WO 2005/063266 A1

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date

(10) International Publication Number
WO 2005/063266 A1

(51) International Patent Classification:
A61K 35/78

(21) International Application Number:
PCT/BG2004/000024

(22) International Filing Date: 7 December 2004 (07.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

(71) Applicants and Inventors:
NAYDENOV, Vladimir, Yosifov [BG/BG];
88, Ing. Ivan Ivanov Boul., 1303 Sofia (BG).
KURDOV, Kiril, Dimitrov [BG/BG]; j.k. Serdika, bl. 17A, entr. B,
1379 Sofia (BG).

(74) Agent: GEORGIEVA, Lilia, Tsvetkova; j.k. Banishora,

(81) Designated States (unless otherwise indicated, for every kind of national protection available):
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available):
ARIO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, MC, ML, NL, PL, PT, RO,
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,
GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— of inventorship (Rule 4.17(iv)) for US only

Published:
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTICAL COMPOSITION FOR THE TREATMENT OF DERMATOSIS COMPRISING AN EXTRACT OF CALENDULA OFFICINALIS AND HYPERICUM PERFORATUM

(57) Abstract: Therapeutic composition, containing an extract of the medicinal herbs Calendula officinalis and Hypericum perforatum in a ratio from 1:1 to 3:1 parts by weight. The extract contains low-molecular peptides and free amino acids to a total amount of 0.5-6.0% of the extract dry mass, more specifically histidine, cystine, serine, alanine, valine, leucine, isoleucine, phenylalanine, glycine, lysine, proline, tyrosine, glutamine, asparagine and methionine; unsaturated fatty acids 1.0-10.0%, more specifically linoleic acid, linolenic acid and oleic acid; vitamins 1.0-6.0%, including retinoids 0.6-3.0%; and minerals and microelements 1.0-6.0% of the extract dry mass.
THERAPEUTICAL COMPOSITION FOR THE TREATMENT OF DERMATOSIS

FIELD OF THE INVENTION

The present invention relates to a therapeutical composition for the treatment of dermatosis such as psoriasis, neurodermatitis, trophic sores, eczemas, acne and other disorders of the skin, which has anti-inflammatory, regenerative and trophic effect and normalizes the metabolism in the dermal and epithelial tissues.

BACKGROUND OF THE INVENTION

It is known that in the treatment of dermatitis, in particular psoriasis, extracts from different combinations of medicinal herbs are used, which have anti-inflammatory, regenerative and bactericidal action.

WO91/15218 describes a therapeutical composition against psoriasis based on an extract of a combination of the herbs Chelidonium L. and Hypericum L., and optionally Bardanum L., Calendula L., Achilea L. and Matricaria Chamomilla L. More specifically the composition contains acetone extract of the herbs, included in different carriers for external application.

US 6225342 and US 6313099 describe the use of sesquiterpene glucosides, isomers and other derivatives thereof from Calendula L. for the treatment of disease involving cell hyperproliferation, psoriasis in particular, obtained by multiphase extraction of Calendula species.

WO 02/051427 describes a stabilized extract of Hypericum perforatum L. and its use in the treatment of disease involving cell proliferation and inflammation, psoriasis in particular. The extract has a lower chlorophyll and pro-anthocyanidinen content and contains hyperforin, hypericin and flavon, as well as a stabilizer selected from ester of ascorbinic acid, thiolic compounds, cysteine, glutathione, etc. The extract contains essential oils, carotenoids, anthraquinone derivatives, flavonoides, catechins and epicatechins, tan compounds, phenolic acids, sterols, wax, paraffin, in specific quantities.

Despite the multitude of known therapeutical compositions, the problems in treating dermatosis, in particular psoriasis, still exist because these known drugs solve separate aspects of the disease. There is a need for improvement of the known
drugs, effective in individual cases, by taking into account the basic factors related to the disease, the prime causes and the intimate mechanism of the anomalies in the diseased cells.

