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SUPPLEMENTARY EUROPEAN SEARCH REPORT

Application Number
EP 04 78 0744

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
L,X	WO 95/10292 A (CALIFORNIA BIOMEDICA INC [US]) 20 April 1995 (1995-04-20) L: Priority * the whole document *	1-18	INV. A61K38/16 C07K14/415
X	US 5 980 902 A (SHANMUGASUNDARAM EDAYATIMANGAL [IN] ET AL) 9 November 1999 (1999-11-09) * columns 4-10 *	1-18	
P,L,X	US 2004/091559 A1 (CHATTERJI ARUN K [US]) 13 May 2004 (2004-05-13) L: Priority * the whole document *	1-18	
X	ANONYMOUS: "Madhumeha Vinasini Vatika" KEY ATTRIBUTES OF TKDL AK15/200, 1953, pages 1-3, XP003025246 * the whole document *	1,5,6	
E	WO 2004/078139 A (AYURVEDIC LIFE INTERNATIONAL L [US]; CHATTERJI ARUN K [US]) 16 September 2004 (2004-09-16) * the whole document *	1-18	TECHNICAL FIELDS SEARCHED (IPC) A61K C07K
A	FLETCHER J I ET AL: "High-resolution solution structure of gurmarin, a sweet-taste-suppressing plant polypeptide" EUROPEAN JOURNAL OF BIOCHEMISTRY, BLACKWELL PUBLISHING, BERLIN, DE, vol. 264, no. 2, 1 September 1999 (1999-09-01), pages 525-533, XP002977280 ISSN: 0014-2956 * the whole document *	1-14	

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
The Hague	11 August 2009	Cupido, Marinus

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

EPO FORM 1503 03.82 (P04C04)

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

Description, Pages

1-4, 6-14	as published
5	as annexed to the Int. Prel. Examination Report

Claims, Numbers

1-18	received on	25.04.2006	with letter of	25.04.2006

The present invention claims a therapeutic dosage form useful for treatment of diabetes, comprising an insulinotropically effective amount of isolated gurmarin and a non-metabolizable polysaccharide.

I Documents

The following documents are or may be regarded as relevant; their numbering will be adhered to in the rest of the procedure:

D1: WO 95/10292 A (CALIFORNIA BIOMEDICA INC [US]) 20 April 1995

D2: US-A-5 980 902 (SHANMUGASUNDARAM EDAYATIMANGAL [IN] ET AL) 9 November 1999

D3: US 2004/091559 A1 (CHATTERJI ARUN K [US]) 13 May 2004 (2004-05-13)

D4: ANONYMOUS: "Madhumeha Vinasini Vatika" KEY ATTRIBUTES OF TKDL AK15/200, pages 1-3, XP003025246

D5: WO 2004/078139 A (AYURVEDIC LIFE INTERNATIONAL L [US]; CHATTERJI ARUN K [US]) 16 September 2004

D6: FLETCHER J I ET AL: "High-resolution solution structure of gurmarin, a sweet-taste-suppressing plant polypeptide" EUROPEAN JOURNAL OF BIOCHEMISTRY, BLACKWELL PUBLISHING, BERLIN, DE, vol. 264, no. 2, 1 September 1999, pages 525-533, XP002977280 ISSN: 0014-2956

II Priority

It appears that the invention as described is the isolate described in example 1 and shown to have insulin-releasing activity in RIN-58 cells. However this invention was already applied for as D1, D3, and D5. Consequently the present application is not the first application within the meaning of Article 87 (1)(b) and the priority date of 11 August 2003 for the present application cannot be recognised, and the relevant date is therefore 11 August 2004.

III Novelty and inventive step

D1 discloses the same isolate prepared from leaves of *Gymnema sylvestre* leaves as the present application. D3 is identical in that respect and also states that it the isolate is an insulinotropic active factor of *G. sylvestre* leaves having a molecular weight of at least about 3000 Daltons. The isolate does not comprise an isolated gurmarin. Moreover, the prior art does nowhere suggest to use a mixture of isolated gurmarin and a non-metabolizable polysaccharide for the treatment of diabetes. Consequently the subject-matter of 1-18 is novel and involves an inventive step in view of Articles 54 and 56 EPC.

IV Support and disclosure

Article 84 EPC demands that the claims are supported by the description. Described is an extract from the leaves of *Gymnema sylvestre*, which has been purified to contain a sulphur-containing polypeptide with a MW of more than 3000 Daltons, that is capable to stimulate rat insulinoma cells to release insulin. There is no support for a therapeutic dosage form containing isolated gurmarin. The description mentions a preferred embodiment containing purified gurmarin, but this is not sufficient, see the guidelines C-III, 6.3 requiring that support must be of a technical character an assertions having no technical content provide no basis. From the prior art, see for example D6 or references cited therein, can be deduced that the isolate disclosed in example 1 will contain the 35 amino acids peptide gurmarin, but it is not "isolated" in the sense this term is generally used, i.e free from other *Gymnema sylvestre* molecules.

There is also no support for the presence of a non-metabolizable polysaccharide from *Sterculia urens* exudate in the therapeutic dosage form. It is noted that support is present in co-pending patent application WO 2004/078139 (D5).

The application as a whole also does not enable a skilled person to obtain an isolated gurmarin. This is illustrated by example 5 showing that the lyophilized isolate contains only 3.3% polypeptide by weight. Consequently, this cannot be regarded as an isolated gurmarin, and the present claims and the invention as disclosed do not fulfill the requirements of Articles 83 and 84 EPC.

V Conclusion

It is not at present apparent which part of the application could serve as a basis for a new, allowable claim. Should the applicant nevertheless regard some particular matter as patentable, new claims should be filed. 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.

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

Description, Pages

1-4, 6-14	as published
5	as annexed to the Int. Prel. Examination Report

Claims, Numbers

1-18	received on	25-04-2006	with letter of	25.04.2006

Priority right

Documents D1, D3, and D5 do indeed only disclose the use of a *Gymnea sylvestre* extract for the treatment of diabetes, and not the use of the polypeptide gurmarin for that purpose. The present invention concerns an isolated gurmarin polypeptide, which apparently has insulinotropic properties, and is useful for modulation of glucose metabolism in human patients, alone or in conjugation with a non-metabolisable polysaccharide such as *Sterculia urens* exudate. The present application is the first application within the meaning of Article 87 (1)(b) EPC for this matter, and the priority of US 10/638,811 from 11 August 2003 is therefore recognised.

Disclosure and support

It is clear from the prior art, as for example D6, how an isolated gurmarin can be provided, and in that sense there is no lack of disclosure. Also the non-metabolisable polysaccharide, which may be *Sterculia urens* exudate, is sufficiently disclosed.

However, the claims are directed to a therapeutic dosage form, useful for treatment of diabetes. The application as a whole does not provide any guidance how to obtain such a therapeutic dosage form, it only indicates that the ratio between isolated gurmarin and the non-metabolisable polysaccharide should be in the range of about 1:50 to about 1:5. The claims are a mere invitation to set up further research programs to develop a suitable therapeutic dosage and, it is an undue burden and may involve the use of inventive skill to put the claimed matter into practice. Our objection that the claimed invention is insufficiently disclosed is therefore maintained.

The statement in the description page 5, that gurmarin has insulinotropic properties is not regarded as sufficient support for the claim that gurmarin can be used for the treatment of diabetes in humans (claim 6). D6 mentions that gurmarin is a sweet-

taste-suppressing polypeptide in rats, but it has no apparent effect on humans sweet taste receptors. The data provided in example 2 of the application, show that a *Gymnema sylvestre* isolate induces insulin release in RIN-58 rat-insulinoma cells, and in example 5 that such an isolate is calculated to contain 3.3% polypeptide (gurmarin). From these data, a skilled person can not conclude, that gurmarin will have insulin-releasing activity in human cells. It is speculation that gurmarin is the only active component of the isolate, and will also induce insulin releasing activity in the absence of any other component present in the isolate. Moreover, as purified gurmarin inhibits the sweet taste sensation of rat, but not in humans, it appears that any effect gurmarin has on rat-insulinoma cells cannot automatically be extrapolated to human cells. Therefore, the claim that the present invention provide a therapeutic dosage form useful for treatment of diabetes, is not adequately supported by the description.

