COMPOSITIONS FOR THE TREATMENT OF PERIPHERAL ULCERS OF VARIOUS ORIGINS

Summary of the invention

The present invention relates to compositions containing a combination of a cell proliferation-stimulating agent with vasokinetic properties and an antimicrobial, antifungal and antiviral agent with an anti-inflammatory/analgesic, which is useful in the treatment of peripheral ulcers of various origins, such as diabetic ulcers, ulcers caused by venous stasis of the limbs, bedsores and the associated skin infections. More particularly, the present invention relates to compositions containing catechin polyphenols, anthocyanosides, or *Aesculus hippocastanum*, *Vitis vinifera* or *Ericaceae* extracts containing them, and *Echinacea sp.* extract.

Said compositions are suitable for topical or systemic use.

Technical background

Disorders like peripheral ulcers, whether they are diabetic ulcers, ulcers caused by venous stasis of the limbs, or bedsores and the associated skin infections, have different etiologies although they present common symptoms. Some involve the peripheral circulation and microcirculation, while many are associated with arteriosclerosis which causes occlusions of the small and medium arteries with consequent oedema and, due to accidental causes or scratching caused by itching, can result in a lesion that is difficult to heal due to subsequent bacterial and/or fungal infection.

Ulcers associated with chronic venous insufficiency require lengthy treatments with a combination of substances having different, synergic actions. Diabetic ulcers have similar origins to the former, and are accompanied by peripheral pain and purpura.

Vasokinetic and vasoprotective agents generally improve wound

healing, especially in the case of bedsores. The availability of substances which have a wound-healing and vasokinetic action, together with substances which rapidly eliminate infection and pain, would therefore be desirable. Keeping the arterial microcirculation active and removing protein seepage from the ulcerated area by means of lymph drainage further accelerates tissue re-epithelialisation.

Description of the invention

It has been found that the combination of catechin polyphenols or anthocyanosides and *Echinacea sp.* extract induces surprisingly rapid wound healing, with a reduction of the surrounding oedema and re-epithelialisation, due to the immediate reduction of fibrin production and protein seepage, which allows wound cleaning and rapid proliferation of granulation tissue.

The present invention therefore relates to compositions containing, as active ingredients:

a) catechin polyphenols or anthocyanosides or extracts containing them, and

b) *Echinacea sp.* extract

for the treatment of peripheral ulcers of various origins, such as stasis ulcers, diabetic ulcers, bedsores and the associated skin infections.

Catechin polyphenols are known to possess *in vitro* activity on fibroblast proliferation, antiprotease activity on the ground substance of connective tissue, and vasokinetic activity at venous and lymphatic level. According to the present invention, said polyphenols can be present either as single molecules or in the form of extracts containing them. When they are present in the form of extracts, *Aesculus hippocastanum* or *Vitis vinifera* extracts will preferably be used. Said extracts will preferably be obtained by extraction from the aerial parts of said plants.

According to a preferred aspect, the catechin polyphenols will be present in the form of an extract obtained from *Aesculus hippocastanum* bark, branches and fruit pericarp. Said extract basically contains two classes of substance: procyanidin A2, which is not only a powerful protease inhibitor but also active as a microvasculokinetic agent at venous and lymphatic level, and significant amounts of esculoside, a powerful vasokinetic agent at arterial level.

According to a preferred aspect, the catechin polyphenols will be selected from alcoholic extract of *Aesculus hippocastanum*, proanthocyanidin A2, and oligomeric proanthocyanidins extracted from *Vitis vinifera* seeds.

According to a preferred aspect, the term "anthocyanosides" comprises both anthocyanosides properly so called and their aglycons (anthocyanidins).

The anthocyanosides are preferably derived from Ericacea extracts, in particular extracts of various species of *Vaccinium*.

According to a preferred aspect the anthocyanosides are derived from cranberry fruit and leaf extracts (*Vaccinium macrocarpon, V. oxycoccus, V. erythrocarpum, V. microcarpum, V. oxycoccos*).

According to a further preferred aspect the anthocyanosides are derived from a *Vaccinium myrtillus* extract. Bilberry (*Vaccinium myrtillus*) extract is a product with marked anti-inflammatory activity, especially at topical level, due to its effect on capillary fragility and permeability. The preparation of bilberry extracts containing anthocyanosides is known. Moreover, bilberry anthocyanosides, like procyanidins, have a bacteriostatic action which prevents bacterial and fungal adherence.

