Description

The present invention concerns pharmaceutical and cosmetic compositions comprising extracts of Ammi visnaga and Ammi majus or the vasoactive agents contained therein, particularly visnadine, kelline and other coumarins and flavoncoumarols. The compositions of the invention are useful for the topical, epicutaneous treatment of pathological or paraphysiological conditions of the skin and of the adnexes thereof, characterized by functional or organic deficiencies of the local microcirculation associated with ischemia, stasis and trophic disturbances secondary to impaired microvascular-tissue relationships.

The therapeutic use of extracts of Ammi visnaga and Ammi majus or of active constituents thereof is already known, particularly in the cardiological field for the treatment of ischemic coronaropathies, namely of anginous attacks and of chronic-degenerative myocardial diseases. More recently, it has been reported that some dihydropyranocoumarins and dihydrofuranocoumarins are endowed with platelet anti-aggregant activity similar to that of dipyridamol; this could lead to their therapeutic uses as anti-thrombotic agents and cyclic AMP-phosphodiesterase inhibitors. Some derivatives of visnaginone and of kellinone were reported to be endowed with antibacterial and anti-helmintic activity. High oral doses of visnadine have been used by BENSIMON (G.M. de France, Tome 77, No. 29, 1970, 6269-6275) and by GOURNAY (G.M. de France, Tome 78, No. 3, 1971, 390-391) in the treatment of peripheral arteriopathies affecting large arterial vessels.

The results of said studies show that: the compound is not convenient to use, it asks for high daily doses, it must be administered for prolonged periods and produces favourable responses in an unsatisfactorily low proportion of patients. Moreover, the administration of these high dosages for long period is associated with remarkable side-effects, especially gastric disturbances, insomnia and paresthesiae which may even require discontinuation of the therapy.

The available knowledges refer only to the treatment of disorders affecting large arteries and of pathological conditions of peripheral vascular diseases secondary to occlusion of large arterial vessels, without any mention of a possible effect of the compound on the microcirculation and on the smallest arterio-arteriolar vessels at precapillary level, with particular reference to the cutaneous circulation.

It has now been found according to the present invention that the extracts of Ammi visnaga and Ammi majus containing visnadine and/or coumarins as well as visnadine-like flavoncoumarols and visnadine itself in purified form, have the following properties:

a) they are not "vasodilators" and therefore they do not inhibit the tonus and the sphygmic activity of the muscular media in medium-sized or large arteries. By contrast, they exert a marked stimulatory effect on microvascular motility and on the sphygmic activity of the smooth muscle constituents of the media of small arteries and precapillary arterioles. The supposed "vasodilator effect" is only a consequence of substantial modifications in the microcirculatory haemodynamics;

b) their biological effect is therefore mainly at microcirculatory level. These agents act infact on small arteries and precapillary arterioles and determine as an immediate haemodynamic consequence increase of the volume and of the blood flow-rate in capillary network: the tissue oxygenation increases and the trophic exchanges are enhanced;

c) they are highly effective in antagonizing the vasal spasm induced by cold, particularly in the circulation of the fingertip.

The invention refers therefore to pharmaceutical and cosmetic compositions comprising extracts of Ammi visnaga and Ammi majus containing visnadine and/or visnadine-like coumarins and flavoncoumarols, or visnadine itself in purified form incorporated in a liposomal vehicle for the therapeutic treatment by the topical epicutaneous route of peripheral vascular acrosyndromes, particularly of Raynaud disease and of local perfusion deficiencies of the upper and lower limbs, and for the cosmetic treatment of defects due to insufficient blood perfusion of the skin and of the subcutaneous adipous tissue, particularly for the treatment of precocious senile involution of the face and neck skin, cellulitis, cutaneous stretch marks, alopecias and similar conditions.

The percutaneous administration is not only surprisingly more active and effective but it is also practically devoid of side-effects such as those described for the oral administration of high doses.

The active and effective doses by topical epicutaneous route are by far lower, up to 50 times, than that used for the oral route and the time necessary for the onset of the biological effect, which may be measured by means of instrumental methods, is of some hours whereas the oral route asks for days or months.

