US 20110218249A1

(19) United States

(12) Patent Application Publication

(10) Pub. No.: US 2011/0218249 A1

(43) Pub. Date: Sep. 8, 2011

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(54) **USE OF HYPERICUM PERFORATUM EXTRACTS IN THE TREATMENT OF NEUROPATHIC PAIN**

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(21) Appl. No.: **13/111,386**

(22) Filed: **May 19, 2011**

Related U.S. Application Data

(62) Division of application No. 12/919,360, filed on Sep. 15, 2010, filed as application No. PCT/EP2009/001211 on Feb. 19, 2009.

(30) **Foreign Application Priority Data**

Feb. 27, 2008 (IT) MI2008A 00316

Publication Classification

(51) **Int. Cl.**
A61K 31/122 (2006.01)
A61P 25/00 (2006.01)

(52) **U.S. Cl.** **514/680**

(57) **ABSTRACT**

Disclosed is the use of *hypericum* (*Hypericum perforatum* L.) tip extracts containing hypericin, of hypericin, to prepare medicinal products and/or food supplements for the treatment of neuropathic pain.

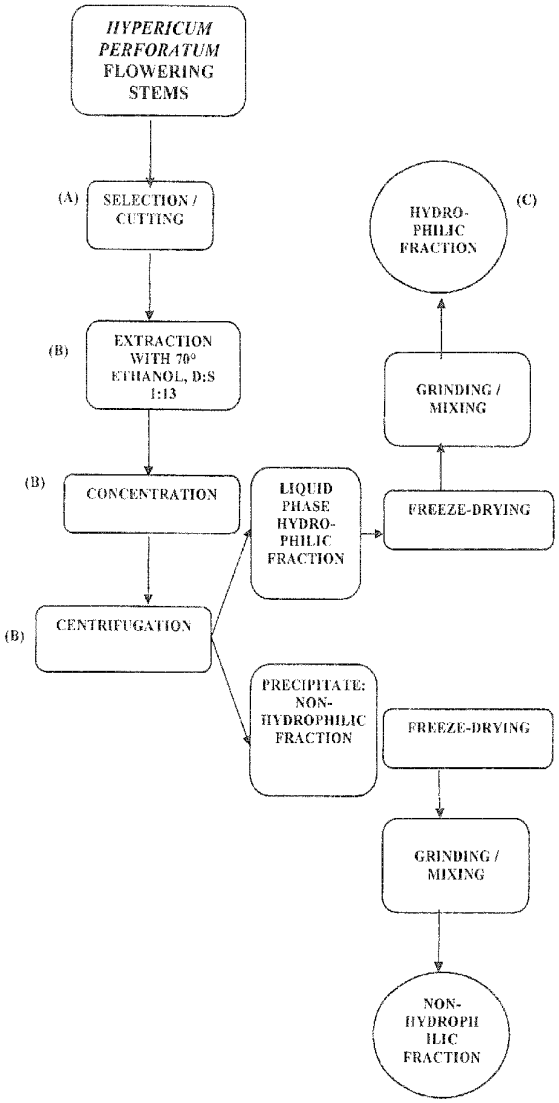


Figure 1

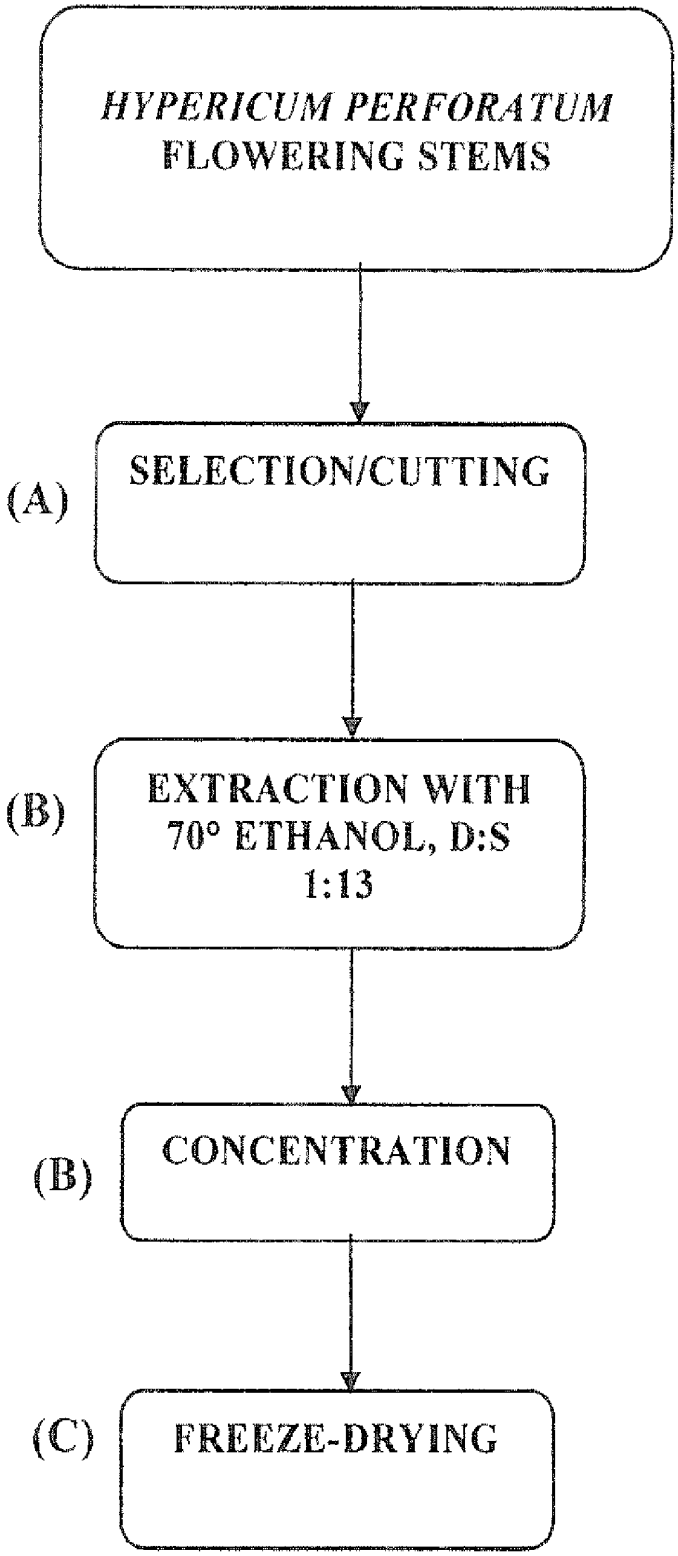
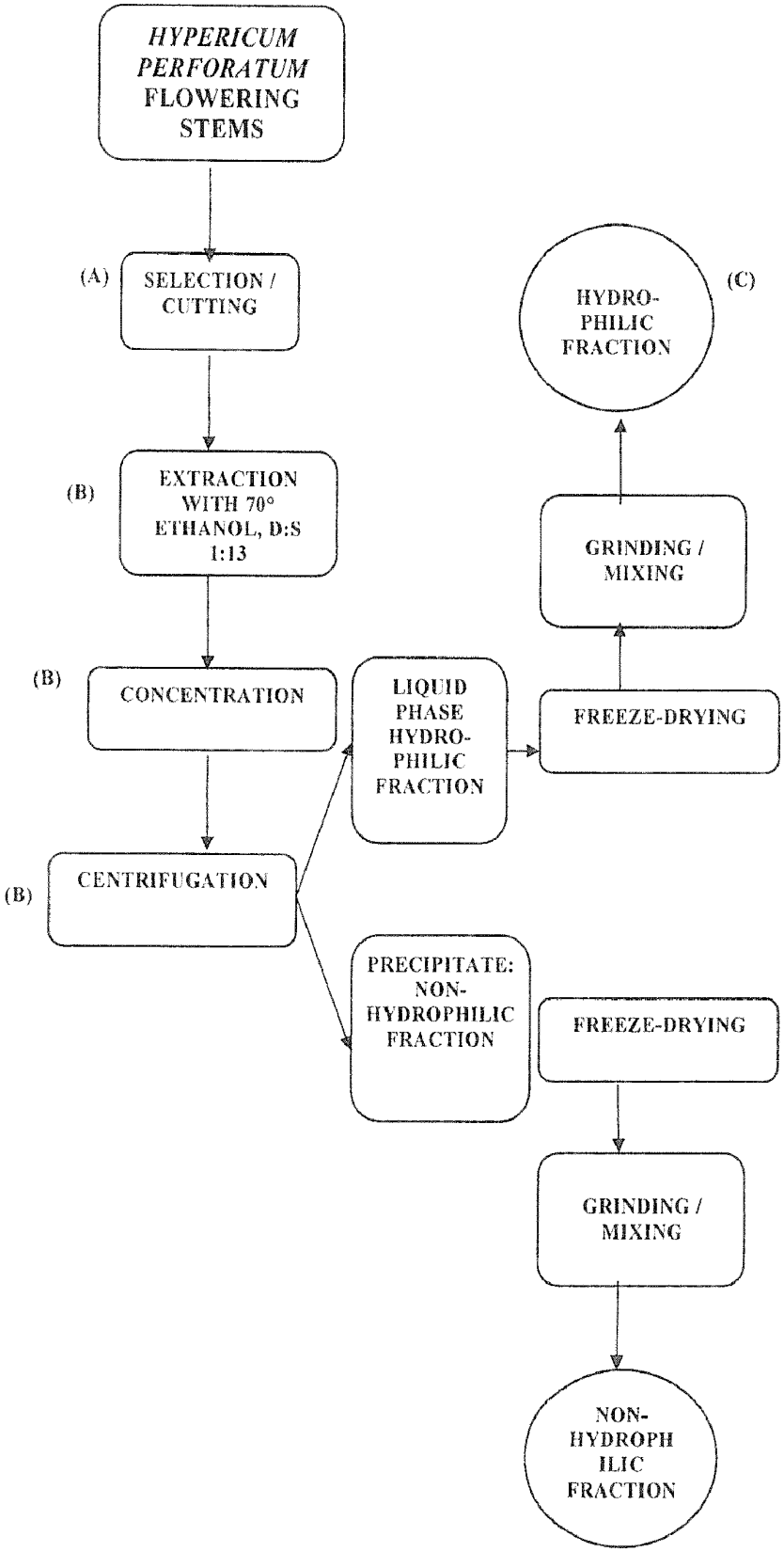

