

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 April 2008 (17.04.2008)

PCT

(10) International Publication Number
WO 2008/045294 A3

(51) International Patent Classification:
A61K 31/353 (2006.01)

(21) International Application Number:
PCT/US2007/021335

(22) International Filing Date: 4 October 2007 (04.10.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/849,416 4 October 2006 (04.10.2006) US

(71) Applicant (for all designated States except US): **MARS, INCORPORATED** [US/US]; 6885 Elm Street, McLean, VA 22101-3883 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHMITZ, Harold, H.** [US/US]; 6109 Rudyard Drive, Bethesda, MD 20814 (US). **KWIK-URIBE, Catherine, L.** [US/US]; 1008 Primrose Avenue, Stroudsburg, PA 18360 (US).

(74) Agent: **JAIN, Nada;** Nada Jain, PC, 560 White Plains Road, Suite 460, Tarrytown, NY 10591 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

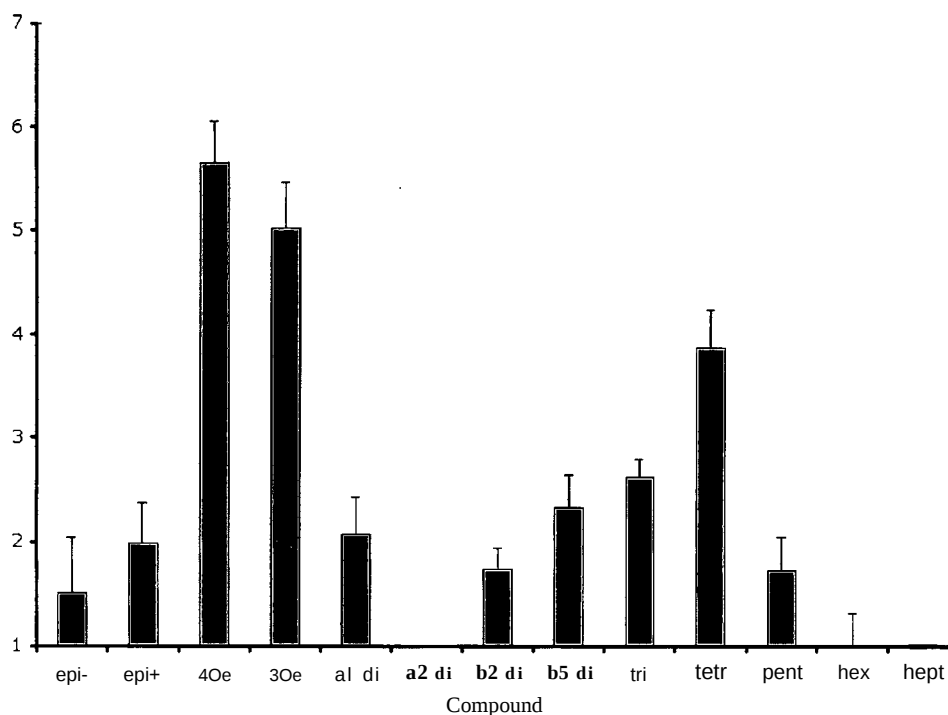
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
27 November 2008

(54) Title: **BOOSTING IMMUNITY**



(57) Abstract: The invention relates to compositions, and methods of use thereof, for boosting immunity, e.g. innate immunity, in a subject in need thereof comprising administering to the subject certain polyphenols such as flavanols, procyanidins, or pharmaceutically acceptable salts or derivatives thereof.

WO 2008/045294 A3

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US07/21335

A. CLASSIFICATION OF SUBJECT MATTER IPC: A61K 31/353(2006.01) USPC: 5 14/456 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) U.S. : 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) Please See Continuation Sheet														
C. DOCUMENTS CONSIDERED TO BE RELEVANT														
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.												
X	Wan et al. "Effects of cocoa powder and dark chocolate on LDL oxidative suseptibility and prostaglandin concentrations in humans"; 2001 ; Am. J. Clin. Nutr.; 74: 596-602; abstract, througout	1-5												
X	Keen "Chocolate: Food as Medicine/Medicine as Food"; 2001; Journal of the American College of Nutrition; 20(5): 436S-439S; abstract, throughout	1-5												
X,P	Kenney et al. "Immune Effects of Cocoa Procyanidin Oligomers on Peripheral Bllood Mononuclear Cells"; 2007 Feb; Exp. Biol. Med.; 232:293-300; abstract, throughout	1-5												
☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.														
<table border="0"> <tr> <td>* Special categories of cited documents</td> <td>"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</td> </tr> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"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</td> </tr> <tr> <td>"E" earlier application or patent published on or after the international filing date</td> <td>"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</td> </tr> <tr> <td>"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)</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td></td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			* 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 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	
* 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 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														
Date of the actual completion of the international search 22 August 2008 (22.08.2008)		Date of mailing of the international search report 17.9FP ?(NR)												
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P O. Box 1450 Alexandria, Virginia 223 13-1450 Facsimile No. (571) 273-3201		Authorized official Ardin Marschel Telephone No. (571) 272-1600												

