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(54) Title: 8-(C-BETA-D-GLUCOPYRANOSYL)-7,3',4'-TRIHIDROXYFLAVONE, PROCESS OF ISOLATION FROM PTEROCARPUS MARSUPIUM AND PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF DIABETES

(57) Abstract: The present invention relates to a novel compound 8-(C-β-D-glucopyranosyl)-7,3', 4' - trihydroxyflavone, isolated from *Pterocarpus marsupium* useful in the treatment of diabetes. The present invention also relates to a method for the preparation of the compound and to the use thereof.



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**8-(C-BETA-D-GLUCOPYRANOSYL)-7,3', 4'-TRIHYDROXYFLAVONE,
PROCESS OF ISOLATION FROM PTEROCARPUS MARSUPIUM AND
PHARMACEUTICAL COMPOSITION FOR TREATMENT OF DIABETES**

5 Field of the invention

The present invention relates to a novel compound, 8-(C-β-D-glucopyranosyl)-7,3', 4'- trihydroxyflavone. The present invention also relates to a process for the isolation of said novel compound 8-(C-β-D-glucopyranosyl)-7,3',4'-trihydroxyflavone from *Pterocarpus marsupium*. The present invention also relates to a pharmaceutical composition containing 8-
10 (C-β-D-glucopyranosyl)-7,3', 4'- trihydroxyflavone and to method for the treatment of diabetes using said compound.

Background of the invention

Pterocarpus marsupium Roxb (*Leguminosae*) also known as Indian Kino tree or Bijasar, is common in the hilly regions of central and peninsular India [Jain, S. K., Medicinal
15 Plants, National Book Trust, New Delhi, 1968, p. 116]. The extracts of leaves, flowers and gum of this tree have been used medicinally in the treatment of diarrhea, toothache, fever, urinary tract and skin infections. [Chopra, R. N., Chopra, I. C., Handa, K. L. and Kapur, L. D., Indigenous Drugs of India, 2nd Ed., Dhar, U. N. and Sons Private Limited, Calcutta, 1958, p. 522]. The extract of the bark has long been regarded as useful in the therapy of
20 diabetes [Kirtikar, K. R. and Basu, B. D., Indian Medicinal Plants, 2nd Ed., edited by Blatter, E., Cailes, J. F. and Mhaskar, K. S., Singh and Singh, Delhi, India, 1975, p. 2135]. It is reported by Chakravarthy et al [Chakravarthy, B. K., Gupta, S. and Gode, K. D., *Lancet*, 1982, 272 (and references cited therein)] that the active hypoglycemic principle of the bark is (-)-epicatechin and that its effect is due to the regeneration of pancreatic beta cells. However,
25 this claim has been questioned by Kolb et al [Kolb, H., Kiesel, U., Grenlich, B. and Bosch, J. V. D., *Lancet*, 1982, 1303.] and Sheehan et al [Sheehan, E. W., Zemaitis, M. A., Slatkin, D. J. and Schiff, Jr., P. L., *Journal of Natural Products*, 1983, 46, 232]. It is now felt that further investigation is necessary before (-)-epicatechin can be considered a viable antidiabetic agent for use in human clinical studies.

30 Practitioners of the Indian System of Medicine are of the view that the heartwood rather than the bark of *Pterocarpus marsupium* is useful for treatment of diabetic patients and that older the plant more efficacious is its heartwood. It is also claimed that only heartwood that is distinctly red in colour and which imparts a red colouration with bluish green fluorescence to water in which it is kept soaked is suitable for use as an antidiabetic drug.

Hypoglycaemic effects of aqueous or alcoholic extracts of heartwood of *Pterocarpus marsupium* have been verified by experimental [Shah, D. S., *Indian Journal of Medical Research*, 1967, 55, 166 and references cited therein; Gupta, S. S., *Indian Journal of Medical Research*, 1963, 51, 716] and clinical studies [Septha, G. C. and Bose, S. N., *J. Ind. Med. Assoc.*, 1956, 27, 383; Kedar, P. and Chkrabarti, C. H., *Maharashtra Med. J.*, 1981, 28, 165].

