Abstract: The present invention relates to a food supplement containing α-lipoic acid and hydroxytyrosol. An optional third component is lactoferrin. The present invention also relates to the use of α-lipoic acid and hydroxytyrosol for the preparation of a food supplement intended for the treatment of neuropathies, particularly poly-neuropathies referable to degenerative processes caused by the formation of free radicals.
FOOD SUPPLEMENT FOR THE TREATMENT OF NEUROPATHIES

The present invention relates to food supplement and particularly it relates to a composition of substances useful for administering to subjects suffering from neuropathies.

It is known that in many cases food supplements are formulated in such a way that they can be useful for administering to subjects suffering from particular deficiency conditions or in a state of increased need of specific nutrients. In the case of metabolic diseases such as diabetes, a lack of fundamental substances for the metabolism can occur and result in a need of specific nutrients. Neuropathies are, among other diseases, very common among subjects suffering from diabetes. These can also be caused by a nutritional deficit and are defined acquired neuropathies, or by inherited diseases, and also in these cases a need of specific nutrients can result.

Genetic diseases are at the base of hereditary neuropathies, whereas the acquired neuropathies are due to diseases acquired in the course of life, or caused by a nutritional deficit. The common denominator of acquired neuropathies is that the symptoms are bound to a severe and/or protracted oxidative stress, independently on the affected structures. It is known that oxidative stress is associated to an increase of the free radicals, that are the toxic oxygen species which, by seriously damaging the host cells, are cause or concomitant cause of a number of pathologies, including those due to ageing of the subject.

It is also known that the toxic effects of the free radicals can be canceled by antioxidant substances, or prevented by substances which prevent their formation. The administration of substances which cancel the damaging effects of the free radicals or prevent their formation can be beneficial for treating people suffering from neuropathies whose origin is often referable to the same free radicals.

It is also known to use α-lipoic acid and polyphenols of vegetal origin as antioxidant substances in compositions for alimentary or pharmaceutical use. However, the known compositions also comprise other substances, such as carnitine, which in order to be effective has to be administered in high doses (from about 200 mg to about 600 mg per day).
Patent application JP2007262054A2 describes a liquid composition comprising α-lipoic acid, vitamin B2 and polyphenols, however hydroxytyrosol is not mentioned amongst polyphenols.

WO2007/084839 describes a composition containing carnitine, α-lipoic acid and polyphenols. Tea and wine are mentioned as substances containing polyphenols. The described composition contains from 280 mg to 3500 mg of carnitine, from 7 to 700 mg of α-lipoic acid and from 2.1 mg to 70 mg of polyphenols, indicated as a daily dose for a person of 70 kg. The ratio between polyphenols and α-lipoic acid is included between 0.003 and 10. The examples given in said document also teach that the composition is administered 2 to 6 times a day, since a single tablet comprising the daily dose of all the three active principles would be too large.

Therefore, there is the need to provide a food supplement which employs at best the beneficial properties of α-lipoic acid in the treatment of the neuropathies, without including a number of other active substances such as carnitine and vitamin B2, which may imply the need of numerous daily administrations.

It is therefore an object of the present invention to provide a food supplement that is particularly useful in the diet of subjects suffering from poly-neuropathies, comprising α-lipoic acid and hydroxytyrosol as active principles.

Said object is obtained according to the present invention by means of a food supplement whose main features are specified in the first claim, whereas other features are specified in the following claims. Claim 7 and subsequent claims are use claims.

The food supplement according to the present invention comprises two substances which are per se already known but they are associated in a new and balanced way suitably for administration to subjects suffering from neuropathies.

Particularly, the food supplement according to the present invention offers the advantage of an increase of the efficacy of the components α-lipoic acid and hydroxytyrosol, due to an unexpected complementary and synergic effect. Another advantage of the food supplement according to the present invention is that the two components can be administered together, thus obtaining clear advantages from the point of view of administration ease, lower number of dosage units to be taken, and
minimum hindrance of the dose.

Preferably, the two components are associated together in the same dosage unit, in the form of a tablet, syrup, capsule, mycropellet, or similar dosage units.

