EP 2303298

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

Description, Pages

1-24 as published

Claims, Numbers

1-15 filed with entry into the regional phase before the EPO

Drawings, Sheets

1/13-13/13 as published

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D8 Arkaprakasah:
In: Indradeva Tripathi: "Lankapatiravana", 1995, Krishnadas Academy, Varanasis, India
page 117,

D9 D. V. Panditarao: 1990, Govt of India: Sahastrayoga, New Delhi
page 63,

D10 AMMON H P T: "BOSWELLIASAEUREN (INHALTSSTOFFE DES WEIHRAUCHS) ALS WORKSAME PRINZIPIEN ZUR BEHANDLUNG CHRONISCH ENTZUENDLICHER ERKRANKUNGEN//Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases",
WIENER MEDIZINISCHE WOCHENSCHRIFT, SPRINGER WIEN, AT, vol. 152, no. 15-16, 1 January 2002 (2002-01-01), pages 373-378, XP009096034,
ISSN: 0043-5341, DOI: 10.1046/J.1563-258X.2002.02056.X

The following documents have been cited in the international search report; the numbering will be adhered to in the rest of the procedure.

D1 US 2006/040000 A1 (GOKARAJU ET AL.) 23 February 2006 (2006-02-23)

D2 CHEMICAL ABSTRACTS, 27 November 2009 (2009-11-27), Columbus, Ohio, US;
abstract no.: 147:533852,

SHARMA, A. ET AL.: "Phytochemical profile of Boswellia serrata: an overview.", ; & PHARMACOGNOSY REVIEWS,
vol. 1, no. 1, 2007, pages 137-142,

D3 CHEMICAL ABSTRACTS, 27 November 2009 (2009-11-27), Columbus, Ohio, US;
abstract no.: 146:350251,

WADA, K. ET AL.: "Bioactivities of Boswellia gum resin.", ; & AROMA RESEARCH,
vol. 7, no. 3, 2006, pages 234-241,

D4 ARUL, V. ET AL.: "Mechanisms of the contractile effect of the alcoholic extract of Aegle marmelos Corr. on isolated guinea pig ileum and tracheal chain.",
PHYTOMEDICINE,
vol. 11, 2004, pages 679-683, XP004956773,

D5 SAVITHRAMMA, N. ET AL.: "Ethnobotanical survey of plants used to treat asthma in Andhra Pradesh",
JOUMAL OF ETHNOPHARMACOLOGY,
vol. 113, 2007, pages 54-61, XP022162817,
INDIA.

D6 JP 10 072357 A (LOTTE CO LTD) 17 March 1998 (1998-03-17)

D7 ULBRICHT, C.: "Boswellia: An Evidence-Based Systematic Review by the Naturasl Standard Research Collaboration.",
JOURNAL OF HERBAL PHARMACOTHERAPY,
vol. 4, no. ISS.3, April 2005 (2005-04), pages 63-83, XP009067501,

The third-party observation received on 25-05-2011 pursuant to Art. 115 EPC; in particular documents D8, D9, calls into question the patentability of the subject-matter claimed for the reasons given below. Thus, documents D8, D9 will be taken into account in the proceedings (Guidelines E-VI, 3) and the numbering will be adhered to in the rest of the procedure.

The present communication contains remarks under the following sections:

I Amendments (Art. 123(2) EPC)

III Clarity (Art. 84 EPC) and sufficiency of disclosure (Art. 83 EPC)

V Novelty (Art. 54(1) and (2) EPC)

VI Inventive Step (Art. 56 EPC)

VII Formal Aspects

VIII Conclusion

I Amendments (Art. 123(2) EPC)

Claim	Basis in the application as filed	Basis sufficient
1	1	yes
2	claim 13	yes
3	claims 2	yes
4	claim 14	yes
5	claim 3	yes
6	claim 4	yes
7	claim 5	yes
8	claim 6	yes
9	claim 7	yes

10	claim 8	yes
11	claim 9	yes
12	claims 10-12	no
13	claim 15	yes
14	claim 17	yes
15	claim 19	yes

Regarding the multiple dependencies introduced to the claims filed upon entry into the regional phase, p14§5 - p18§1 provide also a basis, alongside the originally filed claims.

Claim 12

There is no basis for the embodiment of claim 12 wherein the composition is made into both a dosage form for oral administration and for parenteral administration at the same time (Art. 123(2) EPC). The "and/or" has to be amended to "or" in claim 12.

