Title: COMPOSITIONS BASED ON SAFFRON FOR THE PREVENTION AND/OR TREATMENT OF CORNEAL DYSTROPHIES.

Abstract: The present invention relates to a pharmaceutical, dietary and/or food composition, comprising saffron for use in the prevention and/or treatment of corneal dystrophies. The present invention also relates to a combination comprising saffron and at least one antioxidant and to a pharmaceutical dietary and/or food composition comprising said combination for use in the prevention and/or treatment of corneal dystrophies.

FIG. 1

[Continued on next page]
Published:

— with international search report (Art. 21(3))

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))
Title

Compositions based on saffron for the prevention and/or treatment of corneal dystrophies.

*** ***

The present invention is direct to a pharmaceutical, dietary and/or food composition, comprising saffron for use in the prevention and/or treatment of corneal dystrophies.

The present invention is also direct to a combination comprising saffron and at least one antioxidant and to a pharmaceutical dietetic and/or food composition comprising said combination for use in the prevention and/or treatment of corneal dystrophies.

PRIOR ART

The transparency of the cornea is essential to maintain visual function and depends on the perfect integrity of all the components thereof.

Corneal dystrophies are a group of progressive disorders of non-inflammatory nature, usually bilateral and mostly genetically determined, which cause opacification of the cornea.

They are characterised by a morpho-functional alteration resulting from modifications in normal corneal trophism and by abnormal accumulation of foreign matter in one or more of the five layers of the cornea, namely the epithelium, Bowman's layer, stroma, Descemet's membrane, and the endothelium.

This material can cause the loss of transparency in the cornea or significant impairment of visual acuity.

One symptom common to many forms of corneal dystrophy is recurrent corneal erosion, where the outermost layer of the cornea (epithelium) does not adhere correctly to the eye. Recurrent corneal erosion can cause discomfort or pain, abnormal sensitivity to light (photophobia), the feeling of a foreign body in the
eye, and blurred vision.
Recurrent corneal erosion can be treated with specific contact lens (soft bandage) or with antibiotics such as doxycycline.
Doxycycline can, however, cause several side effects and can interfere with many drugs.
The age of corneal dystrophies onset varies from the first to fourth decade, depending on the relative frequency of recurrent epithelial erosions and vision deficit.
Corneal dystrophies can be classified into three groups based on the sole or predominant anatomical location of the anomalies: some affect primarily the corneal epithelium (epithelial corneal dystrophies), some the Bowman's layer (corneal dystrophies of Bowman's layer), others the corneal stroma (stromal corneal dystrophies), or the Descemet's membrane and the corneal endothelium (posterior or endothelial corneal dystrophies).
The group of epithelial corneal dystrophies includes epithelial basement membrane dystrophy (also known as "map-dot-fingerprint dystrophy" or anterior corneal dystrophy) and Meesmann's dystrophy.
Possible corneal dystrophies of the Bowman's layer include Reis-Bucklers dystrophy, Thiel-Behnke dystrophy, and Schnyder's central crystalline dystrophy.
The group of stromal corneal dystrophies includes lattice corneal dystrophy, lattice corneal dystrophy type 1 (Biber-Haab-Dimmer), lattice corneal dystrophy type 2 (Meretoja syndrome), lattice corneal dystrophy types 3 and 3A, Avellino dystrophy, macular corneal dystrophy and gelatinous drop dystrophy.
The endothelial corneal dystrophies include Fuchs' endothelial dystrophy and posterior polymorphous dystrophy.
Corneal dystrophy is the most common epithelial basement membrane dystrophy (EBMD).
It is a bilateral anterior corneal dystrophy, characterised by the presence, within the epithelium, of greyish lines in a fingerprint pattern, of irregular map-like areas with ground-glass appearance, and of small opaque spheroidal alterations (microcysts) visible under slit lamp examination.

The 50% of patients presenting recurrent corneal erosions are suffering from EBMD.

Treatment of corneal dystrophies usually involves the use of tear substitutes or, in cases of severe impairment of visual acuity, laser use is necessary or a corneal transplant must be performed.