Even more preferably, in the composition of the food supplement according to the present invention the weight ratio between the quantity of hydroxytyrosol and the quantity of α-lipoic acid is included in the range of 0.004-3.

It is to be noted that the higher limit of said ratio is lower than that of the composition known from WO07/084839 wherein the higher limit is 10. This is a clear evidence that the applicant has found the existence of said synergic effect, due to the substantially contemporaneous taking of α-lipoic acid and hydroxytyrosol with respect to the separated use of the single substances. Said synergic effect has been verified through a number of experimental tests of which examples will be given in the following.

The first component for the food supplement according to the invention is α-lipoic acid, a natural substance of which the antioxidating properties are already known and which therefore does not need a detailed description. In a preferred embodiment α-lipoic acid is present in the food supplement in a quantity included between 200 mg and 1200 mg, preferably between 300 mg and 1200 mg, more preferably between 300 mg and 600 mg, according to the dose of assumption and of the form of administration.

The other component of the food supplement according to the present invention is hydroxytyrosol, also a natural substance which properties are already known and therefore do not require a specific detailed description, in a preferred embodiment of the present invention, hydroxytyrosol is introduced in the food supplement in quantities included between 2 mg and 100 mg, preferably between 5 mg and 100 mg, more preferably between 25 mg and 50 mg, according to the dose of assumption and of the form of administration.

Hydroxytyrosol, a natural polyphenol present in olives, is industrially obtained by extraction of the vegetation waters derived from the production of olive oil, or by semisynthetic approach starting from a natural substance called Oleuropein, also derived from olives and olive leaves.

In a preferred embodiment of the invention, the two components α-lipoic acid and
hydroxytyrosol are the only active principles of the food supplement. This embodiment has the advantage of allowing a further reduction of the weight and volume of the dosage unit of the food supplement.

In another embodiment of the present invention, the supplement may comprise a third component having the purpose of advantageously modifying some of the therapeutic features thereof. For example, as a third component lactoferrin can be used, a natural substance extracted from human or bovine milk. It is already known that this substance has the property to chelate two ferric ions per molecule, thus preventing the formation of oxygen toxic species. Therefore, it does not require a specific detailed description.

In a preferred embodiment of the invention, lactoferrin is contained in the food supplement in quantities included between 0.5 and 50 mg, preferably between 1 and 50 mg, more preferably between 30 and 40 mg, according to the dose of assumption and of the form of administration.

Depending on the dose and the administration form, the food supplement according to the present invention can also comprise other substances having antioxidant effect such as for example Vitamin E or, as above mentioned, human or bovine lactoferrin and excipients, flavors and other substances having known activity in function of the desired object. Said substances are for example maltodextrin, microcrystalline cellulose, magnesium stearate, colloidal silica, etc. The optimal quantities of said substances also have to be selected on a case by case basis as a function of the dosage and of the administration form of the food supplement according to the present invention. The preparation technique of the composition according to the present invention is also selected as a function of the administration type and other practical considerations as shown in the following examples.

As above explained, in order to prove the synergy of the two components of the food supplement, the results of in vitro tests carried out with samples of α-lipoic acid and hydroxytyrosol used singularly or in combination in four samples having different dosages, and with the addition of lactoferrin, as a third specific component, are shown in the following.
EXAMPLE 1

The test was carried out in vitro on a cell line of dopaminergic neurons, named SH-SU5Y, which in vivo represent the target of peripheric neuropathies. The above mentioned cells were cultivated and stimulated with external agents to the purpose of producing reactive species of oxygen and nitrogen so as to reproduce conditions similar to those described in vivo in neuropathies. Then, two parameters were analyzed for evaluating the neuroprotective effects of the tested substances, that is apoptotic neuronal death and total antioxidating activity (TAA), as index of the cellular antioxidating state (ABTS test).