The heartwood of *Pterocarpus marsupium* is rich in phenolics. Chemical investigation on heartwood of *P. marsupium* dates back to 1946 but early works [Bhargava, P. N., *Proc. Ind. Acad. Sci.*, 1946, 24A, 496] on this drug are fragmentary in nature. Previous reported studies on this plant disclose the following chemical constituents.

1. Ether extract of *P. marsupium* heartwood furnished isoflavonoid glycol 4,4'-dihydroxy- α -methylhydrobenzoin designated Marsupol [Rao, A. V. S., Mathew, J., *Phytochemistry*, 1982, 21, 1837], a benzofuranone derivative, 2,4',6-trihydroxy-4-methoxybenzo(b)furan-3(2H)-one designated carpusin [Mathew, J. and Rao, A. V. S., *Phytochemistry*, 1983, 22, 794], 2-propanol derivative, 1,3-bis (4-hydroxyphenyl)propan-2-ol, designated propterol [Rao, A. V. S., Mathew, J. and Shankaran, A. V. B., *Phytochemistry*, 1984, 23, 897], 1-(2,4-dihydroxyphenyl)-3-(4-hydroxyphenyl)propan-2-ol designated propterol B [Mathew, J., Rao, A. V. S. and Rambhav, S. *Current Science*, 1984, 53, 576], 6-hydroxy-7-O-methyl-3-(3-hydroxy-4-O-methyl benzyl) chroman-4-one [Jain, S. C., Sharma, S. K., Kumar, R., Rajwansh, V. K. and Babu, V. R., *Phytochemistry*, 1997, 44, 765].
2. Ethylacetate soluble fraction of alcoholic extract of heartwood furnished pterosupin β ,2',4,4'-tetrahydroxy-3'(c- β -D-glucopyranoside)dihydrochalcone [Adinarayana, D., Syamsundar, K. V., Seligmann, O., & Wagner, H., (*Z. Naturforsch.*, 1982, 37C, 145)], Marsupinol [Trivedi, J. J., *Indian J. Phys. Pharmacol*, 1997, 15, 51], 5,4'-dimethoxy-8-methylisoflavone-7-O- α -L-rhamnopyranoside, retusin-O- β -D glucopyranoside and irisolidine-7-O- α -L-rhamnopyranoside [Mitra, J. and Joshi, T., *Phytochemistry*, 1982, 21, 2429] and 5,7'-dihydroxy-6-methoxy-7-O- α -L-rhamnopyranoside [Mitra, J. and Joshi, T., *Phytochemistry*, 1983, 22, 2326] obtained from ethylacetate soluble fraction of alcoholic extract of heartwood.
3. Benzofuranone derivative, 2,6-dihydroxy-2-(p-hydroxybenzyl)-4-methoxy-3(2H)-benzofuranone designated as marsupin [Maurya, R., Ray, A. B., Duah, F. K., Slatkin, D. J. & Schiff, P. L. Jr., *Heterocycles*, 1982, 19, 2103] & pterostilbin, (2S)-hydroxyflavone, isoliquiritigenin, liquiritigenin, 7,4'-dihydroxyflavone, 5-deoxykaempferol & 3,7,4'-trihydroxyflavone [Maurya, R., Ray, A. B., Duah, F. K., Slatkin, D. J. & Schiff, P. L. Jr.,

*J.Nat.Prod.*1984,47,179], two C-glycosides, 8-C- β -D-glucopyranosyl-3,7,4'-trihydroxy & 3,7,3',4'-tetrahydroxyflavone & 3'-C- β -D-glucopyranosyl- α -hydroxy dihydrochalcone [Bezuidenhoudt,B.C.B., Brandt,E.V., and Ferreira,E.V.,*Phytochemistry*,1987,26,531] from ethylacetate extract of defatted heartwood.