**DISCLOSURE OF THE INVENTION**

The present invention provides a therapeutical composition for the treatment of skin diseases, in particular psoriasis, which contains an extract of the medicinal herbs Calendula officinalis L. and Hypericum perforatum L. in ratio 1:1 to 3:1 parts by weight. The extract contains: low-molecular peptides and free amino acids to a total amount of 0.5-6.0 % by weight of the extract dry mass, more specifically histidine, cystine, serine, alanine, valine, leucine, isoleucine, phenylalanine, glycine, lysine, proline, tyrosine, glutamine, asparagine, methionine; unsaturated fatty acids 1.0-10.0 % by weight of the extract dry mass, more specifically linoleic acid, linolenic acid and oleic acid; vitamins to a total amount of 1.0-6.0 % by weight of the extract dry mass, including retinoids 0.6-3.0 %; and minerals and microelements 1.0-6.0 % by weight of the extract dry mass.

The extract is prepared with water and/or organic solvent and/or oil with medicinal herbs:solvent ratio from 1:5 to 1:25 parts by weight. The quantity of the above-mentioned biologically active substances depends on the type of solvent used.

Besides retinoids, other vitamins contained in the extract according to the present invention are the wide range of vitamins of group B, vitamins C, D, E, P, H.

The group of minerals and microelements contained in the extract includes: Fe$^{3+}$, Mg$^{2+}$, Mn$^{2+}$, K$^+$, Na$^+$, Zn$^{2+}$, sulphur, phosphor, calcium.

Several enzymes activities such as kinases, oxidases, catalases, phosphatases, proteolytic enzymes are detected in the extract.

Products of nucleoproteins decomposition were found in the amount of 0.1-0.8 % by weight of the extract dry mass, which include: amino acids formed by hydrolysis of histones such as cysteine; phosphoric acid; nucleosides; ribose; purines; and pyrimidines, which assist in cell metabolism.

The extract also contains other active components known from the prior art. For example, an extract of Calendula officinalis L. contains: triterpene saponins,
calendulosides, oleanolic acid derivatives, lupeol derivatives, sesquiterpenes -
calenduline and derivatives thereof, essential oil, carotenoids, flavonoids, tan
compounds and mucous compounds, phytosterols, phytohormones, organic acids,
alkaloids, phitonicides. An extract of Hypericum perforatum L. contains: condensed
anthraquinone derivatives (hypericin), essential oils, carotenoids, sesquiterpenes,
flavonoids, biflavons, monomer catehins and epicatehins, tan compounds – tannins,
hyperforins, phenolic acids (chlorogenic acid), sterols, waxes, paraffins.

Proceeding from the biochemistry and the pathology of dermatosis, in
particular psoriasis, and the need for complex intervention, a composition of an
extract of medicinal herbs was created which acts on the anomalies to regulate the
metabolism, in order to restore the structure and function of the dermis tissues. To
this end, in the process of directed extraction the macromolecular compounds are
reduced to low-molecular fragments and constituent elements, where partial physico-
chemical transformations occur among them in a natural ionobalanced medium.

In the extract according to the present invention are found products of the
chlorophyll decomposition in a quantity 0.3-1.5% of the extract dry mass, which
include phytol, magnesium, chlorophyll porphyrins. Practically no chlorophyll in the
extract is detected (HPLC analysis).

The extract contains also compounds such as cycloheptanon and troponon
with cytostatic action regulating hyperproliferation, as well as thiolic compounds.

The high degree of hydrolysis of the polypeptides contributes for their nearly
complete assimilation by the dermis cells. They were found in a step-by-step
synthesis of scleroproteinic structures in the corneous layer of the epidermis,
composed mainly of keratinic proteins, with 14-19% content of the amino acid
cystine, which is synthesized in the presence of methionine, serine and retinoids as
regulator. The disulphidic bonds between the opposite cystinic molecules ensure the
stability of the keratins. Another determining factor for the formation of the
scleroproteinic structures is the essential amino acid histidine, which is dominant in
the formation of the granular layer of the epidermis. The essential amino acids, the
unsaturated fatty acids, the vitamins, including retinoids, the microelements and
other biologically active substances mentioned above have a specific effect on the
trophics and metabolism regulation. They take part in the biosynthesis of high energy compounds – nucleoside phosphates; phospholipids; proteoglycans, and in the metabolism of arachidonic acid and prostaglandins.

