The examination is being carried out on the **following application documents**

Description, Pages

1, 2, 4-9, 13-16, 18, 21, 23, 25, 26, 28-30, 33-36, 39, 41, 43-111, 113-128	as published			
3, 3a, 10, 10a, 11, 12, 17, 19, 20, 22, 24, 27, 31, 32, 37, 38, 40, 42, 112, 129, 130	received on	25-10-2006	with letter of	20.10.2006

Claims, Numbers

1-18	filed with telefax on 11-01-2008

Drawings, Sheets

1/14-14/14	as published

The following documents (D) are referred to in this communication: the numbering will be adhered to in the rest of the procedure:

D1: US 2002 086 070 A1

D2: US-A-6 129 907

D3: US-A-5 370 863

Following documents are cited by the Examiner (documents that were brought to attention by a third party)(see Guidelines C-IV, 7.2 and 7.3 for citation of further documents in examination). Copies of the documents are annexed to the communication and the numbering will be adhered to in the rest of the procedure:

D4: XP55103490

D5: XP55103482

D6: XP55103514

1 THIRD PARTY OBSERVATIONS (Art. 115 EPC)

1.1 Two references from the Traditional Knowledge Digital Library (TKDL) disclose that Rosmarinus officinalis Linn (rosemary) has been known for centuries in the treatment of bronchial asthma, used as anti-inflammatory, and as a medicament for the treatment of chronic inflammation(see D4 and D5). One reference (D6) discloses a composition comprising a variety of plants including Humulus lupulus Linn (hops) as an oral drug for treatment of oedema, inflammation, and ascites. D6 is not more relevant for the examination than D1 and thus will not be further discussed.

2 AMENDMENTS (Art. 123(2) EPC)

2.1 The amendments appear to fulfil the requirements of Article 123(2) EPC.

3 CLARITY (Art. 84 EPC)

3.1 Dependent claim 6 refers to a second component consisting of "rosemary", and "a compound derived from rosemary". However, according to present independent claim 1 the second component can only be an "extract derived from rosemary". Thus said features should be deleted from claim 6 (Article 84 EPC).

3.2 Further medical use claims 14,15,16, and 17 are not acceptable under Article 84 EPC. The therapeutic application is functionally defined by a mechanism of action ("..condition associated with tissue-specific activation of inflammation", "..via inhibiting inducibility or activity of COX-2", or "inflammation-associated disorders") which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease) (F-IV, 4.22 and G-II, 4.2).

The objection could be overcome by either introducing into the claim a list of pathological conditions (diseases) cited in the application, or by showing that means are available which would allow the skilled person to recognise which additional condition/s would fall within the functional definition (F-IV, 6.5).

3.3 Moreover, claims 14 and 16 should read "..for use in treating or inhibiting..." (Art. 84:53(c) EPC).

4 NOVELTY (Art. 54 EPC)

4.1 The present application does appear to meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-18, in as far as allowable under Art. 84 EPC, does appear new in the sense of Article 54(1) and (2) EPC:

Independent claim 1 is directed to a composition comprising (i) a fraction isolated or derived from hops wherein said fraction is reduced isoalpha acid, and (ii) a second component of at least one member selected from an extract derived from rosemary and a triterpene species.

Documents D1-3 disclose compositions and the use of fractions of hops for the therapy of various diseases.

D1, wich is the closest prior art, discloses in par. 14, 16-18: "[0014] Preferably, the benefits of the invention may accrue if the recited COX-2 inhibitor is a botanical COX-2 inhibitor. In a especially preferred embodiment, the botanical COX-2 inhibitor comprises hops (Humulus lupus L) or Polygonum Cuspidatum (a member of the buckwheat family commonly known as japanese knotweed).

[0016] The anti-inflammatory properties of hops extract has been traced to one of the bitter principles or resins in hops called humulon.In one study, humulon inhibited arachidonic acid-induced inflammatory ear edema in mice (Yasukawa, K et al, Oncology 1995, Mar; 52(2): 156-158), and also inhibited skin tumor formation following initiation with a chemical challenge. Humulon, the alpha acid contained in hops, has also been shown to suppress cyclooxygenase-2 induction at the level of transcription (Yamamoto K, et al, FEBS Lett 2000 Jan 14, 465(2-3: 103-106). Humulon, therefor, could be considered a COX-2 inhibitor. Furthermore, humulon suppressed the TNFalpha-dependent cyclooxygenase-2 induction with an IC(50) of about 30 nM, a fairly low concentration.

[0017] Hops according to the invention may be used in its entirety, as whole hops powder for instance, or may be used as extracts of the hops flowers, pure humulon or other active principles isolated from hops.Extraction of hops also yields various essential oils, oleoresins, and alpha and beta acids. The primary beta acids in hops are lupulone, colupulone, and adlupulone. Hops resin is obtained from the yellow vesicles in the flowers of the hops plant. Extraction of hops resin is usually done using accepted extraction techniques with such solvents as hexane or ethyl alcohol, which concentrates the alpha and beta acids.

