

**COMPOSITIONS CONTAINING EXTRACTS OF *CURCUMA LONGA* AND  
*ECHINACEA ANGUSTIFOLIA* WHICH ARE USEFUL TO REDUCE  
PERIPHERAL INFLAMMATION AND PAIN**

Summary of the invention

The present invention relates to compositions containing, as their only active ingredients, an extract of *Curcuma spp*, optionally as curcumin in the form of a complex with phospholipids, and an extract selected from *Echinacea spp* extract or a lipophilic extract of *Zanthoxylum spp*, which are useful in the topical and systemic treatment of peripheral pain and of superficial and deep inflammatory and painful conditions. The compositions according to the invention are particularly effective in the treatment of osteoarthritis and rheumatoid arthritis in patients unable to tolerate long-term treatment with NSAIDs or steroids.

State of the art

Osteoarthritis is one of the major causes of physical disability in elderly people. As well as reducing the quality of life of millions of individuals all over the world, it also causes financial loss to both families and the community, because the costs of the care involved are very high.

Conventional treatments for osteoarthritis involve symptomatic treatment with analgesics and therapeutic treatment with non-steroidal anti-inflammatory drugs, which are known to induce serious side effects that often lead to discontinuance of the treatment. Similar considerations also apply to rheumatoid arthritis. For these reasons, research has also focused on phytotherapy medicaments and natural plant remedies in general.

Lipophilic extracts and alcoholic extracts of *Echinacea spp*. possess both topical and systemic anti-inflammatory activity attributable to their isobutylamide content, isobutylamides being ligands of the CB1 and CB2 cannabinoid receptors and vanilloid receptor TRPV1. The lipophilic extracts of *Echinacea angustifolia*

described in EP 0464298 are particularly effective in this respect, due to their high isobutylamide content.

The roots and rhizomes of turmeric (*Curcuma*) have been used as spices in India since time immemorial, and are also used in many industrialised countries today. Its active constituent is curcumin, the yellow compound that constitutes the main ingredient of curry and other traditional Indian dishes. The uses described in traditional medicine include the treatment of indigestion, flatulence and diarrhoea, and especially of inflammatory conditions and joint pain after long-term treatment. Many of these traditional uses have been confirmed by *in vitro* biochemical tests or pharmacology.

Curcumin is now one of the molecules most frequently investigated from the biochemical standpoint, and in recent years, as well as numerous publications of doubtful scientific value, controlled double-blind clinical trials have also been conducted according to the protocols of modern clinical pharmacology. Preliminary clinical trials have demonstrated the low bioavailability of the molecule, which is unstable at intestinal pH (half-life at pH 7 < 10 min), and its low oral absorption, which limit many of the applications indicated by the *in vitro* tests. Plasma concentrations of 50 ng are reported after administration of 12 g of compound, the secondary metabolites, glucuronides and sulphates also being measured.

Like many polyphenols, curcumin is poorly soluble in water and fats. The Applicant has therefore devised a patent WO2007101551 that describes its complexing with phospholipids to improve its bioavailability. Curcumin in phospholipid-complexed form provides improved systemic and topical absorption, which allows it to be administered to humans.

Clinical trials conducted on patients with osteoarthritis have demonstrated that long-term treatment with phospholipid-complexed curcumin (Belcaro et al, Alternative Medicine Review, 4, 338, 2010) gives favourable but still insufficient results due to the low level of pain reduction, which obliges patients to take NSAIDs.

However, significant improvements were only obtained after 8 months' treatment, and many patients had to use NSAIDs or other analgesics to alleviate the pain.

## DESCRIPTION OF THE INVENTION

5 It has now surprisingly been found that compositions containing as the only active ingredients *Curcuma spp* extract and an extract selected from *Echinacea spp* extract or lipophilic extract of *Zanthoxylum spp* possess potent analgesic and anti-inflammatory activity, which is greater than that found when the extracts are used separately.

10 Particularly favourable results have been observed with compositions containing phospholipid-complexed curcumin and lipophilic extracts of *Echinacea angustifolia*.

Good results have also been obtained by replacing the *Echinacea* extracts with extracts of other plants having a high isobutylamide content, especially  
15 lipophilic extract of *Zanthoxylum spp*.

The object of the invention is therefore compositions substantially consisting of an extract of *Curcuma spp* or curcumin, and an extract selected from *Echinacea angustifolia* extract or lipophilic extract of *Zanthoxylum bungeanum*, mixed with acceptable excipients.

20 The invention relates in particular to compositions substantially consisting of an extract of *Curcuma spp* or curcumin, and an extract selected from *Echinacea angustifolia* extract or lipophilic extract of *Zanthoxylum bungeanum*, mixed with acceptable excipients.

The compositions according to the invention may be administered orally or  
25 topically.

According to a preferred aspect, the compositions for oral administration will contain phospholipid-complexed curcumin in amounts ranging from 100 to 1000 mg, and *Echinacea* extract in amounts ranging from 1 to 200 mg, or

alternatively lipophilic extract of *Zanthoxylum spp.* in amounts ranging from 5 to 25 mg per oral dose unit. According to a particularly preferred aspect, the compositions for oral administration will contain 500 mg of phospholipid-complexed curcumin and 5 mg of *Echinacea extract*, or alternatively 10 mg of lipophilic extract of *Zanthoxylum spp.*, per oral dose unit.

According to a preferred aspect, the compositions for topical administration will contain phospholipid-complexed curcumin in amounts ranging from 0.1 to 0.5% by weight, and *Echinacea extract* in amounts ranging from 0.05 to 0.5% by weight, or alternatively lipophilic extract of *Zanthoxylum spp* in amounts ranging from 0.1 to 1% by weight. According to a particularly preferred aspect, the compositions for topical administration will contain 0.2% by weight of phospholipid-complexed curcumin, and 0.2% by weight of *Echinacea extract*, or alternatively 0.5% by weight of lipophilic extract of *Zanthoxylum spp*.

The compositions according to the invention can be used to treat peripheral pain of all kinds, ranging from diabetic neuropathy to joint and muscle pain of various origins. It is particularly important that the compositions according to the invention do not cause side effects in the gastrointestinal tract, to allow its use by patients with gastric problems who are unable to tolerate NSAIDs.

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 in accordance with EP464298.

Alcoholic extracts of *Echinacea spp* still containing a pharmacologically active amount of isobutylamides have proved effective provided that at least a minimal dose of 1 mg of isobutylamine complex is administered to the patient. The active clinical doses range from 0.5 mg to 10 mg, preferably 5 mg for a mean body weight of 70 Kg.

The lipophilic extract of *Zanthoxylum spp* can be prepared in accordance with WO 00/02570.

However, the compositions according to the invention provide almost immediate relief of patients' symptoms, with no need to use other medicaments. Patients with gastro-oesophageal reflux and at the pre-ulcerative stage are also able to take the compositions according to the invention.

## 5           **Pharmacological tests**

### 1. Tail-flick test in the rat

The analgesic activity of the compositions according to the invention (combination of phospholipid-complexed curcumin and *Echinacea* extract) was compared with that of the individual ingredients administered separately to rats. The  
10 results demonstrated a clear synergy between the two ingredients of the compositions according to the invention, as shown in Table 1 below.

The analgesic activity 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  
15 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 ointment of the composition described in example 4, 5 cm from the base 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  
20 same experimental model, in two separate formulations which contained the same amount of one of the active ingredients 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).

**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       |
| <i>Echinacea angustifolia</i> lipophilic extract | 6.1 ± 0.44   | 35.5       | 4.8 ± 0.63   | 4.4        |
| Phospholipid-complexed curcumin                  | 4.2 ± 0.63   | --         | 4.6 ± 0.48   | --         |

## 2. Analgesic activity in humans

40 patients suffering from bone disease of the knee with constant pain were randomised and treated with two tablets a day according to Example 1, one in the morning and one in the evening, or with a placebo (consisting of the carrier only), or with the individual ingredients added to the placebo formulation at the same concentrations as in the formulation described in example 1.