- 5 4. The petrol extract of *P. marsupium* root afforded selin-4(15)-ene-1 β , 11-diol, β -eudesmol, erythrodol-3-monoacetate and pterostilbene [Adinarayana, D., and Syamasundar, K. V., *Phytochemistry*, 1982, 22, 1083]. Ethanolic extract of *P. marsupium* flowers furnished 4,6,4'-trihydroxyaurone 6-O-rhamnopyranoside and 4,6,4'-trihydroxy-7-methylaurone 4-O-rhamnopyranoside [Mohan, P., and Joshi, T., *Phytochemistry*, 1989, 28, 1287] and
10 ethanolic extract of *P. marsupium* bark furnished (-)-epicatechin [Chakravarthy, B. K., and Gode, K. D., *Planta Medica*, 1985, 56].

However, the prior art does not provide any details about the biological activities associated with such chemical constituents. Also prior art discloses only preparation of ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract but
15 does not disclose any method of preparing water extracts of heartwood of *Pterocarpus marsupium* and attempting to isolate any chemical constituents therefrom.

Objects of the invention

The main object of the invention is to accordingly prepare water extracts of the heartwood of *Pterocarpus marsupium* and to obtain chemical constituents therefrom.

- 20 It is another object of the invention to investigate the water extracts of heartwood of *Pterocarpus marsupium* to obtain bioactive fractions useful in the treatment of diabetes.

Summary of the invention

The above and other objects of the invention are achieved by preparing a n-butanol soluble water extract of investigate the water extract of heartwood of *Pterocarpus marsupium* and isolating a novel bioactive fraction therefrom. Accordingly, the present invention
25 provides a novel compound 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone.

The present invention also provides a process for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
30 (b) extracting the powdered plant material so prepared with a protic solvent,
(c) concentrating the extract to minimum volume and partitioning with different organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,

(d) isolating the 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone from the residue.

In one embodiment of the invention, the protic solvent used for preparing the extract in step (b) is selected from the group consisting of water, methanol, ethanol, propanol, butanol and any mixture thereof.

5 In a further embodiment of the invention the polar solvent used to extract the aqueous layer is selected from ethyl acetate, propanol and butanol.

In another embodiment of the invention, organic solvent used in step (c) to remove non-polar components is selected from group consisting of hexane, pet ether and chloroform.

10 In another embodiment of the invention, the chromatographic methods used for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone is selected from MPLC, HPLC and flash chromatography.

The present invention also relates to a pharmaceutical composition containing a pharmaceutically effective amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in a pharmaceutically acceptable carrier.

15 In one embodiment of the invention, the amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in said composition is in the range of 0.5 mg to 10 mg per kg of body weight of the patient.

The invention also relates to a method for the treatment of diabetes comprising administering a pharmaceutically effective amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone to a patient.

20 In one embodiment of the invention, the amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in said composition is in the range of 0.5 mg to 10 mg per kg of body weight of the patient.

The present invention also relates to the use of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in preparation of a pharmaceutical composition for treatment of diabetes.

Detailed description of the invention

The present invention provides a process for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone which comprises:

- (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
- 30 (b) extracting the powdered plant material so prepared with a protic solvent,
- (c) concentrating the aqueous extract to minimum volume and partitioning with organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue;

(d) isolating the 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone from residue.

The solvent used for preparing the extract may be water, methanol, ethanol, propanol and butanol and like or their mixtures. The organic solvent used in step (c) to remove the non-polar components is selected from the group consisting of hexane, pet ether and chloroform. The polar solvent used to extract the aqueous layer is selected from ethyl acetate, propanol and butanol. The chromatographic methods used for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone may be MPLC, flash chromatography etc.

In the MPLC method the required eluting solvent is pumped through the column and in the flash chromatography solvent is pushed with air pressure. The compound was assigned the molecular formula $C_{21}H_{20}O_{10}$ [FAB-MS, m/z 433[M+1]⁺]. This conclusion was supported by ¹³CNMR and DEPT spectra.

The compound 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone was isolated from the n-butanol soluble fraction of the water decoction of the heartwood of *P. marsupium* which has shown antidiabetic activity in both humans and animals. There is no disclosure in the prior art of this compound since work had been done in the art on the ether extract, ethyl acetate extract and ethyl acetate soluble fraction of the alcoholic extract.