The pharmaceutical or cosmetic compositions of the invention may be prepared using known methods and excipients, such as those disclosed in "Remington's Pharmaceutical Sciences Handbook" Mack Pub. Co., NY, USA.

Examples of suitable formulations include creams, ointments, gel, lotions containing from 1 to 5% of visnadine or the equivalent of extracts or of visnadine-like compounds (visnaginone, kelline, kellinone, coumarins, dihydropyranocoumarins or dihydrofuranocoumarins derived from plants of the Ammi genus).

These formulations may be applied on the skin so as to cover the area to be treated once or more times a day.

Liposomial carriers obtainable from lecithins, unsaturated or saturated phosphatidylcholine or other conventional phospholipids are particularly preferred.

The Ammi extracts may be obtained according to known methods, such as those disclosed in the following Examples wherein specific reference is made to visnadine. It is however apparent that all the above cited extracts containing visnadine or the above cited visnadine-like compounds contained in plants of the Ammi genus may be used in substitution of or in combination with visnadine, in any quantitative ratio.

EXAMPLE 1

Extemporaneous preparation of an aqueous microdispersion of visnadine with pure soy-bean phosphatidylcholine

100 g of visnadine are dissolved together with 400 g of pure soy-bean phosphatidylcholine in 1 l of methylene chloride; the solvent is evaporated under vacuum and the syrupy residue is dispersed in 5 l of water in an high speed turboemulsifier under strong stirring for 5 h; 200 g of mannitol are then added and the mixture is distributed in 10 ml vials and lyophilized. This lyophilized material, suspended in 5 ml of water, is directly applied on the cutis to be treated.

EXAMPLE 2

Preparation of an Ammi visnaga extract with high visnadine titer.

100 Kg of finely ground blossoming tops of the plant are placed in a 400 l extractor suited for the use of gases in hypercritic conditions; the plant material is extracted with carbon dioxide for 1 h at 35°C and under a pressure of 100 bar to remove the undesired fatty substances; after elimination of the extract from the condenser, the extraction with carbon dioxide is continued at 45°C and 180 bar for 3 h or until complete extraction of visnadine from the plant material. The obtained extract (3.4 kg) may be directly used or it may be subjected to purification by partition between immiscible solvents according to the methods of Example 3.

EXAMPLE 3

Preparation of visnadine from lipophilic extracts containing it obtained according to Example 2

2.5 Kg of lipophilic extract prepared according to Example 2 are dissolved in 25 l of 95% aqueous methanol and thoroughly extracted with 20 l of n-hexane until complete extraction of the extractable undesired material; the pooled hexane extracts are counter-washed with 5 l of 95% methanol which are added to the previous methanol phase. The methanol solution is concentrated under vacuum up 10 l and the concentrate is diluted with an equal volume of water; the obtained suspension is counter-extracted with n-hexane until complete extraction of visnadine. After addition of a 3% proportion of ethanol, the hexane solution is concentrated resulting in crystallization of the desired product which exhibits spectroscopic and physico-chemical characteristics equivalent to those described in literature.

EXAMPLE 4

Lotion for the treatment of hair scalp.
100 g of composition contain:

Visnadine	2	g
Soy-bean phosphatidylcholine(96%)	4	g
Softigen^{R} 727	25	g
Volpo^{R} 20	7	g
Octylinone	0,1	g
Imidazolidinylurea	0,3	g

Purified water q.s. to 100 g

EXAMPLE 5

Gel containing as active principle a mixture of visnadine and kelline

100 g of gel contain:

Visnadine	1 g
Kelline	0,5 g
Softigen^{R} 727	25 g
Volpo^{R} 20	7 g
Carbopol^{R} 934	1,5 g
Triethanolamine	1 g
Imidazolidinylurea	0,3 g
Purified water	q.s. to 100 g

CLINICAL PHARMACOLOGY INVESTIGATIONS

Investigation A

The sphygmic activity of small arteries and arterioles of the subpapillary plexus and the cutaneous temperature of the fingertip were determined quantitatively in 30 healthy subjects (divided in two groups A and B) by using computerized infra-red photo-pulse plethysmography (I.r.Ph.P.P.) and direct cutaneous thermometry respectively. The same measurements were repeated at 15, 30 , 45 and 60 minutes after the percutaneous application of a visnadine formulation (prepared according to Example I) in group A and placebo in group B. The application was always followed by a light massage until complete penetration of the product had been achieved.