Inventive step

In view of the above, our opinion that the presently claimed invention involves an inventive step has been revised. The closest prior art is represented by D1-D4, disclosing the use of a *Gymnema sylvestre* extract for the treatment of diabetes in humans. The problem the present application sets out to solve is the provision of further compositions for use in the treatment of diabetes in humans. The claimed solution consists of a therapeutic dosage form useful for treatment of diabetes comprising an insulinotropically effective amount of gurmarin and a non-metabolisable polysaccharide. The question that has to be answered is, whether the present invention does indeed provide a further composition that can be used in the treatment of diabetes in humans.

Amendments

The Applicants are invited to comment on the observations mentioned above and, if possible, to file new claims which take them into account. The requirements of Article 123(2) should be respected.

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

Description, Pages

1-4, 6-14	as published
5	as annexed to the Int. Prel. Examination Report

Claims, Numbers

1-18	received on	25-04-2006	with letter of	25.04.2006

Added matter

We apologise for not having mentioned this in our previous communications. The amended page 5 of the description as annexed to the IPER cannot be accepted as the gurmarin amino acid sequence that has been inserted was not present in the application as filed and therefore the amended page 5 violates Article 123(2) EPC. The sequence is present in the priority document, however the Guidelines specifically state that under Article 123(2) it is impermissible to add to a European application matter present only in the priority document for that application, Chapter VI point 5.3.1. and decision **T260/85** point 3 of the reasons. However, the amino acid sequence of gurmarin was already known in the prior art, e.g. D6.

Support

1. Claim 1 concerns a therapeutic dosage form of **isolated** gurmarin (emphasis added). A passages in the description that may be considered as support for claims to an isolated gurmarin is bridging pages 4 and 5: "The aforementioned isolate containing gurmarin is readily obtainable by aqueous or aqueous ethanolic extraction of the leaves of the species *Gymnema sylvestre*, followed by isolation of a relatively high molecular weight insulinotropically active principle from the extract. The isolated, insulinotropically active principle contains gurmarin, having a molecular size of about 4000 Daltons." This method, when put into practice by the inventors resulted in an isolate containing 3.3% polypeptide (which does not necessarily have to consist only of gurmarin). By no standards such an isolate can be regarded as an isolated gurmarin.

1.1 Your letter of March 26, 2010 mentions that the amino acid sequence from gurmarin is known from D6 and that a skilled person therefore can prepare gurmarin by other means such as Merryfield peptide synthesis or recombinant DNA technologies. Support for this was alleged to be present on page 5 line 19 which states that Gurmarin can be obtained by chemical synthesis. However, the Guidelines C-III, 6.3 demand that support must be of a technical character and that assertions without technical content provide no basis.

2. Support for claim 2, a therapeutic dosage form in accordance with claim1 wherein gurmarin and the non-metabolisable polysaccharide are present in the dosage form in a respective weight ratio in the range of about 1:50 to about 1:5 is said to be supported by the description page 9 lines 1-10. However, this passage states that a usual daily dose would be in the range of about 200 to about 900 milligrams in conjunction with about 300 to about1350 milligrams of polysaccharide, which gives a range of 3:1 to about 1:7 which distinctly differs and even hardly overlaps the claimed range. The same objection is made with respect to claim 3 wherein the ration is 1:25

3. There is no solid support for the claimed insulinotropic activity of isolated gurmarin. The bioassay for insulin-releasing activity in rat insulinoma RIN-58 cells demonstrated that activity was present in the retentate, which has a MW of more than about 3000 Daltons, but also in the permeate with a MW under 3000, see table 2 on page 12. These data are identical to those presented in D5 and no conclusions about the actual agent having the insulin-releasing activity were drawn by the inventors in D5. The additional data, provided in the present application confirm the presence of a sulfur-containing polypeptide in the retentate fraction. It is well possible, in view of the disclosure of D6 that this polypeptide is gurmarin. There are however no data showing that this polypeptide is the insulin-releasing agent in the retentate, and it may well be any of its other constituents that represent the remaining 96.7% of the retentate.

Inventive step

We repeat that the closest prior art is represented by D1-D4, disclosing the use of a *Gymnema sylvestre* extract for the treatment of diabetes in humans, and that the problem the present application sets out to solve is to provide further compositions for use in the treatment of diabetes in humans. The claimed solution consists of a therapeutic dosage form useful for treatment of diabetes comprising an insulinotropically effective amount of isolated gurmarin and a non-metabolisable polysaccharide.