[0018] A more preferred extraction technique is using liquid carbon dioxide under supercritical conditions can be used to separate the alpha and beta fractions. Supercritical fluid technology is a more recent and superior means of extracting and concentrating the active principles that are contained in botanical extracts.Furthermore, supercritical fluid extraction is not a solvent based system, so it

results in solvent free extractions, and is less harmful to the environment, because there is no need to evaporate toxic organic solvents. CO2 is the most commonly used material in supercritical fluid extraction and fractionation. Supercritical CO2 extraction also allows for better separation and fractionation of certain components in hops that may not be necessary for a particular application, such as the elimination of estrogenic components which may not be needed in an anti-inflammatory formula. For instance, ethanol extracts of hops are known undesirably to possess strong estrogenic properties".

Furthermore, it is disclosed in par. 40-43 of D1: "[0040] The pharmaceutical compositions of the present invention may be used to treat, regenerate, and repair connective tissue in mammals; and may also be used to treat osteoarthritis, rheumatoid arthritis or acute pain. Dosing is by conventional means for the dosage selected. Conventional methods (such as dose ranging studies) may be used to determine dosage amounts; alternatively preferable dosage ranges have been disclosed elsewhere herein.

[0041] An advantage of the invention is that the combination of an amino sugar with a recited COX-2 inhibitor can result in a synergistic increase in the analgesic activity of the composition.The mechanism by which this effect occurs is not certain, but may involve altered COX-2 inhibitor metabolism/pharmacokinetics, resulting in effective pain relief at a lower dose. For instance, the synergistic effect may increase the maximum concentration of the recited COX-2 inhibitor in the blood or blood plasma, or may prolong or enhance the bioavailability of the recited COX-2 inhibitor or its metabolites, or may impact other pathways that directly or indirectly interact with the pathways involving cyclooxygenase-2. In an embodiment, the combination of a glucosamine salt with a hops extract could result in a significantly increased analgesic effect from the hops component.Such a synergistic increase in the analgesic activity would be useful for inventive compositions for and methods of treating joint pain or other types of pain, including acute pain, or pain due to trauma or injury, or for improved inhibition of cyclooxygenase-2 in mammals.

[0042] An advantage of the invention is that it provides an anti-inflammatory and pain relieving effect while reducing the danger of gastric erosion from frequent usage, such as would be encountered with a composition that did not comprise a recited COX-2 inhibitor.Still another benefit is the fast onset of pain relief action due to the immediate anti-inflammatory effects of the recited COX-2 inhibitor, which may operate cooperatively with the restorative properties of the joint restorative compound.

[0043] Surprisingly, by combining a joint restorative compound with a recited COX-2 inhibitor, significantly more effective joint pain relief is achieved initially, with continued improvement over time as the joint restorative compound begins to work its way into cartilage metabolism. Additionally, the combination of a joint restorative compound

with the recited COX-2 inhibitor also results in more effective reduction of pain than either the joint restorative compound or the recited COX-2 inhibitor alone. This may translate into a reduction in dose amount, or an increase in the analgesic efficacy of the inventive pharmaceutical composition.Therefore, the inventive pharmaceutical composition may result in significantly greater analgesic effects than either ingredient alone."

Documents D4 and D5 disclose that Rosmarinus officinalis Linn (rosemary) has been been used in traditional medicine for centuries as an anti-inflammatory medicament, used in the treatment bronchial asthma and chronic inflammation.

However, the prior art does not disclose compositions comprising as a first component a fraction isolated from hops (reduced isoalpha acids) and as a second component, at least one member selected from the group consisting an extract derived from rosemary and a triterpene species. Thus, the claimed compositions are new. Consequently, the use such compositions in medicine is also new.

Therefore, the subject-matter of claims 1-18 does appear new in the sense of Article 54 EPC.

5 INVENTIVE STEP (Art. 56 EPC)

5.1 The subject matter of claims 1-18, in as far as allowable under Art. 84 EPC, does appear inventive for the following reason:

The COX-2 inhibitory effects, as well as antimicrobial and anti-cancer effects of hops (Humulus lupus L.) were known. However, a synergistic inhibition of PGE2 synthesis by the combination of a fraction of hops (reduced isoalpha acids) and rosemary extract, or hops (reduced isoalpha acids) in combination with a triterpenoid (e.g. oleanolic acid) is not suggested in the prior art.

A synergistic effect appears supported in the present application for HOPS CO_2 extract in combination with triterpenoids (oleanic acid and ursolic acid)(see Example 7). A synergy of combinations of reduced isomerized alpha acids from hops with rosemary is also demonstrated in the Example 8; Example 6 concerns selective inhibition of PGE2 synthesis by rosemary extract.

Thus, the subject-matter of claims 1-18, in as far as allowable under Art. 84 EPC, does appear inventive (Art. 56 EPC).

6 REMARKS

6.1 The applicant is requested to adapt the description to the claims where necessary (Art. 84 EPC and Rule 69(1) EPC), in particular taking into consideration the provisions of Art. 53(c) EPC (non patentability of methods of treatment on the human or animal body).

6.2 Superfluous statements such as "but not limited to/ not limited", "non-limiting example", "and the like", "incorporated herein by reference" should be deleted from the description, should such terms or statements still be present in the description pages (Art. 84 EPC and Rule 48 (1)(c) EPC)).

6.3 If the applicant wishes to file amended claims, the attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed (Article 123(2) EPC).

6.4 In order to facilitate the examination of the conformity of the amended application with the requirements of article 123(2) EPC, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based. If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed (together with a printed clean copy (Rule 49(8) EPC)).

6.5 To meet the requirements of Rule 42 (1) (b) EPC, the documents D1, and D4-5 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.