As indicated by the data shown in Table 1, the preparation described in Example I induces a statistically significant increase in the arterio- arteriolar sphygmic activity as compared to baseline conditions. This, in turn, determines an increase in volume and velocity of the microcirculatory flow directed to the capillary networks located downstream, with consequent elevation of the cutaneous temperature without reddening and without active hyperemia. The placebo was found to be totally inactive.

TABLE 1

Arterio-arterial sphygmic activity						
Case n°	Baseline			After treatment		
	Second finger	Third finger	Fourth finger	Second finger	Third finger	Fourth finger
1	56.81	112.33	88.12	218.25	111.25	135.50
2	152.00	77.68	34.40	269.33	182.00	138.80
3	178.50	146.20	114.50	54.33	141.75	116.00
4	23.40	16.75	32.00	31.16	46.75	110.00
5	59.90	31.20	40.00	105.10	120.00	100.60
6	50.80	34.30	17.25	76.50	164.50	133.60
mean	86.902	69.743	54.378	125.778	127.708*	122.417*
+/- SD	50.458	40.815	31.297	74.392	65.275	59.549

Significance level (Baseline vs Q36)	
2°finger	t-Student = -0.963 N.S. p < 0.618
3°finger	t-Student = -2.473 p < 0.056*
4°finger	t-Student = -4.003 p < 0.011*

continued

TABLE 1 (continued)

Cutaneous temperature						
Case n°	Baseline			After treatment		
	Second finger	Third finger	Fourth finger	Second finger	Third finger	Fourth finger
1	30.590	30.290	27.910	30.230	30.490	31.560
2	30.450	31.870	26.000	31.200	31.530	32.570
3	30.300	32.830	26.900	30.940	32.220	32.950
4	27.300	24.970	26.830	32.520	31.500	34.210
5	26.180	24.300	24.460	32.560	31.440	34.590
6	25.740	24.010	23.300	32.840	32.050	34.990
mean	28.427	28.045	25.900	31.715*	31.538	33.478*
+/- SD	13.769	13.668	12.534	15.327	15.237	16.183

Significance level (Baseline vs. Q36)		
2° finger	t-Student = -2.438	p < 0.058*
3° finger	t-Student = -2.068 N.S.	p < 0.092
4° finger	t-Student = -6.387	p < 0.002*

These data indicate that, surprisingly, visnadine:

- Acts selectively on the small arteries and arterioles of the cutaneous microcirculation;
- Increases the volume of blood in the capillaries and opens to blood flow previously closed vessels in capillary networks. This results in increased cutaneous temperature and enhanced trophic exchanges even in normal, healthy subjects;
- Is active by direct topical epicutaneous application to the desired site of action at dosages much lower than those used by the oral route.

In addition, the effects of topical epicutaneously applied visnadine are surprisingly more rapid and can be demonstrated readily by instrument-based measurements, as opposed to the situation observed after oral administration of doses at least 50-fold greater.

Investigation B

The arterio-arteriolar sphygmic activity of the fingertip and the cutaneous temperature under baseline conditions and after immersion of the right hand in an ice-water bath for 4 minutes ("cold test") were determined in healthy subjects divided into two groups (group A and group B) as in investigation A. The skin of the fingers and of the palmar and dorsal surface of the hand was treated with a visnadine preparation or with placebo as described in Example I and investigation A. Continuous computerized recordings of arterio-arteriolar sphygmicity and of cutaneous temperature were made as in investigation A until all values had returned to baseline

conditions, and the required time (in minutes) was calculated.