The process of isolating active principle from *Pterocarpus marsupium* comprises partition of the aqueous extract of powdered heartwood with different organic solvents containing 1–6 carbon atoms in the molecule. 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone is isolated from polar fraction by applying modern chromatographic techniques such as medium pressure liquid chromatography (MPLC), high pressure liquid chromatography (HPLC) and flash chromatography using silica gel (230 – 400 mesh) and shows hypoglycaemic activity.

The compound 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone has been evaluated for hypoglycaemic activity in 18 h. fasted Wistar rats. In the dose of 10 mg/kg p. o., hypoglycaemic effect was recorded in all the treated rats. The mean fall recorded was 24mg/100ml. blood, from initial mean of 92 to mean of 68 mg/ 100 ml. blood. As compared to this, the clinically used hypoglycaemic agent, employed as positive control in the study, showed mean fall of 23 mg/ 100 ml. blood.

The compound was proved to be a phenol from its positive phosphomolybdenic acid test (blue), ferric chloride test (green). It was recognised to be a flavone as it responded to the Shinoda test. The presence of hydroxyl, carbonyl, and phenyl nucleus was indicated by the IR absorption at 3228, 1615, 1554, 1448, 1422 cm^{-1} . The UV spectrum of the compound showed

absorption maxima at $\lambda_{\text{max}}^{\text{MeOH}}$ 219, 238, 260, 320, 358 nm which underwent bathochromic shift 219, 238, 267, 320, 367 nm in presence of NaOAc. This observation suggested the presence of a free hydroxyl group located at C-7.

The ^1H NMR spectrum (200MHz, in DMSO- d_6) displayed broadening of signals in the aromatic regions presumably because of the steric crowding of the glucosyl and B-ring. The inspection of spectrum revealed singlet signal at δ 6.98 (1H) characteristic of proton at C-3 of flavone. A doublet proton signal at δ 8.28 (1H, d, $J = 2.1$ Hz) which is low field shifted due to the effect of the neighbouring C=O, is ortho-coupled with the doublet signal at δ 6.95 (1H, d, $J = 8.3$ Hz). This ortho coupling is assigned to the proton at C-5 and C-6 indicating that only these two protons belong to A ring and that C-8 is occupied by a glucosyl group. The proton signal at δ 7.84 (1H, br d, $J = 2.1$ Hz), 7.97 (1H, br dd, $J = 2.1, 8.7$ Hz) and 6.99 (1H, d, $J = 8.7$ Hz) are assigned to the protons at the B-ring. Further ^1H and ^{13}C NMR spectra showed signals attributed to one glucose moiety. The C-C coupling was exemplified by ^1H and ^{13}C heteronuclear correlation of the anomeric proton at δ 5.16 with a carbon doublet at δ 79.3 in the region characteristic of C_1 - substituted glucosides. Further the coupling constant ($J=9.5$ Hz) of the signal resulting from the anomeric proton of the glucopyranoside indicated that the glucosidic linkage has β -configuration. Thus the above analysis led to the structure 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone.

The invention is described in detail by the examples given below which should not be construed to the limit of scope of the present invention.

Example 1

The powdered heartwood of *Pterocarpus marsupium* (1kg) was percolated with 80% aqueous ethanol (3x3 lits.) for a period of 48 hours. The resultant concentrate was partitioned with hexane, chloroform, propanol and butanol in that order. The polar extract was subjected to MPLC using silica gel (100 - 200 mesh) for gross fractions with hexane, chloroform, methanol, ethanol in that order. The active compound was purified by repeated MPLC and flash chromatography over silica gel (230 - 400 mesh) using CHCl_3 - MeOH (19:1) as solvent, to furnish 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone, (yield 0.046), mp. 202 -204°C, $[\alpha]_D^{19} + 25.6^\circ$ (MeOH, c, 0.5).

Example 2

The heartwood of *Pterocarpus marsupium* was extracted with hot water for a period of 4X4 hours. The resultant concentrate was partitioned between hexane, chloroform, propanol and butanol in that order. The polar extract so obtained was subjected to flash

chromatography employing silica gel (100 - 200 mesh) using hexane, chloroform, ethylacetate and methanol as solvent system to afford 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone rich fraction, which on repeated chromatography over silica gel (230 - 400 mesh) using EtOAc - MeOH (19.5:0.5) as solvent, furnished 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone of the formula 1 (yield 0.049%), mp. 202 – 204°C, $[\alpha]_D^{19} + 25.6^\circ$ (MeOH, c, 0.5).

