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(54) Title: METHODS FOR IMPROVING THE AESTHETIC APPEARANCE OF SKIN

(57) **Abrégé/Abstract:**

There are provided methods and compositions for improving the aesthetic appearance of skin, treating rosacea and/or telangiectasia, and treating the signs of dermatological aging. The method is directed to topically applying to an affected area an effective amount of mangostin, an analog thereof, or a combination thereof.



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(54) Title: METHODS FOR IMPROVING THE AESTHETIC APPEARANCE OF SKIN

(57) Abstract: There are provided methods and compositions for improving the aesthetic appearance of akin, treating rosacea and/or telangiectasia, and treating the signs of dermatological aging. The method is directed to topically applying to an affected area an effective amount of mangostin, an analog thereof, or a combination thereof.

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METHODS FOR IMPROVING THE AESTHETIC APPEARANCE OF SKIN

BACKGROUND OF THE INVENTION

5 1. Field of the Invention

10 The present invention relates to methods for improving the aesthetic appearance of skin. The present invention further relates to methods of treating sensitive skin, methods of treating rosacea and/or telangiectasia, and methods of treating dermatological signs of aging. The present invention further relates the topical application of an effective amount of mangostin or an analog thereof.

15 2. Description of the Prior Art

 Cosmetic products, which enhance the appearance of skin, are increasingly in demand. Consumers are interested in mitigating or delaying the signs of chronologically or hormonally aged or photo-aged skin, such as fine lines, wrinkles, drying, and sagging skin. During the aging process, the complexion of the skin, i.e., the color and appearance of the skin, deteriorates slowly from aging and/or exposure to sunlight.

 Numerous cosmetic and medical treatments have been developed in an attempt to treat aged skin, as well as sensitive skin, rosacea, telangiectasia and related conditions. Rosacea and its clinical manifestations are known by those in the art. A description of rosacea and related literature is set forth in U.S. Patent No. 5,972,993 at col. 1, line 15 through col. 2, line 55.

30 Telangiectasia typically presents as superficial cutaneous capillaries near the surface of the skin having a bright red center portion and branching radiations. Such a skin condition is often called "spider veins." When telangiectasia includes capillaries that are burst, leak blood or other fluids and/or become highly branched, the skin condition is commonly

referred to as "broken capillaries." Telangiectasia may be spurred by UV exposure, stress, environmental conditions, injury and/or general skin aging.

5 The prior art discloses treatments for telangiectasia. U.S. Patent No. 5,268,176 provides for treatment via repeated applications of a composition having inositol phosphoric acid or derivatives thereof. U.S. Patent No. 5,698,206 provides for treatment via topical application of natural herbs in a carrier oil and concurrent ingestion of vitamin C.

10

 Persons having rosacea and/or telangiectasia frequently address the skin irregularities brought on by those conditions by the application of cosmetics to mask the appearance of the skin. While the use of cosmetics is not deleterious to the health of the person, they do not mitigate or
15 ameliorate the underlying conditions.

 Mangostin has been employed in the prior art for a variety of purposes, but heretofore has not been employed to treat rosacea, telangiectasia, or aging skin. French Patent No. 2,754,447 relates to
20 sunscreen compositions having mangostin. Japanese Patent Publication No. 10072357 relates to antiallergenic agents and foods having mangostin. The publication, *Antimicrobial Activities of Chemical Constituents from Garcinia mangostana*, J. Sci. Soc. Thailand (1986), 12(4), pages 239-43, relates to the use of mangostin and mangostin derivatives as
25 antimicrobials. The publication, *The Structure of Garcinone E*, Chem. Pharm. Bull. (1993), 41(5), pages 958-60, relates to the use of mangostin analogs as anti-tumor agents.

 It would be desirable to have a topical composition to improve the
30 aesthetic appearance of the skin. It would also be desirable to have an effective treatment for sensitive skin. It would also be desirable to have an effective treatment for rosacea and/or telangiectasia. It would also be desirable to have an effective treatment for the dermatological signs of aging.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for
5 improving the aesthetic appearance of skin.

It is another object of the present invention to provide a method for
treating sensitive skin.