III Clarity (Art. 84 EPC) and sufficiency of disclosure (Art. 83 EPC)

Lack of synergy

The application claims that there is synergy in combining a Boswellia serrata and Aegle marmelos extract when treating respiratory disorders such as asthma. Several in vitro markers, viz. the expression profile of 5-LOX, FLAP and Cys LT-1 receptor in THP-1 macrophage cells, have been assayed in examples 14-16, combining Boswellia serrata with either Aegle marmelos extract (composition 1) or with ginger (composition 2), which is outside the scope of the claims (since lacking Aegle marmelos) and thus irrelevant.

In example 14 it is not indicated at which concentrations the individual compositions were given - no comparison is thus possible. The corresponding fig. 4, 5 have no error bars while the control, LPS values as well as the ratio of control / LPS vary widely between the fig. 4 A, B and fig. 5 A, B, indicating a high error. Synergy cannot be deduced. Fig. 5 relating to composition 2 is irrelevant since composition 2 is outside the scope of the claims.

In example 15, fig. 6, the values of the single extracts are very close to those of the composition while again no error bars are indicated. Synergy seems not to be present.

In example 16, fig. 7, at least for 5-LOX, composition 2 was less effective than ginger (fig. 7A) while for CysLT1 the activity of the single ingredients was in the same range of that of composition 2. Again, no error bars are indicated. Synergy seems not to be present. In any case, example 16 is a comparative example only since composition 2 is outside the scope of the claims.

From the nature of the protein expression experiments of examples 14-16, which appear to measure the intensities of bands in a single Western blot, and from the absence of any error bars, it is clear that each experiment has been conducted only once and also that each extract or extract mixture was only tested at a single given (or not indicated) concentration.

The applicant may want to compare the passage bridging pages 31/32 of XP023796270.

"Measurements made with single doses of drug 1, drug 2 and their mixture can never alone determine synergism since the sigmoidicity of dose-effect curves and the exclusivity of drug effects cannot be determined from such measurements."

The synergy has not been proven scientifically and the claim thereto amounts to mere speculation. It cannot be retained for the analysis of inventive step.

Also, apart from the lack of a theoretical basis for synergy, it is also disputed that the tiny effects observed with the used in vitro markers would result in a quantifiable synergistic effect in the treatment of respiratory disorders, as claimed.

The synergistic effect is insufficiently disclosed (Art. 83 EPC). The claimed synergistic activity has to be deleted from the claims.

Extracts, fractions, pure isolates of Aegle marmelos

According to claim 1, any Aegle marmelos extract or fraction or pure isolate can be used in combination with Boswellia serrata extract. No active principle has been identified in Aegle marmelos, only a crude fruit ethanol extract has been used in the examples. There is no reason to believe that any isolated substance or any fraction or any extract of Aegle marmelos would have the desired activity of not only treating respiratory disorders, but to do so in synergy with a Boswellia serrata extract. The generalisation is insufficiently disclosed (Art. 83 EPC) and claim 1 has to be limited to a fruit ethanol extract of Aegle marmelos.

Protection, control

The terms "protection" and "control" of respiratory disorders do not clearly amount to a method of treatment under Art. 53(c) EPC. It should read "protection **from**". The term "control", however, does not make sense at all in this context and should be deleted.

Scope of protection - respiratory diseases

The application comprises in vitro and in vivo data relating to asthma and an over-reacting immune system, which would enable the treatment of respiratory diseases such as asthma, allergic rhinitis, hay fever, type-1 hypersensitivity and mild allergies. However, the term "respiratory diseases" is much broader since it also comprises diseases such as lung cancer or pneumonia which can clearly not be treated with the composition of the present application, or at least this treatment is insufficiently disclosed. Claim 1 has to be limited to the specific respiratory diseases mentioned in its last line.

Proper wording of a further medical use claim

A claim according to Art. 54(5) EPC should be worded "A ... composition for **use in** the treatment of..." Claim 1 has to be corrected. Further, claims depending on such a claim should read "A composition for use according to claim 1, wherein..."

Functionally defined diseases

Claims 13-15 do not meet the requirements of Article 84 EPC for the following reasons. The therapeutic application of the composition is functionally defined by a mechanism of action, ie by their capability of ameliorating conditions related to aP2, FLAP and/or Cys LT-1 receptor expressions or activities, which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease), see Guidelines C - IV, 4.8, G 1/83 and T 0241/95, OJ 2/2001, 103).

