

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
21 December 2007 (21.12.2007)

PCT

(10) International Publication Number  
**WO 2007/146841 A3**

(51) International Patent Classification:  
A61K 31/352 (2006.01) A61P 41/00 (2006.01)  
A61K 31/353 (2006.01)

(21) International Application Number:  
PCT/US2007/070809

(22) International Filing Date: 8 June 2007 (08.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/812,664 9 June 2006 (09.06.2006) US  
60/918,640 16 March 2007 (16.03.2007) US

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(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

(54) Title: COLLAGEN CROSS-LINKING AGENTS ON DENTAL RESTORATIVE TREATMENT AND PREVENTIVE DENTISTRY

(57) Abstract: The invention relates to the development of compositions and methods for increasing the amount of collagen cross-linking in a mammalian tissue. A typical composition as described herein includes at least one cross-linking agent such as a bioflavonoid compound (e.g., proanthocyanidin), a grape seed extract, a Casein Phosphopeptide-amorphous Calcium Phosphate, or an iridoid compound (e.g., genipin) in an amount effective for increasing collagen cross-linking in the mammalian tissue in a pharmaceutically acceptable carrier. A typical method for increasing the amount of collagen cross-linking in dentin in a mammalian tooth includes the steps of preparing the surface of the tooth to be treated; and applying a composition including at least one of a bioflavonoid compound, a grape seed extract, a Casein Phosphopeptide-amorphous Calcium Phosphate, and an iridoid compound in a pharmaceutically acceptable carrier to the tooth surface for a time period of 0.0001 hours to about 4 hours. In some embodiments, two or more cross-linking agents are included in the compositions described herein. The compositions and methods as described herein are particularly useful for applying to dentin in a mammalian tooth requiring a restorative procedure for improving the mechanical properties of restoration interfaces to withstand degradation over time. Compositions containing one of the collagen cross-linking agents as described herein were applied to dentin collagen and resulted in a significant improvement in ultimate tensile strength indicating the value of these compositions in restorative dentistry. The compositions and methods described herein will also find use in preventive dentistry applications, and can be applied to sound dentin, caries-affected dentin, and dentin that is impaired, weak, or degraded in any way.

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**INTERNATIONAL SEARCH REPORT**

International application No  
**PCT/US2007/070809**

**A. CLASSIFICATION OF SUBJECT MATTER**  
INV. A61K31/352 A61K31/353 A61P41/00

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 practical, search terms used)

**EPO-Internal, WPI Data, BIOSIS, EMBASE, 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	HAN, B. ET AL.: "Proanthocyanidin: A natural crosslinking reagent for stabilizing collagen matrices" J. BIOMED. MATER. RES., vol. 65A, 2003, pages 118-124, XP002460268 cited in the application abstract the whole document	1-3,6, 9-17, 21-24,27
X	RAO C N ET AL: "Influence of bioflavonoids on the metabolism and crosslinking of collagen" ITALIAN JOURNAL OF BIOCHEMISTRY, ROME, IT, vol. 30, no. 4, July 1981 (1981-07), pages 259-270, XP009092804 ISSN: 0021-2938 the whole document abstract	1-3,6, 9-17, 21-24,27

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 document 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.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

**29 November 2007**

Date of mailing of the international search report

**06/06/2008**

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## 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	<p>RAO C N ET AL: "BIOFLAVONOID-MEDIATED STABILIZATION OF COLLAGEN IN ADJUVANT-INDUCED ARTHRITIS" 1983, SCANDINAVIAN JOURNAL OF RHEUMATOLOGY, ALMQVIST &amp; WIKSELL PERIODICAL CO., STOCKHOLM, SE, -PAGE(S) 39-42, XP000981292 ISSN: 0300-9742 the whole document abstract</p>	1-3,6, 9-17, 21-24,27
X	<p>RONZIÈRE M. C. ET AL.: "Influence of some flavonoids on reticulation of collagen fibrils in vitro" BIOCHEMICAL PHARMACOLOGY, vol. 30, no. 13, 1 July 1981 (1981-07-01), pages 1771-1776, XP002460269 England the whole document abstract</p>	1-3,6, 9-17, 21-24,27
X	<p>SHAN TEXEIRA: "Bioflavonoids: Proanthocyanidins and Quercetin and their Potential Roles in Treating Musculoskeletal Conditions" THE JOURNAL OF ORTHOPEDIC AND SPORTS PHYSICAL THERAPY, vol. 32, no. 7, July 2002 (2002-07), pages 357-363, XP002460270 USA the whole document abstract page 357, right-hand column, last paragraph page 358, right-hand column, paragraphs 4,6</p>	1-3,6, 9-17, 21-24,27
X	<p>US 2005/163821 A1 (SUNG HSING-WEN [TW] ET AL) 28 July 2005 (2005-07-28)  paragraphs [0002], [0057], [0100], [0300]</p>	1-3,6, 9-17, 21-24,27
X	<p>US 2005/019404 A1 (SUNG HSING-WEN [TW] ET AL) 27 January 2005 (2005-01-27)  paragraphs [0080], [0086], [0259], [0260]</p>	1-3,6, 9-17, 21-24,27
X	<p>US 2006/067959 A1 (NIMNI MARCEL [US] ET AL) 30 March 2006 (2006-03-30)  the whole document</p>	1-3,6, 9-17, 21-24,27
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## INTERNATIONAL SEARCH REPORT

