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**Datasheet for the decision
of 2 July 2014**

Case Number: T 1453/13 - 3.3.04
Application Number: 00125986.0
Publication Number: 1208849
IPC: A61K38/48, A61P29/00,
A61P37/00, A61P37/08, A61K35/78
Language of the proceedings: EN

Title of invention:

Use of bromelain for the treatment of inflammatory diseases
and for adjuvant therapy during wound healing process

Applicant:

Ursapharm Arzneimittel GmbH & Co. KG

Headword:

Non-protease components of bromelain/URSAPHARM

Relevant legal provisions:

EPC Art. 123(2), 84, 83, 54, 56
RPBA Art. 13(1), 13(3)

Keyword:

"Main request: requirements of the EPC met (yes)"

Decisions cited:

Catchword:



**Beschwerdekammern
Boards of Appeal
Chambres de recours**

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Case Number: T 1453/13 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 2 July 2014

Appellant: Ursapharm Arzneimittel GmbH & Co. KG
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Decision under appeal: **Decision of the Examining Division of the
European Patent Office posted on 10 January 2013
refusing European patent application No.
00125986.0 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairwoman G. Alt
Members: R. Morawetz
M.-B. Tardo-Dino

Summary of Facts and Submissions

I. The appeal of the applicant (hereinafter "appellant") lies against the decision of the examining division posted on 10 January 2013 refusing European patent application No. 00125986.0. The application at issue has the title "*Use of bromelain for the treatment of inflammatory diseases and for adjuvant therapy during wound healing processes*".

II. The decision under appeal is the second refusal of the present application by the examining division. It is based on a main request, auxiliary requests 1 to 12, and a further auxiliary request, also named auxiliary request 6. While the main request was held to lack novelty, none of the auxiliary requests was admitted into the proceedings by the examining division. In particular, the second auxiliary request 6 was not admitted because the examining division held (see paragraph 2.4 of the decision under appeal) that it *prima facie* failed to meet the requirements of Article 123(2) EPC. The sole claim of the main request read:

"1. Use of bromelain for the manufacture of a medicament for adjuvant therapy during wound healing processes by increasing the IL-8 level in an individual to stimulate immune responses, wherein bromelain is used as a food ingredient."

The sole claim of the second auxiliary request 6 read:

"1. Heat inactivated bromelain for use in the treatment of wounds."

III. With its grounds of appeal the appellant filed a new main request of which the sole claim read:

"1. Heat inactivated Bromelain for use in adjuvant therapy during wound healing."

- IV. By a communication of 15 May 2014 the appellant was summoned to oral proceedings to be held on 2 July 2014. In a communication under Article 15(1) RPBA of 26 May 2014 the board expressed its preliminary opinion on the sole request on file.
- V. With a letter of 16 June 2014 the appellant replied to the board's communication and filed auxiliary requests 1 to 6.
- VI. Oral proceedings before the board were held on 2 July 2014. The board further explained why it considered that the main request filed with the grounds of appeal failed to meet the requirements of Article 123(2) EPC. The appellant withdrew all pending requests and filed a new main request, of which the sole claim reads:

"1. Non-protease component or components of bromelain, obtainable by dissolving bromelain base powder in water and heat-treating the solution at 80 °C for 1 hr for use in adjuvant therapy during wound healing."

- VII. The following documents are cited in this decision:

(D2) Taussig S.J. and S. Batkin, Journal of Ethnopharmacology (1988), vol. 22, pages 191-203

(D5) Kelly G.S., Alternative Medicine Review (1996), vol. 1, pages 243-257

- (D6) Gylling U. et al., Acta Chir Scand (1966), vol. 131, pages 193-196
- (D7) Cirelli M.G., Medical Times (1964), vol. 92, pages 919-922
- (D9) Seltzer A.P., The Eye, Ear, Nose and Throat Monthly (1962), vol. 41, pages 813-817
- (D10) Woolf R.M. et al., The Journal of Trauma (1965), vol. 5, pages 491-494
- (D11) Zatuchni G.I. and D.J. Colombi, Obstetrics and Gynecology (1967), vol. 29, pages 275-278
- (D12) Howat R.C.L. and G.D. Lewis, The Journal of Obstetrics and Gynaecology of the British Commonwealth (1972), vol. 79, pages 951-953
- (D13) Rennekampff H.-O. et al., Journal of Surgical Research (September 2000), vol. 93, pages 41-54

VIII. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the new main request filed during the oral proceedings.

