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 KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME,
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(54) Title: ENHANCING AUTOPHAGY OR INCREASING LONGEVITY BY ADMINISTRATION OF UROLITHINS OR PRE-
 CURSORS THEREOF

(57) Abstract: Disclosed are methods, compounds, and compositions useful for increasing autophagy and promoting longevity. The methods, compounds, and compositions relate to urolithins and urolithin precursors and use thereof. Certain urolithins are represented by Formula I, while certain urolithin precursors are represented by Formula IV. The urolithin may be urolithin A, urolithin B, urolithin C, or urolithin D. The urolithin precursor may be ellagic acid or an ellagitannin. The methods include in vivo, ex vivo, and in vitro uses of the compounds and compositions.



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/048310

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	A61K31/366	A61K45/06
	A61P9/00	A61P29/00
	A61P3/10	A61P35/00
		A61K31/00
		A61P25/00
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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)		
A61K A61P		
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)		
EPO-Internal, EMBASE, WPI Data, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/016554 A1 (NATREON INC [US]) 7 February 2008 (2008-02-07)	10-16, 22-34, 91-97, 103-107
Y	particularly Examples 1, 2, 8, 13, 15, 19, 20, 26; Fig. 1 ----- -/--	35-41,47
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "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) "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 "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 "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 "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 "&" document member of the same patent family		
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Scheithe, Rupert

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LANDETE J M: "Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health", FOOD RESEARCH INTERNATIONAL, ELSEVIER APPLIED SCIENCE, BARKING, GB, vol. 44, no. 5, 17 April 2011 (2011-04-17) , pages 1150-1160, XP028375003, ISSN: 0963-9969, DOI: 10.1016/J.FOODRES.2011.04.027 [retrieved on 2011-04-22] chapter 8	10-16, 22-34, 91-97, 103-107
X	----- WO 2007/127263 A2 (UNIV CALIFORNIA [US]; SEERAM NAVINDRA P [US]; HEBER DAVID [US]) 8 November 2007 (2007-11-08) the whole document	10-16, 22-34, 91-97, 103-107
X	----- SASHI G. KASIMSETTY ET AL: "Colon Cancer Chemopreventive Activities of Pomegranate Ellagitannins and Urolithins", JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY, vol. 58, no. 4, 24 February 2010 (2010-02-24), pages 2180-2187, XP055078529, ISSN: 0021-8561, DOI: 10.1021/jf903762h the whole document	10-16, 22-34, 91-97, 103-107
X	----- ANNA K KISS ET AL: "Epigenetic modulation of mechanisms involved in inflammation: Influence of selected polyphenolic substances on histone acetylation state", FOOD CHEMISTRY, ELSEVIER LTD, NL, vol. 131, no. 3, 26 September 2011 (2011-09-26), pages 1015-1020, XP028104633, ISSN: 0308-8146, DOI: 10.1016/J.FOODCHEM.2011.09.109 [retrieved on 2011-10-02] abstract, Fig. 4a	10-16, 22-34, 91-97, 103-107
X	----- US 2011/263521 A1 (MOUTET MARC [FR] ET AL) 27 October 2011 (2011-10-27)	10-16, 22-34
Y	claim 22	35-41, 47
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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2013/048310

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TAOTAO CHEN ET AL: "Rapamycin and other longevity-promoting compounds enhance the generation of mouse induced pluripotent stem cells", AGING CELL, vol. 10, no. 5, 14 June 2011 (2011-06-14), pages 908-911, XP055078410, ISSN: 1474-9718, DOI: 10.1111/j.1474-9726.2011.00722.x abstract	35-41,47
X,P	----- WO 2012/088519 A2 (AMAZENTIS SA [CH]; ANDREAUX PENELOPE [CH]; SCHNEIDER BERNARD [CH]; RIN) 28 June 2012 (2012-06-28) the whole document	10-16, 22-41, 47, 91-97, 103-107
A	----- NADINE SAUL ET AL: "Diversity of Polyphenol Action in Caenorhabditis elegans : Between Toxicity and Longevity", JOURNAL OF NATURAL PRODUCTS, vol. 74, no. 8, 26 August 2011 (2011-08-26), pages 1713-1720, XP055078143, ISSN: 0163-3864, DOI: 10.1021/np200011a particularly abstract; Fig. 1, 2 -----	10-16, 22-41,47

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/048310

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:

see additional sheet

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 an 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.:

1-9, 11-16, 24-34, 36-41, 92-97(completely); 10, 22, 23, 35, 47, 91
103-107(partially)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 11-16, 24-34, 36-41, 92-97(completely); 10, 22, 23, 35, 47, 91, 103-107(partially)

A method of increasing autophagy or longevity according to claims 1, 10, 24, 91, wherein the urolithin is urolithin A, urolithin B, urolithin C or urolithin D.

A composition according to claim 35, wherein the urolithin is urolithin A, urolithin B, urolithin C or urolithin D.

2. claims: 19, 44, 100(completely); 10, 17, 18, 22, 23, 35, 42, 43, 47, 91, 98, 99, 103-107(partially)

A method of increasing autophagy or longevity according to claims 10, 91, wherein the urolithin precursor is ellagic acid.

A composition according to claim 35, wherein the urolithin precursor is ellagic acid.

3. claims: 20, 21, 45, 46, 101, 102(completely); 10, 17, 18, 22, 23, 35, 42, 43, 47, 91, 98, 99, 103-107(partially)

A method of increasing autophagy or longevity according to claims 10, 91, wherein the urolithin precursor is an ellagitannin.

A composition according to claim 35, wherein the urolithin precursor is an ellagitannin.

4. claims: 48-64(completely); 78-90, 108-113(partially)

A method of increasing autophagy or longevity according to claims 80, 83, 86, 108, wherein the compound is a compound according to Formula II or III.

A composition according to claim 78, wherein the first compound is a compound according to Formula II or III.

A compound according to claims 48, 56.

5. claims: 65-77(completely); 78-90, 108-113(partially)

A method of increasing autophagy or longevity according to claims 80, 83, 86, 108, wherein the compound is a compound according to Formula V or VI.

A composition according to claim 78, wherein the first compound is a compound according to Formula V or VI.

A compound according to claims 65, 71.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2013/048310

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008016554 A1	07-02-2008	CA 2659892 A1	07-02-2008
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