The results of this investigation clearly show that epicutaneous treatment with the preparation described in Example I causes a statistically significant reduction of the time required for flow conditions to return to baseline, while placebo treatment is without effect. These results demonstrate that visnadine:

- After topical epicutaneous application, counteracts rapidly and effectively the vasoconstriction and the associated decrease in arterio-arteriolar sphygmic activity which follow exposure to cold ("cold test") in healthy subjects;
- Potently antagonizes at microcirculatory level the cold-induced ischemia of the tissue;
- May be used for the topical epicutaneous treatment of functional or organic peripheral vascular acrosyndromes due to microangiopathies and/or histangiopathies and characterized by hypoxic episodes affecting the extremities, secondary to abnormal cold-induced vasoconstriction and deficiency of the mechanisms regulating the local microcirculatory flow;
- After topical epicutaneous application with an adequate vehicle, counteracts the physiological cold-induced vasoconstriction at very low doses.

Investigation C

Investigation C was performed in subjects with venous stasis and/or chronic venous insufficiency of the lower limbs and functional-anatomic alterations of the cutaneous arterio-arteriolar afferrents. The subjects were divided into two groups (group A and group B) as in investigation A. The filling time of the superficial venous plexus of the dorsum of the foot was recorded in these subjects by means of light reflectance rheography before and after 15 timed rhythmical flexion-extension movements of the foot. The profile of the resulting recording represents a mirror image of the venous pressure in the system. These measurements were repeated by using the same procedure after 3 weeks of epicutaneous treatment with a visnadine preparation of the type described in Example I or in Example 5. The preparation was applied twice daily over the entire surface of the lower limb, including the thigh. The experimental protocol was carried out according to a placebo-controlled, double-blind design. The arterio-arteriolar sphygmic activity of the subpapillary plexus of the supra-lateral region of the thigh was recorded in parallel by means of computerized infra-red plethysmography.

The results of this investigation indicate that the filling time of the superficial cutaneous venous plexus of the pretibial region is clearly prolonged in subjects treated with visnadine as compared to those treated with placebo, which is on the contrary without effect. Moreover, in visnadine-treated subject the sphygmic activity of the small arteries and arterioles of the subpapillary plexus of the supralateral region of the thigh increases by more than 50% compared to baseline conditions, with a clear-cut improvement in local microcirculatory flow. The subjects treated with the active preparation show an appreciable subjective improvement in the feeling of leg heaviness, paresthesiae and frequency of diurnal and nocturnal muscle cramps.

The instrument-based findings demonstrate that:

- In the presence of capillaro-venular stasis causing a slowing and a pathological alteration of the microvascular-tissue exchanges, low dosages of topical epicutaneously applied visnadine are surprisingly effective in increasing the velocity and volume of the cutaneous microcirculatory flow, thus counteracting the blood stasis;
- Topically applied visnadine is effective in reducing the microcirculatory stasis and the capillaro-venular dilation typically associated with stasis conditions and/or chronic venous insufficiency. Surprisingly, this activity is already observed at very low doses compared with those used by the oral route. The rapid onset of activity and the efficacy of this treatment can be documented by instrument based observations and are statistically significant as compared to placebo.

Investigation D

Investigation D was performed in a group of male subjects with alopecia aerata. The local microcirculatory conditions in the scalp area affected by the disease were evaluated by means of high-resolution contact thermometry and infra-red photo-plethysmography before and 60 minutes after the application of a hair lotion containing visnadine prepared according to Example 4.

The instrument-based findings demonstrate that:

- Topical epicutaneous application of visnadine over the areas of alopecia is effective in increasing arterio-arteriolar sphygmic activity and cutaneous temperature. These effects are associated with an increase in volume/minute and velocity of microcirculatory flow, resulting in improved perfusion of the hair follicle;
- Visnadine does not cause reddening secondary to cutaneous vasodilation, unlike, other drugs or compounds which induce scalp hyperemia and reduce at the same time the volume of the local microcircu-

latory flow;
- The vehicle (especially phospholipidic liposomes) exerts surprisingly an antiseborrhoic action and reduces the lipidic content of greasy hair. This allows a drastic reduction of the weekly frequency of the required hair washings;
- The dose of visnadine which is active on the scalp microcirculation is much lower than those used orally for the vasodilating treatment of arterial diseases and/or coronary heart disease;
- The action of the compound is exerted essentially by the topical route in the presence of an appropriate (preferably liposomal) vehicle.