International application No

PCT/US2007/070809

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT.

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/060547 A (ALIGN TECHNOLOGY INC [US]; LI CHUNHUA [US]; CARLYLE WENDA C [US]; DE S) 8 June 2006 (2006-06-08) paragraphs [0097] - [0100]	1-3,6, 9-17, 21-24,27
X	WO 03/020031 A (UNIV SOUTHERN CALIFORNIA [US]; HEDMAN THOMAS P [US]) 13 March 2003 (2003-03-13) page 5, line 9 - line 13 page 7, line 27 - page 8, line 2	1-3,6, 9-17, 21-24,27
P,X	BEDRAN-ROUSSO, A.-K., B. ET AL.: "Application of Crosslinkers to Dentin Collagen ENhances the Ultimate Tensile Strength" J. BIOMED. MATER. RES., vol. 80B, 9 June 2006 (2006-06-09), pages 268-272, XP002460271 USA the whole document	1-3,6, 9-17, 21-24,27
X	MUNKSGAARDE.,C.: "Amine-induced polymerization of aqueous HEMA/aldahyde during action as a dentin bonding agent" JOURNAL OF DENTAL RESEARCH, vol. 69, no. 6, June 1990 (1990-06), pages 1236-1239, XP002460488 USA the whole document abstract	1-3,6, 9-17, 21-24,27
X	RITTER, A.,V. ET AL.: "Effects of phosphoric acid and glutaraldehyde-HEMA on dentin collagen" EUROPEAN JOURNAL OF ORAL SCIENCES, vol. 109, no. 5, October 2001 (2001-10), pages 348-353, XP002460489 DENMARK abstract the whole document	1-3,6, 9-17, 21-24,27

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2007/070809

## 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 allsearchable 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.:

see annex

### 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(partially), 2-3, 6 (partially), 9, 10, 11-16 (all partially), 17, 21-23 (all partially), 24, 27(partially)

Compositions comprising phenylchromans [flavonoids and grape seed extract (proanthocyanidins)] and methods for increasing collagen cross-linking in a mammalian tooth comprising the use of said compositions

2. claims: 1(partially), 6 (partially), 11-16 (all partially), 21-23 (all partially), 27 (partially).

Compositions comprising casein phosphopeptide-amorphous calcium phosphate and methods for increasing collagen cross-linking in a mammalian tooth comprising the use of said compositions  
Your attention is drawn that in connection with casein phosphopeptide-amorphous calcium phosphate the description does not provide any evidence that said compounds crosslinks collagen. It appears that the compound acts rather as a remineralizing agent than a cross-linking agent.

3. claims: 1(partially), 4, 5, 6 (partially), 11-16 (all partially), 20, 21-23 (all partially), 27 (partially)

Compositions comprising a synthetic collagen cross-linker e.g. glutaraldehyde and methods for increasing collagen cross-linking in a mammalian tooth comprising the use of said compositions

4. claims: 1 (partially), 7, 8, 11-16 (all partially), 18-19, 21-23 (all partially) 25-26, 27 (partially)

Compositions comprising iridoids e.g. genipin and methods for increasing collagen cross-linking in a mammalian tooth comprising the use of said compositions

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2007/070809

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2005163821	A1	28-07-2005	NONE
US 2005019404	A1	27-01-2005	NONE
US 2006067959	A1	30-03-2006	NONE
WO 2006060547	A	08-06-2006	EP 1824410 A2 29-08-2007 US 2006115785 A1 01-06-2006
WO 03020031	A	13-03-2003	CA 2458821 A1 13-03-2003 CN 1578624 A 09-02-2005 EP 1432312 A1 30-06-2004 JP 2005501874 T 20-01-2005