10 It is also an object of the present invention to provide a method for
treating rosacea.

It is also an object of the present invention to provide a method for
treating telangiectasia.

15

It is still another object of the present invention to provide a method
for treating the signs of dermatological aging.

These and other objects and advantages of the present invention
20 are achieved by a method of topically applying to an affected area an
effective amount of mangostin and/or an analog thereof.

These and other objects of the invention are also achieved by a
method of topically applying to an affected area an effective amount of a
25 natural extract of mangostin and/or an analog thereof.

DETAILED DESCRIPTION OF THE INVENTION

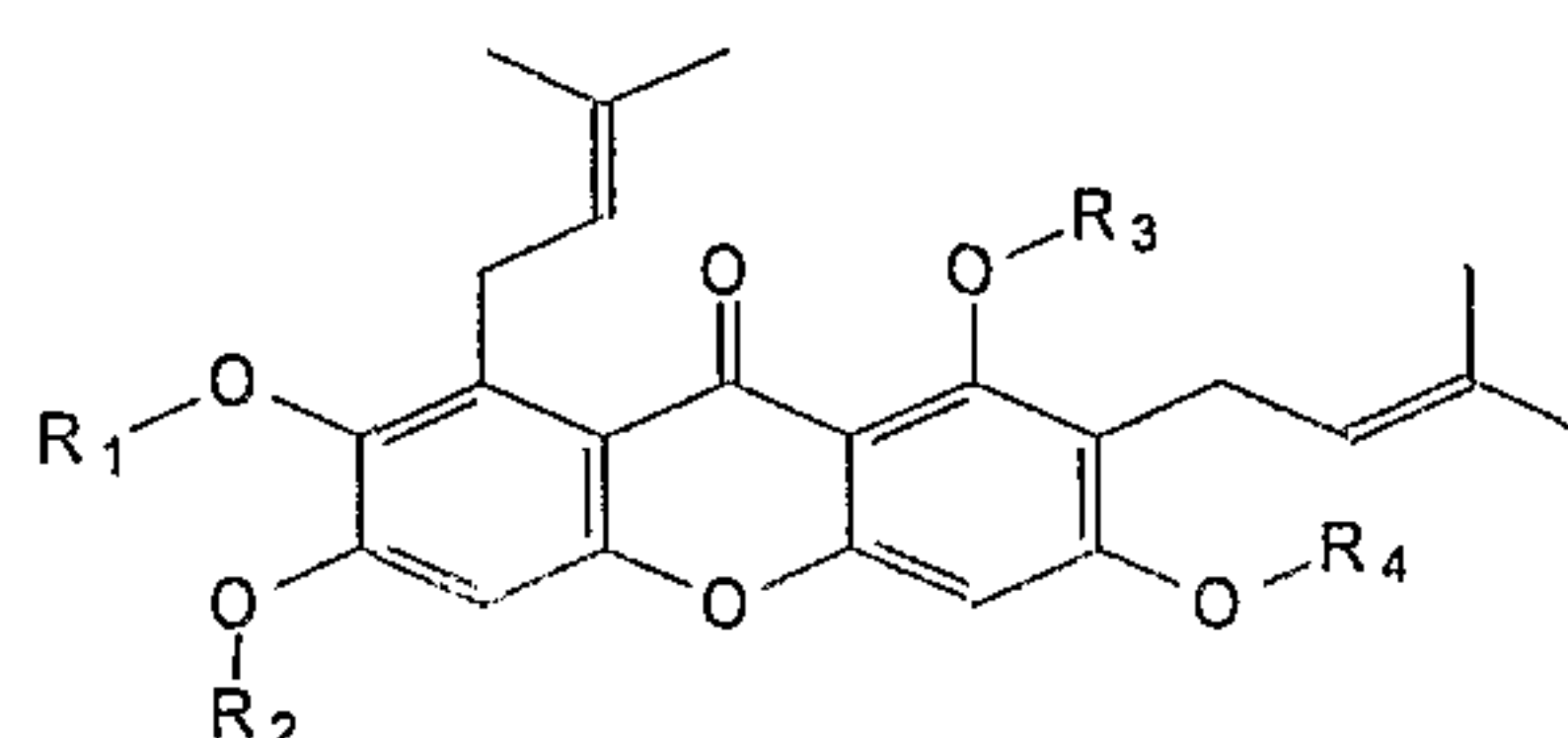
It was found surprising that there are methods for improving the
30 appearance of skin, treating sensitive skin, treating rosacea and/or
telangiectasia, and treating the signs of dermatological aging, particularly
with respect to the face, legs and/or torso. It was also surprisingly found
that such methods are effected by topically applying to the affected area an
effective amount of mangostin or an analog thereof.

The terms "treating" or "treat" as used in the present invention mean reduce, diminish, ameliorate, or prevent. To improve skin appearance means to partially or fully restore the normal appearance of the skin.

5

Mangostin and its analogs are compounds that can be derived from natural sources (e.g., *Garcinia mangostana* L., *Guttiferae* as described in Schmid, Ann. 93, 83 (1855)) and/or synthesized.

10 Mangostin and its analogs can be represented by the following general formula:



15 wherein R₁, R₂, R₃ and R₄ may, independently, be any of the following: a hydrogen atom; a carbohydrate; an acyl group, substituted or unsubstituted, straight-chain or branched, fully saturated or having one or more unsaturated bonds, that has from 1 to 22, preferably 1 to 18, and most preferably from 1 to 12, carbon atoms; an alkyl group, substituted or
 20 unsubstituted, straight-chain or branched, fully saturated or having one or more unsaturated bonds, that has from 1 to 22, preferably 1 to 18, and most preferably from 1 to 12, carbon atoms; an alkenyl group, substituted or unsubstituted, straight-chain or branched, fully saturated or having one or more unsaturated bonds, that has from 1 to 22, preferably from 1 to 18,
 25 and most preferably from 1 to 12 carbon atoms; an alkynyl group, substituted or unsubstituted, straight-chain or branched, fully saturated or having one or more unsaturated bonds, that has from 1 to 22, preferably 1 to 18, and most preferably from 1 to 12, carbon atoms; a phenyl group, substituted or unsubstituted; a benzyl group, substituted or unsubstituted; a
 30 cycloalkyl group, substituted or unsubstituted, that has from 3 to 8, preferably from 4 to 7, and most preferably from 5 to 6, carbon atoms; a

cycloalkenyl group, substituted or unsubstituted, that has from 4 to 8, preferably from 4 to 7, and most preferably from 5 to 6, carbon atoms; and an oxaalkyl, oxaalkenyl, or oxaalkynyl group having at least one oxygen atom in its backbone structure, substituted or unsubstituted, and straight-
5 chained or branched. Suitable carbohydrates include but are not limited to glucose, lactose, fructose, rhamnose, trehalose, or fucose. Glucose and fucose are preferred carbohydrates. Preferably, at least two of R₁, R₂, R₃ and R₄ are hydrogen atoms. Most preferably, R₁ is an alkyl group or acyl group having from 1 to 12 carbon atoms and R₂, R₃ and R₄ are each
10 hydrogen atoms.

Mangostin has the chemical name of 1,3,6-trihydroxy-7-methoxy-2,8-di(3-methyl-2-butenyl)xanthone or, alternately, 1,3,6-trihydroxy-7-methoxy-2,9-bis(3-methyl-2-butenyl)-9H-xanthen-9-one. The physical
15 properties of mangostin are set forth in *The Merck Index*, 10th Edition (1983), page 818.

Analogues of mangostin can be derived from plant or natural sources or be prepared via conventional organic synthesis procedures such
20 catalytic esterification, ethoxylation, and etherification. Such analogues include the following: alpha mangostin, beta mangostin, bicyclomangostin, gamma mangostin, 3-O-methylmangostin, mangostin triacetate, and mangostin-3,6-di-O-glucoside.