Reasons for the Decision

Main (sole) request

Admissibility

1. The main request now under consideration was filed during the oral proceedings. It is in the board's discretion whether or not to admit this request in the

appeal proceedings (Article 13(1) and(3) RPBA).

2. The amendments made in this request are straightforward, they do not raise new issues, do not contribute to the complexity of the appeal case and did not require a postponement of the oral proceedings. The board, exercising its discretion under Article 13(1) and (3) RPBA, admits the request in the proceedings.

Article 123(2) EPC

3. The application as filed discloses the use of bromelain and components thereof for use as an adjuvant therapy during wound healing (see page 1, lines 6 to 9). According to page 4, lines 1 to 3, of the application as filed: "*[t]he one or more components of bromelain is/are preferably non-protease component(s) thereof, since the stimulating activity of bromelain is even retained when bromelain has been subjected to high temperature treatment (...).*" Finally, the application as filed discloses on page 4, lines 20 to 25, that the protease activity of bromelain is destroyed by dissolving bromelain base powder in water and heating the solution at 80 °C for 1 hour. The application as filed thus discloses directly and unambiguously that the non-protease component or components of bromelain which are used in adjuvant therapy during wound healing are obtainable by dissolving bromelain base powder in water and heating the solution at 80 °C for 1 hour. The board is satisfied that the subject-matter of claim 1 finds a basis in the application as filed and that therefore the requirements of Article 123(2) EPC are fulfilled.

Article 84 EPC - clarity

4. The application as filed discloses that heat treatment of a bromelain base powder solution destroys the protease activity while maintaining the interleukin-8 (IL-8) inducing activity of bromelain. The board is satisfied that the protease activity and the IL-8 inducing activity can be readily tested by the person skilled in the art. The board concludes that the skilled person can determine whether or not a non-protease component of bromelain falls within the scope of claim 1. Claim 1 thus fulfils the clarity requirement of Article 84 EPC.

Article 83 EPC

5. The application discloses that bromelain that has been heated at 80 °C for 1 hour increases the secretion of IL-8 from neutrophils, whereas neutrophils not activated with heat-treated bromelain do not show any secretion of IL-8 into the supernatant. The skilled person is also generally aware that IL-8 enhances wound healing. Thus, document (D13) teaches (see abstract, page 41, right hand column, first paragraph) that wound healing is a sequential biological process that involves the integration of chemotaxis of neutrophils, mitosis and migration of keratinocytes, and remodelling of the scar. It proceeds in three phases: the inflammation phase, the proliferation phase, and the maturation phase, and endogenous IL-8 is involved in all three of these phases. Thus, IL-8 is the major bioactive chemoattractant for polymorphonuclear leukocytes in e.g. human blister and skin graft donor wound fluids. IL-8 is also able to stimulate keratinocyte proliferation, and *in vivo* topically applied IL-8 on human skin grafts in a chimeric mouse

model enhances reepithelialisation due to elevated numbers of keratinocytes. Finally, wound contraction is significantly diminished by topically applied IL-8. Therefore the board is satisfied that the non-protease component or components of bromelain can be made and that the demonstration in the application as filed of the induction of IL-8 secretion from neutrophils by heat-treated bromelain renders the claimed therapeutic application - adjuvant therapy during wound healing - plausible for the skilled person. The requirements of Article 83 EPC are fulfilled.

Article 54 EPC

6. Document (D5), a literature review on bromelain and its therapeutic applications, discloses (see page 243, 2nd paragraph) that bromelain's primary component is a sulfhydryl proteolytic fraction but that it also contains a peroxidase, acid phosphatase, several protease inhibitors, and organically bound calcium. Document (D5) further discloses (see page 249, right hand column, second and third paragraphs) that bromelain applied topically as a cream can be beneficial in the elimination of burn debris and in acceleration of healing. According to document (D5) a non-proteolytic component of bromelain, termed escharase, is responsible for this effect. Topical bromelain separates eschar at the interface with living tissue. It is hypothesised that bromelain activates collagenase in living tissue, which then attacks the denatured collagen in the eschar. This produces a demarcation between living and dead tissue, which allows all of the eschar to be removed, and a bed suitable for grafting results. Document (D5) thus discloses to the skilled person the use of bromelain as an adjuvant therapy for wound healing. However, the

bromelain used according to document (D5) also contains the active proteolytic fraction, as it has not been treated with heat. Document (D2) also discloses (see page 197, lines 6 to 32) the use of bromelain which has not been treated with heat for the debridement of third-degree burns.