Therefore, there is a need to find alternative therapies, preferably neither surgical nor invasive, which are effective in the prevention and/or treatment of corneal dystrophies without generating side effects.

Saffron, that is the stigmas of the *Crocus Sativus* plant, is known for its antioxidant/anti-inflammatory activity. Recently, it was shown that its crude extract, and purified derivatives thereof, are able to prevent tumors formation, atherosclerosis, and liver and kidney damage.

The chemistry of saffron is complex and there are many types of saffron, obtained from different varieties and differently prepared, which differ in the amount of their main components, such crocins, picrocrocin, campherols and safranal.

Chemically, crocins are compounds of formula I, that is diesters of the dicarboxylic acid crocetin, wherein the carboxy groups are esterified by \( R_1 \) and \( R_2 \), wherein both \( R_1 \) and \( R_2 \) groups may be, independently, gentiobiose, glucose and many other sugars:

![Formula I](image)

Formula I
Different crocins may therefore be distinguished, in which the crocetin acid groups are esterified with different saccharides.

In the different varieties of saffron, the more abundant crocins are *trans-crocin* $T_1$ (*trans*-crocin-4-gentiobiose-gentiobiose), of formula II

![Formula II](image1)

where $R_1=R_2$ = gentiobiose,

and *trans*-crocin $T_2$ (*trans*-crocin-3-gentiobiose-glucose), of formula III

![Formula III](image2)

$R_1$ = gentiobiose and $R_2$ = glucose.

Also belong to the group of crocins analogues which have a different configuration of the 5-6 double bond of crocetin alkyl chain, *i.e.* compounds that have the *cis* configuration instead of the *trans* configuration, so called *cis*-crocins.

The investigations carried out on varieties of saffron of different geographical origin have revealed that these different varieties of saffron mainly differ in their contents of *trans* and *cis* crocins.

The main object of the present invention is to provide a composition which allows treatment and also prevention of corneal dystrophies.

By "treatment", according to the present invention, it is meant the complete remission of the disease, but also the arrest or even a partial improvement of the
recognized symptoms of corneal dystrophies existing at the beginning of therapy. By "prevention", according to the present invention, it is meant the administration of a medicament which slows down or inhibits the onset of the symptoms of corneal dystrophies; preferably, the administration as a preventive measure is indicated for genetically predisposed patients, or those presenting a gene mutation typical of the aforementioned corneal dystrophies, or for which have already been diagnosed with corneal dystrophy of genetic origin.

**DESCRIPTION OF THE INVENTION**

This object is achieved with a pharmaceutical, dietary and/or food composition, containing effective amounts of saffron.

An object of the present invention is therefore to provide a pharmaceutical, dietary and/or food composition, preferably a food supplement, containing effective amounts of saffron for use in the treatment and/or prevention of corneal dystrophies.

The corneal dystrophies to which the present invention is addressed are epithelial corneal dystrophies, Bowman's layer corneal dystrophies, stromal corneal dystrophies, or posterior or endothelial corneal dystrophies.

Preferably, the corneal dystrophies to which the present invention is addressed are the epithelial corneal dystrophies, and more preferably epithelial basement membrane dystrophy (EBMD).

By "saffron" in the present invention it is meant a mixture comprising crocins, picrocrocin, campherols and safranal, obtained through the pulverisation of the stigmas of *crocus sativus*.

In a preferred aspect, the saffron contained in the composition of the invention is a mixture in which the *trans*-crocin-4-gentiobiose-gentiobiose is present in an amount equal to or greater than 16.9 % by weight, based on the total weight of saffron, and in which the *trans*-crocin-3-gentiobiose-glucose is preferably present
in an amount equal to or higher than 8% by weight, based on the total weight of the saffron.

A further aspect of the present invention is a pharmaceutical, dietary and/or food composition comprising effective amounts of saffron in association with at least one physiologically acceptable excipient in the same dosage unit.

The daily dose and the duration of the treatment vary according to the treatment indication, the age and the patient's clinical situation.

The use of said composition for the prevention and/or treatment of corneal dystrophies provides for the daily dose administration of saffron ranging between 5 and 50 mg/day, preferably ranging between 10 and 40 mg/day, still more preferably a daily dose of 20 mg/day or 30 mg/day.

