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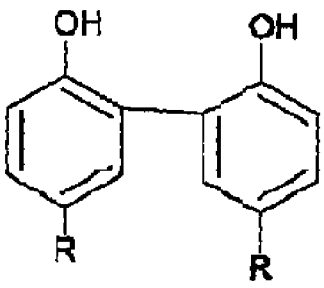

(1)

(57) Abstract: A skin external preparation, which comprises 0.1 to 5% by mass of a biphenyl compound represented by the general formula (1), and 0.01 to 5% by mass of salt of ascorbyl 2-phosphate 6-palmitate. (In the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

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DESCRIPTION

SKIN EXTERNAL PREPARATION AND METHOD OF PRODUCING THE SAME

TECHNICAL FIELD

[0001]

The present invention relates to a skin external preparation and a method of producing the same.

Priority is claimed on Japanese Patent Application No. 2011-140502, filed on June 24, 2011, the content of which is incorporated herein by reference.

BACKGROUND ART

[0002]

Conventionally, a whitening agent has been combined with a skin external preparation such as a cosmetic. However, a skin external preparation including a whitening agent sometimes causes stimulation to a person having sensitive skin. The stimulation generally means transient stimulation, wherein a material which is adhered to the surface of a skin passes through a skin barrier, arrives at keratinized cells to stimulate the keratinized cells, and causes an inflammatory reaction on the skin.

Accordingly, various studies have been performed in order to reduce skin-stimulation which is caused by a skin external preparation including a whitening agent. For example, Patent Document 1 discloses a skin external preparation wherein a specific nonionic surface-active agent is used in combination with a whitening agent to relieve stimulation. Patent Document 2 discloses a cosmetic wherein an antibacterial phospholipid is used in combination with a whitening agent to control the occurrence of transient stimulation.

It has also been proposed that a biphenyl compound such as 2,2'-dihydroxy-5,5'-dialkyl-biphenyl be used as a whitening agent. The biphenyl compound prevents the generation of melanin and exerts whitening effects since the biphenyl compound inhibits tyrosinase activity, which is enzyme concerning the generation of melanin. Therefore, a biphenyl compound is considered to have higher

safety as compared with hydroquinones, which are another kind of whitening agent (refer to Patent Document 3), and therefore addition of a biphenyl compound to a cosmetic or the like has been studied.

For example, in Patent Document 4, a whitening cosmetic is disclosed wherein N-acyl sarcosine alkyl is used in combination with a biphenyl compound in order to increase the solubility of a biphenyl compound and improve usage feeling when the cosmetic is used.

BACKGROUND ART LITERATURE

(Patent documents)

[0003]

Patent Document 1: Japanese Unexamined Patent Application, First Publication No. 2003-300857

Patent Document 2: Japanese Unexamined Patent Application, First Publication No. 2004-26657

Patent Document 3: Japanese Patent No. 2719300

Patent Document 4: Japanese Unexamined Patent Application, First Publication No. 2002-241254

DISCLOSURE OF INVENTION

[0004]

However, after the studies of the present inventors, it was found that even if a biphenyl compound is used as a whitening agent in a skin external preparation, a skin external preparation including a biphenyl compound does not always prevent transient stimulation. Furthermore, although Patent Document 4 reported that no subjects suffered from a skin stimulus reaction or a skin sensitization reaction due to a whitening cosmetic when 2,2'-dihydroxy-5,5'-dialkyl-biphenyl and N-acyl sarcosine alkyl were used in combination, the test method and the results thereof are not clearly described in the document.

The present invention is realized in view of the aforementioned circumstances, and the purpose of the present invention is to provide a skin external preparation which includes a biphenyl compound such as 2,2'-dihydroxy-5,5'-dialkyl-biphenyl, which is a whitening agent, but has low skin irritation, and a method of producing the skin external preparation.

Means for solving the problems

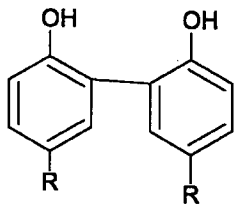
[0005]

The present inventors have intensively studied so as to solve the aforementioned problems, and found that, due to the combination of a salt of ascorbyl 2-phosphate 6-palmitate and a biphenyl compound such as 2,2'-dihydroxy-5,5'-dialkyl-biphenyl, which is a whitening agent, skin irritation induced by the biphenyl compound is alleviated, and achieved the present invention.

