

ORAL COMPOSITIONS FOR THE TREATMENT OF CELLULITE



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The present invention relates to oral pharmaceutical and cosmetic compositions containing ingredients of vegetable origin for the treatment of cellulite.

More particularly, the present invention relates to pharmaceutical and
5 cosmetic oral compositions for the treatment of cellulite containing *Vitis vinifera* extracts, dimeric *Ginkgo biloba* flavonoids and *Centella asiatica* triterpenes as the active ingredients.

According to the present invention, the active ingredients are in the free form or complexed with phospholipids.

10 Cellulite affects a remarkable and increasing percentage of the western population, especially women, including many adult women with normal body weight not affected by obesity. Cellulite is related to a condition of panniculopathy, characterized by poor peripheral circulation, oedema, fibrosis and altered lipocytes metabolism, and an ideal treatment should take into
15 account all these aspects.

A number of pharmaceutical or cosmetic compositions for the treatment of cellulite are presently available on the market: they are generally based on active principles of vegetable origin, such as ivy, horse-chestnut or kola tree (*Centella asiatica*) extracts, caffeine, beta-adrenergic stimulants,
20 methylxanthines and the like. However, none of them has proved really effective so far and the improvements are often due to the diet regimen generally associated with the use of the compositions, rather than to the compositions themselves.

It has now been found that oral pharmaceutical and/or cosmetic
25 compositions containing a combination of active principles of vegetable



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origin, which are object of the present invention, allow to obtain optimal results in the treatment of cellulite, significantly reducing the deposits of subcutaneous fat and "orange peel" skin, thanks to the combination of the different activity of the various components, which exert antioedema, antiphosphodiesterasis and vasokinetic activity, and promote collagen production. The compositions of the invention have also proved effective in the treatment of venous insufficiency of the lower limbs.

All the active principles of the compositions of the invention are known and used in pharmaceuticals and/or in cosmetics; however, it should be noted that the compositions show a synergistic effect and that the activity of the single actives used separately is by far lower than that of the actives used in combination.

The compositions of the present invention can contain from 10 to 500 mg per dose unit of *Vitis vinifera* standardized extracts, from 10 to 500 mg of dimeric *Ginkgo biloba* flavonoids and from 10 to 500 mg of *Centella asiatica* or an equivalent amount of the corresponding phospholipid complexes.

Components a)-c) in the free form are commercially available.

Phospholipid complexes of *Vitis vinifera* standardized extract (also referred to as "components a") are disclosed in European Patent 275.224. Said extract, consisting of the polyphenols fraction contained in *Vitis vinifera* seeds, contains gallic acid, catechin and epicatechin monomers, dimers, trimers, tetramers, pentamers, hexamers and eptamers in the free form or esterified with gallic acid.

In vitro and in vivo studies have demonstrated the high antioxidant activity of the extract (from 10 to 200 times higher than that of vitamin E, depending on the experimental model), which allows to eliminate the most reactive radical species and counteract their harmful effects. Moreover, the extract is able to inhibit xanthine-oxidase and chelate Cu^{++} and Fe^{+++} , thus

preventing enzyme-catalysed production of free radicals in tissues. Last, the *Vitis vinifera* extract inhibits collagenase and other proteases, thereby protecting the connective tissue and the skin from the noxious action of proteolytic enzymes released upon UV irradiation and in the course of inflammatory responses in the skin; moreover, the extract has selective affinity for the skin and circulatory structures, such as microvessels and capillaries, thus also exerting a protective action on the circulatory apparatus.

The complexes of dimeric *Ginkgo biloba* flavonoids with phospholipids (also referred to as "components b"), disclosed in EP 0 275 005, have the same activity of *Ginkgo biloba* flavones dimers in the free form, but induce a more prolonged release of the active principles and have a better bioavailability. *Ginkgo biloba* flavonoids dimers are extremely potent vasoactive agents due the fact that they inhibit the release of histamine and cAMP phosphodiesterase from mast cells. In particular, the inhibition of cAMP phosphodiesterase causes an increase of cAMP levels; since cAMP is able to activate lipocytes metabolism, these complexes exert a lipolytic action and improve microvascular perfusion and cutaneous trophism.