The presence of the free amino acids cystine, histidine, serine, methionine, glycine, proline, lysine, as well as retinoids, vitamins C, B and D and iron (Fe^{3+}) in the extract according to the present invention provides the basic constructive factors for the keratins, collagen and elastin. On the other hand, the cystine, serine, tyrosine and histidine content in combination with the electrophilic groups of Mg^{2+}, Mn^{2+}, Fe^{3+}, K^+, Na^+, Zn^{2+} are the basic constructive factors for the enzymes active center.

The functional groups of the serine, tyrosine, cysteine sulphhydryl group and particularly of the histidine imidazole group contained in the extract, which have a nucleophilic activity, in combination with the electrophilic groups of Mg^{2+}, Mn^{2+}, Fe^{3+} and the NH_3^+ groups of the proteids are the basic constructive factors for the enzymes catalytic centers. Vitamins B1, B2, B3, B5, and the metal ions Zn^{2+}, K^+, Na^+ participate as co-factors for many enzymes.

The complex extraction of Calendula officinalis L. and Hypericum perforatum L. in the above mentioned ratio produces an extract with multilateral modifications and biotransformations in a natural biological medium, which determines a different composition of the extract compared with the prior art and the obtaining of a pharmacological and pharmaco-kinetic effect significantly higher than in the separate application of the two extracts.

In one embodiment of the invention, in order to enhance the anti-inflammatory, painkilling, anti-itching, hyperproliferation-normalizing and/or sore-healing effect, the extract may contain additionally extractions of at least one of the medicinal herbs selected from the group: Lycopodium Clavatum L., Matricaria chamomilla L., Ruta graveolens L., Urtica dioica L., Uncaria tomentosa, Achillea millefolium L., Melissa officinalis L., Chelidonium majus L., Salvia officinalis L., Thymus sp. diversa, Taraxacum officinale Web., Genista tinctoria L., Alloe arborescens Mill, Uncaria tomentosa, Cotinus coggyria, Juglans regia L., Allium sativum L., Equisetum arvense L., Crataegus monogyna Jacq., Plantago lanceolata L., Symphytum officinale L., Juniperus communis L., Pithecolobium unguiscati, Hedera
helix L. The ratio of these medicinal herbs to the total mass content of Calendula officinalis L. and Hypericum perforatum L. is determined so as the quantities of low-molecular peptides and free amino acids, fatty acids, vitamins, minerals and microelements in the end extract would be higher than the lower limit of the above indicated quantities of these substances.

For example, an extract of Licopodium Clavatum L. in a quantity 15-35% of the total mass of Calendula officinalis L. and Hypericum perforatum L. added to the basic extract strengthens the curative effect of the main extract in cases of hyperproliferation, slowing down and regulating cell hyperproliferation, and also has an anti-itching effect.

In another embodiment of the invention, to the basic extract of Calendula officinalis L. and Hypericum perforatum L. is added an extract of at least one apian product: honey, royal jelly, beeswax, bees’ pollen, propolis, in a quantity 10-25% by weight of the basic extract of Calendula officinalis L. and Hypericum perforatum L. The apian products content in the extract widens the range of amino acids, enzymes, microelements and vitamins. They have a trophic, anti-inflammatory and metabolism-regulatory action.

The method for preparing the extract according to the invention is the following:

30 to 70% fresh plant material from Calendula officinalis L. and Hypericum perforatum L. is used and dried plant material for the remaining percentage up to 100%. The dried plant material is of particle size from 1 to 10 mm, and the fresh one – from 10 to 20 mm. The extraction is carried out with water, organic solvent and organic food oils, e.g. Olium olivarum (olive oil), in a herb:solvent ratio from 1:5 to 1:25. During the extraction constant contact between the components is ensured by optimum stirring.

The extraction is carried out at a temperature between 10°C and 78°C with duration as follows:

- Water extraction: 1/2 of the plant material intended for extraction is extracted with water in a ratio 1:6 for a period of 20 days at a temperature of 18°C.
The extract is decanted and 5 parts by weight of water are added to the residue. The extraction is carried out in 2 to 4 phases of total duration about 50 days, and at the phase borders the extract is stabilized with known preservatives and stabilizers such as esters of para-hydrobenzoic acid, nipagin, nipazol. The extracts are mixed, filtered, stabilized and concentrated.

