

**COMBINATIONS OF VASOACTIVE AGENTS, THEIR USE IN THE
PHARMACEUTICAL AND COSMETIC FIELD, AND
FORMULATIONS CONTAINING THEM**

FIELD OF INVENTION

This invention relates to combinations of vasoactive substances which act at venous or arterial level with phosphodiesterase inhibitors, including c-GMP phosphodiesterase V.

5 **BACKGROUND TO THE INVENTION**

Visnadine is a coumarin mainly found in the seeds of *Ammi visnaga*, a plant traditionally used to treat anginoid disorders. The compound has been used in the pharmaceutical field as a coronary dilator.

10 It has also been demonstrated that this compound, when applied topically, has a strong vasokinetic action on the precapillary arteries and arterioles, and increases blood flow and tissue perfusion (EP 0418806). The supply of blood to the tissue involves better nutrition and the elimination of metabolic waste, with consequent benefits for the treated area. Visnadine also has an anti-phosphodiesterase activity.

15 Esculoside, a coumarin glucoside present in many plants, such as *Aesculus hippocastanum*, *Fraxinus communis* etc., possesses a vasokinetic action and venotropic activity at both venous and arterial levels.

20 Icarin and derivatives thereof, which possess activity on cGMP phosphodiesterase V, are useful activators of the microcirculation in certain areas.

Amentoflavone is a biflavone present in modest amounts in numerous plants, such as *Ginkgo biloba*, *Brakeringea zanguebarica* and *Taxus sp.*

The saponins of horse chestnut or *Centella asiatica* act on the venous and lymphatic system, where they perform an anti-oedematous action that

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facilitates lymph drainage.

DESCRIPTION OF THE INVENTION

The invention relates to pharmaceutical, dietetic, cosmetic or nutraceutical compositions comprising:

- 5 - visnadine or esculoside;
- at least one compound selected from icarin or derivatives thereof or extracts containing it, *Ginkgo biloba* dimeric flavones in the free form or complexed with phospholipids, and amentoflavone;
- at least one compound selected from escin, escin beta-sitosterol
10 complexed with phospholipids, sericoside, sericoside complexed with phospholipids or *Centella asiatica* extract in the free form or complexed with phospholipids.

The combination of vasoactive substances according to the invention, which act simultaneously at arterial and venous level and on lymph drainage,
15 reduces stasis oedema, which is one of the first symptoms of chronic venous insufficiency, with pathological consequences ranging from cellulitis to crural ulcers of various aetiologies. The warning signs of circulatory deficiency of the lower limbs include below-normal skin temperature, a feeling of heaviness in the legs, and acroasphyxial syndromes with peripheral pain. Various
20 attempts have been made to treat these symptoms, but with modest success.

It has now surprisingly been found that the formulations according to the invention, containing compounds with different action mechanisms, prevent peripheral vascular and tissue degeneration.

The most common case is cellulitis or degenerative panniculopathy.
25 Before the formation of painful fibrous nodules or fat deposits due to degeneration of the adipocytes, cellulitis is caused by seepage of fluids and protein into the perivascular spaces as a result of venous insufficiency. The resulting oedema, due to mechanical compression, reduces the free circulation of

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the arterial bloodstream. Under these circumstances the adipocytes accumulate fats, become enlarged and take away space from other cells. Treatment with anti-cellulitis formulations should begin at this point if the maximum success is to be achieved. The association according to the invention enables the condition to be
5 treated at the pre-pathological stage, in order to prevent it from progressing to peripheral damage. The same formulations can also be used successfully even when the disorder has become chronic, to eliminate painful sensations and reduce unwanted adipose masses with long-term treatments, by means of lipase stimulation induced by the persistence of cyclical nucleotides in the tissues.

10 Icarin derivatives which can be used according to the invention as an alternative to icarin include 7-hydroxyethyl-icarin, 7-ethylamino-icarin, 7-aminoethyl-icarin, 7-hydroxyethyl-3-O-ramnosyl-icarin, 7-aminoethyl-3-ramnosyl-icarin, 8-dihydro-icarin and its glucosides in 7 and 3, and 7-hydroxyethyl-7-desgluco-icarin.

15 The compositions according to the invention preferably contain visnadine.

The compositions according to the invention typically have the following concentration ranges by weight:

- visnadine or esculoside: 0.05-2%;
- 20 - amentoflavone or *Ginkgo biloba* dimers in the free form or complexed with phospholipids: 0.1-1%;
- icarin or derivatives thereof or extracts containing it: 0.1-1%;
- at least one compound selected from among escin, escin beta-sitosterol complexed with phospholipids, sericoside, sericoside
25 complexed with phospholipids or *Centella asiatica* extract, in the free form or complexed with phospholipids: 0.5%-2%.

These compounds can be incorporated in the most common pharmaceutical and cosmetic formulations, such as oil-in-water and water-in-oil

emulsions, suitably carried by excipients, surfactants and solubilisers.

Moreover, products can be formulated in cream, milk and gel form for treatment of large areas of the skin.

The following examples illustrate the invention in detail.

