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(54) Title: PROTEASES FOR DEGRADING GLUTEN

(57) Abstract: Gluten-degrading proteases derived from insects, including flour beetles, are isolated, and the purified, and recombinant forms can be used to make gluten-containing food safe for patients suffering from gluten intolerance.

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US 11/30472

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(8) - A61K 38/16; C07K 1/00 (2011.01)

USPC - 514/21.2; 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
USPC: 514/21.2; 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
PubWEST (USPT, PGPB, EPAB, JPAB), Google Patents/Scholar: insect, gluten protease, glutenase, recombinant, vector, celiac, grain, proline-specific protease  
GenCore 6.3: SEQ ID NO:1

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Elpidina et al. Digestive peptidase in <i>Tenebrio molitor</i> and possibility of use to treat celiac disease. <i>Entomological Research</i> 2007, 37:139-147; abstract, pg 140, right col, para 2; pg 145, left col, para 4 to right col, para 1, pg 145, right col, para 1-2	1, 10 ----- 2-9, 11-18
Y	NCBI Direct Submission XP_971305.1. 21 July 2008. [Retrieved from the Internet 18 July 2011: <URL: http://www.ncbi.nlm.nih.gov/protein/XP_971305.1>]; entire document	2-7, 11-18/(2-7)
Y	US 2009/0280555 A1 (Hausch et al.) 12 November 2009 (12.11.2009) para [0021]-[0022], [0031], [0068], [0071], [0081], [0107], [0126], Fig. 7	1,6, 8-9, 11-18/(1,6,8-10)

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

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**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/US 11/30472

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:  
Group I+: claims 1-18, drawn to an isolated gluten-degrading protease from an insect that feeds on gluten containing dried grain products, and a method of using said protease. The first invention is restricted to SEQ ID NO: 1 and GenBank Accession U19384.  
Should an additional fee(s) be paid, Applicant is invited to elect an additional insect protease(s) of a specified SEQ ID NO: and/or non-insect protease(s) to be searched.

The inventions listed as Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

- Please see extra sheet for continuation -

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-18 restricted to SEQ ID NO: 1 and GenBank Accession U19384

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

\*\*\*\*\* Supplemental Box \*\*\*\*\*

Continuation of:

Box NO III. Observations where unity of invention is lacking

The inventions of Group I+ share the technical feature of an isolated gluten-degrading protease from an insect that feeds on gluten containing dried grain products. However, this shared technical feature does not represent a contribution over prior art as being anticipated by the article entitled "Digestive peptidase in *Tenebrio molitor* and possibility of use to treat celiac disease" by Elpidina et al. (Entomological Research 2007, 37:139-147) (hereinafter 'Elpidina') that discloses a gluten-degrading protease (pg 145, right col, para 2; *T. molitor* diestive cysteine cathepsin L also readily hydrolyzes peptide after Gln in an acidic environment...has a potential for celiac disease treatment) from an insect (pg 145, right col, para 2, *T. molitor*) that feeds on gluten containing dried grain products (pg 145, left col, para 4 to right col, para 1, The major proteins of wheat grain are prolamine that can be efficiently hydrolyzed by larval digestive enzyme located in the anterior midgut: the major cysteine protinase) in purified form (abstract, pg 140, right col, para 2; The major activity belongs to cathepsin L which has been purified and characterized). As said method was known in the art at the time of the invention, this cannot be considered a special technical feature that would otherwise unify the groups.

Another special technical feature of the inventions listed as Group I+ is an insect protease of the specific amino acid sequence recited therein. As no significant structural similarities can readily be ascertained among the sequences, the inventions do not share a special technical feature. Without a shared special technical feature, the inventions lack unity with one another.

Another special technical feature of the inventions listed as Group I+ is a pharmaceutical formulation comprising the specific non-insect protease recited therein. The inventions do not share a special technical feature, because 1) US 2009/0280555 A1 to Hausch et al. (hereinafter 'Hausch') discloses a pharmaceutical formulation suitable for oral administration admixed with one or more pharmaceutically acceptable excipients (para [0031], a composition comprising glutenase in a pharmaceutical formulation suitable for oral administration (para [0068]) admixed with one or more pharmaceutically acceptable excipients (para [0022]), wherein said pharmaceutical formulation further comprises one or more non-insect protease (Hausch, para [0031]), and 2) no significant structural similarities can readily be ascertained among the claimed non-insect proteases. Without a shared special technical feature, the inventions lack unity with one another.

Groups I+ therefore lack unity under PCT Rule 13 because they do not share a same or corresponding special technical feature.