

FORMULATIONS CONTAINING COUMARINS AND THE USE THEREOF
IN THE PHARMACEUTICAL AND COSMETIC FIELDS

5 The present invention relates to the use of novel
formulations for the topical use containing
combinations of coumarins, such as esculoside,
esculetin, extracts containing them or mixtures
thereof, with dimeric and oligomeric proanthocyanidins
for the treatment of peripheral vasculopathies related
to an impaired peripheral microcirculation; moreover,
the invention relates to the use of said coumarin
derivatives in combination with proanthocyanidins in
10 the cicatrization processes and in the complications of
chronic venous stasis (leg heaviness, ulcus cruris) and
in the treatment of internal and external hemorrhoids.
In a strictly cosmetic field, the combinations are used
in the treatment of unestetisms related to superficial
15 capillaries (couperose), rosacea, telangiectasias and
the like. It has surprisingly been found that a strong
synergism exists between these coumarin derivatives and
proanthocyanidins.

20 The microvasculokinetic activity of esculoside,
responsible for many of the properties of the
combinations (cicatrizing and antihemorrhoid) was
evaluated by non-invasive techniques such as infrared
photopulsoplethysmography, Laser-Doppler and video-
capillaroscopy which allows to check the districtual
25 microangiotectionic and the capillary morphological
changes before and after the treatment with the tested
substances. Esculoside induces favourable changes in

the capillary density, up to 300% higher than the basal values.

5 In the combinations according to the invention, the weight ratio of coumarin derivatives to proanthocyanidins preferably ranges from 4:1 to 1:4. For example, combinations of three parts of esculoside and one part of proanthocyanidins (selected from proanthocyanidin A2 and the procyanidole oligomers of a different origin, preferably those extracted from Vitis
10 vinifera or Camellia sinensis) exert synergistic activities which are qualitatively different from those of the single components; a non-limiting interpretation of this fact is that esculoside increases the proanthocyanidin absorption at the topical level as a
15 consequence of the increase in districtual blood flow, and therefore of water. Particularly synergistic is the modulating activity on the cicatrization process, wherein a stimulation of the tissue restoration and a regular orientation alongside the cicatricial axis are
20 observed, thus preventing the formation of keloids.

Analogously, these combinations are favourably used in the unestetisms and on the reduction of the couperose. In the latter case, 20 individuals of both sexes were treated on one side of the face in the
25 temporal-zygomatic area with a 1.5% esculoside and 0.5% of proanthocyanidin A2 formulation and on the other side with placebo. The treatment continued for 60 days twice a day; the evaluation of the intensity of the unestetism was performed by means of scores and with
30 objective evaluations measuring the colour intensity of the area treated with the combination of the invention



compared with that treated with placebo. After the treatment, a 41% reduction in the unesthetism was observed, using the patient himself as control.

5 Particularly important is the healing effect of the combinations according to the invention, which effect can be used in plastic surgery as well as in decubitus and venous stasis ulcers. To evaluate the cicatrization effect, patients were selected which had undergone superficial surgery, having wounds of a size
10 suitable to the simultaneous treatment with the combination of the invention and with placebo. For example: cauterized wounds larger than 2 cm, so as to allow, after suturation, the treatment of 1 cm with a placebo formulation and of 1 cm with a formulation
15 containing 1.5% esculoside and 1.5% procyanidole oligomers from Vitis vinifera. Immediately after the treatment, the adhesion edges and nearby areas of the wound were checked with a videocapillaroscope
20 (Scopeman-Moritex Video Imaging System, Alpha Strumenti, Milan), fitted with a halogen-light optical probe with 50 to 400 x magnifications, measuring the capillary density (number of blood-perfused capillaries per area unit) and evaluating the space orientation of the capillaries and their morphology. 15 Minutes after
25 the treatment, the capillary density increased by 100% compared with the basal one and with the placebo-treated control. Surprisingly it has been found, and it is a part of the present invention, that following the improved districtual circulation (the cicatricial area
30 is usually poorly vascularized, contrary to what was believed up to now) and the fibroblast proliferation

stimulation, a remarkable induction of a regular capillarogenesis takes place. The wound healing with the products of the present invention turned out to be accelerated and at the same time modulated. In bedsores and torpid ulcers, the larger blood flow to the necrotic area leads to a restoration of the tissue healing properties and a reduction and disappearance of the ulcer. Analogous results are obtained in the hemorrhoidal pathology, in which the simultaneous effect on arteries and veins allows a fast regression of venous stasis.

