Description

This invention relates to the use of kojic acid or kojic acid β-cyclodextrin inclusion complex for making drugs for preventing elastosis.

The human dermis has collagen fiber bundles at its upper layer, and nearly parallel elastic fibers run along or across these collagen fiber bundles, which are evenly distributed over the entire dermal layer.

An increase in the number of elastic fibers and the consequent dissociation and breakage of collagen fiber bundles are often found in exposed parts of the skin of aged persons. This dermal abnormality, called elastosis, causes wrinkles on the skin, and is also known to be closely correlated to the occurrence of malignant carcinomas, particularly senile keratosis, keratoacanthoma, squamous cell carcinoma and basal cell carcinoma, because it is invariably found around these carcinomas.

No drug capable of curing or preventing elastosis has yet been discovered. Such a drug, if developed, would be of great use for protection of the skin and prevention of various skin cancers.

Kojic acid is a compound produced by Aspergillus oryzae or other kojic-acid-producing microorganisms, and many studies have been reported on its applications. These include skin-whitening cosmetics containing kojic acid (Japanese Patent Kokai No.3538/1978), antiinflamatory agents (Japanese Patent Publication No. 34446/1983), ultraviolet preventive agents (Japanese Patent Kokai No.157509/1980), and analgesic agents (Japanese Patent Kokai No.131915/1983).

We have discovered that kojic acid is effective in preventing elastosis --- an effect distinctly different from the skin-whitening, antiinflammatory, analgesic and ultraviolet preventing effects mentioned above. This invention was accomplished based on this finding. Thus this invention relates to the use of kojic acid or kojic acid/β-cyclodextrin inclusion complex according to claim 1.

Kojic acid used in this invention is a known compound obtainable by the static or shake culture of a kojic-acid-producing strain belonging to the genus Aspergillus or Penicillium in a liquid culture medium containing glucose or the like as carbon source.

The kojic acid/β-cyclodextrin inclusion complex used in this invention can be prepared by slowly adding kojic acid to an aqueous suspension of β-cyclodextrin with agitation and by continuing stirring until a clear solution is obtained. The solution of inclusion complex thus prepared may be freeze-dried, as required, for use in the drugs of this invention.

The preventive drugs for elastosis of this invention containing, as an effective ingredient, kojic acid or its inclusion complex with β-cyclodextrin are preferably applied in the form of an ointment, cream, emulsion, pack or solution.

The amount of the effective ingredient contained in said drugs may be varied depending on the type and severity of dermatitis being treated, the spread of said drugs on the affected skin and the frequency of application, but is preferably in the range from 0.1 to 5% by weight.

The toxicity of kojic acid is extremely low, its LD_{50} for mice and rats (both male and female) being 2.5 to 3.5 g/Kg when it is orally administered. Its safety to the skin is also very high, with no danger of irritation or of causing allergic reaction.

The pharmaceutical preparations of kojic acid or its inclusion complex with β-cyclodextrin can be manufactured by commonly used techniques.

Solutions, for example, may be prepared by dissolving, in pure water, the effective ingredient (kojic acid or its inclusion complex with β-cyclodextrin), a humectant (e.g., glycerol and propylene glycol) and nourishing agents; dissolving preservatives and perfumes in ethanol; and mixing the two solutions obtained above at room temperature to effect solubilization.

Cream can be prepared by dissolving, in pure water, the effective ingredient (kojic acid or its inclusion complex with β-cyclodextrin) and a humectant (e.g., glycerol and sorbitol); mixing solid fatty substances (e.g., beeswax, paraffin wax, microcrystalline wax, ceresin, higher fatty acids and hardened oil), semi-solid fatty substances (e.g., vaselin, lanolin and glycerol), oily substances (e.g., squalane, liquid paraffin and various liquid esters), and oily additives (e.g., preservatives and surface-active agents); gently agitating the aqueous solution obtained above at an elevated temperature; and slowly adding, to this aqueous solution, the oily mixture prepared above and previously heated to the same temperature as said aqueous solution, thereby effecting emulsification.

Emulsions are manufactured by mixing pure water, the effective ingredient (kojic acid or its inclusion complex with β-cyclodextrin), a humectant (e.g. glycerol) and a pH regulator (acid or alkali) at an elevated temperature, followed by addition of ethanol; mixing solid fatty substances (e.g., beeswax and paraffin wax), oily substances (e.g., squalane, liquid paraffin and various liquid esters), and oily additives (e.g., preserva-

tives and surface-active agents) at an elevated temperature; effecting preliminary emulsification by adding the oily mixture to the aqueous solution; and completing emulsification in a homogenizer in the presence of a protective colloid, such as a carboxyl-containing vinyl polymer and carboxymethylcellulose.

Packs can be prepared by dissolving, in pure water, the effective ingredient (kojic acid or its inclusion complex with β-cyclodextrin) and a humectant (e.g. glycerol); adding a film-forming agent (e.g., polyvinyl alcohol) to the solution, followed by addition of powdery fillers (e.g., kaolin, talc and zinc oxide), as required; further adding ethanol containing perfume, preservatives and other additives dissolved therein; and kneading the resulting mixture until a homgeneous paste is obtained.

