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(54) Title: USE OF BIOTIN TO PREVENT PHOTOAGING

(57) Abstract: Use of biotin, preferably in a combination of biotin and (-)-epigallocatechin gallate (EGCG) in a specific ratio, to prevent sunlight-induced aging (photoaging) of the skin.

WO 2008/138524 A1

USE OF BIOTIN TO PREVENT PHOTOAGING

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The present invention relates to a novel use of biotin, preferably in a combination of biotin and (-)-epigallocatechin gallate (EGCG) in a specific ratio, to prevent sunlight-induced aging (photoaging) of the skin.

10

If the skin is chronically exposed to UV radiation this leads to epidermal and dermal damage, such as hyperkeratosis, keratinocyte dysplasia and dermal elastosis in the affected skin areas, clinically presenting as photoaged skin with actinic or solar keratosis. The molecular mechanisms of skin photodamage and photoaging have been subject of extensive research. UV radiation activates a whole range of cell surface growth factors and cytokine receptors (Rittie and Fisher 2002). This ligand-independent receptor activation induces multiple downstream signaling pathways that converge to stimulate the transcription factor AP-1. Among the genes that are up-regulated by AP-1 are several matrix metalloprotease (MMP) family members.

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MMPs are therefore amongst other things responsible for solar UV radiation-induced skin damage, affecting skin tone and resiliency leading to premature aging. MMPs degrade collagen and elastin in the extracellular matrix of skin. Increased MMP expression and activity causes enhanced collagen proteolysis, and together with reduced collagen expression results in skin elastosis and wrinkling (Berneburg 2003). The symptoms of that include leathery texture, wrinkles, mottled pigmentation, laxity and sallowness.

25

MMPs are among the most important and well established photoaging associated genes. To establish the protective abilities of substances with regard to photoaging the investigation of their effect on suppression of UVA-induced MMPs is therefore of major interest.

30

Biotin is a water soluble vitamin, which is important for the function of skin, hair and nails: Biotin deficiency leads to scaly and rough skin and brittle nails. Furthermore Biotin is a cofactor responsible for carbon dioxide transfer in several carboxylase enzymes, such as acetyl-CoA carboxylase, methylcrotonyl-CoA carboxylase, mitochondrial propionyl-CoA carboxylase and mitochondrial pyruvate carboxylase.

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- 2 -

5 (–)-Epigallocatechin gallate (EGCG) is among the dietary compounds which suppress various skin collagenases (Lee et al., 2005). The term "EGCG" as used herein denotes (–)-epigallocatechin gallate and/or one or more of its derivatives (e. g. esterified forms, glycosides, sulphates) thereof.

10 It was an object of the present invention to provide active ingredients that prevent sunlight-induced aging (photoaging) of the skin. The term "sunlight" as used herein refers to natural and/or artificial sunlight and encompasses in addition to UV radiation especially also IR radiation. Accordingly the active ingredients should prevent UV- radiation induced aging as well as IR induced aging of the skin.

15 It has now surprisingly been found, that the object of the present invention is achieved by the use of biotin for reduction of sun-light induced collagen and/or elastin degradation, wrinkles and fine lines and/or skin aging collagenases and/or for suppression of sun-light induced collagenases.

20 Even more surprisingly, it has been found that the object of the present invention is in an even more preferred way achieved by a synergistic combination of biotin with EGCG. It is therefore further preferred to use a synergistic combination of biotin with EGCG for reduction of sun-light induced collagen and/or elastin degradation, wrinkles and fine lines and/or skin aging collagenases and/or for suppression of sun-light induced collagenases.

25 The active ingredient(s) may be administered via oral or topical / cosmetic compositions, whereas oral applications are preferred.

30 The term "oral composition" as used herein denotes compositions that are administered orally. Thus, oral compositions according to the present invention can serve as supplements to food, feed and beverages, as dietary supplements or as pharmaceutical formulations which may be solid – such as capsules or tablets – or liquid – such as solutions or suspensions. Furthermore the term "oral composition" also comprises food, feed and beverages containing one or both
35 active ingredients according to the present invention.