The present invention has the following aspects.

(1) A skin external preparation, which comprises 0.1 to 5% by mass of a biphenyl compound represented by the general formula (1), and 0.01 to 5% by mass of a salt of ascorbyl 2-phosphate 6-palmitate.

[0006]



... (1)

(In the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

[0007]

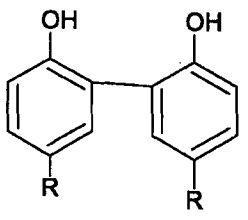
(2) The skin external preparation described in the above (1), wherein a mass ratio of the salt of ascorbyl 2-phosphate 6-palmitate to the biphenyl compound is 0.005 to 1.

(3) The skin external preparation described in the above (1) or (2), wherein the salt of ascorbyl 2-phosphate 6-palmitate is sodium ascorbyl 2-phosphate 6-palmitate.

(4) The skin external preparation described in the above (1) or (2), wherein the skin external preparation is a cosmetic.

(5) A production method of a skin external preparation, wherein a biphenyl compound represented by the general formula (1) and the salt of ascorbyl 2-phosphate 6-palmitate are mixed to form a mixture wherein 0.1 to 5% by mass of the biphenyl compound and 0.01 to 5% by mass of the salt of ascorbyl 2-phosphate 6-palmitate are included in the total amount of the skin external preparation.

[0008]



... (1)

(In the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

[0009]

(6) The production method of a skin external preparation described in the above (5), wherein the mixing is performed so that a mass ratio of the salt of ascorbyl 2-phosphate 6-palmitate to the biphenyl compound is in the range of 0.005 to 1.

[0010]

A salt of ascorbyl 2-phosphate 6-palmitate is a derivative of ascorbic acid, and it is known as a compound which shows effects and efficacy such as a whitening effect, an antioxidant action, and an acceleration effect of collagen synthesis. However, none of Patent Documents 1 to 4 disclose or suggest that transient stimulation caused by a skin external preparation including a biphenyl compound represented by the general formula (1) can be controlled by blending a salt of ascorbyl 2-phosphate 6-palmitate.

Effects of the invention

[0011]

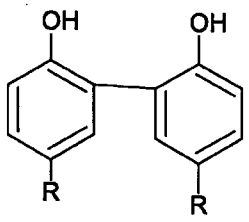
According to the present invention, it is possible to provide a skin external preparation which includes a biphenyl compound such as 2,2'-dihydroxy-5,5'-dialkyl-biphenyl as a whitening agent and is a low stimulus preparation; and also provide a method of producing the skin external preparation.

BEST MODE FOR CARRYING OUT THE INVENTION

[0012]

A skin external preparation of the present invention includes a biphenyl compound represented by the general formula (1) (hereinafter, referred as a biphenyl compound (1)), and a salt of ascorbyl 2-phosphate 6-palmitate

[0013]



... (1)

(In the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

[0014]

(Biphenyl compound (1))

In the general formula (1), R may be a hydrogen atom, or a hydrocarbon group. The hydrocarbon group shown by R may be a linear chain group or a branched chain group. The hydrocarbon group may be a saturated hydrocarbon group (alkyl group) or an unsaturated hydrocarbon group, but an alkyl group is preferable from the viewpoint of stability.

The number of carbons included in the hydrocarbon group is preferably 1 to 5. As examples of the hydrocarbon group, a methyl group, an ethyl group, an n-propyl group, an n-butyl group, an allyl group and the like are cited as concrete examples of the linear chain hydrocarbon group; and an isopropyl group, a t-butyl group, an isopentyl group and

the like are cited as concrete examples of the branched chain hydrocarbon group. However, examples of the hydrocarbon group are not limited thereto.

R is preferably a hydrogen atom or an alkyl group, more preferably a linear chain alkyl group, and still more preferably an n-propyl group. That is, 2,2'-dihydroxy-5,5'-di-n-propyl-biphenyl is particularly preferable as the biphenyl compound (1).

[0015]

As the biphenyl compound (1), one kind thereof may be used alone, or two or more kinds thereof may be used in combination.

Among the skin external preparations of the present invention, the content of the biphenyl compound (1) is 0.1 to 5% by mass based on the total amount of the skin external preparation, and is more preferably 0.3 to 3% by mass. When the amount of the biphenyl compound (1) is less than 1% by mass, a whitening effect achieved by the biphenyl compound (1) is insufficient. Even when the amount of the biphenyl compound (1) exceeds 5% by mass, an increased whitening effect which corresponds to the increased amount cannot be obtained.