Example 3

The heartwood of *Pterocarpus marsupium* was boiled with water (16 times) till 1/4 volume of water is left. Filtered, concentrated and partitioned between hexane, chloroform, ethyl acetate, propanol and n-butanol in that order. The polar extract obtained was subjected to column chromatography employing silica gel (60-120 mesh) using hexane, chloroform, ethyl acetate and methanol as solvent system to afford 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone rich fraction. The 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone rich fraction on repeated column chromatography over silica gel (100-200 mesh) using mixture of ethyl acetate - acetone (8:2), furnished 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone (yield 0.051%), mp. 202 – 204°C, $[\alpha]_D^{19} + 25.6^\circ$ (MeOH, c, 0.5).

Advantages:

1. The compound obtained 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone is a novel molecule with antidiabetic activity.
2. The method of isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone is comparatively simple.

We claim:

1. 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone.
2. 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone as claimed in claim 1 isolated from *Pterocarpus marsupium*.
- 5 3. Process for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone which comprises:
 - (a) powdering the heartwood of the plant *Pterocarpus marsupium*,
 - (b) extracting the powdered plant material so prepared with a protic solvent,
 - (c) concentrating the extract to minimum volume and partitioning with different
10 organic solvents of increasing polarity to remove non-polar components, extracting the aqueous layer with polar solvent, removing the solvent to get the residue.,
 - (d) isolating the 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone from residue.
4. Process as claimed in claim 3 wherein the protic solvent used in step (b) is selected
15 from water, methanol, ethanol, propanol, butanol and any mixture thereof.
5. Process as claimed in claim 3 wherein the organic solvent used in step (c) to remove the non-polar components is selected from hexane, pet ether and chloroform.
6. Process as claimed in claim 3 wherein the polar solvent used to extract the aqueous layer is selected from ethyl acetate, propanol and butanol.
- 20 7. Process as claimed in claim 3 wherein the chromatographic methods used for the isolation of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone is selected from MPLC, HPLC and flash chromatography.
8. Pharmaceutical composition comprising an pharmaceutically effective amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in a pharmaceutically acceptable
25 carrier.
9. Composition as claimed in claim 8 wherein the amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in said composition is in the range of 0.5 mg to 10 mg per kg of body weight of the patient.
10. Method for the treatment of diabetes comprising administering a pharmaceutically
30 effective amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone to a patient.
11. Method as claimed in claim 10 wherein the amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in said composition is in the range of 0.5 mg to 10 mg per kg of body weight of the patient.

12. Use of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in the preparation of a pharmaceutical composition for the treatment of diabetes.
13. Use as claimed in claim 12 wherein the amount of 8-(C- β -D-glucopyranosyl)-7,3',4'-trihydroxyflavone in the pharmaceutical composition is in the range of 0.5 mg to 10 mg per kg of body weight of the patient.

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INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H7/06

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)

IPC 7 C07H

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, 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.
A	BEZUIDENHOUDT B C B ET AL: "FLAVONOID ANALOGUES FROM PTEROCARPUS SPECIES" PHYTOCHEMISTRY, PERGAMON PRESS, GB, vol. 2, no. 26, 1987, pages 531-535, XP008005725 ISSN: 0031-9422 cited in the application the whole document * in particular compounds 13 and 15 *	1-13
A	MAURYA R ET AL: "CONSTITUENTS OF PTEROCARPUS MARSUPIUM" JOURNAL OF NATURAL PRODUCTS, XX, XX, vol. 1, no. 47, 1984, pages 179-181, XP001086563 ISSN: 0163-3864 cited in the application the whole document --- -/--	1-13

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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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.
A	<p>US 5 886 029 A (DHALI WAL KIRPAL S)</p> <p>23 March 1999 (1999-03-23)</p> <p>the whole document</p> <p>* in particular claims 15 and 20 *</p> <p>-----</p>	1-13

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5886029	A	23-03-1999	NONE