Echinacea extract exerts an analgesic, antiviral, anti-inflammatory and antimicrobial activity, leading to a global improvement in wound healing; it

also has a significant effect on all forms of itching, a condition that often accompanies the formation of sores caused by venostasis, and is useful in the healing, and above all prevention, of sores.

According to a preferred aspect of the invention, the *Echinacea* sp extract is an alcoholic extract of *Echinacea angustifolia* or *purpurea*.

The percentages of active ingredients can range between 0.05 and 2% for catechin polyphenols, anthocyanosides, or extracts containing them, whereas for *Echinacea sp.* extract, the concentrations can range between 0.01 and 1%.

According to a preferred aspect, the compositions according to the invention will therefore contain the active ingredients within the following percentage intervals:

a) catechin polyphenols, anthocyanosides, or extracts containing them: 0.05 to 2%;

b) *Echinacea sp.* extract.: 0.01 to 1%.

According to a particularly preferred aspect, the compositions will contain the active ingredients within the following percentage intervals:

a) catechin polyphenols, anthocyanosides, or extracts containing them: 0.1 to 1%;

b) *Echinacea* sp extract.: 0.05 to 0.5%.

The compositions according to the invention can be administered topically or systemically, for example as water/oil emulsions, aseptic dusting powders or occlusive formulations.

According to a preferred aspect, the occlusive formulations will be in solid form, designed to be hydrated at the time of application, containing alginic acid as gelling polysaccharide.

The preferred excipients for use in the formulations are polysaccharides, such as hyaluronic acid and chondroitin sulphate or

alginic acid, which help to form a protective film that stimulates wound healing.

In human pharmacological treatment the formulations are applied to the wound, and left to be absorbed. Particularly infected wounds should be covered with sticking plaster to form an occlusive dressing. The wound treatment is repeated one to three times a day, taking care to protect the wound or sore against mechanical traumas.

The compositions according to the invention will be prepared according to well-known conventional methods, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA, together with suitable excipients.

The following examples illustrate the invention in detail.

PREPARATION EXAMPLES

Example 1 - Preparation of *Aesculus hippocastanum* bark extract

Procyanidin A2 and esculoside are repeatedly extracted from 5 Kg of bark from finely ground *Aesculus hippocastanum* branches with 95% ethanol until exhausted. The extraction solvent is concentrated to an equal weight with the starting biomass, and the concentrate is filtered to eliminate undesirable substances. The filtrate is concentrated until dry under vacuum at a temperature not exceeding 40°C. 570 g of a beige extract with a 35% esculoside content and an 11.2% procyanidin A2 is obtained. This extract can be used "as is" in the formulations according to the invention.

Example 2 - Preparation of *Echinacea angustifolia* root extract

Echinacoside, caffeoylquinic acids and isobutylamides are extracted from 2 Kg of finely ground *Echinacea angustifolia* roots with 95% ethanol at the temperature of 50°C until exhausted. Thin-layer chromatography is used to test for exhaustion, with echinacoside as the marker. The extraction solvent is concentrated under vacuum at a temperature of 25°C, taking care not to distil

the basic oil containing the isobutylamides in steam current. By concentrating the solvent until dry, 150 g of extract with a 4% echinacoside content and an 0.5% isobutylamide content is obtained. This extract can be used "as is" in the formulations according to the invention.

PHARMACOLOGICAL EXAMPLE

Example 3 - Effect on ulcers caused by venous stasis of the lower limbs

50 patients (10 per group), suffering from venous stasis ulcers of the lower limbs, not complicated by other vascular disorders, were included in the study.

The patients were treated with the preparation described in example 7, applied to the lesion twice a day. The treated lesions were then covered with a bandage to ensure that the cream was not removed, and to protect them against external agents and/or mechanical traumas. The lesions were monitored for 21 days, and re-epithelialisation was assessed by measuring the two diameters. The results were expressed as the mean of the two diameters measured.

The results are set out in the table below.