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Application No.: 04 780 744.1

Decision of the Examining Division

In the oral proceedings held on 14.06.2012, the examining division has decided:

The European patent application is refused on the basis of Article 97(2) EPC. The reasons for the decision are attached (Form(s) 2916).

15 06 2012
Date

Kools, Patrick
Chairman

Wiame, Ilse
1st examiner

Lejeune, Robert
2nd examiner

Enclosure(s): Form 2916
Main Request dated 25-04-2006 and Auxiliary Request 1 dated 14-05-2012

The decision is based on the **following application documents**

Main Request

Description, Pages

1-4, 6-14	as published			
5	received on	10-10-2011	with letter of	10-10-2011

Claims, Numbers

1-18	received on	25-04-2006	with letter of	25-04-2006

Auxiliary Request 1

Description, Pages

1-4, 6-14	as published			
5	received on	10-10-2011	with letter of	10-10-2011

Claims, Numbers

1-18	received on	14-05-2012	with letter of	14-05-2012

SUMMARY OF FACTS AND SUBMISSIONS

1.1 PCT application number WO2004US25959 was filed on 11-08-2004 claiming priority from US20030638811 filed on 11-08-2003. The application was published on 03-03-2005 with number WO2005018546. An International Search Report was issued by the USPTO.

1.2 The request for entry into the regional phase before the EPO was received on 10-03-2006 for the corresponding European patent application EP04780744. The request was accompanied by amended claims and an amended page 5 of the description.

1.3 A further set of amended claims to be taken as the basis for further proceedings before the EPO was filed on 25-04-2006, which are also the claims of the present Main Request.

1.4 A Supplementary European Search Report was issued on 18-08-2009.

1.5 With letter dated 22-10-2009, the Applicant expressed his desire to proceed further with the European patent application.

1.6 A first communication C1 was issued on 30-11-2009 raising doubts about the priority claim and raising objections under Articles 83 and 84 EPC.

1.7 With letter of reply R1 dated 26-03-2010 the Applicant submitted arguments in response to the objections in C1.

1.8 A second communication C2 was issued on 31-08-2010, maintaining the objections under Articles 83 and 84 EPC.

1.9 With letter of reply R2 dated 23-12-2010 the Applicant submitted arguments in response to the objections in C2.

1.10 A third communication C3 was issued on 31-05-2011, raising an objection under Article 123(2) EPC for amended page 5 of the description, raising an objection of lack of inventive step and maintaining the objections under Articles 83 and 84 EPC.

1.11 With letter of reply R3 dated 10-10-2011 the Applicant submitted amended page 5 of the description and arguments in response to the objections in C3.

1.12 Summons to Oral Proceedings on 14-06-2012 were issued on 25-01-2012, maintaining the objection under Article 83 EPC.

1.13 With letter of reply R4 dated 14-05-2012, the Applicant submitted a first Auxiliary Request in addition to the claims on file and arguments in response to the objection under Article 83 EPC.

1.14 The Applicant did not appear at the Oral Proceedings. Oral Proceedings were held in the absence of the Applicant.

1.15 The claims on which the decision is based are annexed.

1.16 The following documents (D) and their numbering have been referred to during the procedure and may be referred to in this decision:

[cited in the International Search Report]

D1 WO 95/10292 A (CALIFORNIA BIOMEDICA INC [US]) 20 April 1995 (1995-04-20)

[cited in the Supplementary European Search Report]

D2 US 5 980 902 A (SHANMUGASUNDARAM EDAYATIMANGAL [IN] ET AL) 9 November 1999 (1999-11-09)

D3 US 2004/091559 A1 (CHATTERJI ARUN K [US]) 13 May 2004 (2004-05-13)

D4 ANONYMOUS: "Madhumeha Vinasini Vatika", KEY ATTRIBUTES OF TKDL AK15/200, 1953, pages 1-3, XP003025246,

D5 WO 2004/078139 A (AYURVEDIC LIFE INTERNATIONAL L [US]; CHATTERJI ARUN K [US]) 16 September 2004 (2004-09-16)