The cells were cultivated in a DMEM growth medium (Dulbecco's modified Eagle's Medium) containing 10% of FBS (Fetal Bovine Serum) previously deactivated at 57°C for 30 minutes, 1% of Penicillin-Streptomycin (Penicillin 5000 UI and Streptomycin 5 mg/ml) and 1% of L-Glutamine (previously prepared by dissolving 0,146 g of glutamine in 5 ml ofH₂O bidistilled and by filtering with a filter 0,22 µm of cellulose acetate) in plates for cellular growth having a diameter of 100 mm and treated according to the following procedure:

1) cell growth in said growth medium based on DMEM in humidified atmosphere at 37°C with 5% CO₂;

2) detachment of the cells when arrived at the so-called state of detachment with a solution of EDTA-Trypsin 0,02-0,05% and dilution 1:5 or 1:10 in new plates having the same diameter;

3) cell removal and counting with a Burker chamber, after coloring with Trypan blue.

The study of apoptosis was carried out in plates containing 12 ml of a cell suspension of the cells at the density of 1,25-10⁵ cells/ml.

The study of the antioxidating activity was carried out with further new plates containing 12 ml of a cell suspension of the cells at the density of 3,5-10⁵ cells/ml.

α-lipoic acid or hydroxytyrosol in liquid solution, at the concentration to be studied, was added to the plates prepared as above described.

They were subjected to further incubation for 24 hours at 37°C and 5% CO₂ in order to allow formation of a cell mono-layer.
The culture step is followed by stimulation in order to promote oxidative stress by using a neurotoxin, 6-hydroxydopamine (6-OHDA), at the concentration of 100 µM or hydrogen peroxide H₂O₂ at the concentration of 300 µM.

Then, analysis of the cell cultures followed. Neuronal death of apoptotic type was analyzed by the TUNEL method which uses the immunofluorescence technique in order to determine the number of apoptotic nuclei characterized by DNA fragmentation. In detail, the In situ Cell death Detection Kit, TMR (Roche Diagnostics, Mannheim, Germany) was used, which shows the fragmented DNA through a fluorophore which absorbs in the red region, which was then analyzed by fluorescence microscopy. The apoptosis degree was determined as ratio between the number of the apoptosis TUNEL positive nuclei and the total number of the nuclei.

Besides, the total antioxidant activity (TAA) was investigated, as index of the cellular antioxidant state, by means of absorbance microscopy. The TAA was evaluated by using an extinction radical, the radical cation of 2,2'-amino-bis(3-ethylbenzothiazoline-6-sulfonic) acid (ABTS) a blue/green chromophore having characteristic absorption at 734 nm.

In the studies, a product provided by Labochim S.p.A. Milano was used as α-lipoic acid and a product provided by Monteloeder, Alicante, Spain was used as hydroxytyrosol. The growth medium was prepared based on DMEM by BioWhittaker, Walkersville, MD, USA, with additions of FBS by Sigma Chemical, St. Luis, MO, USA and glutamine of the same supplier.

Samples of four concentrations were analyzed both for α-lipoic acid, and for hydroxytyrosol, for the purpose of finding for each component the minimum concentration effective in reducing the production of reactive oxygen species and apoptosis and free from cytotoxic effects. Tables 1 and 2 give the results of these experiments for α-lipoic acid and hydroxytyrosol at the same time.

<table>
<thead>
<tr>
<th>α-lipoic acid single dosage</th>
<th>2mg/ml</th>
<th>3mg/ml</th>
<th>6mg/ml</th>
<th>12mg/ml</th>
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<tr>
<td>Apoptosis reduction</td>
<td>-9%</td>
<td>-12%</td>
<td>-25%</td>
<td>-28%</td>
</tr>
<tr>
<td>Free radical total reduction</td>
<td>-10%</td>
<td>-15%</td>
<td>-27%</td>
<td>-28%</td>
</tr>
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Table 2

<table>
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<tr>
<th>Hydroxytyrosol single dosage</th>
<th>20μg/ml</th>
<th>50μg/ml</th>
<th>500μg/ml</th>
<th>1mg/ml</th>
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<tbody>
<tr>
<td>Apoptosis reduction</td>
<td>-7%</td>
<td>-10%</td>
<td>-22%</td>
<td>-32%</td>
</tr>
<tr>
<td>Free radical total reduction</td>
<td>-15%</td>
<td>-18%</td>
<td>-25%</td>
<td>-35%</td>
</tr>
</tbody>
</table>

EXAMPLE 2

The same substances, active principles and human neuronal cells prepared and stimulated as described in example 1 were used. In four different samples, quantities of α-lipoic acid and hydroxytyrosol were used, for each sample corresponding respectively to dosages of 200 mg and 2 mg, 300 mg and 5 mg, 600 mg and 50 mg, 1200 mg and 100 mg of one dosage unit of the food supplement. The used concentrations were lower than the values which are considered to be cytotoxic for the two components, and are indicated in table 3.