5 The term "topical composition" as used herein refers to a cosmetic composition that can be topically applied to mammalian keratinous tissue. The term "cosmetic composition" as used in the present application refers to cosmetic compositions as e.g. defined under the heading "Kosmetika" in Römpp Lexikon Chemie, 10th edition 1997, Georg Thieme Verlag Stuttgart, New York.

10 In a preferred embodiment the invention also relates to an oral composition containing a synergistic combination of biotin and EGCG in a ratio in the range of 1 : 1 to 1 : 5000.

15 It was not to be foreseen by the person skilled in the art that the combination of biotin with EGCG would demonstrate superior synergistic activity in suppressing UVA-induced MMP1 and thus provide an antiaging/anti-wrinkling effect. The synergistic combination of biotin and EGCG also prevents photoaging when given days to weeks before actual sun-/UV-light exposure. It also protects when taken shortly before during and/or after intensive sun exposure, i.e. sun bathing.

20 If biotin is applied in combination with EGCG it is according to the present invention preferred to use (–)-epigallocatechin gallate itself. In further preferred embodiments of the present invention the used EGCG has a purity of at least 80 %, preferably of at least 85 %, more preferably of at least 90 %, even more preferably of at least 92 %, most preferably of at least 94 %.

25 Especially preferred is also an aqueous green tea extract containing EGCG in an amount of at least 80 % (preferred of at least 85 %, more preferred of at least 90 %, even more preferred of at least 92 %, most preferred of at least 94 %), based on the total amount of the extract, as e.g. and preferably obtained by any of the processes described in US 6,383,392, EP 1 103 550, US 10/246 112 and EP 1 077 211. Preferably the total amount of other polyphenols and catechins such as gallocatechin gallate, catechin gallate, epicatechin gallate, epigallocatechin, gallocatechin and epicatechin is less than or equal to 5 % by weight, based on the total weight of the green tea extract. More preferably the amount of gallocatechin gallate is less than or equal to 2.5 % by weight, and/or the amount of epicatechin gallate is less than or equal to 5 % by weight (preferably less than or equal to 3 % by weight).

35 According to the present invention it is advantageous if the amount of caffeine in the green tea extract is less than or equal to 2.5 % by weight, preferably less than or equal to 0.1 % by weight, and/or the amount of gallic acid is less than or equal to 0.1 % by weight, each based on the total weight of the green tea extract.

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If biotin is applied in combination with EGCG it is according to the present invention advantageous if the ratio of biotin to EGCG is in the range of 1 : 1 to 1 : 5000, preferred in the range of 1 : 3 to 1 : 3000, most preferred in the range of 1 : 5 to 1 : 1000.

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If the active ingredients are intended for oral application it is according to the present invention advantageous to administer the active ingredients in a way that their effective daily amounts ("daily dosages") are in the ranges given below. It is thereby irrelevant if the daily dosage is applied all at once (by a single dosage) or in multiple dosages.

15

Biotin: daily dosage for humans with a body weight of about 70 kg should not exceed 40 mg, preferably not exceed 25 mg; the daily dosage for humans with a body weight of about 70 kg is advantageously between 0.03 to 40 mg, more preferably between 0.06 to 25 mg.

20

EGCG: daily dosage for humans with a body weight of about 70 kg: 50 to 600 mg, preferred daily dosage for humans with a body weight of about 70 kg: 150 to 300 mg.

25

If the composition is prepared in form of tablets, capsules, granules or powder for oral administration, there may be used excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, dextrans and/or maltodextrins, calcium carbonate, calcium phosphate and/or calcium hydrogen phosphate, kaolin, crystalline and/or microcrystalline cellulose and/or silicic acid as carriers; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch and/or hydrolyzed starch solution, gelatin solution, carboxymethylcellulose, hydroxypropylcellulose, hydroxypropylstarch, shellac, methylcellulose, ethylcellulose, calcium phosphate and/or polyvinyl pyrrolidone; disintegrators such as dry starch, croscarmellose, crospovidone, sodium alginate, agar powder, laminaran powder, sodium hydrogencarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch and/or lactose; disintegration-preventing agents such as stearic acid, cacao butter and/or hydrogenated oils; absorbefacients such as quaternary ammonium bases and/or sodium lauryl sulfate; humectants such as glycerol and/or starch; adsorbents such as starch, lactose, kaolin, bentonite and/or colloidal silica; lubricants such as purified talc, stearic acid salts, boric acid powder and/or polyethylene glycol; taste corrigents such as sucrose, orange peel, citric acid and/or succinic acid; and the like.