Ointment may be prepared by dissolving, in pure water, the effective ingredient (kojic acid or its inclusion complex with β-cyclodextrin) and a humectant (e.g. glycerol); adding solid fatty substances (e.g., animal and vegetable wax, paraffin wax, ceresin and higher fatty acids), and semi-solid fatty substances (e. g., vaselin and lanolin); and thoroughly kneading the mixture thus obtained.

Typical examples of pharmaceutical preparations of the drugs of this invention are described below.

Example 1 (Cream)	
Kojic acid	1.0%
Polyoxyethylene stearyl ether	2.09%
Polyoxyethylene cetyl ether	2.91%
Beeswax	4.0%
Cetanol	3.0%
Isopropyl palmitate	2.0%
Liquid paraffin	15.0%
Polyethylene glycol monostearate	0.5%
Pure water	69.4%
Methyl p-oxybenzoate	0.1%

Example 2 (Emulsion)	
Kojic acid/β-cyclodextrin inclusion complex	2.0%
Self-emulsifiable glycerol monostearate	1.11%
Polyoxyethylene cetyl ether	1.89%
MC stearic acid	2.0%
Cetanol	1.0%
Isopropyl myristate	2.0%
Pure water	89.90%
p-Oxybenzoic acid	0.1%
Perfume	Trace

Example 3 (Pack)	
Kojic acid	0.6%
Ethanol	3.0%
Methyl p-oxybenzoate	0.1%
Carboxyl-containing vinyl polymer	1.0%
Calcium carbonate	0.3%
Titanium dioxide	0.02%
Pure water	94.98%
Perfume	Trace

Example 4 (Solution)	
Kojic acid/β-cyclodextrin inclusion complex	3.0%
Ethanol	10.0%
p-Oxybenzoic acid	0.1%
Citric acid	0.2%
Perfume	Trace
Pure water	86.7%

Example 5 (Ointment)	
Kojic acid	2.0%
Glycerol monostearate	10.0%
Cetanol	0.5%
Stearic acid	5.0%
Lanolin	2.0%
Propylene glycol	2.0%
Liquid paraffin	3.0%
Pure water	75.5%

The effects of this invention will be apparent from the result of animal test described below.

(Test method)

Ten head of female Spraguex-Dawley rats 4-weeks of age were used for the test. The back of each rat was divided into two zones along its center line; one (test zone) was coated with 1% suspension of kojic acid in 1% aqueous solution of carboxymethylcellulose, and the other (control zone) was coated with 1% aqueous solution of carboxymethylcellulose. The coated solution was washed off with hot water one hour later, and each zone was then irradiated with ultraviolet rays for 20 minutes using four UV tubes (Toshiba, Model 20S;E30) placed 62 cm away from the back of each rat. This operation was performed three times a week (on Monday, Wednesday and Friday) and continued over a period of six months. The drug solution and control solution were applied every day (even on days when UV irradiation was omitted). After that, the coating operation alone was continued for an additional six months.

Severity of erythema developed on each zone was observed immediately after the start of test, and 2, 4, 6, 8, 10 and 12 months later. The result is summarized in Table 1 below.

Table 1

	Month	Test Zone	Control Zone
Irradiation Period	0	-	-
	2	+	+ + +
	4	+ +	+ + +
	6	+ +	+ + +
Coating Alone	8	-	±
	10	-	-
	12	-	-

-: No erythema ±: Very slight erythema
+: Slight erythema + +: Medium erythema
+ + +: Severe erythema

At the end of the test, tissues were excised from the test and control zones of each rat, paraffin sections of the skin, prepared from the tissues taken out, were submitted to Hematoxylin-Eosin, Weigert and Orcein-Giemsa staining process, and the condition of the elastic fiber was observed. The result is summarized in Table 2 below.

Table 2

Evaluation	Test Zone	Control Zone
-	3	0
±	3	0
+	3	0
+ +	1	2
+ + +	0	8
Total	10	10

-: No elastosis ±: Very slight elastosis
+: Slight elastosis + +: Medium elastosis
+ + +: Severe elastosis

As can be seen from the table, the drugs of this invention are effective in preventing or minimizing the occurrence of elastosis (complete restoration even when slight elastosis was observed).

Claims

1. Use of kojic acid or kojic acid/β-cyclodextrin inclusion complex for making drugs for preventing elastosis.

2. Use according to claim 1, characterized in that said drugs being in the form of an ointment, cream, emulsion, pack or solution.

Revendications

1. Utilisation de l'acide Kojic ou du complexe d'inclusion acide Kojic/bêta-cyclodextrine en vue de la fabrication de médicaments pour prévenir l'élastosis.

2. Utilisation selon la revendication 1, caractérisée en ce que les dits médicaments sont sous la forme d'une pommade, d'une crême, d'une émulsion, d'un emplâtre ou d'une solution.

Patentansprüche

1. Verwendung von Kojisäure oder Kojisäure/β-Cyclodextrin-Einschlußkomplexen zum Herstellen von Arzneimitteln zur Verhütung von Elastoidosis.

2. Verwendung nach Anspruch 1, dadurch gekennzeichnet, daß die Arzneimittel in Form einer Salbe, Creme, Emulsion, Packung oder Lösung sind.

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