The association of α-lipoic acid and hydroxytyrosol for each sample showed in all the tested concentrations a surprising synergic effect with respect to the substances used alone in the same dosages. The synergic effect can be summarized in the following Table 3, which shows the percentages of reduction of apoptosis and of the free radicals:

Table 3

<table>
<thead>
<tr>
<th>Combined dosage</th>
<th>sample 1</th>
<th>sample 2</th>
<th>sample 3</th>
<th>sample 4</th>
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<tr>
<td>α-lipoic acid dosage</td>
<td>2 mg/ml</td>
<td>3 mg/ml</td>
<td>6 mg/ml</td>
<td>12 mg/ml</td>
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<tr>
<td>Hydroxytyrosol dosage</td>
<td>20 μg/ml</td>
<td>50 μg/ml</td>
<td>500μg/ml</td>
<td>1 mg/ml</td>
</tr>
<tr>
<td>Apoptosis reduction</td>
<td>-20%</td>
<td>-26%</td>
<td>-55%</td>
<td>-68%</td>
</tr>
<tr>
<td>Free radical total reduction</td>
<td>-32%</td>
<td>-40%</td>
<td>-60%</td>
<td>-78%</td>
</tr>
</tbody>
</table>

The apoptosis, evaluated as reduction of the TUNEL positive apoptotic nuclei number, was significantly lower than the results of example 1. The results show an improvement of nearly double free radical total reduction with respect to the results of example 1.

EXAMPLE 3

The same substances, active principles and human neuronal cells prepared and
SIB - 8 - BW527M

stimulated as in example 1 were used.

In four different samples, quantities of α-lipoic acid, hydroxytyrosol and lactoferrin were used, for each sample corresponding respectively to final dosages of a dosage unit of the food supplement of 200 mg, 2 mg, and 0.5 mg; 300 mg, 5 mg, and 1 mg; 600 mg, 50 mg, and 10 mg; 1200 mg, 100 mg and 50 mg. The used concentrations were selected in order to find the minimum effective dose which is free from toxic effects, with reference to the dosage of the components as indicated in table 1 and 2, and are indicated in table 4. A bovine lactoferrin supplied by Morinaga Industries, Japan was used.

From the results shown in Table 4 it is apparent that the addition of lactoferrin to the composition of α-lipoic acid and hydroxytyrosol adds further advantages.

Table 4

<table>
<thead>
<tr>
<th>Combined dosage</th>
<th>sample 5</th>
<th>sample 6</th>
<th>sample 7</th>
<th>sample 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-lipoic acid dosage</td>
<td>2 mg/ml</td>
<td>3 mg/ml</td>
<td>6 mg/ml</td>
<td>12 mg/ml</td>
</tr>
<tr>
<td>Hydroxytyrosol dosage</td>
<td>20 µg/ml</td>
<td>50 µg/ml</td>
<td>500 µg/ml</td>
<td>1 mg/ml</td>
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<tr>
<td>Lactoferrin dosage</td>
<td>5 µg/ml</td>
<td>10 µg/ml</td>
<td>100 µg/ml</td>
<td>500 µg/ml</td>
</tr>
<tr>
<td>Apoptosis reduction</td>
<td>-27%</td>
<td>-34%</td>
<td>-60%</td>
<td>-65%</td>
</tr>
<tr>
<td>Free radicals total reduction</td>
<td>-38%</td>
<td>-51%</td>
<td>-80%</td>
<td>-90%</td>
</tr>
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</table>

The quantitative determination of the oxygen reactive species and of the apoptosis were carried out according to analytical international procedures briefly described in example 1.