- Extraction with organic solvent (chloroform, hexane, ether, ethanol, acetone): 1/4 of the plant material intended for extraction is extracted with 30% ethanol in a ratio 1:6 for 24 to 48 hours at a temperature of 25°C. The extract is decanted and the residue is further extracted with 4-6 parts by weight of 45% ethanol by means of a reflux condenser for 6 to 12 hours at a temperature of 78°C. The two alcoholic extracts are filtered, mixed and concentrated under vacuum and stabilized.

- Oil extraction: 1/4 of the plant material intended for extraction is extracted with vegetable oils such as olive oil in a ratio 1:5 for 5 days at a temperature of 30°C, 5 days at a temperature of 25°C, and 5 days at a temperature of 20°C.

The obtained water extract and organic solvent extract are mixed. The oil extract is stabilized with known antioxidants and included in the pharmaceutical formulation in the appropriate ratio.

When only water is used as a solvent, the procedure is according to the above described method for water extraction using the entire quantity of the plant material.

The values of pH during the water extraction process vary between 4 and 9.5.

When only oil is used as a solvent, the procedure is according to the above described method for oil extraction using the entire quantity of the plant material.

The extract according to the invention may be obtained by other known methods, which ensure a content of low-molecular peptides, free amino acids, unsaturated fatty acids, vitamins, minerals and microelements in the quantities specified above.

The composition for treatment of skin diseases according to the invention can be used in the following pharmaceutical formulations: unguent, cream, emulsion, gel, shampoo. When it is for internal application in the form of emulsion, sterile filtration of the extract is done.
As ointment base in the unguent is used liquid paraffin, glycerin stearate, vaseline, lanolin, white wax, cetaceum in a ratio from 9:1 to 15:1 to the extract quantity. The ointment base provides maximum percutaneous resorption of the biologically active substances contained in the medicinal herb extract. The unguent may also contain surface-active agent, as well as preservatives and stabilizers, for example sodium benzoate, nipagin, potassium sorbate.

Emulsion of the extract according to the invention is obtained by subjecting the extract to sterile filtration and then corrigence and stabilizer are added.

To obtain gel, the extract is filtered and diluted, then known preservatives and stabilizers are added in a ratio 1.5-4.0 parts by weight to 100 parts by weight of the extract, and also antioxidants, polymers and activators from 0.6 to 1.6 parts by weight.

The composition according to the invention is used for the treatment of dermatosis such as psoriasis, neurodermatitis, trophic sores, eczemas, acne, etc.

The advantages of the therapeutical composition against dermatosis according to the invention are the following: The drug acts upon the anomalies for elimination of the pathological aberrations in the metabolism. Wide-scoped and targeted support of the trophics is achieved in accordance with the specific requirements for correction of the anomalies. The drug has marked anti-inflammatory, soothing, anti-allergic, antimicrobial, targeted trophic, antioxidant and antitoxic effect. It regulates and stimulates the metabolic processes, normalizing the hyperproliferation (cytostatically) and the regeneration of the dermis tissues.

EXAMPLES

The present invention will now be illustrated by the following non-limiting Examples.

Example 1.

Water-ethanol-oil extract is obtained from: Calendula officinalis L. 3 parts by weight and Hypericum perforatum L. 2 parts by weight.

The extract contains low-molecular peptides and free amino acids to a total amount of 4.5%, more specifically histidine, cystine, serine, alanine, valine, leucine,
isoleucin, phenylalanine, glycine, lysine, proline, tyrosine, glutamine, asparagine, 
methionine; unsaturated fatty acids 5%, more specifically linoleic acid, linolenic acid 
and oleic acid; vitamins 4.5%, including retinoides 2%; minerals and microelements 
5

The method for preparing the extract is the following:

70% fresh plant material and 30% dried plant material from Calendula 
officinalis L. and Hypericum perforatum L. is used. The particle size of the dried 
plant material is from 1 to 10 mm, and of the fresh plant material – from 10 to 20 
mm. The extraction is made with water, 30% ethanol and 45% Olium olivarum. 
10

During the extraction constant contact between the components is ensured by 
stirring. The extraction is carried out step-by-step with duration as follows: Water 
 extraction: 1/2 of the plant material intended for extraction is extracted with water in 
a ratio 1:5 for 20 days at a temperature of 18°C. The extract is decanted and 5 parts 
by weight of water are added to the drug. The extraction continues for another 25 
days at a temperature up to 25°C and 5 days at a temperature of 30°C. The extracts 
15
are mixed, filtered, concentrated and stabilized.