Preferably, said composition is administered with a posology of one daily dose, as stated above, divided into two doses over the day (morning and evening).

It was also shown that the combination of saffron with a proper amount of at least one antioxidant allows obtaining a further advantage in terms of effectiveness in the prevention and/or treatment of corneal dystrophies.

A further object of the present invention is therefore a pharmaceutical, dietary and/or food composition, preferably a food supplement, containing effective amounts of saffron in combination with effective quantities of at least one antioxidant for use in the treatment and/or prevention of corneal dystrophies.

Preferably, the antioxidant belongs to the polyphenols class; still more preferably, said antioxidant is selected from the group comprising flavonoids, such as quercetin and curcumin, and stilbenes, such as resveratrol.

Still more preferably, the antioxidant is selected from the group comprising quercetin, curcumin, and resveratrol.

The composition of the invention comprising the combination of saffron and at least one antioxidant can perform greater activity than a composition containing
the saffron or the antioxidant alone, thereby demonstrating a synergistic effect due to the combination of saffron and the antioxidant. In a further aspect, the present invention is directed to pharmaceutical, dietary and/or food composition, comprising saffron, in which the amount of trans-crocin-4-gentiobiose-gentiobiose is present in an amount equal to or greater than 16.9% by weight, based on the total weight of the saffron, and in which trans-crocin-3-gentiobiose-glucose is preferably present in an amount equal to or greater than 8% by weight, based on the total weight of the saffron, and at least one antioxidant and in combination with at least one physiologically acceptable excipient, for use in the prevention and/or treatment of corneal dystrophies. The use of said composition and/or combination for the prevention and/or treatment of corneal dystrophies provides for the daily dose administration of saffron ranging between 5 and 50 mg/day, preferably ranging between 10 and 40 mg/day, still more preferably a daily dose of 20 mg/day or 30 mg/day, in combination with an amount of at least one antioxidant ranging between 50 and 250 mg/day, preferably 100 mg/day or 200 mg/day. In a particularly preferred aspect of the present invention, the combination of saffron and at least one antioxidant is characterised in that said saffron is administered at a daily dose of 20 mg/day or 30 mg/day and said at least one antioxidant, selected from the group comprising quercetin, curcumin and resveratrol, is administered at a daily dose of 100 mg/day or 200 mg/day. Preferably, said combination of saffron and at least one antioxidant is administered with a posology of one daily dose, as stated above, divided into two doses over the day (morning and evening). In a preferred aspect, the pharmaceutical, dietary and/or food compositions in this invention are administered systemically, in particular orally. The pharmaceutical, dietary and/or food compositions of the present invention are
preferably formulated in a solid form, said solid form being selected from tablet, 
granulate, dragee, or capsule, and more preferably tablet.

To obtain the pharmaceutical dietary and/or food compositions, according to the 
present invention the following classes of known excipients are preferably used: 
anti-caking agents, sweeteners, surfactants (cationic, anionic or non-ionic), 
diluents, aggregating agents or binders, lubricants, glidants, stabilisers, 
solubilizers, emulsifiers, humectants, flavourings, coating agents, colouring 
agents, acidity regulators, or a mixture thereof.

In one preferred aspect, the pharmaceutical, dietary and/or food compositions of 
this invention comprise saffron and at least one antioxidant, wherein said 
antioxidant preferably belongs to the polyphenol class, stil! more preferably, said 
antioxidant is selected from the group comprising flavonoids, such as quercetin 
and curcumin, and stilbenes, such as resveratrol, in association with at least one 
physiologically acceptable excipient in the same dosage unit in tablet form for 
oral administration.

In a preferred aspect, the combination and/or the pharmaceutical compositions of 
this invention are administered to mammals, especially to humans.

**BRIEF DESCRIPTION OF THE FIGURES**

Additional features and advantages of the invention will become more clearly 
apparent by the following description of some preferred embodiments thereof, 
given hereinbelow by way of illustration and not of limitation, with reference to 
the attached drawings. In such drawings:

- Figure 1 is a graph illustrating the size of the damaged area (mm²), in the 
four experimental groups (A-D), over the course of the seven days following 
surgery;

- Figure 2 is a graph illustrating the degree of opacity in the four 
experimental groups (A-D), over the course of the seven days following surgery.
The following examples are intended to better understand the invention, without in any way limiting it.