The treatment above described relates to the treatment of cauterized wounds and or healing wounds, or of cutaneous ulcers, or of venous stasis conditions. Further, it has surprisingly been found that the administration of a formulation containing 1% esculetin and 0.3% procyanidanole oligomers from Camellia sinensis on newly formed scars leads to a faster disappearance of the cicatritial outcome, with a remarkable reduction in the hyperhaemic area compared with the controls. The result of such a treatment is particularly important in the exposed body areas, where facial esthetic surgery, removal of naevi and the like are performed.

Moreover, it has been found that the above cited coumarins, alone or in combination with proanthocyanidins, are markedly effective in the treatment of atopic dermatitis and haematomas of any origin. Therefore, topical administrations of a formulation containing 2% esculetin on atopic dermatitis induce a reduction of the dermatitis within one week or in even shorter times, depending on the severity and degree of

the pathology. The same formulation, applied on haematomas, made them to disappear within a few days, probably thanks to the microvasculokinetic activity of the product.

5 Particularly useful as excipients for the formulations of the invention proved to be phospholipids, pure or in form of the natural mixtures thereof, which allow a quick absorption of the substances themselves, even though other excipients can advantageously carry the products of the invention, enhancing
10 their therapeutical or dermocosmetic functionalities.

The formulations according to the invention contain, besides the above defined active principles, carriers, additives, preservatives and the like known
15 in pharmaceutical technique, such as those listed in the examples reported hereinbelow, which illustrate the invention without limiting its scope.

Example I - Gel containing esculoside and procyanidole oligomers from Vitis vinifera. 100 g of gel contain:

20	Esculoside	1.50 g
	96% Procyanidole oligomers	1.50 g
	Hydrogenated castor oil 40(OE)	
	(Cremophor RH40 - BASF)	1.00 g
	Propylene glycol	1.50 g
25	Preservatives	0.10 g
	Hydroxyethyl cellulose	
	(Natrosol 250 HHX - Aqualon)	3.00 g
	Purified water	q.b. a 100 g

Example II - Alcoholic fluid gel containing esculoside and proanthocyanidin A2. 100 g of gel contain:

30	Esculoside	1.50 g
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	Proanthocyanidin A2	0.50 g
	Hydrogenated castor oil 40(OE)	
	(Cremophor RH40 - BASF)	5.00 g
	Propylene glycol	3.00 g
5	Carbomer 940 (Carbopol 980 - Goodrich)	1.00 g
	Ethanol 95°	45.00 g
	Phosphatidylcholine	
	(Phospholipon 90- Natterman)	1.60 g
	Glyceryl 6(OE) Caprilate/Caprylate	
10	(Softigen 767)	15.00 g
	Preservatives	0.40 g
	Butylhydroxytoluene	0.05 g
	α -Tocopherol	0.20 g
	Ascorbic acid	0.30 g
15	Dimethicone copolyol	
	(SF 1188 - General Electric)	2.00 g
	10% Triethanolamine	5.00 g
	Purified water	q.s. to 100 g
	Example III - Cream containing esculoside and	
20	proanthocyanidin A2.	
	100 g of cream contain:	
	Esculoside	2.50 g
	Proanthocyanidin A2	
	Hydrogenated castor oil 40(OE)	1.00 g
25	(Cremophor RH40 - BASF)	2.00 g
	Propylene glycol	2.00 g
	Carbomer 934 (Carbopol 934 P - Goodrich)	0.50 g
	Alkyl C ₁₀₋₃₀ -Acrylate (Carbopol 1382 - Goodrich)	0.50 g
	Ethanol 95°	15.00 g
30	Preservatives	0.40 g
	Cetyl Palmitate	