Extract of 1/4 of the plant material is extracted with 30% ethanol in a ratio 
1:6 for 30 hours at a temperature of 25°C. The extract is decanted and the residue is 
further extracted with 45% ethanol by means of a reflux condenser for 8 hours at a 
temperature of 78°C. It is evaporated to a dry extract. The alcoholic extracts are dried 
20
under vacuum to obtain a dry extract.

Oil extraction: the remaining 1/4 of the plant material is extracted with olive 
oil in a ratio 1:8 during 5 days at a temperature of 30°C, 5 days at a temperature of 
25°C and 5 days at a temperature of 20°C. The extracts are mixed.

25

Example 2

Water extract of Calendula officinalis L. 3 parts by weight and Hypericum 
perforatum L. 1.5 parts by weight.

The extract contains low-molecular peptides and free amino acids to a total 
amount of 5%, more specifically histidine, cystine, serine, valine, leucine, isoleucin, 
phenylalanine, glycine, lysine, proline, tyrosine, glutamine, alanine, asparagine and
methionine; unsaturated fatty acids 2.0%, more specifically linoleic acid, linolenic acid and oleic acid; vitamins 4%, including retinoides 2%; minerals and microelements 4%.

The method for obtaining the water extract is the following: The whole quantity of the plant material is extracted with water in a ratio 1:5 for 20 days at a temperature of 18°C. The extract is decanted and 5 parts by weight of water are added to the drug. The extraction continues for another 25 days at a temperature up to 25°C, and 5 days at a temperature of 30°C. The extracts are mixed, filtered, concentrated and stabilized.

Example 3
Oil extract of Calendula officinalis L. 3 parts by weight and Hypericum perforatum L. 2.5 parts by weight.

The extract contains low-molecular peptides and free amino acids to a total amount of 1%, more specifically histidine, cystine, serine, valine, leucine, isoleucin, phenylalanine, glycine, lysine, proline, tyrosine, glutamine, alanine, asparagin and methionine; unsaturated fatty acids 9%, more specifically linoleic acid, linolenic acid and oleic acid; vitamins 3.5%, including retinoides 2.5%; minerals and microelements 1%.

The method for obtaining the extract is the following: The whole quantity of the plant material is extracted with olive oil in a ratio 1:5 for 5 days at a temperature of 30°C, 5 days at a temperature of 25°C, 5 days at a temperature of 20°C.

Example 4
To the water-ethanol-oil extract in Example 1 is added an extract of Licopodium Clavatum L. in a ratio of 1.2 parts by weight to the total quantity of Calendula officinalis L. and Hypericum perforatum L. Licopodium Clavatum L. provides anti-itching, painkilling, anti-rheumatic, anti-hyperproliferation action.

Example 5
To the water-ethanol-oil extract in Example 1 is added an extract of bees' pollen in a ratio of 0.5 parts by weight and an extract of propolis 0.5 parts by weight to the total quantity of Calendula officinalis L. and Hypericum perforatum L. These
apian products extend the scope of the trophic, anti-inflammatory, regenerative and metabolism-regulatory effect.

Examples 6 – 27

Table 1 describes extracts of Calendula officinalis L. and Hypericum perforatum L., obtained by the method described in Example 1, included in a pharmaceutical formulation. In Examples 7-21 the unguent contains extracts of the medicinal herbs listed in the table, obtained by known methods.

Example 28

613 patients suffering from different forms of psoriasis were treated. The cycle of treatment was 55 days on the average.

483 results were recorded in an average cycle of 55 days.

The control tests were made on the 15, 30, 45, 60 and 90 day. In 148 patients were registered 22 accompanying diseases, among which hypertonia – 53 patients, allergy – 10 patients, diabetes – 17 patients, hepatitis – 19 patients, podagra – 4 patients, ulcers – 9 patients. Hereditarily defective with psoriasis were 128 patients.