7. According to document (D6), the proteolytic enzyme combinate bromelain had no effect on post-operative oedema when given orally (see page 196, left-hand column, second paragraph). Document (D7) reports on the clinical experience with bromelains in proteolytic enzyme therapy of inflammation and edema and discloses (page 922, right hand column, first and second paragraph) that patients recovered more rapidly when given bromelains. Document (D9) discloses (see page 817, paragraph bridging the columns) that the use of bromelain, a concentrate of proteolytic enzymes, minimises post-operative oedema and ecchymoses. Document (D10) reports (see page 492, third paragraph, and page 493, last paragraph) that the use of the proteolytic enzyme bromelain results in a more rapid resolution of an artificially induced hematoma. Document (D11) discloses (see page 278, right hand column, first and second paragraphs) that oral administration of a proteolytic enzyme of the bromelain group leads to a statistically significant decrease in oedema, inflammation and pain associated with mediolateral episiotomy. Document (D12) reports (see abstract, page 951, left-hand column, first paragraph; page 953, left-hand column, second paragraph) on a double blind controlled clinical trial to assess the effect of orally administered bromelain, a group of closely related proteolytic enzymes, on episiotomy wounds. No statistically significant differences could be seen between patients treated with bromelain and

those given placebos.

8. The board concludes from the above that all those documents on file which are concerned with the use of bromelain in adjuvant therapy during wound healing disclose the use of a bromelain preparation containing the active proteolytic fraction. The subject-matter of claim 1 is thus not anticipated by any of the prior art documents on file. The requirements of Article 54 EPC are fulfilled.

Article 56 EPC

Closest prior art document and the problem to be solved

9. In the board's judgment document (D5) can be considered to represent the closest prior art. The relevant disclosure of this document has been discussed above (see point 6). The subject-matter of claim 1 differs from the teaching of document (D5) in that one or more non-protease components of bromelain, obtainable by dissolving bromelain base powder in water and heat-treating the solution at 80 °C for 1 hr, are used in adjuvant therapy for wound healing. While according to document (D5) escharase, a hydrolytic enzyme component of bromelain (see document (D2), page 197, lines 6 to 32, and page 201, last two lines), removes eschar in the treatment of burns by activating collagenase, the treatment according to claim 1 relies on the chemotactic and mitotic properties of IL-8.
10. Accordingly, the problem to be solved is defined as the provision of alternative means for adjuvant therapy during wound healing.

Obviousness

11. It remains to be answered whether the skilled person, when facing the technical problem defined above, would have modified the teaching in the closest prior art document (D5) - possibly in the light of other teachings in the prior art - so as to arrive at the claimed invention in an obvious manner.

12. The active principle of bromelain responsible for the wound healing property of bromelain according to document (D5) is the enzyme escharase. The skilled person is generally aware that enzymes, like all other proteins, are denatured by heat-treatment, resulting in a loss of activity. Faced with the problem defined above, the skilled person would thus not be motivated to heat-treat the bromelain of document (D5) when trying to solve the problem formulated above. The board concludes that document (D5) on its own provides no hint to provide one or more non-protease components of bromelain, obtainable by dissolving bromelain base powder in water and heat-treating the solution at 80 °C for 1 hr, when trying to solve the technical problem formulated above.

13. Document (D2) discloses that bromelain heated at 70°C for 30 minutes retains its anti-cancer effect (see page 194, second paragraph). Document (D2) is however silent as regards the mechanisms underlying the dose-dependent growth retardation caused by bromelain in tumor cell lines *in vitro*. Consequently, document (D2) provides no hint that one or more non-protease components of bromelain, obtainable by dissolving bromelain base powder in water and heat-treating the solution at 80°C for 1 hr, could be used to solve the technical problem

defined above.

14. Documents (D6), (D7), (D9), (D10), (D11) and (D12) rely on proteolytically active bromelain in adjuvant therapy during wound healing (see point 7 above) and provide no motivation to heat-inactivate the proteolytic activity of bromelain when faced with the problem formulated above.
15. In fact, none of the prior art documents on file discloses that a non-protease component of bromelain induces the secretion of IL-8 from neutrophils or that this activity is maintained even after heat-treatment of bromelain.
16. In summary, the board concludes that none of the documents on file provides any hint that would have motivated the skilled person to modify the teaching in the closest prior art document (D5) so as to arrive at the claimed invention in an obvious manner. The requirements of Article 56 EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The case is remitted to the department of first instance with the order to grant a patent on the basis of the sole claim of the new main request filed during oral proceedings, Figure 1 and the description to be adapted thereto.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated