



EUROPEAN SEARCH REPORT

Application Number  
EP 11 17 6493

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 6 291 533 B1 (FLEISCHNER ALBERT M [US]) 18 September 2001 (2001-09-18) * See composition of column 11, lines 10-33 comprising: Quercetin dihydrate, licorice extract, Ginkgo Biloba, Ginseng root extract *	1-15	INV. A61K31/352 A61K36/185 A61K36/484 A61K36/258 A61K36/87 A61K36/489
Y	WO 2006/079243 A (LONG MIAN [US]) 3 August 2006 (2006-08-03) * the whole document * & EP 1 847 265 A (LONG MIAN [US]) 24 October 2007 (2007-10-24) * column 1, lines 7-9, paragraph 1 * * column 1, lines 20-22,41-48 * * See column 2, line 35, and claims 4, 5, 16, 17, 18, figure 1 and 3: quercetin; column 2 * * See figure 3: activity of quercetin on fibroblast proliferation. * * See column 4, line 6, 44: and par. [0039]: activity of flavonoid kaempferol on BMP 2 *	1-15	A61P19/00 A61P19/10
Y	US 5 478 579 A (SAWRUK STEPHEN [US]) 26 December 1995 (1995-12-26) * column 2, lines 8-14 * * column 2, lines 29-61 *	1-15	TECHNICAL FIELDS SEARCHED (IPC) A61K
Y	WO 02/17909 A (KOREA INST OF ORIENTAL MEDICIN [KR]; KIM CHUNG SOOK [KR]; HA HYE KYUNG) 7 March 2002 (2002-03-07) * page 1, lines 5-20; claims * * page 8, lines 10-16 * * page 10, lines 30-37 * * examples 1-4; tables *	1-15	
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The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 December 2011	Examiner Veronese, Andrea
<p>CATEGORY OF CITED DOCUMENTS</p> <p>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</p> <p>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</p> <p>&amp; : member of the same patent family, corresponding document</p>			

EPO FORM 1503 03/02 (P04G01)



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EP 11 17 6493

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	WO 2005/077396 A (MEDITECH KOREA PHARM CO LTD [KR]; CHUNG KYU-HYUCK [KR]; OH SEUNG-MIN []) 25 August 2005 (2005-08-25) * claims 1,2 * * page 4, lines 19-23 * * paragraph [0020] * * examples 1,2 *	1-15	TECHNICAL FIELDS SEARCHED (IPC)
Y	----- DATABASE WPI Week 200634 Thomson Scientific, London, GB; AN 2006-324949 XP002474157, & JP 2006 117550 A (KAGOME) 11 May 2006 (2006-05-11) * abstract *	1-15	
Y	WO 01/32191 A (GAVISH GALILEE BIO APPLIC LTD [IL]; VAYA JACOB [IL]; TAMIR SNAIT [IL]) 10 May 2001 (2001-05-10) * page 6, lines 1-6,10-12 * * claims 1,5 *	1-15	
Y	----- DATABASE WPI Week 200419 Thomson Scientific, London, GB; AN 2004-192368 XP002474158, & CN 1 446 549 A (MEDICINE SCI & TECHNOLOGY DEV CENT GUANG) 8 October 2003 (2003-10-08) * abstract * ----- -/--	1-10, 20-23	
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 December 2011	Examiner Veronese, Andrea
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	

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EPO FORM 1503 03.02 (P04/C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TIAN, YUHUI ET AL: "Effect of soybean isoflavone on expression of bone BMP2 and TGF - .beta.1 in ovariectomized rats", XP002474155, retrieved from STN Database accession no. 2005:577261 * abstract * &amp; ZHONGGUO GONGGONG WEISHENG , 20(9), 1079-1080 CODEN: ZGWEE3; ISSN: 1001-0580, 2004,</p> <p style="text-align: center;">-----</p>	1-10, 20-23	
Y	<p>DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHEN, ZHENGYUE ET AL: "Effects of Celosia cristata L flavonoid on expression of bone morphogenetic protein and function of tubular reabsorption of rats with diabetes mellitus", XP002474156, retrieved from STN Database accession no. 2006:927340 * abstract * &amp; ZHONGGUO LINCHUANG KANGFU , 9(39), 188-190 CODEN: ZLKHAH; ISSN: 1671-5926, 2005,</p> <p style="text-align: center;">-----</p> <p style="text-align: center;">-/--</p>	1-10, 20-23	<p>TECHNICAL FIELDS SEARCHED (IPC)</p>
The present search report has been drawn up for all claims			
Place of search <b>Munich</b>		Date of completion of the search <b>2 December 2011</b>	Examiner <b>Veronese, Andrea</b>
CATEGORY OF CITED DOCUMENTS		<p>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 ..... &amp; : member of the same patent family, corresponding document</p>	
<p>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</p>			

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	ZHOU SHUANHU ET AL: "Estrogens activate bone morphogenetic protein-2 gene transcription in mouse mesenchymal stem cells.", MOLECULAR ENDOCRINOLOGY (BALTIMORE, MD.) JAN 2003, vol. 17, no. 1, January 2003 (2003-01), pages 56-66, XP002474163, ISSN: 0888-8809 * abstract * * See page 59 and Figure 7: stimulation of mouse BMP-2 promoter by Genistein * * See page 60, second column, last paragraph * * See page 63, column 1 and 2 * -----	1-10, 20-23	TECHNICAL FIELDS SEARCHED (IPC)
Y	WATTEL ALICE ET AL: "Flavonoid quercetin decreases osteoclastic differentiation induced by RANKL via a mechanism involving NF kappa B and AP-1.", JOURNAL OF CELLULAR BIOCHEMISTRY 15 MAY 2004, vol. 92, no. 2, 15 May 2004 (2004-05-15), pages 285-295, XP002474154, ISSN: 0730-2312 * the whole document * -----	1-10, 20-23	
Y	DATABASE EPODOC EUROPEAN PATENT OFFICE, THE HAGUE, NL; 21 April 2004 (2004-04-21), "Effective parents of Sophorae Flavone production and the use thereof", XP002474218, * abstract * & CN 1 490 321 A (WEI XIANHUA [CN]) 21 April 2004 (2004-04-21) ----- -/--	1-10, 20-23	
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 December 2011	Examiner Veronese, Andrea
CATEGORY OF CITED DOCUMENTS			
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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
X	US 6 733 797 B1 (SUMMERS WILLIAM K [US]) 11 May 2004 (2004-05-11) * See compositions of table 3, column 10, comprising Siberian Ginseng and quercetin *	9,10	TECHNICAL FIELDS SEARCHED (IPC)
Y	WO 02/00236 A (SCHWABE WILLMAR GMBH & CO [DE]; ERDELMEIER CLEMENS [DE]; JAGGY HERMANN) 3 January 2002 (2002-01-03) * See claims 4 and 19: sophora japonica * * See page 1, lines 27 and page 10, line 24: osteoporosis *	9,10	
Y	KR 2004 0038481 A (REXGENE BIOTECH CO LTD) 8 May 2004 (2004-05-08) See isoflavones from sophora japonica and their use to treat menopause disorders; * abstract *	9,10	
Y	KR 2003 0095669 A (REXGENE BIOTECH CO LTD [KR]) 24 December 2003 (2003-12-24) See isoflavones from sophora japonica and their use to treat menopause disorders; * abstract *	9,10	
Y	KROPOTOV A V ET AL: "Effects of Siberian ginseng extract and ipriflavone on the development of glucocorticoid-induced osteoporosis", BULLETIN OF EXPERIMENTAL BIOLOGY AND MEDICINE, vol. 133, no. 3, August 2002 (2002-08), pages 252-254, XP002485799, ISSN: 0007-4888 * the whole document *	9,10	
----- -/--			
The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 December 2011	Examiner Veronese, Andrea
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	

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EPO FORM 1503 03.02 (P04/C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y,P	<p>WANG ET AL: "Pharmacological studies of the large-scaled purified genistein from Huaijiao (Sophora japonica - Leguminosae) on anti-osteoporosis", PHYTOMEDICINE, vol. 13, no. 9-10, 3 November 2006 (2006-11-03), pages 718-723, XP005847527, GUSTAV FISCHER VERLAG, STUTTGART ISSN: 0944-7113</p> <p>* Note: article available on-line on 27-10-2005 *</p> <p>* See effects of genistein from Sophora Japonica on osteoporosis *</p> <p>-----</p>	9,10	<p>TECHNICAL FIELDS SEARCHED (IPC)</p>
X	<p>WO 03/057141 A (AVON PROD INC [US]; PTHELINTSEV DMITRI S [US]) 17 July 2003 (2003-07-17)</p> <p>* See page 3, lines 30-31: treatment of rosacea and teleangiectasia *</p> <p>* See compositions of example 1 and 6: pomegranate extract and grape seeds extract *</p> <p>-----</p>	11,13-16	
X	<p>WO 03/041636 A (AVON PROD INC [US]; LU MICHELLE [US]; DUGGAN MICHELLE [US]; MENON GOPI) 22 May 2003 (2003-05-22)</p> <p>* See compositions of example 2 and 3: pomegranate extract and grape seeds extract *</p> <p>* See page 6, protective effects on the skin *</p> <p>-----</p> <p style="text-align: center;">-/--</p>	11,13-16	
The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
Munich		2 December 2011	Veronese, Andrea
<p>CATEGORY OF CITED DOCUMENTS</p> <p>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</p> <p>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</p> <p>..... &amp; : member of the same patent family, corresponding document</p>			

3 EPO FORM 1503 03 02 (P04C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	DATABASE WPI Week 200065 Thomson Scientific, London, GB; AN 2000-667393 XP002485802, & JP 2000 247896 A (SNOW BRAND MILK PROD CO LTD) 12 September 2000 (2000-09-12) See abstract: pomegranate prevents reduction in bone weight; * abstract *	11-19	
Y	----- DATABASE WPI Week 200528 Thomson Scientific, London, GB; AN 2005-270104 XP002485803, & KR 2004 101 694 A (HEALTHMASTER) 3 December 2004 (2004-12-03) * abstract * * See abstract: compositions comprising pomegranate to treat osteoporosis *	11-19	TECHNICAL FIELDS SEARCHED (IPC)
Y	----- DATABASE WPI Week 200615 Thomson Scientific, London, GB; AN 2006-137870 XP002485804, & CN 1 680 240 A (WANG Y) 12 October 2005 (2005-10-12) * abstract * * See abstract: grape fruit extracts increase skeletal density * ----- -/--	11-19	
3 The present search report has been drawn up for all claims			
Place of search Munich		Date of completion of the search 2 December 2011	Examiner Veronese, Andrea
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 03.02 (P04C01)



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Y	<p>DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; June 2005 (2005-06), YAHARA N ET AL: "Mechanical assessment of effects of grape seed proanthocyanidins extract on tibial bone diaphysis in rats", XP002485800, Database accession no. EMB-2005453730 * See abstract: pomegranate has beneficial effects on bone formation * &amp; JOURNAL OF MUSCULOSKELETAL NEURONAL INTERACTIONS 200506 GR, vol. 5, no. 2, June 2005 (2005-06), pages 162-169, ISSN: 1108-7161</p> <p style="text-align: center;">-----</p>	11-19	
Y	<p>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; February 2005 (2005-02), ISHIKAWA MAKOTO ET AL: "Grape seed proanthocyanidins extract promotes bone formation in rat's mandibular condyle", XP002485801, Database accession no. PREV200500146664 * See abstract: grae seed extracts promotes bone formation * &amp; EUROPEAN JOURNAL OF ORAL SCIENCES, vol. 113, no. 1, February 2005 (2005-02), pages 47-52, ISSN: 0909-8836</p> <p style="text-align: center;">-----</p> <p style="text-align: right;">-/--</p>	11-19	<p>TECHNICAL FIELDS SEARCHED (IPC)</p>
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3 EPO FORM 1503 03.02 (P04C01)



DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	DATABASE TKDL [Online] Council of Scientific and Industrial Research; 1994, "Megathy Kuligai", XP002664997, Database accession no. PD03/114 * See abstract: pomegranate to decrease bone loss *	1-15	TECHNICAL FIELDS SEARCHED (IPC)
Y	DATABASE TKDL Council of Scientific and Industrial Research; 1879, "Appiraka Chendoorram", XP002664998, Database accession no. AM05/2268 * See pomegranate for use to prevent diminution of bone tissue *	1-15	
Y	DATABASE TKDL [Online] Council of Scientific & Industrial Research; 1900, "Madhumalini Vasant", XP002664999, Database accession no. RS22/631 * Pomegranate to promote bodily bulk *	1-15	
Y	EP 1 514 540 A1 (HAYASHIBARA BIOCHEM LAB [JP]) 16 March 2005 (2005-03-16) * See paragraph [0005] and claims 1, 4: quercetine for strenghtening bones and increasing bone mass *	1-15	
The present search report has been drawn up for all claims			
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EPO FORM 1503 03.92 (P04C01)

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
Y	<p>DATABASE WPI Week 200301 Thomson Scientific, London, GB; AN 2003-003189 XP002665000, &amp; JP 2002 179585 A (MARUZEN SEIYAKU KK) 26 June 2002 (2002-06-26) * abstract * * Licorice extract to prevent osteoporosis, and for promoting osteoblast cell growth *</p>	1-15	<p>TECHNICAL FIELDS SEARCHED (IPC)</p>
Y	<p>----- DATABASE WPI Week 200272 Thomson Scientific, London, GB; AN 2002-667899 XP002665001, &amp; CN 1 359 671 A (SUN Q) 24 July 2002 (2002-07-24) * See abstract: licorice root for promoting bone growth *</p>	1-15	
Y	<p>----- AHN S W: "Production of green tea pills effective for eliminating constipation, maintaining skin resiliency and strengthening bones, comprises using green tea and herbal plants", WPI/DERWENT,, vol. 2005, no. 52, 3 March 2005 (2005-03-03), XP002485987, * Green tee for strengthening bones *</p> <p>----- -/--</p>	1-15	
The present search report has been drawn up for all claims			
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Y	<p>CHUNG-HWAN CHEN ET AL: "Green tea catechin enhances osteogenesis in a bone marrow mesenchymal stem cell line", OSTEOPOROSIS INTERNATIONAL ; WITH OTHER METABOLIC BONE DISEASES, vol. 16, no. 12, 1 December 2005 (2005-12-01), pages 2039-2045, XP019380888, SPRINGER-VERLAG, LO ISSN: 1433-2965, DOI: 10.1007/S00198-005-1995-0 * See abstract: Green tea catechin enhances osteogenesis *</p> <p>-----</p>	1-15	
Y	<p>DATABASE TKDL [Online] Council of scientific and industrial research; 1996, "Ikvdightam", XP002665002, Database accession no. HG/1903 * See licorice to decrease bone loss *</p> <p>-----</p>	1-15	<p>TECHNICAL FIELDS SEARCHED (IPC)</p>
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EPO FORM 1503 03.82 (P04C01)

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

**Description, Pages**

1-68 as originally filed

**Claims, Numbers**

1-15 as originally filed

**Documents relevant for the proceedings**

The documents listed below have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages indicated in the Search Report:

- D1:** US-B1-6 291 533 (FLEISCHNER ALBERT M [US]) 18 September 2001 (2001-09-18)
- D2:** WO 2006/079243 A (LONG MIAN [US]) 3 August 2006 (2006-08-03)
- D3:** US-A-5 478 579 (SAWRUK STEPHEN [US]) 26 December 1995 (1995-12-26)
- D4:** WO 02/17909 A (KOREA INST OF ORIENTAL MEDICIN [KR]) 7 March 2002 (2002-03-07)
- D5:** WO 2005/077396 A (MEDITECH KOREA PHARM CO LTD [KR]) 25 August 2005 (2005-08-25)
- D6:** DATABASE WPI Week 200634 Derwent Publications Ltd., London, GB; AN 2006-324949 XP002474157 & JP 2006 117550 A (null) 11 May 2006 (2006-05-11)
- D7:** WO 01/32191 A (GAVISH GALILEE BIO APPLIC LTD [IL]) 10 May 2001 (2001-05-10)
- D8:** DATABASE WPI Week 200419 Derwent Publications Ltd., London, GB; AN 2004-192368 XP002474158 & CN 1 446 549 A (MEDICINE SCI & TECHNOLOGY DEV CENT GUANG) 8 October 2003 (2003-10-08)
- D9:** DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TIAN, YUHUI ET AL: "Effect of soybean isoflavone on expression of bone BMP2 and TGF - .beta.1 in ovariectomized rats" XP002474155 retrieved from STN Database accession no. 2005:577261
- D10:** DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; CHEN, ZHENGYUE ET AL: "Effects of Celosia cristata L flavonoid on expression of bone morphogenetic protein and function of tubular reabsorption of rats with diabetes mellitus" XP002474156 retrieved from STN Database accession no. 2006:927340
- D11:** ZHOU SHUANHU ET AL: "Estrogens activate bone morphogenetic protein-2 gene transcription in mouse mesenchymal stem cells." MOLECULAR ENDOCRINOLOGY (BALTIMORE, MD.) JAN 2003, vol. 17, no. 1, January 2003 (2003-01), pages 56-66, XP002474163 ISSN: 0888-8809

**D12:** WATTEL ALICE ET AL: "Flavonoid quercetin decreases osteoclastic differentiation induced by RANKL via a mechanism involving NF kappa B and AP-1." JOURNAL OF CELLULAR BIOCHEMISTRY 15 MAY 2004, vol. 92, no. 2, 15 May 2004 (2004-05-15), pages 285-295, XP002474154 ISSN: 0730-2312

**D13:** DATABASE EPODOC EUROPEAN PATENT OFFICE, THE HAGUE, NL; 21 April 2004 (2004-04-21), "Effective paretis of Sophorae Flavone production and the use thereof" XP002474218

**D14:** US-B1-6 733 797 (SUMMERS WILLIAM K [US]) 11 May 2004 (2004-05-11)

**D15:** WO 02/00236 A (SCHWABE WILLMAR GMBH & CO [DE]; ERDELMEIER CLEMENS [DE]; JAGGY HERMANN) 3 January 2002 (2002-01-03)

**D16:** KR 2004 0038481 A (REXGENE BIOTECH CO LTD) 8 May 2004 (2004-05-08)

**D17:** KR 2003 0095669 A (REXGENE BIOTECH CO LTD [KR]) 24 December 2003 (2003-12-24)

**D18:** KROPOTOV A V ET AL: "Effects of Siberian ginseng extract and ipriflavone on the development of glucocorticoid-induced osteoporosis" BULLETIN OF EXPERIMENTAL BIOLOGY AND MEDICINE 200208 US, vol. 133, no. 3, August 2002 (2002-08), pages 252-254, XP002485799

**D19:** WANG ET AL: "Pharmacological studies of the large-scaled purified genistein from Huaijiao (Sophora japonica - Leguminosae) on anti-osteoporosis" PHYTOMEDICINE, GUSTAV FISCHER VERLAG, STUTTGART, vol. 13, no. 9-10, 3 November 2006 (2006-11-03), pages 718-723, XP005847527 ISSN: 0944-7113

**D20:** WO 03/057141 A (AVON PROD INC [US]; PTHELINTSEV DMITRI S [US]) 17 July 2003 (2003-07-17)

**D21:** WO 03/041636 A (AVON PROD INC [US]; LU MICHELLE [US]; DUGGAN MICHELLE [US]; MENON GOPI) 22 May 2003 (2003-05-22)

**D22:** DATABASE WPI Week 200065 Thomson Scientific, London, GB; AN 2000-667393 XP002485802 & JP 2000 247896 A (SNOW BRAND MILK PROD CO LTD) 12 September 2000 (2000-09-12)

**D23:** DATABASE WPI Week 200528 Thomson Scientific, London, GB; AN 2005-270104 XP002485803 & KR 2004 101 694 A (HEALTHMASTER) 3 December 2004 (2004-12-03)

**D24:** DATABASE WPI Week 200615 Thomson Scientific, London, GB; AN 2006-137870 XP002485804 & CN 1 680 240 A (WANG Y) 12 October 2005 (2005-10-12)

**D25:** DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; June 2005 (2005-06), YAHARA N ET AL: "Mechanical assessment of effects of grape seed proanthocyanidins extract on tibial bone diaphysis in rats" XP002485800 Database accession no. EMB-2005453730

**D26:** DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; February 2005 (2005-02), ISHIKAWA MAKOTO ET AL: "Grape seed proanthocyanidins extract promotes bone formation in rat's mandibular condyle" XP002485801 Database accession no. PREV200500146664

Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

**D27** DATABASE TKDL [Online]  
Council of Scientific and Industrial Research; 1994,  
"Megathy Kuligai",  
Database accession no. PD03/114

**D28** DATABASE TKDL [Online]  
Council of Scientific and Industrial Research; 1879,  
"Appiraka Chendooram",

**D29** DATABASE TKDL [Online]  
Council of Scientific & Industrial Research; 1900,  
"Madhumalini Vasant",  
Database accession no. RS22/631

**D30** EP 1 514 540 A1 (HAYASHIBARA BIOCHEM LAB [JP]) 16 March 2005 (2005-03-16)

**D31** DATABASE WPI  
Week 200301  
Thomson Scientific, London, GB;  
AN 2003-003189  
& JP 2002 179585 A (MARUZEN SEIYAKU KK) 26 June 2002 (2002-06-26)

**D32** DATABASE WPI  
Week 200272  
Thomson Scientific, London, GB;  
AN 2002-667899  
& CN 1 359 671 A (SUN Q) 24 July 2002 (2002-07-24)

**D33** AHN S W: "Production of green tea pills effective for eliminating constipation, maintaining skin resiliency and strengthening bones, comprises using green tea and herbal plants",  
WPI/DERWENT,,  
vol. 2005, no. 52, 3 March 2005 (2005-03-03), XP002485987,

- D34 CHUNG-HWAN CHEN ET AL: "Green tea catechin enhances osteogenesis in a bone marrow mesenchymal stem cell line", OSTEOPOROSIS INTERNATIONAL ; WITH OTHER METABOLIC BONE DISEASES, SPRINGER-VERLAG, LO, vol. 16, no. 12, 1 December 2005 (2005-12-01), pages 2039-2045, XP019380888, ISSN: 1433-2965, DOI: 10.1007/S00198-005-1995-0
- D35 DATABASE TKDL [Online]  
Council of scientific and industrial research; 1996,  
"Ikvdightam",  
Database accession no. HG/1903

**Subject matter extending beyond parent application as filed (Article 76 EPC)**

Claims 2 and 3 relate to ternary compositions. In as far as these relate to compositions comprising pomegranate, grape seed and green tee, they extend beyond the content of the parent application as filed. In order to obtain this ternary composition from paragraphs [0019] of the parent application as filed, it is necessary to operate three selections from a relative long list of ingredients. This creates new subject matter. Paragraph [0020] can also not be used as basis, since it is restricted to a composition comprising four ingredients and not three. The other sections of the application comprising the three aforementioned ingredients, relate to compositions where specific amounts of the active agents are selected or other ingredients are present.

Conversely, claim 4 would appear to have basis in [0020 and 0024].

Claim 5 extends beyond the parent application, because it generalises the teaching of the example in table 12. Table 12 relates to specific combinations characterised by other features which are not included in claim 5.

Claim 7 has no basis in paragraph [0085]. The selection of the extreme of a range as defined in [0085] and subsequent combination with other specific ranges, infringes Article 76 EPC. The same applies to claim 9.

Claim 10 extends beyond the parent application, because it generalises the teaching of the example in table 12. See the reasons above relating to claim 5.

Claim 11 extends beyond the parent application as filed because [0085], as well as [0027] are limited to quercetin dihydrate and anhydrate.

Claim 15 extends beyond the parent application as filed because the amount of 300 mg of pomegranate is not disclosed in [0094]. Paragraph [0085] cannot be used as basis, because it relates to a different embodiment. Paragraph [0094] does further not disclose the claimed amounts of quercetin (in general), but only of quercetin anhydrate and dihydrate.

### **Novelty (Art.54 EPC)**

The application relates to the provision of medicines for the treatment of bone diseases involving increase of bone resorption. Although not explicitly mentioned in the claims, osteoporosis appears to be a preferred disease to be treated according to the invention (see paragraph [0004]). In order to treat such diseases, the inventors propose a composition comprising pomegranate and grape seed as defined in claim 1. According to other embodiments, other ingredients are present, such as ipriflavone and green tea (see claims 2-4) or further ingredients (Siberian ginseng, Sophora Japonica, Liquorice extract.

**D20** (WO03057141, see examples 1 and 6) discloses compositions comprising extracts of pomegranate and grape seeds and their use to treat skin disorders (rosacea and teleangiectasia).

**D21** (WO03041636, see examples 2 and 3) discloses compositions of comprising pomegranate extract and grape seeds extract, and their use to prevent skin ageing.

These documents do not mention the use of the relevant compositions for treating diseases involving bone resorption. Accordingly, the claimed matter is new.

### **Inventive step (Art.56 EPC)**

The present application relates to the provision of medicines for the treatment of bone diseases. Although not explicitly mentioned in the claims, osteoporosis appears to be a preferred disease to be treated according to the invention (see paragraph [0004]). The applicant reports the discovery that various combinations of plant derived extracts can be used to treat these diseases. These extracts contain flavonoids or other related derivatives. In the applicant's opinion, this effect is mediated by a mechanism of action involving an increase in the expression of BMP-2 or the modulation of RANK-L.

In order to treat the aforementioned conditions, the applicant proposes combinations of pomegranate and grape seed extracts, optionally in combinations with other ingredients, such as ipriflavone, green tee, Siberian Ginseng, Sophora Japonica, Lliquorice extracts.



The use of these plant extracts to treat bone diseases (e.g. osteoporosis) is well known. It is also known that flavonoid compounds, (e.g. quercetin) stimulate osteoblast activity, promote bone growth and can be used for the treatment of osteoporosis:

*Pomegranate*

**D22** teaches that pomegranate prevents reduction in bone weight and **D23** discloses the use of compositions comprising pomegranate to treat osteoporosis. Documents **D27-D29** indicate that the use of compositions comprising pomegranate and other herbal extracts was part of the traditional knowledge.

*Grape fruit extracts*

**D24** discloses the use of compositions comprising grape fruit extracts to increase skeletal density and **D25** and **D26** teach that grape seeds extracts have beneficial effect on bone formation and promote bone formation.

*Green tea*

Documents **D33** and **D34** teach that green tea and its active components enhance osteogenesis and strengthen bones.

*Ipriflavone*

**D18** teaches that Siberian Ginseng and ipriflavone protect against Glucocorticoid induced osteoporosis.

*Documents relating to the use of quercetin*

**D2** (see corresponding translation EP1847265) discloses the use of flavonoids, including quercetin to stimulate osteoblast activity, promote bone growth and to treat osteoporosis. The involvement of BMP-2 in the bone forming activity is also disclosed. See in particular paragraphs [0001, 0002, 0003, 0010, 0016, 0022], claims 1, 8, 9; "quercetin" in paragraph [0009]; claims 4, 16, 17, 18 and figure 3: activity of quercetin on fibroblast proliferation).

**D3** (see e.g. column 2, lines 8-14, 29-61, claims) discloses the use of quercetin to treat bone diseases (e.g. osteoporosis).

**D4** (see page 1, lines 5-20, page 8, lines 10-16, page 10, lines 30-37, examples 1-4, tables and claims) discloses the proliferative activity of quercetin on osteoblasts, its inhibitory activity on osteoclasts and its uses to treat osteoporosis.