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- 5 -

5 If the composition is prepared in the form of tablets, these may be provided as tablets coated with usual coatings, for example, sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film-coated tablets, double coated tablets, multilayer-coated tablets and the like. The capsules are prepared by mixing the compounds according to the present invention with the various carriers exemplified above or according to the current state of the art and charging the
10 mixture into hard gelatin capsules, soft capsules and the like.

A multi-vitamin and mineral supplement may be added to the compositions according to the present invention, e.g. to maintain a good balanced nutrition or to obtain an adequate amount of an essential nutrient missing in some diets. The multi-vitamin and mineral supplement may also
15 be useful for disease prevention and protection against nutritional losses and deficiencies due to lifestyle patterns and common inadequate dietary patterns sometimes observed in diabetes.

The composition according to the present invention can be a food or beverage composition. Beverages can be e.g. sports drinks, energy drinks or other soft drinks, or any other suitable
20 beverage preparation.

A sports drink is a beverage which is supposed to rehydrate athletes, as well as restoring electrolytes, sugar and other nutrients. Sports drinks are usually isotonic, meaning they contain the same proportions of nutrients as found in the human body.

25 Energy drinks are beverages which contain (legal) stimulants, vitamins (especially B vitamins) and/or minerals with the intent to give the user a burst of energy. Common ingredients include caffeine, guarana (caffeine from the Guarana plant) and/or taurine, various forms of ginseng, maltodextrin, inositol, carnitine, creatine, glucuronolactone, coenzyme Q10 and/or ginkgo
30 biloba. Some may contain high levels of sugar, or glucose, whereas others are sweetened completely or partially with a sugar alcohol and/or an artificial sweetener like Ca-cyclamate or Aspartame. Many such beverages are flavored and/or colored.

A soft drink is a drink that does not contain alcohol. In general, the term is used only for cold
35 beverages. Hot chocolate, tea, and coffee are not considered soft drinks. The term originally referred exclusively to carbonated drinks, and is still commonly used in this manner.

- 6 -

- 5 If the composition is prepared in form of one of the following food articles it is according to the present invention advantageous if the amount of biotin and – if desired – the amount of EGCG in the composition are selected from the ranges given in the following table:

Food Category	typical serving size	mg biotin per kg food	mg EGCG per kg food (if applicable)	Ratio (biotin : EGCG) (if applicable)
Beverages (final product) (e.g. soft drinks, juices, teas, soups)	250 g	0.1 to 20	100 to 1000	1 : 5 to 1 : 2000
Dairy Products (e.g. milk shakes, yoghurts, ice creams)	150 g	0.5 to 20	100 to 1000	1 : 5 to 1 : 2000
Sweets (e.g. chocolates, candies, mints, jellyies)	1 to 5 pieces of 5 g each per day = 5 to 25 g	5 to 200	2'000 to 10'000	1 : 10 to 1 : 2000
other food items (e.g. cookies, muesli bars)	25 g	1.0 to 200	400 to 2'000	1 : 10 to 1 : 2000

- 10 If the composition is prepared in form of a tablet or a capsule it is according to the present invention advantageous if the amount of biotin and – if desired – the amount of EGCG in the composition are selected from the ranges given in the following table:

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- 7 -

Category	typical size	mg biotin per dose unit	mg EGCG per dose unit (if applicable)	Ratio (biotin : EGCG) (if applicable)
Tablets	1 g 1-2 x per day	0.5 to 10	25 to 600	1 : 50 to 1 : 1200
Capsules	1 g 1-2x per day	0.5 to 10	25 to 600	1 : 50 to 1 : 1200

5 Example 1

Synergistic effects of EGCG and biotin on inhibition of UV-A induced expression of matrix metalloproteinase-1