25

In the present method, mangostin and/or its analogues can be topically applied without a vehicle, i.e. in an amount 100 percent by weight (wt%). More preferably, mangostin and/or its analogues are admixed with a vehicle suitable to form a composition for topical application. When compositions
30 are employed, the composition preferably has about 0.0001 wt% to less than 100 wt%, more preferably about 0.0001 wt% to about 90 wt%, still more preferably about 0.01 wt% to about 50 wt%, and most preferably about 0.5 wt% to about 20 wt%, of mangostin and/or its analogues based on the total weight of the composition.

In the present invention, mangostin and/or its analogs can be used to improve the overall appearance of the skin and treat sensitive skin. Treatable skin conditions include itch, irritation, inflammation, loss of tone
5 (e.g., sagging and/or uneven color), redness, allergic responses, combination (oil/dry/unbalanced) skin, blemishes, flushing and blushing.

Also in the present invention, mangostin and/or its analogs can be used to treat dermatological signs of aging due to, for example,
10 chronological aging, hormonal aging and/or photoaging. Such signs of aging include, but are not limited to, skin fragility; loss of collagen and/or elastin; skin atrophy; appearance and/or depth of lines and/or wrinkles including fine lines; skin discoloration including dark eye circles; skin sagging; skin fatigue and/or stress, e.g., skin breakout due to
15 environmental stress, such as pollution and/or temperature changes; loss of skin tone, clarity or luster; loss of skin firmness; poor skin texture; loss of skin elasticity and/or resiliency; and thin skin.

The compositions of the present invention can be effectively applied
20 daily for about 1, 2 or 4 weeks, or more. Preferably, the compositions are applied daily for about 2 weeks.

Compositions useful in the present method can be formulated in any suitable product form. Such product forms include, but are not limited to,
25 aerosol spray, cream, dispersion, foam, gel, lotion, mask, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, tape and towelette.

Compositions useful in the present method can include a vehicle
30 that is pharmaceutically or cosmetically acceptable. Such vehicles include, but are not limited to, one or more C₁₋₄ alcohols, fatty alcohols, fatty ethers, fatty esters, polyols, glycols, vegetable oils, mineral oils, liposomes, laminar lipid materials, silicone oils, water, or any combinations thereof.

Optionally, compositions useful in the present method can include one or more of the following additional ingredients: amino acids, anesthetics, anti-acne agents, anti-allergens, antifungals, antimicrobials, anti-inflammatory agents, anti-irritants, antineoplastics, antioxidants, antiseptics, antivirals, chelating agents, colorants, depigmenting agents, emollients, emulsifiers, exfollients such as oxa acids and alpha and beta hydroxy acids, film formers, fragrances, humectants, hypopigmenting agents, immune system boosting agents, immune system suppressing agents, insect repellents, lubricants, moisturizers, pharmaceutical agents, photostabilizing agents, preservatives, retinoids, skin protectants, skin penetration enhancers, staining agents, sunscreens, stabilizers, surfactants, thickeners, viscosity and/or rheology modifiers, vitamins, or any combinations thereof.

The following are examples of the present invention.

Example 1

	<u>Oil-in-Water Emulsion</u>	<u>wt%</u>
	Humectant (e.g. Glycols, Glycerols)	0.5-15
20	Thickeners (e.g. Gums, Starches, Polymers)	0.1-4
	Chelants (e.g. Disodium EDTA, Tetrasodium EDTA)	0.001-0.5
	Preservatives	0.01-2
	Sunscreen (e.g. Parsol 1789™, ethylhexylmethoxycinnamate, benzophenone-3)	0.1-50
25	Silicone	0.1-15
	Silica	0.01-10
	Extracts (e.g., one or more of	
	Pomegranate extract,	0.0001-50
	Neem Seed Cell Broth,	
30	Grape Seed Extract,	
	Salvia Miltiorrhiza Extract,	
	Iris Florentina Root Extract,	
	Carrot Extract,	
	Cucumber Extract,	

White Birch(Betula Alba) Bark Extract,
 Rosemary Extract,
 Algae Extract, or any combination)