**D6** (see abstract) discloses the effects of quercetin on osteoclast differentiation and its use to inhibit bone resorption and to treat osteoporosis.

**D30** (see paragraph [0005] and claims 1, 4) discloses compositions comprising quercetin, for strengthening and increasing bone mass.

*Documents relating to the use of liquorice extract*

**D7** (see page 6, line 1-6, 10-12; claims 1, 5) and **D8** (abstract) disclose the use of licorice extract for the treatment and prevention of osteoporosis.

**D31** and **D32** (see abstracts) discloses compositions comprising liquorice extract for the treatment of osteoporosis, which promote osteoblast growth, cell differentiation and osteoclast calcification and promote bone formation.

**D35** (see abstract) discloses compositions comprising liquorice root for promoting bone growth.

*Documents relating to the use of Sophora*

**D13** discloses the use of extracts from the sophora fruit to treat osteoporosis.

**D15** discloses the use of extracts of Sophora (including Sophora Japonica) to treat diseases related to decrease of estrogen levels, including osteoporosis.

**D16** and **D17** disclose the use of extracts of sophora japonica to treat menopause syndrome. Osteoporosis is mentioned among the conditions to be cured.

**D19** (available on-line on 27-10-2005) teaches that Genistein from Sophora Japonica has beneficial anti - osteoporosis effects.

*Documents relating to the use of ginseng*

**D18** teaches that Siberian Ginseng and ipriflavone protect against Glucocorticoid induced osteoporosis.

*Documents relating to the use of pomegranate extracts*

**D22** teaches that pomegranate prevents reduction in bone weight and **D23** discloses the use of compositions comprising pomegranate to treat osteoporosis.

Documents **D27-D29** further reveal that compositions comprising extracts of pomegranate were used since long time according to traditional knowledge, for use in the treatment of conditions characterised by reduction of bone tissue and rickets.

*Document relating to the use of Ginkgo Biloba*

**D5** (see page 4, lines 19-23, paragraph [0020], claims 1,2, examples 1, 2) discloses the therapeutic activity of Ginkgo Biloba (comprising quercetin), to treat osteoporosis.

*Documents relating to the use of grape fruits extracts*

**D24** discloses the use of compositions comprising grape fruit extracts to increase skeletal density and **D25** and **D26** teach that grape seeds extracts have beneficial effect on bone formation and promote bone formation.

*Documents relating to the Involvement of BMP.2 and RANK-L*

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The involvement of the bone morphogenetic protein 2 (BMP-2) and of RANK-L in bone metabolism and the modulation of the expression or the activity of these proteins induced by flavonoids is also well known:

**D9** shows that Soybean isoflavone (a flavonoid close to quercetin) increases the expression of BMP - 2, and increases bone mineral density in ovariectomized rats, preventing osteoporosis. **D10** shows that Celosia cristata L flavonoid increases the expression of BMP - 2 in diabetic rats.

**D11** shows that the Genistein (a flavonoid very similar to quercetin) stimulates the BMP - 2 promoter and its use is suggested, together with other estrogens, to treat osteoporosis. This paper teaches that the effect on BMP-2 is shared by different estrogens and phytoestrogens, like Genistein.

**D12** discusses the effects of quercetin on osteoclastic differentiation and the involvement of RANK-L.

*The problem and its solution*

Considering the teaching of the prior art, the problem underlying the subject matter can be seen as the provision of a new medicament to treat bone diseases. In the absence of a clear evidence that the claimed invention produces a new unexpected technical effect, the idea to prepare the claimed combinations would have been obvious. In fact, a skilled person confronted with such problem would have been prompted to combine compounds increasing bone growth according to the invention. Since on the basis of the application as filed no surprising effects can be observed when using combinations falling within the scope of the claims, the subject matter claimed may not be considered to involve an inventive step.

In as far the applicant will argue that unexpected effects are produced by the claimed combinations, adequate evidence will have to be provided to prove that this effect is obtained using any of the claimed combinations and any ratio between the compounds used.

**Clarity (Art.84 EPC)**

The wording "approximatively" used in the claims is a relative term and is unclear.