10 Primary human dermal fibroblasts were cultured in EMEM without glutamine (Earle's Minimum Essential Medium), supplemented with antibiotics / antimycotics, 2 mM L-glutamine and 7.5 % fetal calf serum at 37°C/5% CO₂ and grown to 100 % confluency. Forty-eight hours prior to irradiation the cells were preincubated with the desired substances in EMEM (with AB/AM, L-Glutamine and 2% FCS. After 24 hours the medium was replaced by fresh medium with
15 substances (freshly prepared). For irradiation, the medium was removed and after 6 wash steps with phosphate-buffered saline (PBS) replaced by phosphate-buffered saline (PBS). The plate was then exposed to 30 J/cm² UVA1. The UVA1 output was approximately 150 mW/cm². After irradiation the phosphate-buffered saline in the cell microplate was exchanged against culture medium (+ 7.5% FCS) with the substances (fresh prepared) and the cells were incubated in a
20 CO₂-incubator for further 24 hrs (MMP-1 determination). The culture medium was removed, the cells were rinsed with phosphate-buffered saline and the whole plate was frozen in liquid nitrogen. Total RNA was isolated using RNeasy Total RNA Kits (Qiagen, Hilden; Germany). The RNA concentration was determined via photometric measurement at 260/280. Aliquots of total RNA (75 ng) were applied for cDNA-Synthesis using Superscript™III First-Strand synthesis
25 system for RT-PCR. Two samples for each compound were analyzed. The PCR reactions were carried out on an Opticon 1 (MJ Research, Waltham, MA, USA) using SYBR Green® PCR Master Mix (Applied Biosystems, Darmstadt, Germany). For comparison of relative expression in real time PCR control cells and treated cells the $2^{(-\Delta\Delta C(T))}$ method was used. Results are summarized in Table 1. UV-A treatment induced a ~10-fold increase of MMP-1 RNA
30 compared to the levels detected in non-irradiated cells (not shown). EGCG and biotin reduced this expression by 13 % and 66%, respectively. In contrast, when the substances were combined, UV-A induced MMP-1 expression was completely abolished. This means that EGCG and biotin exert a synergistic effect on the modulation of MMP-1, since a positive value (*i.e.* 21%) was obtained between the observed and expected inhibition (sum of the values of each
35 single compound).

- 9 -

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Table 1: Expression of MMP-1 in skin fibroblasts

<i>treatment</i>	<i>compound</i>	<i>MMP-1 expression relative to UV-A only treated cells</i>	<i>% inhibition</i>	<i>Δ (observed- expected inhibition)</i>
UV-A	-	(100 %)	-	-
UV-A	EGCG 9 μmol/L	87	13	-
UV-A	Biotin 0.03 μmol/L	35	66	-
UV-A	EGCG 9 μmol/L + Biotin 0.03 μmol/L	0	100	21

10 **Example 2:**

Tablet for long-term anti-aging prevention

Composition:

	Potency/tabl.	Amount/tabl.
EGCG (as TEAVIGO™ TG)	300 mg	333 mg
Biotin	5 mg	5 mg
Agglomerated lactose (Tablettose™ 80)		125 mg
Microcrystalline cellulose (Tablettose™ 80)		312 mg
Silicon dioxide (Aerosil™ 200)		5 mg
Crospovidone NF (as Polyplasdone™ XL 10)		20 mg
Magnesium stearate		5 mg
Tablet weight		1000 mg

15

Preparation:

Biotin, Teavigo™ TG, agglomerated lactose, microcrystalline cellulose, silicon dioxide and Crospovidone are added to an appropriate vessel and mixed for 20 minutes by a tumbler mixer.

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5 Magnesium stearate is sieved through a 1 mm sieve, added and the composition again mixed for 2 min.

The powder is compressed to tablets with a Korsch XP1 tablet press, punch size 17x7.87 mm oblong.

10 One tablet per day should be taken starting in spring, i.e. at least two months before increased sun exposure, and maintained throughout season.

Example 3:

Instant drink for boosting anti-aging protection

15

Composition:

	Parts
Xylitol	668.7
Citric acid, anhydrous	220.0
Carboxymethyl cellulose	30.0
Tri-sodium-citrate	22.0
Tri-calcium-phosphate	20.0
Orange flavour	20.0
Biotin	0.7
Ascorbic acid	8.0
Sweetener Twinsweet	4.0
EGCG as Teavigo™	6.6
Powder mix total	1000.0

Preparation:

Sieve all ingredients through a 500 µm sieve.