5	Fatty alcohol/Emulsifiers/Wax/Fatty acid (e.g. ceteth-20 phosphate/cetearyl alcohol /dicetyl phosphate, Tribehenin PEG-20 Ester, sodium Dihydroxycethyl phosphate, cetearyl gloconide, cocoglyceride)	0.5-15
10	Emulsion Stabilizers/Viscosity Modifiers (e.g. acrylates/C ₁₀₋₃₀ alkyl acrylate crosspolymer, acrylate/aminoacrylates/ C ₁₀₋₃₀ alkyl PEG-20 itaconate, sodium acrylate/ acryloyldimethyl taurate copolymer,	0.1-20
15	acrylates/C ₁₀₋₃₀ alkyl acrylate crosspolymer Film Formers (e.g. decene/butene copolymer, acrylates/octylacrylamide copolymer, adipic acid/diethylene glycol/ glycerin crosspolymer)	0.001-2
20	Emollients	0.1-20
	Mangostin	0.5-20
	Demineralized Water	Q.S.

Example 2

25	<u>Water/Silicone Emulsion</u>	<u>wt%</u>
	Sodium PCA 50%	0.1-4
	Sodium Lactate 60%	0.01-10
	Sodium Chloride	0.1-10
	Humectant(Glycerin, Glycols, Glycerols)	0.5-10
30	Ammonium Hydroxide	0.01-10
	Cyclomethicone	0.1-20
	Cyclomethicone/Dimethicone Copolyol	0.1-20
	Emollients(E.G. Cetyl Octanoate)	0.1-20
	Dimethicone Copolyol/Cyclopentasiloxane	0.1-10

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Alpha mangostin

0.01-50

Demineralized Water

Q.S.

5

Example 3

Gelwt%

Carbopol™

0.01-3

Glycerin

0.1-30

Butylene Glycol

0.1-30

10 Disodium EDTA

0.01-2

Methylparaben

0.01-2

Hydroxyethyl Cellulose

0.01-2

Corn (Zea Mays) Starch

0.01-10

C.S. D&C Yellow No.10

0.001-1

15 C.S. FD&C Blue No. 1

0.001-1

POE (20M) Methyl Glucose Ether

0.01-10

Dimethyl Polysiloxane

0.01-10

Peg 50 Shea Butter

0.01-10

Sodium Hydroxide Solution

0.01-5

20 Benzyl Alcohol

0.01-5

Mangostin triacetate

0.001-10

Demineralized Water

Q.S.

25

Example 4

Cleansing Foamwt%

Humectant (Glycerin, Butylene Glycol)

5-25

Polyethylene Glycol

0.1-20

30 Bentonite

0.1-20

Stearic Acid

0.1-30

Myristic Acid

0.1-20

Cetearyl Alcohol/Ceteareth-20

1

Potassium Hydroxide 45%

0.1-20

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Preservatives(E.G. Benzyl Alcohol, 2-Phenoxyethanol, Benzyl Alcohol)	0.1-10
Alpha mangostin	0.15-20
Demineralized Water	Q.S.

5

Example 5

	<u>wt%</u>
Mixed tocopherols	1
Vitamin E succinate 1000 PEG	0.5
10 Gamma Oryzanol	0.2
Lipoic Acid	0.1
Hesperetin	0.1
Naringenin	0.1
Silybin (Silymarin)	0.1
15 Chlorogenic Acid	0.01
Mangostin	0.001-20
Vehicle	Q.S.

20

Example 6

Moisturizing Cream

	<u>wt%</u>
Propyl gallate	1
Rosmantic acid	5
25 N-actyl-cysteine	3.5
Beta-carotene	0.001
Licorice root extract	0.01
Naringenin	2.7
PPG Myristyl Ether Propionate	6.5
30 Oleyl alcohol	3.5
Stearic acid	8.6
Lanolin	1
Pomegranate Extract	0.00-2
Neem Seed Cell Broth	0.01-10

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	Grape Seed Extract	0.01-2
	Salvia Miltiorrhiza Extract	0.00-10
	Iris Florentina Root Extract	0.00-20
	Carrot Extract	0.00-2
5	Cucumber Extract	0.00-2
	White Birch (Betula Alba) Bark Extract	0.00-2
	Rosemary Extract	0.00-2
	Algae Extract	0.00-2
	Glycerin	2.5
10	Triethanolamine	0.5
	Germal	0.1
	Methylparaben	0.01
	Mangostin	0.001-20
	Demineralized water	Q.S.
15		

