-soluble licorice extract containing 50% glabridin	0.2	General purpose	[22]
	niacinamide	5, 4	General purpose	[23][24]
	placenta extract	3	General purpose	[25]
	retinol	0.15	General purpose	[26]
	ascorbic acid 2-O- α -glucoside (AA-2G)	20 (iontophoresis)	General purpose	[27]
	azelaic acid.	20	General purpose	[28]
C No effectiveness for human pigment spots has been published in scientific journals and may be considered, but evidence is insufficient	potassium 4-methoxysalicylate	1, 3	Shiseido Co. Ltd.	
	dexpantenol		POLA ORBIS HOLDINGS INC.	
	Rhododenol	2	Kanebo Cosmetics Inc.	[29]
D Not recommended, because of toxicity data published in scientific journals	Magnolignan	0.5	Kanebo Cosmetics Inc.	[29]
	ascorbyl tetra-2-hexyldecanoate		Nikko Chemicals Co. Ltd.	[30][31][32]

The use of a hydrophilic ointment containing 3% APM for hyperpigmentation (melasma and Riehl melanosis) was reported in 1969 [15]. It was reported in 1996 that APM 10% cream was found to be significantly beneficial in 19 of 34 patients with melasma and senile freckles and in 3 of 25 patients with normal skin [7]. The use of 3% human placenta extract for

treating facial hyperpigmentation in women (47 cases of melasma and 2 cases of freckles) was reported in 1982 [25]. Other topically applied products with good results for melasma include 1% or 2.5% kojic acid [16], 3% arbutin [13], 1% tranexamic acid [12], 0.1% linoleic acid S [18], 0.3% Rucinol [19], and 0.5% ellagic acid [9]. Examples of topically applied products with good results for senile pigmentation include 3% APM [15], 10% APM [7][33], 1% or 2.5% kojic acid [16][17][34], 0.5% ellagic acid [9], 7% arbutin [8], and 0.5% chamomile extract [20]. Topical application of 1% or 2.5% kojic acid [16], 0.5% ellagic acid [9], 1% tranexamic acid [12], and 7% arbutin [8] has been used with good results in the treatment of freckles. In some cases, 1% vitamin C ethyl has shown effectiveness in pigmentation after natural light exposure and burns [14]. The effectiveness of these pharmaceutical skin-lightening cosmetics was not evaluated in a comparative study with a placebo, but instead was assessed in a study that examined the effectiveness of the formulations before and after continuous use, without double-blinding. In examining effectiveness, attention must be paid to changes in skin tone with seasonal variations and the effects of the base agent.

Examples of topical effectiveness in double-blind comparative studies include 0.1% retinoic acid (Tretinoin) [3], 0.2% oil-soluble licorice extract [22], and 20% azelaic acid [28] for melasma. Topical 0.1% retinol has been reported to be effective in photodamaged skin in a double-blind, controlled study [26]. Iontophoresis of 20% AA-2G has been reported to be effective in melasma and postinflammatory hyperpigmentation [27]. For senile pigmentation, both 0.1% retinoic acid (tretinoin) [4] and 2% 4-methoxyphenol/0.01% retinoic acid [5][6] have shown topical effectiveness in double-blind comparative studies, but these are not active ingredients in pharmaceutical cosmetics. Thus, a pharmaceutical skin-lightening cosmetic product is defined as a pharmaceutical product if its effectiveness against melasma and senile pigmentation is statistically demonstrated in actual use in a double-blind comparison test.

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