- 47 patients had complications – atropathy related to psoriasis.
- 268 patients had complete recovery with stable result.
- 126 patients showed clear improvement.
- In 52 patients till the 55 day partial improvement was observed.
- In 37 patients serious counter indications were found.

The majority of the last two groups had the disease for more than 15 years. They suffered the cumulative effect of accompanying diseases, hereditary defectiveness, and application of unsuitable therapy over large periods. This requires extension of the treatment to 90 days on the average and the application of an additional complex therapy. A large part of them show prospects for positive results.

The remaining 130 patients did not complete the average 55-day cycle of treatment. Some of them discontinued their treatment for objective reasons and did not follow the recommendations and prescriptions of the medical team, which is the reason for prolongation of the treatment. Nevertheless, this group also shows a similar picture to that of the group of 483 patients.
| Composition | Example No | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 |
|-------------|------------|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Calendula Officinalis L. | 6,0 | 3,0 | 2,5 | 3,2 | 2,5 | 2,5 | 3,0 | 3,2 | 2,5 | 2,3 | 2,5 | 2,3 | 2,5 | 2,0 | 2,5 | 2,5 | 2,0 | 4,0 | 3,0 | 2,0 | 2,0 | 4,0 |
| Hypericum perforatum L. | 2,0 | 1,5 | 1,8 | 2,0 | 2,5 | 2,5 | 2,0 | 2,1 | 1,8 | 1,8 | 2,0 | 2,0 | 1,5 | 2,0 | 2,5 | 1,8 | 1,5 | 2,0 | 2,0 | 2,0 | 2,0 | 2,5 |
| Plantago lanceolata | 1,4 | 0,8 | 1,0 | 1,0 | 0,5 | 1,0 | 1,0 |
| Matricaria chamomilla L. | 2,8 | 0,4 | 1,0 | 1,0 | 0,8 | 0,5 | 1,2 | 1,0 | 1,0 |
| Ruta graveolens L. | 1,4 | 2,5 | 1,0 | 1,0 |
| Urtica dioica L. | 1,4 | 1,0 | 1,5 | 1,5 | 0,5 | 0,5 | 0,5 |
| Uncaria tomentosa | 1,1 | 1,0 |
| Achillea millefolium L. | 1,3 | 1,0 | 0,5 | 0,5 | 1,0 |
| Melissa officinalis L. | 1,7 | 0,8 | 0,3 |
| Chelidonium majus L. | 1,0 | 1,0 |
| Salvia officinalis L. | 0,5 | 0,5 | 0,3 | 1,0 |
| Thymus sp. diversa | 0,3 | 0,5 | 1,0 | 0,1 | 0,3 |
| Radix Taraxacum officinalis Web. | 1,3 | 1,8 | 1,0 | 0,7 | 1,0 |
| Genista tinctoria | 1,5 | 0,8 |
| Alloe arborescens Mill. | 1,8 | 0,5 |
| Uncaria tomentosa | 1,5 |
| Cotinus coggyria | 1,1 | 1,5 | 0,5 |
| Juglans regia L. | 1,0 |
| Allium sativum L. | 1,5 | 0,5 |
| Equisetum arvense L. | 2,0 | 0,8 |
| Crataegus monogyna | 0,4 |
| Symphytum officinale | 1,0 |
| Juniperus communis L. | 1,0 |
| Picea abies L. | 1,0 |
| Hedera helix L. | 0,3 | 1,0 |
| Lycopodium clavatum L. | 1,8 |
| Royal jelly | 1,0 |
| Bees' pollen | 1,0 |
| Propolis | 1,0 |
| Ointment base | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 | up to 100 |
CLAIMS

1. Therapeutical composition for the treatment of dermatosis, in particular psoriasis, containing an extract of the medicinal herbs Calendula officinalis L. and Hypericum perforatum L., characterized in that the plant material from Calendula officinalis L. and Hypericum perforatum L. are in a ratio from 1:1 to 3:1 parts by weight and the extract includes low-molecular peptides and free amino acids to a total amount of 0.5-6.0% by weight of the extract dry mass, more specifically histidine, cystine, serine, alanine, valine, leucine, isoleucine, phenylalanine, glycine, lysine, proline, tyrosine, glutamine, asparagine and methionine; unsaturated fatty acids 1.0-10.0% by weight of the extract dry mass, more specifically linoleic acid, linolenic acid and oleic acid; vitamins 1-6% by weight, including retinoides 0.6-3.0% by weight of the extract dry mass; and minerals and microelements 1.0-6.0% by weight of the extract dry mass.