TREATMENT	RE-EPITHELIALISATION		
	7 days	14 days	28 days
Placebo	0.02 V 0.01	0.01 ± 0.01	0.03 ± 0.02
Preparation example 7	2.14 ± 0.73**	4.9 ± 1.01**	8.30 ± 1.10**
Placebo + *Vaccinium myrtillus* 0.3%	0.10 ± 0.03	0.23 ± 0.13*	0.50 ± 0.23*
Placebo + *Echinacea angustifolia* 0.3%	0.01 ± 0.01	0.20 ± 0.02*	0.35 ± 0.02*

* P<0.05; **P<0.001 Student's "t" test

Some formulation examples are set out below.

FORMULATION EXAMPLES

Example 4 - Granulate for sachets used to prepare an extempore aqueous gel

Aesculus hippocastanum (bark extract)	0.5 g
Echinacea angustifolia (root extract)	0.1 g
Alginic acid as calcium salt	0.5 g
Carboxymethylcellulose sodium salt	0.3 g
Sorbitol	1.2 g

Example 5 - Aqueous gel

Aesculus hippocastanum (bark extract)	0.5 g
Echinacea angustifolia (root extract)	0.1 g
Alginic acid as calcium salt	0.5 g
Propylene glycol	5.0 g
Carboxymethylcellulose sodium salt	3.5 g
Potassium sorbate	0.1 g
Purified water q.s. for	100.0 g

Example 6 - Dusting powder

Vitis vinifera (seed extract)	1.0%
Echinacea angustifolia (root extract)	0.2%
Colloidal silicon dioxide	2.0%
Talc q.s. for	100.0%

Example 7 - Aqueous gel

Vitis vinifera	0.50 g
Echinacea angustifolia (root extract)	0.10 g
Polyethylene glycol 400	5.00 g
Glycerin	5.00 g
Carbomer	1.00 g
Sodium hydroxide 10% solution	2.00 g
Methyl paraben	0.20 g
Propylparaben	0.05 g
Potassium sorbate	0.15 g
Purified water q.s. for	100 g

Example 8 - Cream (O/W emulsion)

Vaccinium myrtillus dried extract	0.300 g
Echinacea angustifolia (root extract)	0.300
Liquid paraffin	8.000 g
Stearic acid	10.000 g
Methyl para-hydroxybenzoate	0.028 g
Propyl para-hydroxybenzoate	0.012 g
Polysorbate 80	2.000 g
Glycerin	12.000 g
Purified water q.s. for	100.000 g

CLAIMS

1. Compositions comprising:

a) catechin polyphenols, or anthocyanosides or extracts containing them, and

b) extract of *Echinacea sp.*

2. Compositions as claimed in claim 1, wherein the extracts which contain catechin polyphenols are extracts of *Aesculus hippocastanum* or *Vitis vinifera.*

3. Compositions as claimed in claim 1, wherein the extracts which contain anthocyanosides are extracts of *Ericaceae*.

4. Compositions as claimed in claim 2, wherein the extract of *Aesculus hippocastanum* is an alcoholic extract of bark, branches and fruit pericarp.

5. Compositions as claimed in claim 2, wherein the extract of *Vitis vinifera* is an extract of the seeds.

6. Compositions as claimed in claim 3, wherein the extract of *Ericaceae* is an extract of V. myrtillus, V. macrocarpon, V. oxycoccus, V. erythrocarpum or V. microcarpum.

7. Compositions as claimed in claim 1, wherein the extract of *Echinacea* sp is an alcoholic extract of *Echinacea angustifolia* or *purpurea.*

8. Compositions as claimed in claim 1, containing the active ingredients within the following percentage ranges:

a) catechin polyphenols, or anthocyanosides or extracts containing them: 0.05 to 2%;

b) extract of *Echinacea sp.*: 0.01 to 1%.

9. Compositions as claimed in claim 8, containing the active ingredients within the following percentage ranges:

a) catechin polyphenols, or anthocyanosides or extracts containing them: 0.1 to 1%;

b) extract of *Echinacea sp.*: 0.05 to 0.5%.

10. Compositions according to the above claims, for topical or systemic administration.

11. Compositions comprising:

a) catechin polyphenols, or anthocyanosides or extracts containing them, and

b) extract of *Echinacea* sp,

for the treatment of peripheral ulcers of various origins, and the related skin infections.

12. Compositions as claimed in claim 11, wherein the ulcers are diabetic ulcers, venous stasis ulcers of the limbs, or bedsores.