HYPERICUM PERFORATUM FLOWERING STEMS
(A)
SELECTION/CUTTING
(B)
EXTRACTION WITH 70° ETHANOL, D:S 1:13
(B)
CONCENTRATION
(C)
FREEZE-DRYING

Figure 2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(C)
HYDRO-PHILIC FRACTION
PRECIPITATE: NON-HYDROPHILIC FRACTION
FREEZE-DRYING
GRINDING / MIXING
NON-HYDROPH ILIC FRACTION

USE OF HYPERICUM PERFORATUM EXTRACTS IN THE TREATMENT OF NEUROPATHIC PAIN

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a divisional application which claims the benefit of pending U.S. patent application Ser. No. 12/919,360, filed Sep. 15, 2010, which is a National Stage entry of International Application No. PCT/EP2009/001211, filed Feb. 19, 2009, and claims priority of Italian Patent Application No. MI 2008 A 000316, filed Feb. 27, 2008. The disclosures of the prior applications are hereby incorporated herein in their entirety by reference.

[0002] The present invention relates to the use of extracts of *hypericum* (*Hypericum perforatum* L.) flowering stems and the components thereof for the preparation of pharmaceutical preparations and/or food supplements for the treatment of various forms of neuropathic pain (caused by chemotherapy drugs, mononeuropathy or osteoarthritis).

BACKGROUND TO THE INVENTION

[0003] Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".

[0004] Within this definition a particular type of pain associated with neurological abnormalities, called neuropathic pain, is becoming increasingly important due to its significant, growing worldwide prevalence. Neuropathic pain is defined as "pain initiated or caused by a primary lesion or dysfunction in the nervous system", which may take the form of dysaesthesia, allodynia, hyperpathy, stinging or stabbing pain.

[0005] Neuropathic pain is distinguished from other types of commonly reported (nociceptive) pain, including headache, backache, and other types of musculoskeletal pain, and comprises a heterogeneous group of conditions which cannot be explained by a single etiology or a particular anatomical lesion.

[0006] These disorders of the structures of the central or peripheral nervous system include various neuropathies (diabetic neuropathy, post-herpetic neuropathy, inflammatory neuropathies, neuropathy caused by alcohol abuse and neuropathy associated with HIV/AIDS infection), and can derive from various toxins (such as neurotoxins), acute trauma (including surgical traumas), chronic trauma (such as repetitive stress syndrome), mononeuropathies, such as carpal tunnel syndrome (the most common type of mononeuropathy, which affects 2.8% to 4.6% of the adult population), and disorders of the central nervous system (such as stroke, multiple sclerosis, cerebral ischaemia, Parkinson's disease, spinal cord lesions and head injuries).

[0007] The disorder is not easy to diagnose, because although the nerve produces continual painful discharges, it is often anatomically intact.

[0008] Neuropathic pain covers a variety of pathological states and presents with a variety of symptoms, which have the following common denominators:

[0009] pain is perceived in the absence of a permanent, identifiable tissue lesion or process;

[0010] unpleasant, abnormal or unusual sensations (dysaesthesia) are present, frequently described as stinging or electric shocks;

[0011] brief episodes of paroxystic stabbing or piercing pain are present;

[0012] the pain appears some time after the lesion that triggered it

[0013] the pain is perceived in a region with a sensory deficit;

[0014] even mild stimuli are painful (allodynia);

[0015] marked summation and persistent activity occur after the application of repeated stimuli.

[0016] It is estimated that neuropathic pain affects up to 3% of the population, and that some 1 to 5% of European adults suffer from chronic pain.

[0017] According to the literature, in the USA the problem of neuropathic pain is potentially onerous for the national insurance systems, with a prevalence of 1.5%.

[0018] 80% of patients with tumours at an advanced stage present neuropathic symptoms.

[0019] Chronic neuropathic pain is a major problem in neurology because it is frequent and often disabling, due to its unpleasant, chronic nature.

[0020] It is also a type of pain which does not respond well to the most common analgesics, such as acetylsalicylic acid, paracetamol or the most common non-steroidal anti-inflammatory drugs.

[0021] The aim of pharmacological treatments should be to prevent pain, but in practice, the most that can be achieved is to reduce the pain to a bearable level.

[0022] At present, no class of drugs has proved universally effective for patients with neuropathic pain.

[0023] "Off-label" drugs belonging to the following categories are generally used, but cause serious side effects in the long term:

[0024] antidepressants

[0025] anticonvulsants (gabapentin)

[0026] opioids (methadone, oxycodone)

[0027] tramadol

[0028] lidocaine

[0029] cytokine-inhibiting anti-inflammatories.