The objection could be overcome by either introducing in the claims a list of pathological conditions (diseases) cited in the application, or by showing that means are available (in the form of experimental tests or testable criteria, either disclosed in the patent application or known from the common general knowledge), which would allow the skilled person to recognise which additional conditions fall within the functional definition (Guidelines C - III, 4.22 and T 0241/95, section 3.1.1 & 3.1.2).

Claim 7 is wider in scope than claim 1

Claim 7 is unclear in that its scope is wider than that of claim 1 on which it depends: claim 7 relates to the use of the composition of claim 1 for the treatment of eczema, psoriasis and wrinkles which are not "respiratory disorders" as indicated in claim 1 on which claim 7 depends. The use of terms such as "useful for the treatment" does not alter this.

Adaptogens, bio-protectants, bioavailability enhancers

It is unclear to which specific compounds the terms "adaptogens, bio-protectants or bioavailability enhancers" in claim 10 refer to. These compounds appear not to be part of the common general knowledge and are thus insufficiently disclosed (Art. 83 EPC). They have to be replaced with structurally defined compounds.

Inconciseness

Optional features in independent claims make the claims inconcise and should be made the object of a dependent claim - see eg claim 1, "optionally selected from asthma..." (Art. 84 EPC).

The same applies to dependent claims with such optional features appended to them, see claims 7 and particularly claim 12 which is a merger of originally filed claims 10-12 wherein the latter already contained optional features which were inconcise as such (Art. 84 EPC).

Percentages

The percentages of claims 2, 4, 8 are not identified as being on a volume or weight basis, and further it is unclear whether they refer to a liquid extract of unknown concentration or on a dry substance basis. In consequence, those claims are unclear and not limiting in any way.

The same objection is raised against claim 6 since it refers to "30% AKBA" while not indicating whether this is referring to a weight or dry matter concentration.

Unclear category

Claim 12 appears to be a claim depending on claim 1 but sets out that "the composition is made into...", which appears to turn the claim into a process claim. The category of claim 12 is unclear (Art. 84 EPC).

Unclear dosage

Claim 14 specifies a dosage of 0.01 - 500 mg/kg body weight, while it is not stated whether this applies to a dry composition or a liquid composition of unspecified concentration. Claim 14 is unclear and its feature does not limit the subject-matter in any way.

5-Loxin

Claim 6 refers to a commercial product, "5-Loxin", to clarify the term "an extract standardised to 30% AKBA". The composition of a commercial product can change at any moment and cannot serve as a reference point. The term "5-Loxin" should be deleted.

V Novelty (Art. 54(1) and (2) EPC)

V.1 Invention

Examples 1-10: A commercial Boswellia serrata extract, 5-Loxin(R), which is standardised to 30% 3-O-acetyl-11-keto-beta-boswellic acid (AKBA), is mixed with:

- Bael fruit ethanol extract (Aegle marmelos),
- ginger "extract" (Zingiber officiniale) or "ginger hydroalcohol extract", and/or
- Garcinia mangostana "extract".

Example 11: Human THP-1 monocyte-macrophage cells were pretreated with one of the four different extracts or two different positive controls. Thereafter, the cells were stimulated with LPS to induce an inflammatory response. The expression of adipocyte fatty-acid binding protein (aP2) was down-regulated by each of the four extracts (fig. 1A-D).

Example 12: In the same experimental set-up as in example 11, 5-Loxin reduced expression of 5-lipooxygenase (5-LOX), 5-lipooxygenase activating protein (FLAP) and cysteinyl leukotriene 1 receptor (Cys LT-1 receptor) (fig. 2).

Example 13: Asthmatic airway inflammation was induced in rats with intrathoracic administration of Sephadex LH-20. Rats were fed either 50 or 100 mg/kg of 5-Loxin, which caused a dose-dependent reduction of pro-inflammatory markers TNFalpha and IL-4 in both serum and lung tissue (fig. 3).

Example 14: In the same experimental set-up as in example 11, compositions 1 and 2 of examples 1 and 2, respectively, were shown to decrease the expression of aP2. In comparison to their individual ingredients, viz. 5-Loxin and Bael or ginger extract, the compositions had a higher suppression of expression of aP2, which was supposedly synergistic (fig. 4, 5).

Example 15: Like example 11, but testing 10 ug/mL of composition 1 and 5-Loxin or Bael extract alone on the expression of 5-LOX, FLAP and Cys LT-1 receptor, demonstrating a reduction which is supposedly synergistic in case of composition 1 (fig. 6).