INTERNATIONAL SEARCH REPORT

International application No

PCT/US07/21335

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.: 6-1 1
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:
Please See Continuation Sheet
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:
Please See Continuation 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 additional fees, this Authority did not invite payment of any 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.: 1-5 (oligomeric compound of formula An)

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.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US07/21 335

Continuation of Box II Reason 2:

Claims 6-11 are objected to under PCT Rule 66.2(a)(v) as lacking clarity under PCT Article 6 because claims 6-11 are indefinite for the following reason(s):

Claim 6 does not appear in the claims; claims 7-11 each depend on the missing claim 6. This renders the instant claims indefinite with respect to the subject matter of the claims.

BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

- (i) an oligomeric compound of formula A_n (with a single bond linkage between monomeric units A; claim 1);
- (ii) epicatechin or a monomeric derivative not included in species (iii)-(xii) (claim 12);
- (iii) catechin (claim 12);
- (iv) 3'-O-methyl-(+)-catechin (claim 16);
- (v) 3'-O-methyl-(-)-epicatechin (claim 16);
- (vi) 4'-O-methyl-(+)-catechin (claim 16);
- (vii) 4'-O-methyl-(-)-epicatechin (claim 16);
- (viii) 3'-O-, 4'-O-dimethyl-(+)-catechin (claim 16);
- (ix) 3'-O-, 4'-O-dimethyl-(-)-epicatechin (claim 16);
- (x) 4'-O-methyl epicatechin-O- β -D-glucuronide (claim 17);
- (xi) 3'-O-methyl epicatechin-O- β -D-glucuronide (claim 17);
- (xii) epicatechin-O- β -D-glucuronide (claim 17);
- (xiii) an oligomer composed of n monomeric 3-flavan-3-ol of claim 23 (with at least two linkages between monomeric units).

The claims are deemed to correspond to the species listed above in the following manner:

- (i) claims 1-5
- (ii) claims 12-15, 18-22
- (iii) claims 12-13
- (iv)-(ix) claims 12-13, 15-16
- (x)-(xii) claims 12-13, 15, 17
- (xiii) claims 23-30

The following claim(s) are generic: claims 12-22 are generic.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

INTERNATIONAL SEARCH REPORT

International application No.
PCTAJS07/21335

The technical feature linking the species is a compound of the species administered to a subject in need of boosting innate immunity. Berg et al. "Effects of Flavonoid Compounds on the Immune System Response"; 1988; Plant Flavonoids in Biology and Medicine II: Biochemical, Cellular and Medicinal Properties, Alan R. Liss, Inc., pp. 157- 171) teaches induction of two branches of the immune response, including the non-specific response (innate immunity) (p. 158, Figure 1); phagocytosis of bacteria in the presence of cianidanol (catechin; p. 159), and enhancement of phagocytic capacity of guinea pig Kupffer cells in vivo upon administration of 3-palmitoyl-(+)-catechin-3 (a catechin derivative), feeding of mice high cianidanol doses (p. 163, middle paragraph, last sentence). While it noted that Berg acknowledges that the biological effects of bioflavonoids on specific immune responses in vivo remain poorly understood (p. 169, 11. 5-7), and Berg does not resolve the specific effect of innate immunity in the responses noted, the administration to individuals with an immune challenge (subjects in need of boosting innate immunity) of the compounds of the instant invention inherently would boost innate immunity. Therefore, since the method of the instant claims has been taught with at least two compounds of the invention, the technical feature linking the species lacks novelty; the technical feature is not "special". Accordingly, the species are not so linked by the same or a corresponding special technical feature to form a single general inventive concept.

Continuation of B. FIELDS SEARCHED Item 3:

STN, PubMed

Search Terms: PROCYANIDIN, PROANTHOCYANIDIN, FLAVANOL, cocoa

Innate immunity, human