Efficacy was scored on an international analogue pain scale with scores from 0 to 10, 10 points indicating maximum pain and 0 the disappearance of pain. The effect was evaluated on the second day after administration of the tablet, in the mornings 60 and 120 minutes after treatment.

The results are set out in Table 2 below.

**Table 2**

| Treatment                                        | Pain scores at time |           |           |
|--------------------------------------------------|---------------------|-----------|-----------|
|                                                  | 0                   | 60 min    | 120 min   |
| Placebo                                          | 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 |
| <i>Echinacea angustifolia</i> lipophilic extract | 8.7 ± 1.4           | 7.4 ± 1.2 | 7.1 ± 2.6 |
| Phospholipid-complexed curcumin                  | 8.2 ± 1.6           | 7.9 ± 0.6 | 8.6 ± 1.8 |

### 3.Effect on osteoarthritis

Table 3 shows the results obtained, after treatment for up to three months with the composition according to the invention, on the global effect of osteoarthritis on the patients recruited, following the Karnofsky Scale for both selection and evaluation of efficacy ( J.Clin.Oncology 1984; 2:187-193).

The evaluation was conducted by measuring the distance travelled without pain, and with different degrees of pain, on a treadmill set to 3 Km/h and an inclination of 10%. 80 patients suffering from osteoarthritis of the knee were divided into two groups. After randomisation, one group was treated with the placebo and the other with the composition described in example 1. Pain was evaluated weekly during the treatment with the WOMAC index, and the humoral parameters, which constitute indexes of inflammatory parameters, were evaluated every month. (Table 4).

**Table 3. Results of distance travelled on treadmill**

| Treatment                          | Distance travelled at time |              |            |
|------------------------------------|----------------------------|--------------|------------|
|                                    | 0                          | 1 month      | 3 months   |
| Placebo                            | 84.6 metres                | 90.1 metres  | xx         |
| Composition described in example 1 | 78.4 metres                | 186.4 metres | 370 metres |

xx patients who left the trial for ethical reasons or were treated with other medicaments

5                    **Table 4. Evaluation of some inflammation markers**

| Inflammation indexes   | Placebo                    Composition<br>of example 1 |          |          |           |
|------------------------|--------------------------------------------------------|----------|----------|-----------|
|                        | T. 0                                                   | 3 months | 3 months | reduction |
| IL - 1 $\beta$ (pg/ml) | 0.91                                                   | 0.89     | 0.36*    | 60.4%     |
| IL - 6 (pg/ml)         | 1.37                                                   | 1.36     | 1.02*    | 26%       |
| sCD4OL                 | 2.47                                                   | 2.46     | 1.39*    | 43.9%     |
| ESR (mm/h)             | 35.64                                                  | 37.59    | 26.3*    | 26.2%     |

Pharmaceutical compositions in the form of gels, creams and ointments have proved particularly useful in the topical treatment of peripheral pain and of superficial and deep inflammatory and painful conditions. The combination can be applied directly to the skin in the oil in which it is solubilised, or incorporated in  
10                    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.

According to a further aspect, the compositions according to the invention  
15                    may be administered together with other substances having a useful or complementary activity.

The 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 - Tablets containing phospholipid-complexed curcumin and lipophilic extract of Echinacea**

|    |                                                            |           |
|----|------------------------------------------------------------|-----------|
|    | <b>Phospholipid-complexed curcumin</b>                     | 600.00 mg |
| 5  | <b><i>Echinacea ang.</i> extracted with CO<sub>2</sub></b> | 5.00 mg   |
|    | <b>standardised to 25% isobutylamides</b>                  |           |
|    | Mannitol                                                   | 345.25 mg |
|    | Sodium bicarbonate                                         | 120.00 mg |
|    | Magnesium carbonate                                        | 66.75 mg  |
| 10 | Croscarmellose sodium                                      | 39.00 mg  |
|    | Silicon dioxide                                            | 39.00 mg  |
|    | Talc                                                       | 20.00 mg  |
|    | Hydroxypropylcellulose                                     | 10.00 mg  |
|    | Magnesium stearate                                         | 5.00 mg   |
| 15 | Opadry White                                               | 35.00 mg  |
|    | Opadry Yellow                                              | 15.00 mg  |