Example 7

	<u>Moisturizing Cream</u>	<u>wt%</u>
	Tocopherol	2
20	Quercetin/Lycopene	2.5
	Carbopol™	0.3
	Triethanolamine	0.5
	Mineral Oil	1.5
	Safflower oil	0.3
25	Squalene	1.7
	Dimethicone	0.7
	Allantoin	1
	Oleyl alcohol	0.6
	Cholesterol	4.5
30	Lanolin oil	0.6
	Mangostin	0.001-20
	Vehicle	Q.S.

It should be understood that the foregoing description is only illustrative of the present invention. Various alternatives and modifications can be devised by those skilled in the art without departing from the invention. Accordingly, the present invention is intended to embrace all
5 such alternatives, modifications and variances which fall within the scope of the appended claims.

Claims

1. Use of a composition, comprising mangostin or analog thereof selected from the group consisting of alpha mangostin, beta mangostin, bicyclomangostin, gamma mangostin, 3-O-methylmangostin, mangostin triacetate and mangostin-3,6-di-O-glucoside; and

a cosmetically acceptable vehicle, in the preparation of a medicament for the treatment of telangiectasia or rosacea.

2. The use according to claim 1, wherein the composition is in a product form selected from the group consisting of aerosol spray, cream, dispersion, foam, gel, lotion, mask, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, tape, and towelette.

3. The use according to any one of claims 1 or 2, wherein mangostin or analog thereof is present in an amount ranging from 0.0001 wt% to less than 100 wt% based on the total weight of the composition.

4. The use according to any one of claims 1 or 2, wherein mangostin or analog thereof is present in an amount ranging from 0.0001 w% to 90 wt% based on the total weight of the composition.

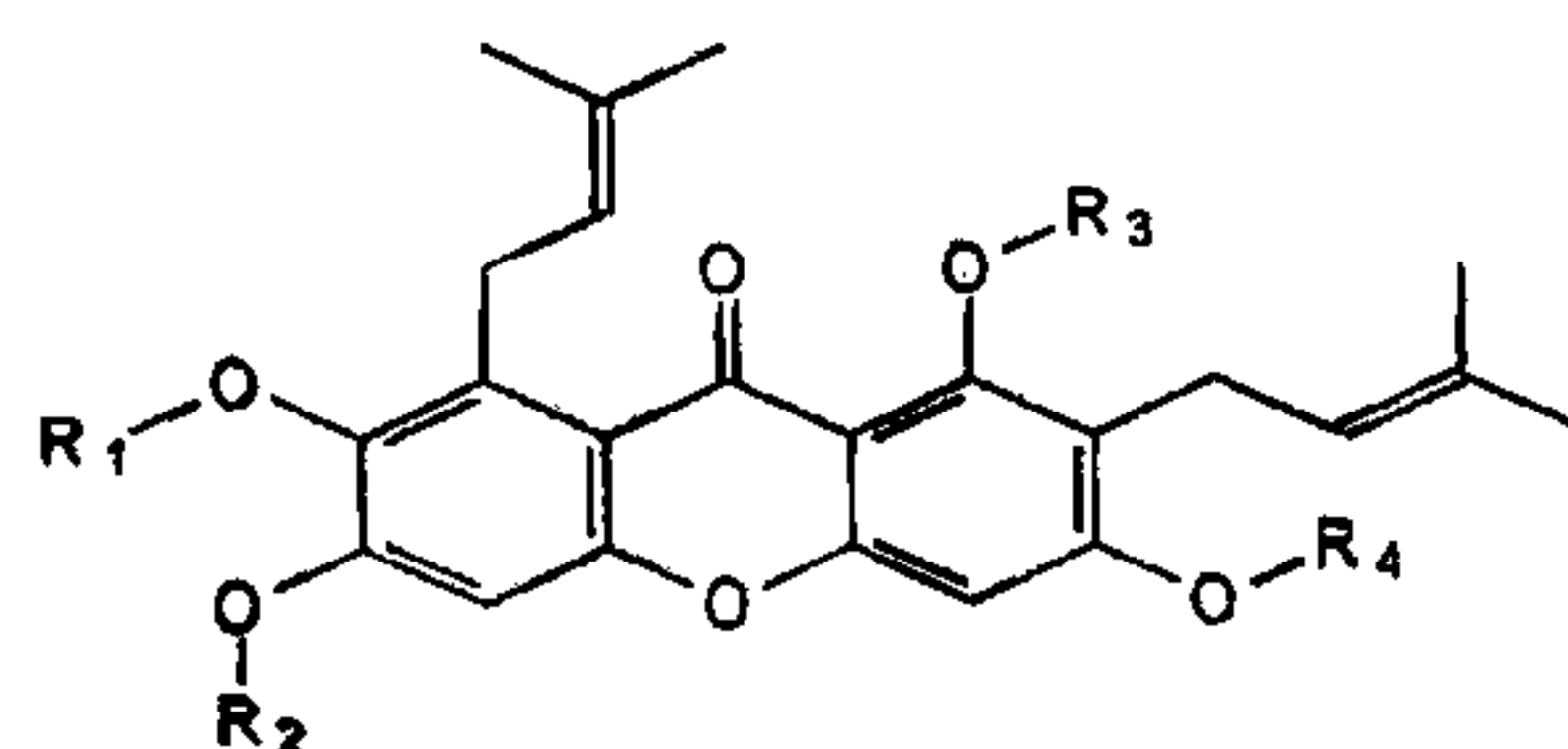
5. The use according to any one of claims 1 or 2, wherein mangostin or analog thereof is present in an amount ranging from 0.01 wt% to 50 wt% based on the total weight of the composition.