**Experimental part**

**EXAMPLE 1**

It has been demonstrated that administration of a composition comprising effective doses of saffron to a patient suffering from epithelial basement membrane dystrophy was effective in the treatment of such disease.

The epithelial basement membrane dystrophy had been diagnosed based on clinical manifestations of recurrent corneal erosions and infections that the patient had suffered for several years prior to start drug-based treatment.

The patient complained of acute pain in the eyes, above all during the latter stages of sleep and upon waking.

The patient had initially been treated with steroids and doxycycline (100 mg/day) for 10 months, with concomitant use of tear substitutes.

The treatment proved effective and the symptoms subsided.

Nevertheless, the discontinuation of the doxycycline resulted in the return of the symptoms within a few days and likewise the acknowledged side effects.

The patient discontinued treatment with doxycycline and subsequently started treatment with two tablets per day of a saffron composition containing:

- saffron 10 mg
- curcumin 50 mg

The patient immediately noted the absence of symptoms related to recurrent corneal erosions.

Given the tolerability of the composition, treatment with saffron was continued and today, approximately two years after starting treatment, the patient is no longer suffering from any symptoms.

**EXAMPLE 2**
A patient suffering from epithelial basement membrane dystrophy and the same clinical history as described in Example 1 was treated with two tablets per day of a saffron composition containing:

- saffron 15 mg
- quercetin 50 mg
- resveratrol 50 mg

The patient immediately noted the absence of symptoms related to recurrent corneal erosions.

The treatment with saffron was continued and today, approximately two months after starting treatment, the patient is no longer suffering from any symptoms.

It has therefore been demonstrated that administration of a composition comprising effective doses of saffron, quercetin and resveratrol to a patient suffering from epithelial basement membrane dystrophy was effective in the treatment of such disease.

**EXAMPLE 3**

A patient suffering from epithelial basement membrane dystrophy and the same clinical history as described in Example 1 was treated with two tablets per day of a saffron composition containing:

- saffron 10 mg

The patient immediately noted the absence of symptoms related to recurrent corneal erosions.

During treatment with saffron, the patient stopped taking steroids and doxycycline and only used the tear substitutes occasionally.

Today, approximately two years after starting treatment, the patient is no longer suffering from any symptoms.

**EXAMPLE 4**
(Evaluation of the effects of orally administered saffron solution on the corneal wound healing process on a murine model of surgical corneal lesion)

For the experiment, 40 animals (mice) of the MUS MUSCULUS species were used, all male, healthy, and aged three months.

The saffron used had an amount of trans-crocin-4-gentobiosio-gentobiosio amounting to 16.9% and of trans-crocin-3-gentobiosio-glucose amounting to 8%.

Both eyes of each mouse were subjected to PRK (photorefractive keratectomy), which consists of a surgery on the central cornea, with a 2 mm ablation area, 45 microns of depth (reaching the epithelium), using an excimer laser.

The corneal wound healing process was monitored using a stereoscopic microscope, immediately after surgery and at 1, 2, 3 and 7 days thereafter. With a colorimetric test with fluorescein (Alcon Cusi, Barcelona, Spain) the degree of damage to the corneal epithelium was evaluated. This is because the fluorescein accumulates in the areas where the epithelium is damaged; with the wound healing evolution, the marked (coloured) area decreases. The level of opacity of the cornea was evaluated according to the method of Fante et al. (1990) which involves four levels of opacity, ranging from 0 to 4, where 0 = completely clear cornea, 4 = severe opacity. All clinical evaluations were performed separately, by two operators.

The animals were divided into four experimental groups:

Group A: mice with corneal injury, not treated with saffron (drinking water only);

Group B: mice with corneal injury, treated with aqueous saffron solution;

C and D are used to show the groups of animals used as an internal control, which were treated, respectively, with plasma rich in PRGF and Cacicol growth factors (CACICOL-RGTA 20; Thea Laboratoires). The saffron treatment was orally administered (in the diet), while in the two control groups, the treatment was administered topically.
The ocular features were studied daily just before administration of treatments by microscopic analysis. Each group was analysed at four times: 1, 2, 3 and 7 days of treatment. These time points were selected because they include important events in the wound healing process.