**Example 2 - Soft gelatin capsules**

|    |                                                            |           |
|----|------------------------------------------------------------|-----------|
|    | <b>Phospholipid-complexed curcumin</b>                     | 300.00 mg |
|    | <b><i>Echinacea ang.</i> extracted with CO<sub>2</sub></b> | 5.00 mg   |
| 20 | <b>standardised to 25% isobutylamides</b>                  |           |
|    | Linseed oil                                                | to 700 mg |

**Example 3 - Tablets containing phospholipid-complexed curcumin and alcoholic extract of *Echinacea***

|    |                                                |           |
|----|------------------------------------------------|-----------|
|    | <b>Phospholipid-complexed curcumin</b>         | 400.00 mg |
|    | <b><i>Echinacea ang.</i> alcoholic extract</b> | 100.00 mg |
| 5  | <b>standardised to 1% isobutylamides</b>       |           |
|    | Mannitol                                       | 345.25 mg |
|    | Sodium bicarbonate                             | 120.00 mg |
|    | Magnesium carbonate                            | 66.75 mg  |
|    | Croscarmellose sodium                          | 39.00 mg  |
| 10 | Silicon dioxide                                | 39.00 mg  |
|    | Talc                                           | 20.00 mg  |
|    | Hydroxypropylcellulose                         | 10.00 mg  |
|    | Magnesium stearate                             | 5.00 mg   |
|    | Opadry White                                   | 35.00 mg  |

15 **Example 4 - Ointment containing phospholipid-complexed curcumin and lipophilic extract of *Echinacea angustifolia***

|    |                                                            |                |
|----|------------------------------------------------------------|----------------|
|    | <b>Phospholipid-complexed curcumin</b>                     | 200.00 mg      |
|    | <b><i>Echinacea ang.</i> extracted with CO<sub>2</sub></b> | 200.00 mg      |
|    | <b>standardised to 25% isobutylamides</b>                  |                |
| 20 | Linseed oil                                                | 4 g            |
|    | Stearic acid                                               | 12 g           |
|    | Glycerin                                                   | 10 g           |
|    | Cetostearyl alcohol                                        | 2 g            |
|    | Potassium hydroxide                                        | 0.9 g          |
| 25 | Paraben                                                    | 0.2 g          |
|    | Demineralised water                                        | q.s. for 100 g |

**CLAIMS**

1. Compositions consisting of phospholipid-complexed curcumin and an *Echinacea angustifolia* extract, mixed with acceptable excipients, wherein the  
5 compositions contain 0.2% w/w of curcumin complexed with phospholipids and 0.2% w/w of the *Echinacea angustifolia* extract or 500 mg of curcumin complexed with phospholipids and 5 mg of the *Echinacea angustifolia* extract.
2. Compositions according to claim 1 wherein the *Echinacea angustifolia*  
10 extract is prepared by extraction with supercritical carbon dioxide.
3. Compositions according to claim 1 or 2, for oral administration.
4. Compositions according to claim 1 or 2, for topical administration.  
15
5. Compositions according to any one of claims 1-4 for use in the treatment of peripheral pain, joint and muscle pain, inflammatory conditions, superficial pain and deep pain conditions.
- 20 6. Compositions according to any one of claims 1-4 for use in the treatment of osteoarthritis and rheumatoid arthritis.
7. Use of compositions according to any one of claims 1-4 in the manufacture of a medicament for the treatment of peripheral pain, joint and muscle pain,  
25 inflammatory conditions, superficial pain and deep pain conditions.
8. Use of compositions according to any one of claims 1-4 in the manufacture of a medicament for the treatment of osteoarthritis and rheumatoid arthritis.