Example 16: Like example 15, but with 10 ug/mL of composition 2, 5-Loxin or ginger extract, demonstrating a reduction of expression of 5-LOX, FLAP and Cys LT-1 receptor and again a supposedly synergistic reduction for composition 2 (fig. 7).

Example 17: In the same rat asthma model of example 13, compositions 1, 2 and 3 were administered at various concentrations (compare p6/7 for details), resulting in a rather insignificant effect on TNFalpha, IL-4 and IFNgamma (compare fig. 8), even though the application pretends otherwise. The ratio of IL-4 to IFNgamma as an indicator of the Th2 / Th1 balance is also indicated.

Example 18: In the rat asthma model composition 1 was given once daily for 10 days at 100 or 200 mg/kg. On the 10th day, airway inflammation was induced. TNFalpha and IL-4 expression was slightly reduced (fig. 9A, B) with no dose-dependency detectable, while IFNgamma expression was slightly up-regulated, again without dose-dependency, resulting in a small decrease of the IL-4/IFNgamma ratio upon treatment. The granulocyte count in peripheral blood 12h after induction revealed no significant reduction for the 100 mg dose and a supposedly significant slight decrease for the 200 mg dose (fig. 10). The effect is lost entirely after 24h, where the 100 mg dose increased the granulocyte concentration and the 200 mg dose had an insignificant effect (fig. 11). The number of granulocytes in bronchoalveolar lavage fluids (BAL) were reduced slightly but significantly for both doses in a dose-dependent manner (fig. 12). The eosinophil count in blood 12h and 24h after induction showed a strong dose-dependent reduction upon treatment (fig. 13).

V.2 Prior Art

If not otherwise specified, subject matter of cited documents relates to the passages indicated in the search report.

D1 - US2006040000 - ISR

D1 concerns an extract from Boswellia serrata that contains 30% AKBA and is distributed under the trademark 5-Loxin(R).

D2 - Sharma et al., 2007 - ISR

D2 describes the 5-LOX inhibition of boswellic acids from Boswellia serrata. The treatment of asthma and allergic manifestations is mentioned.

D3 - Wada et al., 2006 - ISR

D3 reveals that Boswellia gum resin is used against bronchial asthma since antiquity. Boswellia preparations are used as dietary supplements or folk medicine.

D4 - Arul et al., 2004 - ISR

D4 deals with Aegle marmelos and extracts thereof which are used for the treatment of asthma.

D5 - Savithramma et al., 2007 - ISR

D5 concerns Indian plants for the treatment of asthma. Tables 1-4 demonstrate that Zingiber officinale and extracts thereof are used.

D6 - JP10072357 - 1998 - ISR

D6 pertains to pharmaceutical preparations which contain an extract from Garcinia mangostana. The extract is used for the treatment of hay fever, allergic rhinitis and asthma.

D7 - Basch et al., 2004 - ISR

D7 discloses the use of Boswellia serrata extracts in asthma. The lipid-lowering effect is described as well.

D8 - Exhibit 5 of 3rd party observation - Lankapatiravana

Disclosed is a formulation containing extracts of both A. marmelos and Z. officinale along with a few other ingredients used for the treatment of Allergic rhinitis / vasomotor rhinorrhoea.

D9 - Exhibit 6 of 3rd party observation - Panditarao

Disclosed is a formulation containing extracts of both A. marmelos and Z. officinale along with a few other ingredients used for the treatment of Bronchial asthma through oral administration.

D10 - XP009096034 - Ammon et al., 2002

Preparations made from the resin of Indian frankincense (= Boswellia serrata) are used in Indian traditional medicine for the treatment of inflammations. The active ingredients are the boswellic acids, which inhibit in a non-competitive manner the activity of 5-lipoxygenase and which lead to the inhibition of the leucotriene biosynthesis in the model of neutrophil granulocytes. In clinical studies the administration was demonstrated to to be effective in patients with eg asthma bronchiale.

V.3 Objections

Percentages in the claims are ignored for assessing novelty since they are not limiting the scope of the invention, compare section III above.

The combination of an extract of B. serrata with one of A. marmelos for use in the treatment of respiratory disorders is not disclosed in the art found during the search nor in the art cited in the 3rd party observation.

Claims 1-15 are novel.

VI Inventive Step (Art. 56 EPC)

Lack of synergy

The synergistic effect is insufficiently disclosed, compare section III above. In consequence, synergy is not retained for the analysis of inventive step.