Thanks to the synergic effect of α-lipoic acid and hydroxytyrosol, preferably obtained through a single daily dosage unit, the food supplement according to the present invention has proven to be efficacious in the treatment of neuropathies at remarkably lower concentrations than those of the known art, which makes possible the administration to the patient in a single daily dose.

EXAMPLE 4

Rapid release tablet

For the preparation of a food supplement in a dosage unit in the form of rapid
release deglutible tablets containing 600 mg of α-lipoic acid and 25 mg of pure hydroxytyrosol, 5 mg of Vitamin E, 10 mg of lactoferrin, the following steps were carried out:

a) granulating of α-lipoic acid and maltodextrin in a ratio of 90:10;
b) mixing the obtained granulated product with calcium phosphate, microcrystalline cellulose, powder 10% hydroxytyrosol, Vitamin E CWS 50%, bovine lactoferrin, polyvinylpyrrolidone, talc, magnesium stearate in such a proportion that 1 g of mixture contains 600 mg of α-lipoic acid and 250 mg of 10% hydroxytyrosol;
c) compressing in a compressing machine having polytetrafluoroethylene (PTFE) punches in order to improve the detachment of the tablets from the punches. Lozenge punches are preferred since this shape allows easy ingestion;
d) spinning of the tablets in a GS spinning machine with hydroxypropylmethylcellulose, stearic acid, titanium dioxide and dyes.

The obtained product or dosage unit is a tablet having lozenge shape and weight of about 1200 mg, coated and colored in order to improve the aspect and ease of assumption. The obtained tablets have a disintegration time lower than 15 minutes and a very fast dissolution such as to release the active principles in less than 30 minutes.

EXAMPLE 5

Liquid syrup

The preparation of a liquid syrup, as dosage unit, may be very useful for patients having deglutition difficulties with tablets, and for dosing in a suitable way the active principles as a function of the individual needs.

The preparation of a food supplement with dosage unit in form of a syrup may be carried out in the following way:

a) in a dissolver equipped with mixer, α-lipoic acid is solubilized in water through chemical reactions suitable for obtaining the potassium or sodium salts thereof. The obtained solution contains 3% of α-lipoic acid and is a clear solution having a straw-yellow color;
b) the obtained solution is stabilized through addition of sodium alginate having low viscosity produced by FMC BioPolymers of Philadelphia, USA, in such a quantity as to prevent an excessive increase of the final viscosity;

c) addition of liquid hydroxytyrosol under mixing in quantity of 0.2% of the solution and suitable flavoring in order to improve the taste of the final product.

The syrup may be packaged in 10-20-30 ml single-dose bottles or in 300-500 ml bottles. The active substance content in 10 ml of product is 300 mg of α-lipoic acid and 20 mg of hydroxytyrosol.

EXAMPLE 6

Controlled release micropellets

In order to obtain a controlled release of the active principles, preparation of micropellets may be carried out, as dosage units containing the active principles and coated with substances allowed by the food regulations which allow a slow and controlled release.

This technology is very well known for pharmaceutical preparations and consists in depositing on sugar or other substance micropellets the active principles that are then also coated with excipients such as shellac which, being gastro resistant, delays the active principles release.

Micropellets containing active principles and excipients in a ratio of 30:70 may be prepared.

Mixtures of micropellets with a different shellac coating may have different release profiles.

For example, three grams of micropellets may contain 800 mg of α-lipoic acid and 100 g of hydroxytyrosol.

The micropellets may be used for filling gel capsule in the following proportions:

Type "O" capsule: 600 mg of capsule containing 180 mg of active principles.

Type "1" capsule: 400 mg of capsule containing 120 mg of active principles.

In order to reach higher dosages, the micropellets may be dispersed in a mixture
of sorbitol and carrageenans with flavors and intensive sweeteners for preparing an extemporaneous beverage which is thickened by the carrageenans so that the micropellets remain in suspension and can be easily assumed.