[0030] When these drugs are effective, they reduce pain by 25-40% in 40-60% of patients.

[0031] Moreover, numerous adverse effects are caused by continuous use of these drugs.

[0032] Neuropathic pain therefore represents a major clinical challenge due to its severity, chronic nature, resistance to the usual treatments and serious effect on the quality of the life.

[0033] The main research into this disorder uses experimental metabolic, pharmacological or trauma models in rodents, which reproduce the characteristics of human pain symptoms (Ref 1-7).

[0034] *Hypericum*, also known as St. John's Wort, consists of the flowering stems of *Hypericum perforatum*. It contains a large number of different classes of substances: naphthodianthrone derivatives such as hypericin, pseudohypericin and isohypericin, and phloroglucinol derivatives such as hyperforin. It also contains flavonoids such as hyperoside, rutin, I3,II8-biapigenin, quercetin, quercitrin and isoquercitrin, procyanidins, essential oil and xanthones.

[0035] It is widely used in modern phytotherapy to treat some forms of mild or moderate depression and psychovegetative problems, with effective results at the dose of 500-

1050 mg of extract/day divided into 2-3 doses, for 2-4 weeks, and fewer side effects than treatment with synthetic antidepressants.

[0036] *Hypericum perforatum* extracts have been tested in many experimental pharmacological and clinical trials, which fully support its use for depression, but many questions about its characteristics still remain unanswered. A number of action mechanisms have been suggested to explain its antidepressant effects: 1) non-selective serotonin, noradrenaline and dopamine reuptake inhibition; 2) increased density of the serotoninergic, dopaminergic and GABA receptors; 3) increased affinity for the GABA receptors; 4) inhibition of the enzyme monoamine oxidase (MAO). The identity of the active components is still in doubt, and its pharmacological activity seems to be complex and determined by the concomitant effects of a number of active substances. Hypericin has been identified as "the" active ingredient, but a new component, hyperforin, which was recently identified, seems to play an important part in the efficacy of the plant, while flavonoids, in particular rutin, have been identified as compounds which can influence its activity (Ref. 8-15).

[0037] A clinical trial (16) published in 2000 describes the inefficacy of a *hypericum* extract in the treatment of neuropathies.

[0038] Other studies describe the analgesic activity of *hypericum*, but they were conducted on different species from *Hypericum perforatum*, the extracts were not chemically characterised, the administration route was often not oral, and above all, they were evaluated on non-neuropathic pain models (hot plate test, writhing test, Ref. 16-22).

BRIEF DESCRIPTION OF THE DRAWINGS

[0039] FIG. **1** shows a flow chart of a method of preparing total freeze-dried extracts: and

[0040] FIG. **2** shows a flow chart of a method of preparing freeze-dried extracts of a hydrophilic fraction of *hypericum.*

DESCRIPTION OF THE INVENTION

[0041] Freeze-dried extracts of *hypericum* (*Hypericum perforatum*) flowering stems and one of its components, hypericin, have proved effective in reducing the symptoms of neuropathic pain in various experimental models, following oral administration.

[0042] The studies were conducted on rodents, which have always constituted a good animal model to reproduce the characteristics of human pain symptoms and predict possible remedies.

[0043] The freeze-dried extracts can derive from freeze-drying of either the whole plant material extracted with water-ethanol solvent, or of the most hydrophilic component of the plant.

[0044] The active closes of freeze-dried *hypericum* extracts range from 10 mg/kg to 100 mg/kg.

[0045] The freeze-dried extracts preferably derive from extraction of the whole plant with water-alcohol solvents (0-100% ethanol, methanol, isopropanol, etc.) or water-acetone solvents (0-100%) and separation and freeze-drying of a more hydrophilic component from the plant.

[0046] Freeze-dried *hypericum* extracts preferably have a content of naphthodianthrone derivatives (hypericin+pseudohypericin) amounting to not less than 0.25%, evaluated by the HPLC method (minimum 0.025 mg per kg of body weight).

[0047] One of the naphthodianthrone derivatives, hypericin, has proved active at a dose corresponding to its concentration in freeze-dried extracts.

[0048] The phloroglucinol derivatives isolated (hyperforin and adihyperforin) have proved unable to reduce neuropathic pain.

[0049] Up to the dose of 3000 mg/kg per os the freeze-dried extract does not change the animal's behaviour, as demonstrated by the fact that the number of falls from the rotating rod consecutively declines as the sessions are repeated, demonstrating that the animals' motor coordination is wholly comparable to that of the controls (Ref. 29 Rota Rod test).

[0050] When analyzed in terms of numerous parameters (behaviour, movement, muscle tone, autonomic signs), the extracts did not cause any alteration. The scores of the treated animals did not differ from those of the controls (Ref. 28 Irwin test).

[0051] The invention is described in greater detail in the Examples and Preparations below.

[0052] Preparation 1. Total Freeze-Dried Extract

[0053] FIG. **1** shows the flow chart of the preparation method. The freeze-dried *hypericum* (*Hypericum perforatum*) flowering stem extract is prepared from *hypericum* flowering stems. After drying and selection of the tips, extraction is performed with a water-ethanol solution containing, 50-80% alcohol, with a plant:solvent ratio of 1:13.

[0054] The solution is concentrated under reduced pressure to remove the ethanol, and dried by a freeze-drying process in suitable freeze-dryers.

[0055] Preparation 2. Freeze-Dried Extract of the Hydrophilic Fraction

[0056] FIG. **2** shows the flow chart of the preparation method.

[0057] The freeze-dried extract of the hydrophilic fraction of *hypericum*, containing polar water-soluble substances, was prepared by a process of physical separation of the non-hydrophilic substances, and centrifugation with a decanter. The two fractions were then freeze-dried separately.

[0058] The freeze-dried extract was chemically characterised by HPLC analysis, which showed a total hypericin concentration (hypericin+pseudohypericin) of 0.27 to 0.37%.

Example 1

Oxaliplatin-Induced Neuropathy

[0059] A reduction in the pain threshold was induced by administering oxaliplatin 2.4 mg/kg for 5 consecutive days for a total of 3 weeks. By the end of the treatment period, the pain perception threshold of the rats was statistically lower than that of the controls (Ref. 23).

[0060] The total freeze-dried extract at the dose of 30 and 60 mg/kg of body weight proved to be active to a statistically significant extent.

TABLE 1a

DOSE-RESPONSE CURVE OF *HYPERICUM* EXTRACT ON OXALIPLATIN-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)			
TREATMENT i.p.	TREATMENT MG/KG P.O.	Pre-test	3rd week + 15 min.	3rd week + 30 min	3rd week + 45 min
SALINE	CMC	57.4 ± 3.5	61.8 ± 5.4	67.4 ± 6.3	62.3 ± 5.4
OXALIPLATIN	CMC	22.6 ± 4.6	25.1 ± 6.1	26.9 ± 5.4	24.3 ± 6.6
OXALIPLATIN	*HYPERICUM* EXTRACT 30 mg/kg	21.7 ± 1.2	58.1 ± 3.5*	67.8 ± 2.0*	29.1 ± 2.0
OXALIPLATIN	*HYPERICUM* EXTRACT 60 mg/kg	24.5 ± 1.3	48.2 ± 4.6*	25.7 ± 2.4	21.5 ± 0.0

Oxaliplatin 2.4 mg/kg−1 for 5 consecutive days a week (15 i.p. injections - cumulative dose 36 mg/kg)

^P < 0.05

*p > 0.01

[0061] The freeze-dried extract of the hydrophilic fraction at the dose of 30 mg/lag of body weight proved active to a statistically significant extent in the oxaliplatin-induced neuropathy pain test.

TABLE 1 b

DOSE-RESPONSE CURVE OF HYDROPHILIC FRACTION OF *HYPERICUM* EXTRACT ON OXALIPLATIN-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)			
TREATMENT i.p.	TREATMENT MG/KG P.O.	PRE-TEST	3rd week + 15 min.	3rd week + 30 min	3rd week + 45 min
SALINE	CMC	57.4 ± 3.5	61.8 ± 5.4	67.4 ± 6.3	62.3 ± 5.4
OXALIPLATIN	CMC	22.6 ± 4.6	25.1 ± 6.1	26.9 ± 5.4	24.3 ± 6.6
OXALIPLATIN	HYDROPHILIC *HYPERICUM* EXTRACT 30 mg/kg	21.0 ± 2.0	42.0 ± 1.9*	63.0 ± 1.9*	14.5 ± 1.0

Oxaliplatin 2.4 mg/kg−1 for 5 consecutive days a week (15 i.p. injections - cumulative dose 36 mg/kg)

^ P < 0.05

*p > 0.01

Example 2

Mononeuropathy Induced by Ligature of the Sciatic Nerve

[0062] Neuropathic pain is characterised by the development of an altered perception of pain, which is manifested as continuous spontaneous pain and hyperalgesia. In this model, the rats were anaesthetised with chloral hydrate 400 mg/kg i.p. or sodium pentobarbital 40 mg/kg i.p. The sciatic nerve was then exposed at thigh level by retracting the femoral biceps. Proximally to the trifurcation of the sciatic nerve, approx. 7 mm of nerve was released from the membranes and 4 loose ligatures were tied round the nerve, approx. 1 mm apart. In another group of animals an identical incision was made, but without the nerve ligature (sham operation). Neuropathy developed in 14 days. The tests with the potentially analgesic substances were performed on the 14th and 21st days after the operation using the paw pressure test (ref. 24).

[0063] The total freeze-dried extract at the dose of 10, 30, 60 and 100 mg/kg of body weight proved to be active to a statistically significant extent.