Investigation E

Two groups of patients (group A and group B) with primary or secondary Raynaud's phenomenon were treated topically by epicutaneous application with an active preparation (prepared as described in Examples I and V) or with placebo according to a double-blind design.

At baseline and after 30 days of treatment the patients were evaluated clinically and instrumentally by means of impedance plethysmography performed on the second, third and fourth finger of both hands.

The data obtained in this investigation indicate that the percutaneous treatment with the active preparation induces an appreciable clinical improvement which was rated as "excellent" in 43% of the cases and "good" in 26% of the cases. The placebo preparation was found to be ineffective.

The instrument-based data indicate that the sphygmic waves of the arteries in the fingertip of treated fingers exhibit after treatment a statistically significant increase in amplitude as compared to placebo.

The clinical and instrument-based findings demonstrate that:
- When applied topically over the extremities of limbs affected by pathological ischemic conditions or arterio-arteriolar spasms causing capillary hypovolemia, visnadine induces a statistically significant improvement of clinical symptoms and instrument-based measurements. These effects are surprisingly already seen at dosages which are 30 to 50-fold lower than those used for the oral treatment of "arteritis", e.g. for their action at the level of large and medium sized arteries.
- The vehicle used to facilitate the penetration across the epidermal barrier is preferably liposomal;
- After topical "transepidermal" administration in pathological conditions (functional spasms of the microcirculation), visnadine exerts an hyperactivating action on the microcirculatory flow which is identical to that observed and documented in the "cold test" performed in healthy subjects (investigation B).

Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, LI, CH, BE, AT, LU, DK

1. Pharmaceutical and/or dermatocosmetic and cosmetic compositions containing extracted or semi-synthetic derivatives of Ammi visnaga and Ammi majus, incorporated in a liposomal vehicle.

2. Pharmaceutical and/or dermatocosmetic and cosmetic compositions according to claim 1, in which the liposomal vehicle is based on unsaturated phosphatidylcholine from soy-beans or other extractable animal sources, extracted phospholipidic mixtures, saturated phosphatidylcholine.

3. Pharmaceutical and/or dermatocosmetic and cosmetic compositions according to claim 1 and containing visnadine, kelline, kellinone, visnaginone and the other flavoncoumarols , coumarins, dihydropyrano- and dihydrofuranocoumarins derived from Ammi visnaga and Ammi majus, as mixtures or in purified form.

4. The use of extracted or semi-synthetic derivatives of Ammi visnaga and Ammi majus for the preparation of a medication exerting microvasculo-kinetic effects or stimulatory effects on the sphygmic activity of small arteries and arterioles.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of Ammi visnaga and Ammi majus extracts for use as active principles of pharmaceutical and cosmetic topical compositions comprising the extraction of plant materials with carbon dioxide in hypercritic conditions and the optional purification of visnadine by partition between immiscible solvents.

latory flow;

- The vehicle (especially phospholipidic liposomes) exerts surprisingly an antiseborrhoic action and reduces the lipidic content of greasy hair. This allows a drastic reduction of the weekly frequency of the required hair washings;
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Two groups of patients (group A and group B) with primary or secondary Raynaud's phenomenon were treated topically by epicutaneous application with an active preparation (prepared as described in Examples I and V) or with placebo according to a double-blind design.

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The data obtained in this investigation indicate that the percutaneous treatment with the active preparation induces an appreciable clinical improvement which was rated as "excellent" in 43% of the cases and "good" in 26% of the cases. The placebo preparation was found to be ineffective.

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2. A process for the preparation of an aqueous micro-dispersion of visnadine or visnadine-like compounds comprising the dissolution of visnadine or of visnadine-like compounds and of lecithins or pure saturated or unsaturated phosphatidylcholine in methylene chloride, followed by evaporation and dispersion in water by means of turboemulsifier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Pharmazeutische und/oder dermatokosmetische und kosmetische Präparate, dadurch **gekennzeichnet,** daß sie, eingearbeitet in einen Liposomenträger, extrahierte oder semi-synthetische Derivate von Ammi visnaga und Ammi majus enthalten.