2. Therapeutical composition according to claim 1, characterized in that the extract is water extract and/or organic solvent extract and/or oil extract with medicinal herbs: solvent ratio from 1:5 to 1:25.

3. Therapeutical composition according to claim 1, characterized in that the extract may contain additionally extracts of at least one of the medicinal herbs selected from the group: Lycopodium Clavatum L., Matricaria chamomilla L., Ruta graveolens L., Urtica dioica L., Uncaria tomentosa, Achillea millefolium L., Melissa officinalis L., Chelidonium majus L., Salvia officinalis L., Thymus sp. diversa, Taraxacum officinale Web., Genista tinctoria L., Alloe arborescens Mill, Uncaria tomentosa, Cotinus coggyria, Juglans regia L., Allium sativum L., Equisetum arvense L., Crataegus monogyna Jacq., Plantago lanceolata L., Symphytum officinale L., Juniperus communis L., Pithecolobium unguisca, Hedera helix L.

4. Therapeutical composition according to claims 1 and 3, characterized in that the ratio of the said medical herbs according to claim 3 to the total mass content of Calendula officinalis and Hypericum perforatum is determined so as the quantities of low-molecular peptides and free amino acids, fatty acids, vitamins, minerals and
microelements in the end extract would be higher than the lower content limit of these substances.

5. Therapeutical composition according to claims 1 and 3, characterized in that to the said extract of Calendula officinalis L. and Hypericum perforatum L. is added an extract of at least one apian product: honey, royal jelly, beeswax, bees' pollen, propolis, in a quantity 10-25% by weight of the said extract of Calendula officinalis L. and Hypericum perforatum L.
INTERNATIONAL SEARCH REPORT

PCT/BG2004/000024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K35/78

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, NAPRALERT, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>RU 2 099 410 C1 (BOCHAROVA OLGA ALEKSEEVNA) 20 December 1997 (1997-12-20) abstract; examples 1,2</td>
<td>1-4</td>
</tr>
<tr>
<td>X</td>
<td>WO 97/42963 A (SHIKHASHVILI, NINO; DARSAVELIDZE, ZURAB) 20 November 1997 (1997-11-20) page 7, line 21 - page 8, line 11; claim 1; examples 1-3</td>
<td>1-5</td>
</tr>
<tr>
<td>X</td>
<td>GB 2 164 253 A (* DELTA VAS- MUANYAG-ES SZOLGALTATO IPARI SZOVETKEZET) 19 March 1986 (1986-03-19) page 1, right-hand column, line 90 - line 117 page 2, left-hand column, line 23 - line 47 claims 3,4,8; examples 1,2</td>
<td>1-5</td>
</tr>
</tbody>
</table>

X Further documents are listed in the continuation of box C. X Patent family members are listed in annex.

* Special categories of cited documents:
*A* document defining the general state of the art which is not considered to be of particular relevance
*E* earlier document but published on or after the international filing date
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
*O* document referring to an oral disclosure, use, exhibition or other means
*P* document published prior to the international filing date but later than the priority date claimed

*s* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*x* document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*y* document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search
11 April 2005

Date of mailing of the international search report
18/04/2005

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo ml, Fax (+31-70) 340-3016

Authorized officer
Ganschow, S
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>RU 2099410</td>
<td>20-12-1997</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BG 102995 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69709682 D1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 69709682 T2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 952839 T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0952839 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES 2142781 T1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 9742963 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL 126987 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 5997876 A</td>
</tr>
<tr>
<td>GB 2164253</td>
<td>19-03-1986</td>
<td>HU 33391 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH 662733 A5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3432793 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2570277 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 4614652 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 7674491 A</td>
</tr>
</tbody>
</table>