Give the powder in an appropriate container and mix on a tumbler blender for at least 20 min.

20 Use 35 g powder for one litre of beverage by adding water.

The instant drink contains 50 mg EGCG and 0.5 mg biotin per serving of 240 ml ready drink.

Up to 3 servings per day during and after extensive or sun bathing is recommended.

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- 11 -

5 Example 4

Mints for continuous basic anti-aging protection:

Composition:

	Potency/mint	Amount/mint
EGCG (as TEAVIGO™ TG)	10 mg	11.1 mg
Biotin	0.075 mg	0.075 mg
Vitamin C as Ascorbic Acid fine granular		10.5 mg
Sorbitol as Neosorb 60 W		163.6 mg
Silicon dioxide (Aerosil™ 200)		1 mg
Aroma Frescoforte Permaseal 60470-31 (Givaudan)		10 mg
Aroma Eiszucker Permaseal 60153-73 (Givaudan)		6.0 mg
Sweetener as Twinsweet		1.6 mg
PEG 6000		20.0 mg
Magnesium stearate		1.2 mg
Total Weight		225.0mg

Preparation:

10 Mix Teavigo™ TG, biotin, Ascorbic Acid fine granular, Sorbitol, the aromas, sweetener and PEG 6000 into a drum and mix for 10 minutes with a tumbler mixer. Sieve Sorbitol and silicon dioxide through a 1 mm sieve and mix it in a separate drum for 10 minutes. Combine the two powder mixtures and mix again for 10 minutes. Add Magnesium stearate after sieving through a 1 mm sieve and mix for 2 minutes.

15

The powder is compressed to tablets with a Korsch XP1 tablet press, punch size 8mm round.

Up to 5 mints per day are recommended.

20 TEAVIGO™ TG: Tradeproduct of DSM Nutritional Products;
 Tablettose™ 80: Tradeproduct of Brenntag N.V.;
 Aerosil™ 200: Tradeproduct of Degussa;
 Polyplasdone™ XL 10: Tradeproduct of ISP.

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Claims:

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1. Use of biotin for suppression of sun-light induced collagenases.

2. Use of biotin for reduction of sun-light induced collagen and/or elastin degradation.

3. Use of biotin for prevention and/or reduction of sun-light induced wrinkles and fine lines and/or skin aging.

15

4. Use of biotin according to any of claims 1 to 3 in a synergistic combination with (-)-epigallocatechin gallate (EGCG).

20

5. Use according to claim 4 characterized in that the ratio of biotin to EGCG in the combination is in the range of 1 : 1 to 1 : 5000.

6. Use according to claim 4 characterized in that the ratio of biotin to EGCG in the combination is in the range of 1 : 3 to 1 : 3000.

25

7. Use according to claim 4 characterized in that the ratio of biotin to EGCG in the combination is in the range of 1 : 5 to 1 : 1000.

8. Use of biotin and – if applicable – EGCG according to any of claims 1 to 7 as active principle in a composition that is suitable for oral consumption.

30

9. Oral composition containing the combination of biotin and (-)-epigallocatechin gallate (EGCG) characterized in that the ratio of biotin to EGCG is in the range of 1 : 1 to 1 : 5000.

35

10. Composition according to claim 1 characterized in that the ratio of biotin to EGCG is in the range of 1 : 3 to 1 : 3000.

11. Composition according to claim 1 characterized in that the ratio of biotin to EGCG is in the range of 1 : 5 to 1 : 1000.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/4188 A61K31/353 A61K8/49 A61K8/67 A61K8/97
 A61Q17/00 A61Q17/04 A61Q19/08 A61P17/18

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 A61P A61Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, FSTA, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 2005/048012 A1 (JERMANN ROLAND [CH] ET AL) 3 March 2005 (2005-03-03) page 1, paragraphs 1,2,6,12	1-3,8
Y	page 3, paragraphs 34,39,41,47 ----- -/--	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

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