2. Pharmazeutische und/oder dermatokosmetische und kosmetische Präparate nach Anspruch 1, dadurch **gekennzeichnet,** daß der Liposomenträger auf ungesättigtem Phosphatidylcholin aus Sojabohnen oder anderen extrahierbaren Tierquellen, extrahierten phospholipidischen Gemischen, gesättigtem Phosphatidylcholin basiert.

3. Pharmazeutische und/oder dermatokosmetische und kosmetische Präparate nach Anspruch 1 , dadurch **gekennzeichnet,** daß sie Visnadin, Kellin, Kellinon, Visnaginon und andere Flavoncumarole, Cumarine, Dihydropyrano- und Dihydrofuranocumarine, die sich von Ammi visnaga und Ammi majus ableiten, als Gemische oder in gereinigter Form enthalten.

4. Verwendung extrahierter oder semi-synthetischer Derivate von Ammi visnaga und Ammi majus für die Herstellung eines Arzneimittels, das mikrovaskuläre-kinetische Wirkungen oder stimulierende Wirkungen auf die sphygmische Aktivität der kleinen Arterien und Arteriolen zeigt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung von Ammi visnaga- und Ammi majus-Extrakten für die Verwendung als aktive Wirkstoffe in pharmazeutischen und kosmetisch topischen Präparaten, dadurch **gekennzeichnet,** daß die Pflanzenmaterialien mit Kohlendioxid in hyperkritischem Zustand extrahiert werden und daß gegebenenfalls das Visnadin durch Teilung zwischen unmischbaren Lösungsmitteln gereinigt wird.

2. Verfahren zur Herstellung einer wäßrigen Mikrodispersion von Visnadin oder visnadinartigen Verbindungen, dadurch **gekennzeichnet,** daß Visnadin oder visnadinartige Verbindungen und Lecithine oder reines gesättigtes oder ungesättigtes Phosphatidylcholin in Methylenchlorid aufgelöst werden, anschließend verdampft wird und in Wasser mittels eines Turbo-Emulgiergeräts dispergiert wird.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Compositions pharmaceutiques et/ou dermatocosmétiques et cosmétiques contenant des dérivés extraits ou semi-synthétiques d'Ammi visnaga et d'Ammi majus, incorporés dans un véhicule liposomial.

2. Compositions pharmaceutiques et/ou dermatocosmétiques et cosmétiques selon la revendication 1, dans lesquelles le véhicule liposomial est à base de phosphatidylcholine insaturée extraite du soja ou d'autres sources animales extractibles, de mélanges phospholipidiques extraits, de phosphatidylcholine saturée.

3. Compositions pharmaceutiques et/ou dermatocosmétiques et cosmétiques selon la revendication 1 et contenant de la visnadine, de la kelline, de la kellinone, de la visnaginone et les autres flavonecoumarols, coumarines, dihydropyrano- et dihydrofuranocoumarines dérivés d'Ammi visnaga et d'Ammi majus, sous forme de mélanges ou sous forme purifiée.

4. L'utilisation de dérivés extraits ou semi-synthétiques d'Ammi visnaga et d'Ammi majus pour la préparation

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d'une médication exerçant des effets microvasculo-cinétiques ou des effets stimulants sur l'activité sphygmique des petites artères et artérioles.

Revendications pour les Etats contractants suivants : ES, GR

1. Un procédé de préparation d'extraits d'Ammi visnaga et d'Ammi majus pour utilisation comme principes actifs de compositions pharmaceutiques et cosmétiques topiques, qui comprend l'extraction de matières de plantes avec du dioxyde de carbone dans des conditions hypercritiques, et la purification optionnelle de la visnadine par partage entre des solvants non-miscibles.

2. Un procédé de préparation d'une microdispersion aqueuse de visnadine ou de composés similaires à la visnadine, qui comprend la dissolution de visnadine ou de composés similaires à la visnadine et de lécithines ou de phosphatidylcholine, saturée ou insaturée, pure dans du chlorure de méthylène, suivie d'un évaporation et d'une dispersion dans de l'eau à l'aide d'un turbo-émulseur.

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