D6 FLETCHER J I ET AL: "High-resolution solution structure of gurmarin, a sweet-taste-suppressing plant polypeptide", EUROPEAN JOURNAL OF BIOCHEMISTRY, BLACKWELL PUBLISHING, BERLIN, DE, vol. 264, no. 2, 1 September 1999 (1999-09-01), pages 525-533, XP002977280, ISSN: 0014-2956

REASONS FOR THE DECISION

2 Main Request

2.1 The claims relate to a therapeutic dosage form useful for the treatment of diabetes comprising an insulinotropically effective amount of isolated gurmarin and a non-metabolisable polysaccharide (claims 1-17) and to use of isolated gurmarin for the preparation of a pharmaceutical composition for modulating glucose metabolism in a patient (claim 18).

2.2 Gurmarin is 35 aa polypeptide from the leaves of *Gymnema sylvestre*, a plant which has long been used in Ayurvedic medicine as a treatment for diabetes (see document D6). The MW of gurmarin is approximately 4 kDa.

2.3 The examples of the present application show the preparation of an extract from *Gymnema sylvestre* leaves, identical to example 1 of document D1, which is further fractionated into a permeate fraction having a MW less than about 3 kDa and a retentate fraction having a MW of at least about 3 kDa. Both the permeate and the retentate have insulin-releasing activity on rat cells, with the activity of the retentate being 4 times higher than that of the permeate. The retentate is furthermore shown to contain protein.

2.4 The description of the present application (p. 4, l. 16-18) contains the statement that glucose metabolism in a human patient can be effectively modulated by oral administration of gurmarin, optionally in combination with a non-metabolizable polysaccharide. This statement is not supported by technical data. The Applicant is of the opinion that said statement should be accepted at face value because allegedly there is no provision in the EPC that would set out the level of detail which is required to disclose the property of a compound. The Examining Division does not share this view because the Guidelines (C-III, 6.3 of GL2010 or F-IV, 6.3 of GL2012) state that support in the description must be of a technical character and that vague statements or assertions having no technical content provide no basis.

2.5 The subject-matter of claims 1-18 is not sufficiently disclosed in the sense of Article 83 EPC because it is not credibly shown that isolated gurmarin is insulinotropic or is capable of modulating glucose metabolism. Although the protein-containing retentate fraction having a MW of at least about 3 kDa is shown to possess insulin-releasing activity, there are no technical data in the application which make it credible that gurmarin is responsible for the insulin-releasing activity of the retentate. Other polypeptide or non-polypeptide compounds in the retentate may be responsible for the insulin-releasing activity. Moreover, the permeate having a MW less than about 3 kDa also has insulin-releasing activity, from which it can be concluded that the extract from *G. sylvestre* leaves contains at least one compound with insulin-releasing activity which is not gurmarin.

It is established case law (see the Case Law book of the Boards of Appeal, 6th ed., section II.A.4.3, first par.) that for the acceptance of sufficient disclosure of a therapeutic application, the patent application must provide some information showing that the claimed compound, in this case isolated gurmarin, has a direct effect on a metabolic mechanism specifically involved in the disease, in this case insulin-releasing activity. This is not at present the case.

In C4, the Applicant submits that the serious doubts raised by the Examining Division are not substantiated by verifiable facts. However, said verifiable facts are in the application itself, combined with the common general knowledge of the skilled person. The dry matter of the fraction retentate fraction having a MW of at least about 3 kDa is shown in example 5 the present application to contain 3.3 wt% of protein. This implies that it also contains 96.7% of non-protein compounds which could be responsible for the insulin-releasing activity.

3 First Auxiliary Request

3.1 The First Auxiliary Request differs from the Main Request mainly in that the term "isolated gurmarin" has been replaced with "gurmarin". The subject-matter of the claims of the First Auxiliary Request is not sufficiently disclosed in the sense of Article 83 EPC because it is not credibly shown that gurmarin is insulinotropic or is capable of modulating glucose metabolism. The arguments given above for the Main Request apply *mutatis mutandis* to the First Auxiliary Request.

DECISION

Therefore, the present application is refused according to Article 97(2) EPC on the grounds of insufficient disclosure (Article 83 EPC).