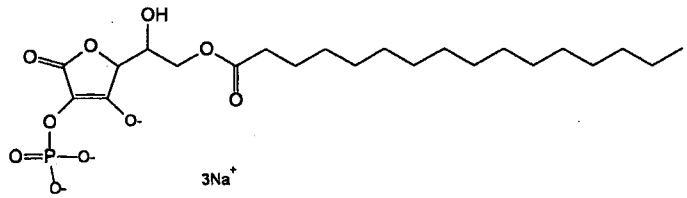
[0016]

(Salt of ascorbyl 2-phosphate 6-palmitate)

A salt of ascorbyl 2-phosphate 6-palmitate is a compound,in which phosphoric acid forms an ester linkage with a hydroxy group, which bonds with the second carbon atom of ascorbic acid; palmitic acid forms an ester linkage with a hydroxy group, which bonds with the sixth carbon atom of ascorbic acid; and hydrogen is removed from at least one selected from two hydroxyl groups, which bonds with a phosphorus atom included in the phosphate group, and a hydroxyl group, which bonds with the third carbon atom of ascorbic acid, to form a salt. Examples of the salt include a sodium salt, potassium salt and the like. For example, sodium ascorbyl 2-phosphate 6-palmitate is represented by the following chemical formula.

When the skin external preparation is a cosmetic, sodium ascorbyl 2-phosphate 6-palmitate is particularly preferable as a salt of the ascorbyl 2-phosphate 6-palmitate from the viewpoint of ease of handling thereof.

[0017]



[0018]

As a salt of ascorbyl 2-phosphate 6-palmitate, one kind thereof may be used alone, or two or more kinds thereof may be used in combination.

Among examples of a skin external preparation of the present invention, the content of the salt of ascorbyl 2-phosphate 6-palmitate is 0.01 to 5% by mass based on the total amount of the skin external preparation, and is more preferably 0.5 to 3% by mass. When a salt of ascorbyl 2-phosphate 6-palmitate is included in such an amount in a skin external preparation, it is possible to provide a skin external preparation which has low skin irritation. When the amount of a salt of ascorbyl 2-phosphate 6-palmitate is less than 0.01% by mass, the occurrence of skin irritation which is caused by the biphenyl compound (1) may be insufficiently controlled. Even when the amount of a salt of ascorbyl 2-phosphate 6-palmitate exceeds 5% by mass, an increased control effect which corresponds to the increased amount thereof cannot be obtained, and therefore it is not economical.

Furthermore, within the above content ranges, a mass ratio of a salt of ascorbyl 2-phosphate 6-palmitate to a biphenyl compound is preferably to 0.005 to 1, and more preferably 0.1 to 0.5. When the ratio is within the above range, a skin external preparation which still has lower stimulus can be obtained, despite the usage of a small amount of an ascorbyl 2-phosphate 6-palmitate salt.

[0019]

(Other optional components)

A skin external preparation of the present invention can include at least one kind of compound which is selected from ascorbic acid, salts of ascorbic acid, and derivatives

of ascorbic acid which are other than a salt of ascorbyl 2-phosphate 6-palmitate, in so far as the effects of the present invention are not inhibited.

Examples of a salt of ascorbic acid include sodium salt and potassium salt. As the derivatives of ascorbic acid other than a salt of ascorbyl 2-phosphate 6-palmitate, an ascorbyl-3-phosphate-6-higher fatty acid ester and salt thereof, an ascorbyl-6- higher fatty acid ester and salt thereof, an ascorbyl-2,6-di higher fatty acid ester and salt thereof, an ascorbyl-2,3,5,6-tetra higher fatty acid ester and salt thereof, an ascorbyl-2-sulfite and salt thereof, an ascorbyl-2-glucoside and the like can be used. Examples of a salt used for the compounds include sodium salts and potassium salts. As the higher fatty acid, a fatty acid having 8 to 22 carbon atoms can be cited.

Concrete examples of the derivatives of ascorbic acid include sodium ascorbyl 3-phosphate 6-palmitate, ascorbyl-6-palmitate, ascorbyl-2,6-dipalmitate, ascorbyl-2,3,5,6-tetraiso palmitate, disodium ascorbyl-2-sulfate, and ascorbyl-2-glucoside.

[0020]

As well as the aforementioned compounds, a skin external preparation of the present invention can optionally include additional components such as a carrier, an additive and the like, which are generally used in skin external preparations and are permitted from a pharmaceutical viewpoint.

Examples of such components include: hydrocarbons, natural waxes, fatty acids, higher alcohols, alkylglyceryl ethers, esters, silicone oils, poly alcohols, monofunctional lower alcohols, saccharides, polymers, anionic surfactants, cationic surfactants, ampholytic surfactants, nonionic surfactants, natural surfactants, ultraviolet absorbing agents, powders, color materials, amino acids, peptides, vitamins, vitamin-like active factors, antiseptic agents, antioxidizing agents, chelating agents, moisturizing agents, anti-inflammatory agents, pH adjusting agents, salts, organic acids, essential oils, terpenes, fragrances; and water.

[0021]

Examples of a skin external preparation of the present invention include a cosmetic and a pharmaceutical.

When a skin external preparation of the present invention is a cosmetic, generally-known existing raw materials which have been used for cosmetics can be further added to the external preparation at a general concentration thereof. For example, all raw materials known for cosmetic use can be used in the present invention.
These are described in documents such as: Japanese Standards of Cosmetic Ingredients (Keshouhin Genryo Kizyun), second edition, explanatory notes, edited by Society of Japanese Pharmacopoeia, 1984 (Yakuji Nippo Ltd.); Standards of Raw Materials of Cosmetics, Nonstandard Ingredients (Keshouhin Genryo Kizyun-gai Seibun Kikaku), under the editorship of the Evaluation and Registration Division, Pharmaceutical Affairs Bureau, Ministyr of Health and Welfare, 1993 (Yakuji Nippo Ltd.); Standards of Raw Materials of Cosmetics, Nonstandard Ingredients, Supplement (Keshouhin Genryo Kizyun-gai Seibun Kikaku Tsuiho), under the editorship of the Evaluation and Registration Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, 1993 (Yakuji Nippo Ltd.); Comprehensive Licensing Standards of Cosmetic by Categpry (Keshouhin Syubetsu Kyoka Kizyun), under the editorship of the Evaluation and Registration Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, 1993 (Yakuji Nippo Ltd.); Japanese Cosmetic Ingredients Codex (Keshouhin Syubetsu Haigou Seibun Kikaku), under the editorship of the Evaluation and Registration Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, 1997 (Yakuji Nippo Ltd.); Dictionary of raw materials of cosmetics (Keshouhin Genryou Jiten), 1991 (Nikko Chemicals Co., Ltd.), and the like.

[0022]

The type of skin external preparation of the present invention is not limited in so far as the agent contacts with the skin of a user when the agent is used, and the type is optionally selected according to use thereof. For example, the pharmaceutical form of a skin external preparation of present invention may be a lotion, a milky liquid, a cream, a pack and the like.

[0023]

A skin external preparation of the present invention can be generated by mixing a biphenyl compound represented by the aforementioned general formula (1), a salt of ascorbyl 2-phosphate 6-palmitate and another compound which may be added optionally to form a preparation. The formulation of a skin external preparation can be performed by general methods according to the dosage form thereof.

[0024]

By mixing a biphenyl compound (1) and a salt of ascorbyl 2-phosphate 6-palmitate, a skin external preparation which has low skin-stimulation and by which transient stimulation caused by a biphenyl compound (1) is controlled can be obtained. Accordingly, the present invention is useful for general skin external preparations including cosmetics and pharmaceuticals, and is particularly useful for cosmetics. An emulsifier-type skin external preparation is particularly preferable for the present invention due to ease of preparation thereof.

EXAMPLES

[0025]

The present invention is described more concretely with reference to the following Examples, but it should be construed that the invention is in no way limited to those Examples.

Skin-stimulation of a skin external preparation (lotion) obtained in Examples, Comparative Examples, and Reference Examples described below was evaluated according to the following procedure.

<Evaluation method of skin-stimulation>

Skin stimulation was evaluated using prepared lotions in a 24-hour closed-patch test, which was performed using a group of five guinea pigs as a model of skin injury (Hartley albino male guinea pigs of approximately 300 to 400 g in weight, whose hair was removed by shaving followed by stripping with tape three times prior to the experiment). Evaluation criteria using the Draize method were used as evaluation criteria as follows:

Score 2: Reaction occurred with edema.

Score 1: Reaction occurred with clear erythema.

Score 0.5: Reaction occurred with unclear erythema.

Score 0: Reaction did not occur.

[0026]

(Example 1, Comparative Example 1, and Reference Example 1)

Lotions according the compositions shown in Table 1 (unit: % by mass) were prepared by the following procedure.

At first, phases A, B, and C were prepared by the following procedure.

Phase A: Among components of phase A shown in Table 1, 2,2'-dihydroxy-5,5'-di-n-propyl-biphenyl and sodium ascorbyl 2-phosphate 6-palmitate were mixed with other components (oil components), and heat-melted at a temperature of 80°C.

Phase B: Each component of phase B shown in Table 1 was mixed and heat-melted at a temperature of 80°C.

Phase C: Arginine was dissolved in pure water.

Subsequently, phase A (oil phase) was added to phase B (aqueous phase) to perform preliminary emulsification, and then emulsification was performed uniformly with a homomixer. After emulsification, the mixture was cooled to 30°C while mixing well, and phase C was added thereto to obtain lotions.

Evaluation of skin stimulation was performed using the obtained lotions. The obtained results are shown in Table 1.

[0027]

Table 1

			Ex. 1	Com. Ex. 1	Ref. Ex. 1
Composition (% by mass)	Phase A	Behenyl alcohol	0.3	0.3	0.3
		Glyceryl stearate	2.0	2.0	2.0
		Polyoxyethylene glyceryl isostearate (60E.O.)	0.5	0.5	0.5
		Squalane	5.0	5.0	5.0
		Cyclomethicone	2.0	2.0	2.0
		Glyceryl tri(2-ethylhexanoate)	1.0	1.0	1.0
		2-Ethylhexyl palmitate	1.5	1.5	1.5
		Propylparaben	0.1	0.1	0.1
		2,2'-Dihydroxy-5,5'-di-n-propyl-biphenyl	2.0	2.0	
		Sodium ascorbyl 2-phosphate 6-palmitate	1.0		
	Phase B	1,3-Butylene glycol	4.0	4.0	4.0
		Glycerin	4.0	4.0	4.0
		Carboxyvinyl polymer	0.2	0.2	0.2
		Xanthan gum	0.2	0.2	0.2
		Methylparaben	0.2	0.2	0.2
		Purified water	70.9	71.9	73.9
	Phase C	Arginine	0.1	0.1	0.1
		Purified water	5.0	5.0	5.0
	Total		100.0	100.0	100.0
Evaluation results of skin-stimulation		Score 2	0	0	0
		Score 1	0	2	0
		Score 0.5	0	3	0
		Score 0	5	0	5

[0028]

As shown in the above results, the composition of Comparative Example 1 wherein 2,2'-dihydroxy-5,5'-di-n-propyl-biphenyl was further added to the composition of Reference Example 1, which did not cause skin stimulus, showed skin stimulus. However, the composition of Example 1, wherein sodium ascorbyl 2-phosphate 6-palmitate was further blended to the composition of Comparative Example 1, did not cause skin stimulus, similar to the results of Reference Example.

[0029]

(Examples 2 to 4, Comparative Example 4 and Reference Example 2)

Lotions each having the composition shown in Table 2 (unit: % by mass) were prepared by the following procedure.

At first, phases A, B, and C were prepared by the following procedure.

Phase A: 2,2'-dihydroxy-5,5'-di-n-propyl-biphenyl and sodium ascorbyl 2-phosphate 6-palmitate were mixed with other components (oil components), and heat-melted at a temperature of 80°C.

Phase B: Each component was mixed and heat-melted at a temperature of 80°C.

Phase C: Potassium hydroxide was dissolved in pure water.

Subsequently, phase A (oil phase) was added to phase B (aqueous phase) to perform preliminary emulsification, and then emulsification was performed uniformly with a homomixer. After emulsification, the mixture was cooled to 30°C while mixing well, and phase C was added thereto to obtain lotions.

Evaluation of skin irritation was performed using the lotions.

The obtained results are shown in Table 2.

[0030]

Table 2

			Ex. 2	Com. Ex. 2	Red. Ex. 2
Composition (% by mass)	Phase A	Ethanol	10.0	10.0	10.0
		Polyoxyethylene oleyl ether (2E.O.)	0.2	0.2	0.2
		Polyoxyethylene cetyl ether (2E.O.)	0.1	0.1	0.1
		Polyoxyethylene hydrogenated castor oil (60E.O.)	0.3	0.3	0.3
		Dimethylpolysiloxane	1.0	1.0	1.0
		Glyceryl tri 2-ethyl hexanoate	1.0	1.0	1.0
		N-Isopropyl lauroyl sarcosinate	5.0	5.0	5.0
		2-Ethylhexyl p-methoxycinnamate	1.0	1.0	1.0
		2,2'-Dihydroxy-5,5'-di-n-propyl-biphenyl	3.0	3.0	
		Sodium ascorbyl 2-phosphate 6-palmitate	1.0		
	Phase B	Sodium lauroyl-l-glutaminate	1.0	1.0	1.0
		Dipropylene glycol	1.0	1.0	1.0
		Concentrated glycerin	2.0	2.0	2.0
		Carboxyvinyl polymer	0.3	0.3	0.3
		Edetate disodium	0.01	0.01	0.01
		Purified water	66.94	67.94	70.94
	Phase C	Potassium hydroxide	0.15	0.15	0.15
		Purified water	5.0	5.0	5.0
	Total		100.00	100.00	100.00
Evaluation results of skin-stimulation		Score 2	0	0	0
		Score 1	0	3	0
		Score 0.5	0	2	0
		Score 0	5	0	5

[0031]

As shown in the above results, the composition of Comparative Example 2, wherein 2,2'-dihydroxy-5,5'-di-n-propyl-biphenyl was further added to the composition of Reference Example 2, which did not cause skin stimulus, showed skin stimulus. However, the composition of Example 2, wherein sodium ascorbyl 2-phosphate 6-palmitate was further blended to the composition of Comparative Example 2, did not cause skin stimulus, similar to the results of Reference Example 2.

[0032]

With respect to the raw materials used in the aforementioned Examples, Comparatives and Reference Examples, "E.O." included in parentheses is an abbreviation of polyoxyethylene, and the number shown before "E.O." represents an average degree of polymerization of an oxyethylene group included in the polyoxyethylene unit.

As a carboxyvinyl polymer, CARBOPOL 980 (trade name) manufactured by Noveon Inc. was used. As a xanthan gum, KELTROL CG (trade name) manufactured by Sansho Co., Ltd. was used.

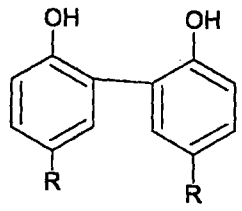
INDUSTRIAL APPLICABILITY

[0033]

A skin external preparation which includes a biphenyl compound such as 2,2'-dihydroxy-5,5'-di-alkyl-biphenyl, which is a whitening agent, but has low skin stimulation, and a method of producing the skin external preparation are provided by the present invention.

CLAIMS

1. A skin external preparation, which comprises 0.1 to 5% by mass of a biphenyl compound represented by the general formula (1), and 0.01 to 5% by mass of a salt of ascorbyl 2-phosphate 6-palmitate;



... (1)

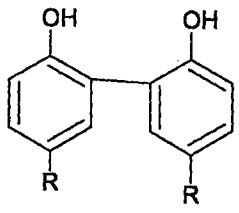
(in the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

2. The skin external preparation according to Claim 1, wherein a mass ratio of the salt of the ascorbyl 2-phosphate 6-palmitate to the biphenyl compound is 0.005 to 1.

3. The skin external preparation according to Claim 1, wherein the salt of ascorbyl 2-phosphate 6-palmitate is sodium ascorbyl 2-phosphate 6-palmitate.

4. The skin external preparation according to Claim 1, wherein the skin external preparation is a cosmetic.

5. A production method of a skin external preparation, wherein a biphenyl compound represented by the general formula (1) and a salt of ascorbyl 2-phosphate 6-palmitate are mixed to form a mixture so that the content of the biphenyl compound in the mixture is 0.1 to 5% by mass and the content of the salt of ascorbyl 2-phosphate 6-palmitate in the mixture is 0.01 to 5% by mass;



... (1)

(in the formula, R represents a hydrogen atom, or a chain hydrocarbon group having 1 to 8 carbon atoms.)

6. The production method of a skin external preparation according to Claim 5, wherein the mixing is performed so that a mass ratio of the salt of ascorbyl 2-phosphate 6-palmitate to the biphenyl compound is 0.005 to 1.