TABLE 2a

EFFECT OF *HYPERICUM* EXTRACT IN A RIGHT-SIDE MONONEUROPATHY MODEL IN RATS, EVALUATED WITH THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)			
TREATMENT		Before	After treatment		
i.p.	PAW	treatment	15 min	30 min	45 min
CMC	L	60.5 ± 3.8	61.8 ± 3.7	64.6 ± 3.3	59.8 ± 3.2
CMC	R	22.8 ± 2.2	21.6 ± 3.5	23.0 ± 2.6	21.9 ± 3.7
HYPERICUM	L	56.2 ± 6.6	56.2 ± 7.2	58.7 ± 3.9	51.2 ± 4.3
EXTRACT	R	20.9 ± 4.0	22.5 ± 3.2	33.7 ± 4.7 ^	18.7 ± 2.4
10 mg/kg					
HYPERICUM	L	63.3 ± 5.7	68.8 ± 4.4	73.3 ± 6.7	51.7 ± 7.5
EXTRACT	R	20.3 ± 4.4	59.8 ± 3.1 *	65.5 ± 1.7 *	31.3 ± 1.7
30 mg/kg					
HYPERICUM	L	62.6 ± 3.0	68.5 ± 4.1	77.6 ± 4.3	60.7 ± 2.2
EXTRACT	R	21.9 ± 2.4	37.0 ± 2.8 ^	41.8 ± 4.4 *	22.7 ± 2.4
60 mg/kg					
HYPERICUM	L	62.8 ± 1.7	72.2 ± 2.4	78.6 ± 2.0	62.5 ± 3.8
EXTRACT	R	21.3 ± 2.7	27.5 ± 4.3	31.5 ± 4.3 *	20.5 ± 2.9
100 mg/kg					

^ $P < 0.05$
* $p > 0.01$

[0064] The freeze-dried extract of the hydrophilic fraction at the doses of 10, 30, 60 and 100 mg/kg of body weight proved active to a statistically significant extent, as shown in Table 2h below.

TABLE 2 b

EFFECT OF HYDROPHILIC FRACTION OF *HYPERICUM* EXTRACT IN A RIGHT-SIDE MONONEUROPATHY MODEL IN RATS, EVALUATED WITH THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)			
TREATMENT		BEFORE	AFTER TREATMENT		
MG/KG P.O.	PAW	TREATMENT	15 min	30 min	45 min
CMC	L	60.5 ± 3.8	61.8 ± 3.7	64.6 ± 3.3	59.8 ± 3.2
CMC	R	22.8 ± 2.2	21.6 ± 3.5	23.0 ± 2.6	21.9 ± 3.7
HYDROPHILIC	L	60.9 ± 4.7	62.5 ± 5.8	61.3 ± 6.0	58.2 ± 3.0
HYPERICUM	R	20.3 ± 2.9	33.5 ± 3.3	41.6 ± 3.5 *	19.8 ± 6.0
EXTRACT					
10 mg/kg					
HYDROPHILIC	L	59.4 ± 4.6	67.5 ± 4.8	63.6 ± 2.4	58.7 ± 3.1
HYPERICUM	R	22.3 ± 2.4	55.1 ± 3.2 *	62.0 ± 3.5 *	26.5 ± 3.3
EXTRACT					
30 mg/kg					
HYDROPHILIC	L	60.4 ± 3.6	65.8 ± 2.0	71.2 ± 3.7	57.7 ± 4.8
HYPERICUM	R	20.2 ± 2.3	52.4 ± 3.7 *	59.7 ± 3.0 *	24.5 ± 3.2
EXTRACT					
60 mg/kg					
HYDROPHILIC	L	63.7 ± 3.5	71.2 ± 4.3	73.0 ± 2.9	61.2 ± 3.1
HYPERICUM	R	23.5 ± 3.9	30.2 ± 3.4	35.8 ± 2.5 *	20.3 ± 3.3
EXTRACT					
100 mg/kg					

^ $P < 0.05$
* $p > 0.01$

Example 3

Paclitaxel-Induced Neuropathy

[0065] The total freeze-dried extract at the doses of 30 and 100 mg/kg of body weight and the extract of the hydrophilic fraction at the dose of 30 mg/kg proved active to a statistically significant extent in the paclitaxel-induced neuropathic pain test (Ref 25)

TABLE 3

EFFECT OF *HYPERICUM* EXTRACT (30 and 100 mg/kg^{-1} p.o.) AND THE HYDROPHILIC FRACTION ON PACLITAXEL-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)			
TREATMENT	TREATMENT	Before treatment			
i.p.	p.o.	Pre-test	15 min	30 min	45 min
SALINE	SALINE	57.2 ± 3.9	62.6 ± 4.4	58.3 ± 4.7	56.9 ± 3.9
PACLITAXEL	SALINE	43.7 ± 4.2	39.6 ± 3.8	41.9 ± 4.3	42.5 ± 4.9
SALINE	*HYPERICUM* EXTRACT 30 mg/kg BATCH 7I0525	62.6 ± 3.3	59.8 ± 4.4	57.6 ± 4.7	60.1 ± 4.6
PACLITAXEL	*HYPERICUM* EXTRACT 30 mg/kg BATCH 7I0525	40.5 ± 3.8	50.3 ± 3.4 *	48.0 ± 4.0	36.6 ± 4.2
PACLITAXEL	*HYPERICUM* EXTRACT 100 mg/kg BATCH 7I0525	39.6 ± 3.3	51.6 ± 3.1 *	46.3 ± 3.9	39.5 ± 4.0
PACLITAXEL	HYDROPHILIC FRACTION 30 mg/kg BATCH 7I0660	38.3 ± 3.9	49.2 ± 3.8 *	44.0 ± 3.5	33.8 ± 3.7

