(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 February 2012 (02.02.2012)

PCT

(10) International Publication Number
WO 2012/013551 Al

(51) International Patent Classification:
A61K 36/28 (2006.01) ***A61P 17/04*** (2006.01)
A61K 36/9068 (2006.01) ***A61P 19/02*** (2006.01)
A61K 9/00 (2006.01)

(21) International Application Number:
PCT/EP20 11/062421

(22) International Filing Date:
20 July 201 1 (20.07.201 1)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2010A001373 26 July 2010 (26.07.2010) IT

(71) Applicant *(for all designated States except US):* INDENA S.p.A. [IT/IT]; Viale Ortles, 12, 1-20139 Milano (IT).

(72) Inventors; and
(75) Inventors/ Applicants *(for US only):* BOMBARDELLI, Ezio [IT/IT]; Via Val di Sole, 22, 1-20141 Milano (IT). MORAZZONI, Paolo [IT/IT]; Viale Ortles, 12, 1-20129 Milano (IT).

(74) Agent: MINOJA, Fabrizio; Bianchetti Bracco Minoja S.r.L, Via Plinio, 63, 1-20129 Milano (IT).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2012/013551 A1

(54) Title: FORMULATIONS CONTAINING EXTRACTS OF ECHINACEA ANGUSTIFOLIA AND ZINGIBER OFFICINALE WHICH ARE USEFUL IN REDUCING INFLAMMATION AND PERIPHERAL PAIN

(57) Abstract: Disclosed is a combination of lipophilic extracts of Zingiber officinale and Echinacea angustifolia for the treatment of itching, peripheral pain, superficial and deep inflammatory and painful states, pain associated with muscle spasms, herpes pain, and radiodermatitis caused by oncological radiotherapy, with or without fungal or bacterial infections.

FORMULATIONS CONTAINING EXTRACTS OF *ECHINACEA ANGUSTIFOLIA* AND *ZINGIBER OFFICINALE* WHICH ARE USEFUL IN REDUCING INFLAMMATION AND PERIPHERAL PAIN

Summary of the invention

The present invention relates to compositions containing lipophilic extracts of *Echinacea* spp. and *Zingiber officinale* which are useful in the topical treatment of itching, peripheral pain, superficial and deep inflammatory and painful states, and pain associated with muscle spasms. The formulations according to the invention are also particularly useful in the treatment of herpes pain and radiodermatitis caused by oncological radiotherapy, with or without fungal or bacterial infections.

The formulations can also be used in the cosmetic field to reduce oedema and irritative states of all kinds.

State of the art

Lipophilic extracts of *Echinacea* spp., preferably those of *Echinacea angustifolia* described in EP 0464298, possess anti-inflammatory activity when administered either topically or systemically. It has been demonstrated that their pharmacological activity is attributable to isobutylamides, ligands of the CB1 and CB2 cannabinoid receptors.

Isobutylamides possess immunostimulating activity which characterises the traditional and pharmaceutical use of *Echinacea* extracts.

The roots and rhizomes of *Zingiber officinale*, variously treated, are used as spices in India and China. The uses described in traditional medicine include the treatment of indigestion, flatulence, diarrhoea, coughing, and other correlated disorders. The extracts of this plant were particularly considered for their antinausea effect. However, the data reported in controlled clinical trials are contradictory, and the US Pharmacopoeia recommends a complete review

of the properties attributed to the plant due to the lack of convincing documentation. Some of the conflicting data are partly due to the instability of the active ingredients in the extracts normally used.

The extract used in the present invention is a lipophilic extract, stabilised and prepared with carbon dioxide under well-defined supercritical conditions.

Description of the invention

It has now surprisingly been discovered that the combination of lipophilic or partly hydrophilic extracts of *Echinacea* spp roots and rhizomes with lipophilic extracts of *Zingiber officinale* produces a potent analgesic and anti-inflammatory activity, greater than can be obtained with uncombined extracts of *Echinacea* and *Zingiber officinale.*

The combination according to the invention can be used in the treatment of peripheral pain of all kinds, ranging from diabetic neuropathy to radiodermatitis, joint and muscle pain of different origins and herpes pain, even in the absence of specific antiviral treatment.