Any Aegle marmelos extract

As indicated in section III above, not just any extract, fraction or pure isolate from Aegle marmelos can be said to have therapeutic activity. The mere presence of such substances in the composition of the claims does not entail the presence of a technical effect associated therewith. The examples 14-18 using composition 1 are limited to that composition comprising an Aegle marmelos fruit ethanol extract. Any technical effect shown therein cannot be extended over the entire scope of the claims.

Lack of therapeutic activity

The data of fig. 8, 9 seems not to be significant. Unlike fig. 3, which relates to the same rat asthma model and which has asterisks for significant differences, fig. 8, 9 have no such asterisks. Given the high error bars and low differences in reduction of TNFalpha / IL-4 or increase of IFNgamma, the conclusion has to be that the effect of compositions 1, 2 and 3 on the pro-inflammatory markers TNFalpha and IL-4 as well as on the Th1 / Th2 shift marker IFNgamma is insignificant.

In view of the lack of synergy the combination of two or more plant extracts known for their use in the treatment of asthma and related diseases lacks an inventive step.

VII Formal Aspects

To meet the requirements of Rule 42(1)(b) EPC, D1, D4, D8, D9 should be identified in the description and its relevant contents should be indicated. The applicant should ensure that it is clear from the description which features of the subject-matter of the independent claims are known from these documents.

VIII Conclusion

At least some of the objections raised above are such that there appears to be no possibility of overcoming them by amendment. Refusal of the application under Article 97(2) EPC is therefore to be expected.

Should the applicant nevertheless regard some particular matter as patentable an independent claim should be filed taking account of Rule 43(1) EPC. The applicant should also indicate in the letter of reply the difference of the subject-matter of the new claim vis-à-vis the state of the art and the significance thereof.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments made, irrespective of whether they concern amendments by addition, replacement or deletion, and indicate the passages of the application as filed (not of amended documents) on which these amendments are based (see Guidelines E-II, 1).

If the applicant considers it appropriate, these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed, accompanied by a clean typed copy.

When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims. Care should be taken during revision, especially of the introductory portion and of any statements of problem or advantage, not to add subject-matter which extends beyond the content of the application as originally filed (Article 123(2) EPC).

Amendments should be made by filing replacement pages. Unnecessary recasting of the description should be avoided. An amended abstract is not required. The applicant should also take account of the requirements of Rule 50(1) EPC. If handwritten amendments are submitted, they should be clearly legible to the printer.

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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 09 76 9808

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	DATABASE TKDL [Online] 1995, "Nasika Rogahara Yoga-2", XP002671003, Database accession no. AK14/315B * the whole document *	1-15	INV. A61K36/324 A61K36/75 A61K36/9068 A61K36/38 A61K31/19 A61P11/00
Y	& Arkaprakasah: In: Indradeva Tripathi: "Lankapatiravana", 1995, Krishnadas Academy, Varanasis, India page 117, * the whole document *	1-15	A61K45/06
Y	DATABASE TKDL [Online] 1990, "Pänalaverädikasäyah", XP002671004, Database accession no. VS/2964 * the whole document *	1-15	
Y	& D. V. Panditarao: 1990, Govt of India: Sahastrayoga, New Delhi page 63, * the whole document *	1-15	TECHNICAL FIELDS SEARCHED (IPC) A61K A61P

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The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
Munich	7 March 2012	Hars, Jesko

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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EPO FORM 1503 03.82 (P04C04)

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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 09 76 9808

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	AMMON H P T: "BOSWELLIASAEUREN (INHALTSSTOFFE DES WEIHRAUCHS) ALS WORKSAME PRINZIPIEN ZUR BEHANDLUNG CHRONISCH ENTZUENDLICHER ERKRANKUNGEN//Boswellic acids (components of frankincense) as the active principle in treatment of chronic inflammatory diseases", WIENER MEDIZINISCHE WOCHENSCHRIFT, vol. 152, no. 15-16, 1 January 2002 (2002-01-01), pages 373-378, XP009096034, SPRINGER WIEN, AT ISSN: 0043-5341, DOI: 10.1046/J.1563-258X.2002.02056.X * the whole document * -----	1-15	
			TECHNICAL FIELDS SEARCHED (IPC)

The supplementary search report has been based on the last set of claims valid and available at the start of the search.

Place of search	Date of completion of the search	Examiner
Munich	7 March 2012	Hars, Jesko

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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