Treatment: Paclitaxel 0.5 mg/kg^{-1} was injected i.p. for four days (days 1, 3, 5 and 8). The cumulative dose of Paclitaxel was 2.0 mg/kg^{-1}. The test was performed 14-15 days after the last injection of paclitaxel. Vehicle: Saline: ethylene oxide 9:1 8 rats per group (two experiments).
* $P < 0.05$; versus rats treated with paclitaxel.

Example 4

Vincristine-Induced Hyperalgesia

[0066] A reduction in the pain threshold was obtained in the rat by i.v. administration of vincristine (150 gamma/kg i.v. every 2 days for 5 days until the cumulative dose of 750 gamma/kg was reached); the test (paw-pressure) was conducted 4 days after the last injection (Ref 26). Alternatively, the vincristine was applied (brushed) directly onto the sciatic nerve. The total freeze-dried extract at the doses of 30 and 100 mg/kg of body weight and the freeze-dried extract of the hydrophilic fraction at the dose of 30 mg/kg proved active to a statistically significant extent.

TABLE 4

EFFECT OF *HYPERICUM* EXTRACT (30 and 100 mg kg−1 p.o.) AND THE HYDROPHILIC FRACTION ON VINCRISTINE-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)				
TREATMENT	TREATMENT	Before treatment				
mg kg−1 i.v.	mg kg−1 p.o.	Pre-test	15 min	30 min	45 min	60 min
SALINE	SALINE	61.6 ± 3.3	57.2 ± 4.5	62.4 ± 4.0	58.3 ± 4.1	61.6 ± 5.3
VINCRISTINE	SALINE	35.2 ± 3.4	33.8 ± 4.5	35.1 ± 3.6	36.2 ± 3.7	34.9 ± 2.8
SALINE	*HYPERICUM* EXTRACT 30 mg/kg BATCH 7I0525	56.3 ± 3.3	63.4 ± 4.0	61.6 ± 3.8	57.3 ± 4.4	58.7 ± 3.3

TABLE 4-continued

EFFECT OF *HYPERICUM* EXTRACT (30 and 100 mg kg−1 p.o.) AND THE HYDROPHILIC FRACTION ON VINCRISTINE-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)				
TREATMENT	TREATMENT	Before treatment				
mg kg−1 i.v.	mg kg−1 p.o.	Pre-test	15 min	30 min	45 min	60 min
VINCRISTINE	*HYPERICUM* EXTRACT 30 mg/kg BATCH 7I0525	34.9 ± 3.1	52.6 ± 4.2*	51.9 ± 4.5*	38.3 ± 5.0	34.9 ± 5.2
VINCRISTINE	*HYPERICUM* EXTRACT 100 mg/kg BATCH 7I0525	33.90 ± 3.5	48.2 ± 4.1*	47.5 ± 4.7*	35.7 ± 4.1	
VINCRISTINE	*HYPERICUM* EXTRACT 30 mg/kg BATCH 7I0660	31.5 ± 3.2	50.9 ± 3.7*	53.4 ± 4.2*	36.5 ± 4.9	31.3 ± 3.8

Treatment with vincristine: five i.v. injections of 150 $\mu g/kg^{-1}$ performed every 2 days up to a cumulative dose of 750 $\mu g/kg^{-1}$ i.v.
The test was performed 4 days after the last injection of vincristine. 7-8 rats per group (two experiments).
^P < 0.05
*P < 0.01 versus rats treated with vincristine
14 rats per group (two experiments).
*P > 0.05 versus rats treated with vincristine.

Example 5

Hypericin in Oxaliplatin-Induced Neuropathy

[0067] Using the same method as in Example 1, the following results were obtained by administering hypericin at the doses indicated in Table 5.

TABLE 5

EFFECT OF HYPERICIN (single administration) ON OXALIPLATIN-INDUCED HYPERALGESIA IN THE RAT PAW PRESSURE TEST

		Pressure on rats' paws (g)					
		Treatment period (weeks of oxaliplatin)					
TREATMENT i.p.	TREATMENT p.o.	Pre-test before all treatments	3rd week Pre-test	3rd week + 15 min	3rd week + 30 min	3rd week + 45 min	3rd week + 60 min
SALINE	SALINE	60.1 ± 2.2	66.2 ± 4.5	65.0 ± 4.3	63.9 ± 3.8	66.5 ± 4.4	68.1 ± 4.1
OXALIPLATIN	SALINE	58.4 ± 4.6	30.5 ± 4.7	28.4 ± 4.1	25.8 ± 3.6	27.1 ± 4.1	29.1 ± 2.8
OXALIPLATIN	HYPERICIN 0.11 mg/kg + CMC	63.2 ± 3.5	32.4 ± 2.0	44.1 ± 2.8*	55.0 ± 2.2*	53.3 ± 2.6*	31.3 ± 3.0
OXALIPLATIN	HYPERICIN 0.11 mg/kg + HYPERISIDE 3.118 mg/kg	60.6 ± 3.8	31.7 ± 2.5	56.3 ± 2.6*	58.5 ± 2.7*	52.5 ± 1.2*	33.0 ± 2.8