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	(Cutina CP - Henkel)	8.00 g
	Polyisoprene (Syntesqual - Vevy)	5.00 g
	Polysorbate 80 (Tween 80 - ICI Americans)	2.00 g
	α -Tocopherol	0.20 g
5	Ascorbyl palmitate	0.10 g
	Hydrogenated lanolin (Lanocerina - Esperis)	5.00 g
	Dimethicone 350 cps (Tegiloxan 350 - Tego)	0.50 g
	Phosphatidylcholine (Phospholipon 90- Natterman)	2.50 g
	10% NaOH sol.	2.40 g
10	Purified water	q.s. to 100 g
Example IV - Gelified emulsion containing esculetin and procyanidanol oligomers from <u>Camellia sinensis</u>. 100 g of emulsion contain:		
	Esculetin	1.00 g
15	96% Procyanidole oligomers	0.30 g
	Isopropyl myristate	5.00 g
	Preservatives	0.40 g
	Perfume	0.10 g
	Polyacrylamide, C ₁₃ -14-isoparaffin and lauric	
20	alcohol 7(OE) (Sepigel 305 - Seppic)	3.00 g
	Purified water	q.s. to 100 g
Example V - Gelified emulsion containing esculetin. 100 g of gelified emulsion contain:		
	Esculetin	2.00 g
25	Isopropyl myristate	5.00 g
	Preservatives	0.40 g
	Perfume	0.10 g
	Polyacrylamide, C ₁₃ -14-isoparaffin and lauric	
	alcohol 7(OE) (Sepigel 305 - Seppic)	3.00 g
30	Purified water	q.s. to 100 g



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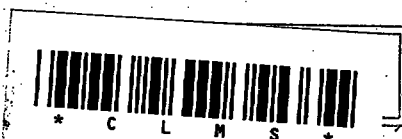
CLAIMS



1. Pharmaceutical and/or cosmetic formulations for
5 the topical use, containing as active principles:
 - a) coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, combined with
 - b) dimeric and oligomeric proanthocyanidins.
- 10 2. Pharmaceutical and/or cosmetic formulations according to claim 1, characterized in that the contained proanthocyanidins are selected from the group consisting of proanthocyanidin A2, procyanidole
15 oligomers extracted from Vitis vinifera and Camellia sinensis, and mixtures thereof.
3. Pharmaceutical and/or cosmetic formulations according to claim 2, characterized in that the contained proanthocyanidin is proanthocyanidin A2.
4. Pharmaceutical and/or cosmetic formulations
20 according to claims 1-3, for the treatment of peripheral vasculopathies connected with impairments of the arterial or venous circles and of unesthetisms related to impaired capillary permeability and fragility, particularly for the treatment of
25 superficial or deep scars; internal and external hemorrhoids; conditions related to chronic venous stasis, such as stasis ulcers and telangiectasias; couperose and peripheral capillaropathies.
5. Pharmaceutical and/or cosmetic formulations for
30 the topical use, containing as active principles coumarins selected from esculoside, esculetin, extracts

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containing them and mixtures thereof, optionally combined with proanthocyanidins, for the treatment of atopic dermatitis and haematomas of any origin.

5 6. Pharmaceutical and/or cosmetic formulations according to any one of the above claims, characterized in that they contain pure phospholipids or mixtures thereof as excipients.

7. The use of coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, combined with dimeric and oligomeric proanthocyanidins, for the manufacturing of a medicament for the topical use, intended for the treatment of peripheral vasculopathies connected with impairments of the arterial or venous circles and of unesthetisms related to impaired capillary permeability and fragility; superficial or deep scars; internal and external hemorrhoids; conditions related to chronic venous stasis, stasis ulcers and telangiectasias; couperose and peripheral capillaropathies.

15 8. The use of coumarins selected from esculoside, esculetin, extracts containing them and mixtures thereof, optionally combined with dimeric and oligomeric proanthocyanidins, for the manufacturing of a medicament for the topical use intended for the treatment of atopic dermatitis and haematomas of any origin.

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