Lipophilic extracts of *Echinacea* spp can be obtained by extraction from the roots or rhizomes with alcohols, ketones or aliphatic ethers, or preferably with carbon dioxide under supercritical conditions.

Extracts of *Zingiber officinale* roots and rhizomes can also be obtained by extraction with carbon dioxide under supercritical conditions.

For the preparation of the extracts contained in the compositions according to the invention, simultaneous extraction of the finely ground roots and rhizomes of *Echinacea* spp. and *Zingiber officinale* with carbon dioxide under supercritical conditions is preferred, in varying ratios which are regulated according to the titre of the biomasses of the active ingredients, in particular according to the isobutylamide content for *Echinacea* (expressed as pellitorine or other specific isobutylamides) and the gingerol content for

Zingiber officinale. The ratio of the two biomasses can range between 1:1 and 1:0.1, preferably 1:0.5. The extraction process with supercritical carbon dioxide guarantees the stability of the active components, preventing the formation of compounds such as shogaol and other inactive products of oxidation.

The finely ground biomasses are extracted for 1-10 hours, preferably 7 hours, at a temperature of between 40 and 60°C, preferably 50°C, and a pressure of between 200 and 260 bars, preferably 235 bars. The extract is collected in the condenser, and after elimination of water by solubilisation of the oily residue in ethyl acetate containing ascorbyl palmitate and dehydration on anhydrous sodium sulphate, it is concentrated until dry under vacuum at a temperature not exceeding 40° centigrade. The extract thus obtained can be directly diluted in oils in the presence of surfactants or phospholipids, or formulated with excipients suitable for administration to animals or humans.

In another embodiment, the invention provides a composition containing the combination of lipophilic or partly hydrophilic extracts of *Echinacea* spp roots and rhizomes with lipophilic extracts of *Zingiber officinale* as above described, together with physiologically compatible vehicles and excipients. In a preferred embodiment, the composition is in a form suitable for topical administration.

The composition according to the invention can be made by mixing the extracts obtained separately, so that the ratio between the isobutylamides obtained from *Echinacea* spp and gingerol from *Zingiber officinale* is between 1:1 and 1:0.1. For this purpose, an *Echinacea angustifolia* extract described in EP 0464298 can be used, and a lipophilic extract of *Zingiber officinale* prepared by extraction from the roots and rhizomes of the plant with carbon dioxide under supercritical conditions similar to those just described,

extracting the powder from the roots and rhizomes at pressures of between 230 and 260 bars, preferably 235 bars, and a temperature of between 40 and 60°C, preferably 50°C, for a time ranging between 1 and 10 hours, preferably seven hours; the extract is collected in the condenser and dehydrated in inert gas dissolved in n-hexane or heptane containing a lipophilic antioxidant, preferably ascorbyl palmitate or tocopherol, and concentrated under vacuum at a temperature not exceeding 40°C.

The *Echinacea angustifolia* root extract typically contains 15 to 45% of isobutyl amides, while the *Zingiber officinale* rhizome extract contains 15 to 30% gingerol together with other terpenes.

The topical compositions according to the invention typically contain 0.1 to 1% by weight of extracts of the two plant species, in particular 0.2 to 0.8% of the compound extract of the two species or 0.1 to 0.3% of *Zingiber officinale* extract and 0.2 to 0.5% of *Echinacea* extract.

The composition has proved particularly useful in the topical treatment of itching, peripheral pain, superficial and deep inflammatory and pain states and pain associated with muscle spasms. The formulations are also particularly useful in the treatment of herpes pain and radiodermatitis caused by oncological radiotherapy, with or without fungal or bacterial infections.

The compositions according to the invention can also be used in the cosmetic field to reduce oedema and irritative states of all kinds, including those caused by excessive exposure to sunlight.

The composition can be applied directly to the skin in the oil in which it is solubilised, or incorporated in creams or ointments suitable for administration. The treatment can be performed one to three times a day, applying a dose of 0.5-5 g of the topical formulation to the part of the body affected by the painful disorder.

The pharmaceutical or cosmetic compositions according to the invention will be formulated according to conventional techniques, such as those described in "Remington's Pharmaceutical Handbook", Mack Publishing Co., N.Y., USA. The examples below further illustrate the invention.

Example 1 - Oil containing compound extract of *Echinacea angustifolia* and *Zingiber officinale*

Extract of *Echinacea angustifolia* and *Zingiber officinale* (isobutylamides 10 mg/ gingerol 1.3 mg)	0.3 g
Vitamin E	1.0 g
Argan oil	q.s. for 100 ml

Example 2 - Oil/water emulsion containing compound extract of *Echinacea angustifolia* and *Zingiber officinale*

Extract of *Echinacea angustifolia* and *Zingiber officinale* (isobutylamides 10 mg/gingerol 1.3 mg)	0.5 g
Ascorbyl palmitate	0.5 g
Evening primrose oil	4.0 g
Polyethylene glycol-20-glyceryl stearate	10.0 g
CIO-C 18 triglycerides	10.0 g
Glycerin	5.0 g
Hydroxylated lanolin	0.5 g
Hydroxyethylcellulose	0.5 g
Parabens	0.2 g
Demineralised water	q.s. for 100.0 g

Example 3 - Cream containing compound extract of *Echinacea angustifolia* and *Zingiber officinale*

Extract of *Echinacea angustifolia* and *Zingiber officinale* (isobutylamides 20 g/ gingerol 2.6 g)	0.6 g
Vitamin E	1.0 g

Linseed oil	4.0 g
Stearic acid	12.0 g
Glycerin	10.0 g
Cetostearyl alcohol	2.0 g
Potassium hydroxide	0.9 g
Parabens	0.2 g
Demineralised water	q.s. for 100.0 g

Example 4 - Oil containing extracts of *Echinacea angustifolia* and *Zingiber officinale*

Echinacea angustifolia extract	0.2 g
Zingiber officinale extract	0.1 g
Ascorbyl palmitate	1.0 g
Argan oil	q.s. for 100 ml

Example 5 - Preparation of compound extract of *Echinacea angustifolia* and *Zingiber officinale*

10 Kg of a mixture of *Zingiber officinale* roots containing approx. 3% gingerol (1 part) and *Echinacea angustifolia* roots containing approx. 1% isobutylamides (3 parts) is finely ground and extracted with carbon dioxide under supercritical conditions at a temperature of 50°C and a pressure of 235 bars for 7 hours. After extraction, the solvent is eliminated and the extracted material, consisting of an oily residue, is recovered in the condenser and taken up with 1.5 L of ethyl acetate containing 0.5 g of ascorbyl palmitate. The organic solution is dehydrated on Na_2SO_4 and concentrated under vacuum at a temperature not exceeding 30°C. 110 g of a thick, dark yellow oil with a 20% isobutylamide and 12% gingerol content is obtained. This extract can be used "as is" in pharmaceutical and cosmetic formulations.

Example 6 - Preparation of lipophilic extract of *Zingiber officinale*

10 Kg of *Zingiber officinale* roots containing approx. 1.2% gingerol is

finely ground and extracted with carbon dioxide under supercritical conditions at a temperature of 50°C and a pressure of 235 bars for 7 hours. After extraction, the solvent is eliminated and the extracted material, consisting of an oily residue, is recovered in the condenser and taken up with 1.5 L of hexane containing 0.5 g of ascorbyl palmitate. The organic solution is dehydrated on Na_2SO_4 and concentrated under vacuum at a temperature not exceeding 40°C. 400 g of a thick, dark yellow oil with a 20% gingerol content is obtained. This extract can be used "as is" in pharmaceutical and cosmetic formulations.

Example 7 - Evaluation of analgesic activity in the rat

The analgesic activity of the composition according to the invention was evaluated with the tail-flick test in the rat. Before treatment, 3 basic measurements were conducted on the animals to ensure that they were suitable for the handling and apparatus involved. The parameters used were 15V of radiant heat and a 15-second cut-off (to prevent irreversible harm to the animals), with evaluation of the tail-flick. The animals were treated with 0.1 ml of oil according to the composition described in example 4, 5 cm from the start of the tail. The analgesic effect was measured 15 and 30 min. after administration. The two individual ingredients of the composition were evaluated with the same experimental model, in a formulation which contained the same amount of active ingredient as the composition described in example 4. The control animals were treated with 0.1 ml of the oil used to dissolve the two ingredients (carrier). The results are set out in Table 1 below.

Table 1

Treatment	Latency time			
	after 15 min.	% increase	after 30 min.	% increase
Carrier	4.5 ± 0.33	--	4.6 ± 0.45	--
Composition described in example 4	12.6 ± 0.61	180	8.5 ± 0.43	84.8
Echinacea angustifolia lipophilic extract	6.1 ± 0.44	35.5	4.8 ± 0.63	4.4
Zingiber officinale Lipophilic extract	4.2 ± 0.63	--	4.6 ± 0.48	--

Example 8 - Evaluation of analgesic activity in patients suffering from osteoarthritis of the knee

40 patients suffering from osteopathy of the knee with constant pain were randomised and treated topically with the oil described in example 1, a placebo (consisting of the carrier alone), or the individual ingredients dissolved in the placebo at the same concentrations as in the oil described in example 1. Efficacy was evaluated on an international analog pain scale with scores from 0 to 10 points, 10 indicating maximum pain and 0 the disappearance of pain. The effect was evaluated 15 and 60 minutes after treatment.

The results are set out in Table 2 below.

Table 2

Treatment	Pain (scores) at time		
	0	15 min.	60 min.
Carrier	8.3 ± 1.7	9.1 ± 2.2	8.2 ± 1.9
Composition described in example 1	9.4 ± 2.6	4.3 ± 0.9	2.5 ± 1.4
Echinacea angustifolia lipophilic extract	8.7 ± 1.4	7.1 ± 1.4	7.8 ± 2.6
Zingiber officinale Lipophilic extract	8.2 ± 1.6	7.2 ± 0.6	8.6 ± 1.8

Example 9 - Effect on radiation-induced itching

10 patients suffering from erythema caused by ultraviolet rays were treated with the quantity of a 0.1% solution in olive oil of the extract described in example 1 required to cover the irritated area. The irritation was significantly reduced only 15 minutes after application, while the itching disappeared immediately after application. The carrier proved to have no activity under the same conditions.

Example 10 - Soft gelatine capsules

Unit composition:

Lipophilic extract of *Zingiber officinale*	12.5 mg
Lipophilic extract of *Echinacea angustifolia*	5.0 mg
Soya lecithin	10.0 mg
Flaxeed oil	110.0 mg

Example 11 - Evaluation of analgesic activity in patients suffering from osteoarthritis of the knee

60 patients suffering from osteopathy of the knee with constant pain were randomised and treated orally with the capsules described in example 10, a placebo (consisting of the carrier alone), or the individual ingredients dissolved in the placebo at the same amount as in the capsules described in example 10. Efficacy was evaluated on an international analog pain scale with scores from 0 to 10 points, 10 indicating maximum pain and 0 the disappearance of pain. The effect was evaluated 60 and 120 minutes after treatment.

The results are set out in Table 3 below.

Table 3

Treatment	Pain (scores) at time		
	0	60 min.	120 min.
Carrier	7.6 ± 0.9	8.9 ± 1.2	7.4 ± 1.9
Capsules of example 10	8.3 ± 1.6	3.5 ± 1.9	2.1 ± 0.6
Echinacea angustifolia lipophilic extract	8.1 ± 0.9	8.1 ± 1.6	7.9 ± 1.6
Zingiber officinale Lipophilic extract	7.9 ± 1.1	7.7 ± 0.9	7.6 ± 0.9

CLAIMS

1. A combination of lipophilic extracts of *Zingiber officinale* and *Echinacea angustifolia* for use in the treatment of itching; peripheral pain; superficial or deep inflammatory and painful conditions; pain connected with muscular spasms; herpes pain; radiodermatitis induced by oncological radiotherapy, with or without fungal or bacterial infections; oedema and irritative skin conditions, including those due to excessive exposure to sunlight.

2. A combination as claimed in claim 1, in which the extracts of both species are obtained by extraction from roots or rhizomes with supercritical carbon dioxide.

3. A combination as claimed in claims 1-2, containing isobutylamides from *Echinacea angustifolia* and gingerol from *Zingiber officinale* in weight ratios ranging from 1:1 to 1:0.1.

4. A combination as claimed in claim 3, containing isobutylamides from *Echinacea angustifolia* and gingerol from *Zingiber officinale* in a weight ratio of 1:0.5.

5. A composition containing the combination of lipophilic extracts of *Zingiber officinale* and *Echinacea angustifolia* according to claims 1-4, together with physiologically-compatible vehicles and excipients, for use in the treatment of itching; peripheral pain; superficial or deep inflammatory and painful conditions; pain connected with muscular spasms; herpes pain; radiodermatitis induced by oncological radiotherapy, with or without fungal or bacterial infections; oedema and irritative skin conditions, including those due to excessive exposure to sunlight.

6. The composition of claim 5, which is in a form suitable for topical administration.

7. The composition of claims 5-6, in which the extracts are formulated in oils in the presence of surfactants or phospholipids.

8. Lipophilic extract of *Zingiber officinale* obtainable by extraction from the roots or rhizomes of the plant with carbon dioxide under supercritical conditions, under pressures ranging from 230 to 260 bars, at a temperature ranging from 40 to 60°C, for a time ranging from 1 to 10 hours.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/062421

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/28 A61K36/9068 A61K9/00 A61P17/04 A61P19/02
ADD.

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)
A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal , BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 2010/083967 A1 (INDENA SPA [IT] ; BOMBARDELLI EZIO [IT]) 29 July 2010 (2010-07-29) the whole document	8
X	WO 2005/053720 A1 (INDENA SPA [IT] ; BOMBARDELLI EZIO [IT]) 16 June 2005 (2005-06-16) page 3, lines 16-24; claims	1-7
X	WO 99/21007 A1 (PHARMAPRINT INC [US] ; UNIV SOUTHERN CALIFORNIA [US] ; KHWAJA TASNEEM A) 29 April 1999 (1999-04-29) page 5, lines 23-26; claims page 8, line 1	1-7

-/- .

[X] Further documents are listed in the continuation of Box C.

[X] See patent family 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" documentwhich 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

"T" 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 docu¬ments, 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	Date of mailing of the international search report
5 October 2011	19/10/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Frederich, Martin

1

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/062421

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2001/046523 A1 (NEWMARK THOMAS [US] ET AL) 29 November 2001 (2001-11-29) paragraphs [0006] - [0007], [0023] - [0027]; claims	8
X	WO 2008/070783 A2 (HERBALSCIENCE SINGAPORE PTE LT [US]; LI DAN [CN]; SYPERT GEORGE W [US]) 12 June 2008 (2008-06-12) page 32, last paragraph; claims	8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2011/062421

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010083967 A1	29-07-2010	CCAA 2750025 A1	29-07-2010
WO 2005053720 A1	16-06-2005	AT 359803 T	15-05-2007
		AU 2004294691 A1	16-06-2005
		BR PI0416846 A	13-02-2007
		CA 2546959 A1	16-06-2005
		CN 1886146 A	27-12-2006
		DE 602004006027 T2	27-12-2007
		DK 1713490 T3	17-09-2007
		EP 1713490 A1	25-10-2006
		ES 2286694 T3	01-12-2007
		IL 175846 A	24-12-2009
		JP 2007512271 A	17-05-2007
		KR 20060097127 A	13-09-2006
		PT 1713490 E	24-07-2007
		RU 2361601 C2	20-07-2009
		US 2007071839 A1	29-03-2007
WO 9921007 A1	29-04-1999	AU 1363499 A	10-05-1999
		CA 2307614 A1	29-04-1999
		EP 1025441 A1	09-08-2000
US 2001046523 A1	29-11-2001	NONE	
WO 2008070783 A2	12-06-2008	US 2008160116 A1	03-07-2008