Phospholipid complexes of *Centella asiatica* standardized extract (also referred to as "components c") are disclosed in EP 0 283 713. This extract consists of a 4:3:3 mixture of three different molecules endowed with high activity on collagen metabolism: asiaticoside, asiatic acid and madecassic acid. These molecules improve the fibroblasts uptake of amino acids, mainly L-proline and L-hydroxyproline, which are the most important amino acids in collagen structure, both from the qualitative and quantitative standpoint. An improved collagen biosynthesis involves a faster replacement of degraded old fibres with new ones.

The compositions of the present invention will be administered orally, in the form of suitable formulations, either liquid (such as syrups, solutions,

suspensions) or solid (such as tablets, sugar-coated pills, capsules, chewable tablets). The formulations will be prepared according to conventional methods, such as those disclosed in "Remington's Pharmaceutical Handbook", Mack Publishing Co., NY, USA, using suitable excipients.

- 5 Examples of compositions according to the invention are reported hereinbelow.

Example I: tablet

Phospholipids complex

	<i>Vitis vinifera</i> extract	240 mg
10	Phospholipid complex of dimeric <i>Ginkgo biloba</i> flavonoids	100 mg
	Phospholipid complex of <i>Centella asiatica</i> triterpenes	60 mg
	Sodium croscarmellose	28 mg
	Silicon dioxide	8 mg
	Talc	4 mg

15 **Example II:**

	<i>Vitis vinifera</i> extract	150 mg
	<i>Ginkgo biloba</i> dimeric flavonoids	100 mg
	<i>Centella asiatica</i> triterpenes	10 mg
	Dihydrate dicalcium phosphate	150 mg
20	Microcrystalline cellulose	100 mg
	Croscarmellose sodium	28 mg
	Silicon dioxide	8 mg
	Magnesium stearate	9 mg
	Talc	3 mg

CLAIMS

1. Oral compositions containing:
 - a) *Vitis vinifera* standardized extract or a complex thereof with phospholipids;
 - b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids;
 - c) *Centella asiatica* or complexes thereof with phospholipids, in admixture with conventional excipients and carriers.
2. Compositions as claimed in claim 1, in which the components a)-c) are in the free form.
3. Compositions as claimed in claim 1, in which the components a)-c) are in the form of complexes with phospholipids.
4. Use of a combination of:
 - a) *Vitis vinifera* standardized extract or a complex thereof with phospholipids;
 - b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids and
 - c) *Centella asiatica* or complexes thereof with phospholipids,for the preparation of oral pharmaceutical and cosmetic compositions for the treatment of cellulite.
5. Use of a combination of:
 - a) *Vitis vinifera* standardized extract or complex thereof with phospholipids;
 - b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids;
 - c) *Centella asiatica* or complexes thereof with phospholipids,

in the preparation of a composition for the treatment of venous insufficiency of the lower limbs.

6. Use of the compositions of claims 1-3 for the cosmetic treatment of cellulite.
- 5 7. A combination of:
 - a) *Vitis vinifera* standardized extract or complex thereof with phospholipids;
 - b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids;
 - 10 c) *Centella asiatica* or complexes thereof with phospholipids, for use in the treatment of venous insufficiency of the lower limbs.
8. A combination of:
 - a) *Vitis vinifera* standardized extract or complex thereof with phospholipids;
 - 15 b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids;
 - c) *Centella asiatica* or complexes thereof with phospholipids, for use in the cosmetic treatment of cellulite.
9. Use of the composition of claims 1-3 in the preparation of a medicament for the cosmetic treatment of cellulite.
- 20 10. A cosmetic method for the treatment of cellulite comprising administering the compositions of any one of claims 1-3 to a subject.
11. Compositions of claim 1-3 for the cosmetic treatment of cellulite.
12. A cosmetic method for the treatment of cellulite comprising administering a combination of:
 - 25 a) *Vitis vinifera* standardized extract or complex thereof with phospholipids;

- b) dimeric *Ginkgo biloba* flavonoids or complexes thereof with phospholipids;
- c) *Centella asiatica* or complexes thereof with phospholipids, to a subject.