In the following Table I the experimental schedule is summarised:

**Table I**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Doses</th>
<th>Sacrifice time</th>
<th>N. of animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left eye</td>
<td>Right eye</td>
<td>ad libitum</td>
<td>7 days</td>
</tr>
<tr>
<td></td>
<td>injured</td>
<td>injured</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>water</td>
<td>water</td>
<td></td>
<td>7 days</td>
</tr>
<tr>
<td>B</td>
<td>Saffron solution</td>
<td>Saffron solution</td>
<td>5mg/kg</td>
<td>7 days</td>
</tr>
<tr>
<td>C</td>
<td>PRGF</td>
<td>PRGF</td>
<td>2.5μL/eye</td>
<td>7 days</td>
</tr>
<tr>
<td>D</td>
<td>Cacicol</td>
<td>Cacicol</td>
<td>2.5μL/eye</td>
<td>7 days</td>
</tr>
</tbody>
</table>

* "Sacrifice time" it is meant the number of days from the surgery through to the time at which the animal is sacrificed.

The aqueous saffron solution was administered daily by syringe at a dose of 5mg/kg/day. The volume of solution administered was 300μl/day. All the treatments (saffron, PRGF, and Cacicol) began seven days prior to surgery and were ended seven days later, with the death of the animal.

The ocular features were evaluated daily by microscopic analysis. After the sacrifice, the eyes were enucleated and duly processed for immune histological analysis.
The results are shown in Figures 1 and 2, wherein the data is expressed, respectively, in units of damaged surface area (mm$^2$) and degree of opacity during the seven days following surgery.

With reference to Figure 1, 1 day after surgery, the greater re-epithelialisation efficiency corresponds to treatment with the saffron solution according to the invention - group B (0.22 ± 0.02 mm). This value is lower than that obtained with the Cacicol- group D (0.43 ± 0.06 mm), although the difference between the two groups was not statistically significant. Significant differences were observed between the untreated control group (A; 0.65 ± 0.11 mm) and the saffron group (B), whereas treatment with Cacicol (group D) showed no significant differences from the mice drinking only water (group A). Treatment with PRGF (group C) was found to be the least efficient in terms of reduction of the injured area (1.19 ± 0.15 mm) with marked differences with respect to the other groups. On the second day, there were no statistically significant differences between the groups, although the smallest average injured area observed was that of the saffron group, in accordance with the invention, i.e. group B (0.02 ± 0.01 mm). Also on the third day, no significant differences between the groups were observed. 7 days after surgery, most of the eyes had completely repaired at the level of the epithelium, while the group treated with drinking water (A) presented epithelial ulcers in 12.5% of cases and the PRGF group (C) in 10 % of cases. A 100% success rate was observed in the animals treated with Cacicol (group D) and with saffron (group B).

With reference to Figure 2, following surgery on the cornea, the tissue became very opaque during the first 24 hours, due to inflammatory processes and oedema. All the groups observed one day after surgery showed a degree of corneal opacity greater than or equal to 3 according to the Fantes' scale.
Two days after treatment, the degree of opacity decreased slightly with respect to level 3 in all groups, except the untreated group (group A), even though statistically significant differences between groups can be observed. On the third day of analysis, there was a marked difference between the groups. Treatment with Cacicol (group D), PRGF (group C), and saffron (group B) significantly improved corneal transparency quality. The Cacicol and PRGF treatments showed opacity levels below level 2, while the saffron group showed an average opacity value of (2.15 ± 0.12). Statistically significant differences between the saffron and Cacicol/PRGF groups were observed on the third day. The seventh day after surgery was particularly interesting because that was when the positive controls (Cacicol and PRGF) showed an optimal degree of corneal transparency. After seven days, the saffron group, according to the invention (group B), showed a significant reduction in corneal opacity, which settled at an average value of (1.77 ± 0.14).