5 EXAMPLE 1 – Gel formulation

	Visnadin	0.25 g
	7-hydroxyethyl-7-desgluco-icarin	0.35 g
	Amentoflavone	0.25 g
	Escin	1.00 g
10	Lecithin	20.00 g
	Cholesterol	0.50 g
	Ethanol	8.00 g
	Butylhydroxy toluene	0.01 g
	Imidazoline urea	0.30 g
15	Hydroxypropyl-methylcellulose	2.00 g
	Water	qs to 100 g

EXAMPLE 2 – Gel formulation

	Esculoside	1.00 g
	Icarin	0.35 g
20	Amentoflavone	0.25 g
	Escin	1.00 g
	Lecithin	20.00 g
	Cholesterol	0.50 g
	Ethanol	8.00 g
25	Butylhydroxy toluene	0.01 g
	Imidazoline urea	0.30 g
	Hydroxypropyl-methylcellulose	2.00 g
	Water	qs to 100 g

EXAMPLE 3 - gel formulation

	Visnadin	0.25 g
	7-Hydroxyethyl-7-desgluco-icaritin	0.35 g
	<i>Gingko biloba</i> dimers complexed	0.25 g
5	with phospholipids	
	Escin beta-sitosterol complexed	1.00 g
	with phospholipids	
	Lecithin	20.00 g
	Cholesterol	0.50 g
10	Ethanol	8.00 g
	Butylhydroxy toluene	0.01 g
	Imidazoline urea	0.30 g
	Hydroxypropyl-methylcellulose	2.00 g
	Water	qs to 100 g

15 EXAMPLE 4 - Gel formulation

	Esculoside	0.25 g
	7-Hydroxyethyl-7-desgluco-icaritin	0.35 g
	Amentoflavone	0.25 g
	Sericoside	1.00 g
20	Lecithin	20.00 g
	Cholesterol	0.50 g
	Ethanol	8.00 g
	Butylhydroxy toluene	0.01 g
	Imidazoline urea	0.30 g
25	Hydroxypropyl-methylcellulose	2.00 g
	Water	qs to 100 g

EXAMPLE 5 - Gel formulation

	Visnadin	0.3 g
	Amentoflavone	0.4 g
	<i>Centella asiatica</i> extract	1.0 g
5	Lecithin	20.00 g
	Cholesterol	0.50 g
	Ethanol	8.00 g
	Butylhydroxy toluene	0.01 g
	Imidazoline urea	0.30 g
10	Hydroxypropyl-methylcellulose	2.00 g
	Water	qb 100 g

CLAIMS

1. Pharmaceutical, cosmetic, dietetic or nutraceutical compositions comprising:

- 5 - visnadin or esculoside;
- at least one compound selected from icarin or derivatives thereof or extracts containing it, *Ginkgo biloba* dimeric flavones either in the free form or complexed with phospholipids, amentoflavone;
- 10 - at least one compound selected from escin, escin beta-sitosterol complexed with phospholipids, sericoside, sericoside complexed with phospholipids or *Centella asiatica* extract in the free form or complexed with phospholipids.

2. Compositions as claimed in claim 1, having the following concentration ranges by weight:

- 15 - Visnadin or esculoside: 0.05-2%;
- amentoflavone or *Ginkgo biloba* dimeric flavones in the free form or complexed with phospholipids: 0.1-1%;
- icarin or derivatives thereof or extracts containing it: 0.1-1%;
- 20 - Escin, escin beta-sitosterol complexed with phospholipids, sericoside, sericoside complexed with phospholipids or *Centella asiatica* extract in the free form or complexed with phospholipids: 0.5%-2%.

3. Compositions as claimed in claim 1 or 2, in which icarin derivatives comprise 7-hydroxyethyl-icarin, 7-ethylamino-icarin, 7-aminoethyl-icarin, 7-hydroxyethyl-3-O-rhamnosyl-icarin, 7-aminoethyl-3-rhamnosyl-icarin, 8-dihydro-icarin and its glucosides in 7 and 3, and 7-hydroxyethyl-7-desgluco-icarin.

4. Compositions as claimed in any one of claims 1-3, in the form of

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creams, gel, lotions, milk.

5. A composition as claimed in claim 1, containing Visnadin.

6. A composition as claimed in claim 1, containing Visnadin, 7-hydroxyethyl-7-desgluco-icarin, amentoflavone and escin.

5 7. A composition as claimed in claim 1, containing esculoside, icarin, amentoflavone, escin.

8. A composition as claimed in claim 1 containing Visnadin, 7-hydroxyethyl-7-desgluco-icarin, *Gingko biloba* dimers in the free form or complexed with phospholipids.

10 9. A composition as claimed in claim 1 containing Visnadin, *Gingko biloba* dimers complexed with phospholipids, escin beta-sitosterol complexed with phospholipids.

10. A composition as claimed in claim 1 containing esculoside, *Gingko biloba* dimers complexed with phospholipids, escin beta-sitosterol complexed
15 with phospholipids.

11. The use of a combination of:

- visnadin or esculoside;
- at least one compound selected from icarin or derivatives thereof or extracts containing it, *Gingko biloba* dimeric flavones either in
20 the free form or complexed with phospholipids, amentoflavone;
- at least one compound selected from escin, escin beta-sitosterol complexed with phospholipids, sericoside, sericoside complexed with phospholipids or *Centella asiatica* extract in the free form or complexed with phospholipids.

25 For the preparation of a composition for the treatment of panniculopathy and of the problems connected with venous insufficiency of the lower limbs.