6. The use according to any one of claims 1 or 2, wherein mangostin or analog thereof is present in an amount ranging from 0.5 wt% to 20 wt% based on the total weight of the composition.

7. The use according to any one of claims 1 to 6, wherein the composition comprises 1,3,6-trihydroxy-7-methoxy-2,8-di (3-methyl-2-butenyl) xanthone.

8. The use according to any one of claims 1 to 6, wherein the composition comprises alpha-mangostin.

9. Use of a composition, comprising mangostin or analogs thereof, represented by the formula



wherein R_1 , R_2 , R_3 and R_4 may, independently, be a hydrogen atom; a carbohydrate selected from the group consisting of glucose, lactose, fructose, rhamnose, trehalose and fucose; an acyl or alkyl group, straight-chain or branched, having from 1 to 12 carbon atoms; a phenyl group; a benzyl group; or a cycloalkyl group having from 3 to 8 carbon atoms; and

a cosmetically acceptable vehicle, in the preparation of a medicament for the treatment of telangiectasia or rosacea.

10. The use according to claim 9, wherein at least two of R_1 , R_2 , R_3 and R_4 are hydrogen atoms.

11. The use according to claim 9, wherein R_1 is an alkyl group or an acyl group having from 1 to 12 carbon atoms, and wherein R_2 , R_3 and R_4 are each hydrogen atoms.

12. The use according to any one of claims 9 to 11, wherein the composition is in a product form selected from the group consisting of aerosol spray, cream, dispersion, foam, gel, lotion, mask, mousse, ointment, powder, patch, pomade, solution, pump spray, stick, tape, and towelette.

13. The use according to any one of claims 9 to 11, wherein mangostin or analog thereof is present in an amount ranging from 0.0001 wt% to less than 100 wt% based on the total weight of the composition.

14. The use according to any one of claims 9 to 11, wherein mangostin or analog thereof is present in an amount ranging from 0.0001 w% to 90 wt% based on the total weight of the composition.

15. The use according to any one of claims 9 to 11, wherein mangostin or analog thereof is present in an amount ranging from 0.01 wt% to 50 wt% based on the total weight of the composition.

16. The use according to any one of claims 9 to 11, wherein mangostin or analog thereof is present in an amount ranging from 0.5 wt% to 20 wt% based on the total weight of the composition.