Treatment: Oxaliplatin 2.4 mg kg^{-1} for 5 consecutive days a week (15 i.p. injections - cumulative dose 36 mg/kg)
8 rats per group (two experiments).
*P < 0.01

Example 6

Hypericin in Neuropathy Induced by Ligature of the Sciatic Nerve

[0068] Using the same method as in Example 2, the following results were obtained by administering hypericin at the doses indicated in Table 6.

TABLE 6

EFFECT OF HYPERICIN IN A RIGHT-SIDE MONONEUROPATHY MODEL IN THE RAT, EVALUATED WITH THE RAT PAW PRESSURE TEST

Treatment		Paw				
		Before	After treatment			
MG/KG. P.O.	PAW	treatment	15 min	30 min	4 min	60 min
CMC	L	60.8 ± 2.9	57.8 ± 3.3	57.4 ± 3.8	59.2 ± 4.9	55.9 ± 3.8
CMC	R	23.2 ± 2.2	24.7 ± 3.5	22.9 ± 2.8	23.6 ± 3.7	20.7 ± 3.5
HYPERICIN 0.11 mg/kg	L	21.6 ± 2.7	23.8 ± 3.3	22.7 ± 2.1	24.8 ± 3.9	21.5 ± 3.0
HYPERICIN 0.11 mg/kg	R	24.3 ± 4.6	28.1 ± 1.2	43.7 ± 2.0*	41.6 ± 2.7*	25.9 ± 2.2

The doses of hypericin, hyperoside and amentoflavone corresponded to 30 mg/kg p.o. of hydrophilic fraction of *hypericum* extract - batch 070305/I)
^P < 0.05;
*P < 0.01.
Each value represents the mean of 8 rats.

Example 7

Effect of Freeze-Dried *Hypericum* Extract and Hypericin in Pain Caused by Monosodium Iodoacetate-Induced Osteoarthritis

[0069] The reduction in the pain threshold was induced by a single administration of monoiodoacetate (MIA) into the paw joint of the rat (Ref. 27).

TABLE 7

EFFECT OF HYPERICIN AND *HYPERICUM* EXTRACT ON PAIN INDUCED BY OSTEOARTHRITIS OF THE KNEE, EVALUATED IN THE RAT PAW PRESSURE TEST

TREAT-	TREATMENT	After treatment				
MENT	mg kg−1 p.o.	Pre-test	15 min	30 min	45 min	60 min
SALINE	CMC	63.9 ± 3.3	64.6 ± 2.5	60.5 ± 3.8	62.6 ± 3.7	64.6 ± 4.0
MIA	CMC	22.6 ± 2.9	20.3 ± 4.1	24.9 ± 2.7	23.2 ± 3.5	24.0 ± 2.7
MIA	HYPERICIN 0.11 mg/kg	23.4 ± 3.3	45.9 ± 2.7*	49.7 ± 3.8*	42.8 ± 3.9*	31.7 ± 3.5
MIA	*HYPERICUM* EXTRACT 60 mg/kg BATCH 7I0525	21.1 ± 2.1	39.7 ± 3.1*	42.7 ± 2.1*	38.4 ± 3.3*	22.1 ± 3.0

Treatment: Monosodium iodoacetate (MIA) 2 mg in a volume of 25 µl was injected into the antechamber of the left knee of non-anaesthetised rats.
Each value represents the mean of 2 experiments (11 rats).
^P < 0.05;
*P < 0.01 by comparison with rats treated with MIA/CMC.
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1. A method of treating neuropathic pain, the method comprising administering to a subject a composition comprising an effective amount of *hypericum* flowering stems extracts containing hypericin, or hypericin.

2. The method of claim **1**, wherein the neuropathic pain is caused by treatment with chemotherapy drugs.

3. The method of claim **2**, wherein the chemotherapy drugs are platinum complexes, vincristine and paclitaxel.

4. The method of claim **1**, wherein the neuropathic pain derives from sciatic pain.

5. The method of claim **1**, wherein the neuropathic pain derives from osteoarthritis.

6. The method of claim **1**, wherein the composition comprises *hypericum* extracts having a naphthodianthrone derivative content of not less than 0.25% by weight, wherein the naphthodianthrone derivative is selected from the group consisting of hypericin, pseudohypericin, and isohypericin.

7. The method of claim **1**, wherein the extract is freeze-dried.

8. The method of claim **7**, wherein the extract is a water-alcohol or water-acetone extract.

9. The method of claim **1**, wherein the flowering stems are from *Hypericum perforatum* L.

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