In terms of speed of epithelial healing, treatment with the aqueous solution of saffron for a duration of 14 days (7 prior to surgery and 7 days after) was as efficient as the Cacicol (which is considered the best treatment in the healing process) and was significantly better than treatment with PRGF. The saffron also significantly reduced the level of opacity compared with the untreated mice (drinking water only), although it was less effective than the other substances such Cacicol or PRGF. Regarding this, it is important to note that the administration route differed for each substance: the Cacicol and the PRGF were applied directly to the cornea, while the saffron solution was administered systemically. The concentration of an active ingredient administered by oral route which acts in the cornea healing process cannot be determined with respect to a topical treatment (drops), but this shows that, although administered systemically, saffron can reduce the level of opacity.
Therefore it has been demonstrated that the orally treatment with saffron, according to the invention, serves in the re-epithelisation of the cornea.
Claims

1. Pharmaceutical, dietary and/or food composition, preferably a food supplement, containing effective amounts of saffron, for use in the treatment and/or prevention of corneal dystrophies.

2. Composition for use according to claim 1, characterised in that in said saffron the amount of trans-crocin-4-gentiobiose-gentiobiose is present in an amount equal to or higher than 16.9% by weight with respect to the total weight of the saffron.

3. Composition for use according to claim 1, characterised in that in said saffron the amount of trans-crocin-3-gentiobiose-glucose is preferably present in an amount equal to or higher than 8% by weight with respect to the total weight of the saffron.

4. Composition for use according to any one of the preceding claims, characterised in that the corneal dystrophies are selected from the group comprising epithelial corneal dystrophies, corneal dystrophies of Bowman's layer, stromal corneal dystrophies, and posterior or endothelial corneal dystrophies.

5. Composition for use according to claim 4, characterised in that said corneal dystrophies are epithelial corneal dystrophies.

6. Composition for use according to claim 5, characterised in that said corneal dystrophy is epithelial basement membrane dystrophy.

7. Composition for use according to any one of the preceding claims, characterised in that said saffron is administered at a daily dose comprised between 5 and 50 mg/day, preferably comprised between 10 and 40 mg/day, and still more preferably 20 mg/day or 30 mg/day.

8. Composition for use according to any one of the preceding claims, characterised in that it further comprises effective amounts of at least one
antioxidant.

9. Composition for use according to claim 8, characterised in that said at least one antioxidant is a polyphenol.

10. Composition for use according to claim 9, characterised in that said polyphenol is selected from the group comprising quercetin, curcumin and resveratrol.

11. Composition for use according to any of claims 8 to 10, characterised in that said saffron is administered at a daily dose comprised between 5 and 50 mg/day, preferably comprised between 10 and 40 mg/day, and still more preferably 20 mg/day or 30 mg/day and said antioxidant is administered at a daily dose of 50 or 250 mg/day, more preferably at a daily dose of 100 mg/day or 200 mg/day.

12. Composition for use according to any one of the preceding claims, characterised in that it is administered to mammals, in particular to a human.

13. Composition for use according to any one of the preceding claims, further comprising at least one physiologically acceptable excipient.

14. Composition for use according to any one of the preceding claims, in the form of a table, granulate, dragee or capsule, preferably a table.
FIG. 1
FIG. 2
**INTERNATIONAL SEARCH REPORT**

**International application No**
PCT/IB2015/057203

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. A61K36/88 A61K31/12 A61K31/7028 A61K31/05 A61K31/352
A61P27/02

**ADD.**

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 , BIOSIS, EMBASE, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>ESMAEAL TAMADDONFARD ET AL: &quot;Effects of intraperi toneal and intracerebroventri cul ar i njec tion of croci n on acute corneal pain i n rats&quot; , PHYTOTHERAPY RESEARCH , vol. 24, no. 10, 17 May 2010 (2010-05-17) , pages 1463-1467, XP055186553</td>
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* 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

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"A" document member of the same patent family

**Date of the actual completion of the international search**
25 November 2015

**Date of mailing of the international search report**
07/12/2015

**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**
Hars, Jesko

Form PCT/ISA/210 (second sheet) (April 2005)
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