For example, 2.4 g of micropellets may be mixed with 6 g of a mixture containing sorbitol and thickening agents. Said preparation, suitably packaged in a single-dose bag, may be suspended in 100 ml of water and is suitable for administration of 800 mg of α-lipoic acid and 100 g of hydroxytyrosol.

The composition according to the present invention has been used for supplementing the diet of persons suffering from neuropathies of the nerve terminals of the eye.
CLAIMS

1. Dietary supplement for the treatment of poly-neuropathies, characterized by comprising, as active ingredients, $\alpha$-lipoic acid and hydroxytyrosol.

2. Dietary supplement according to claim 1, in which $\alpha$-lipoic acid and hydroxytyrosol are contained in the same dosage unit.

3. Dietary supplement according to claim 1 or 2, in which $\alpha$-lipoic acid and hydroxytyrosol are the only active ingredients.

4. Dietary supplement according to claim 1, 2 or 3, in which hydroxytyrosol and $\alpha$-lipoic acid have a weight ratio in the interval from 0.004 to 3.

5. Dietary supplement according to any of the preceding claims, characterized in that $\alpha$-lipoic acid is comprised in amounts between 300 mg and 1200 mg and hydroxytyrosol is comprised in amounts between 5 mg and 100 mg.

6. Dietary supplement according to any of the preceding claims from 1 to 4, characterized in that $\alpha$-lipoic acid is comprised in amounts between 300 mg and 600 mg and hydroxytyrosol is comprised in amounts between 25 mg and 50 mg.

7. Dietary supplement according to the claims 1, 2 and 4 to 6, in which $\alpha$-lipoic acid and hydroxytyrosol are contained in the same dosage unit, the dosage unit also containing lactoferrin.

8. Dietary supplement according to claim 7, in which lactoferrin is comprised in quantities between 1 and 50 mg.

9. Use of $\alpha$-lipoic acid and of hydroxytyrosol for the manufacturing of a dietary supplement intended for the treatment of neuropathies and in particular of poly-neuropathies referring to degenerative processes caused by the formation of free radicals.

10. Use according to claim 9, in which $\alpha$-lipoic acid and hydroxytyrosol are contained in the same dosage unit of the dietary supplement.
11. Use according to claim 9, in which α-lipoic acid and hydroxytyrosol are the only active ingredients of the dietary supplement.

12. Use according to claims 9, 10 or 11, in which α-lipoic acid and hydroxytyrosol have a weight ratio in the interval from 0.004 to 3.

13. Use according to any of the claims from 9 to 12, in which α-lipoic acid is comprised in amounts between 300 mg and 1200 mg and hydroxytyrosol is comprised in amounts between 5 mg and 100 mg.

14. Use according to any of the claims from 9 to 12, in which α-lipoic acid is comprised in amounts between 300 mg and 600 mg and hydroxytyrosol is comprised in amounts between 25 mg and 50 mg.

15. Use according to one of the claims from 9, 10 and 12 - 14, in which the dietary supplement comprises also lactoferrin.

16. Use according to claim 14, in which lactoferrin is comprised in quantities between 1 and 50 mg.

17. Use according to any of the preceding claims from 9 to 16, in which the dietary supplement is designed for the integration of the diet of subjects affected by said neuropathies.

18. Use according to claim 17, in which the dietary supplement is designed for the integration of the diet of subjects affected by neuropathies of the nerve endings of the eye.
# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER

**INV. A23L1/30 A61K31/385 A61K31/05**

According to International Patent Classification (IPC) or to both national classification and IPC.

## B. RELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A23L A61K

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, CHEM ABS Data, FSTA, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
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<td>&amp; JP 2007 330191 A (NIHON'S PREVENTIVE MEDICAL LABORATORY CO)</td>
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<td>27 December 2007 (2007-12-27)</td>
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<td>X</td>
<td>EP 1 897 539 A1 (KANEGAFUCHI CHEMICAL IND [JP]) 12 March 2008 (2008-03-12) claims 1,6-8; examples 1-8</td>
<td>1,2,4</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 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).
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- '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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- 'Y1' 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.
- 'A' document member of the same patent family.

Date of the actual completion of the international search: 16 September 2009

Date of mailing of the international search report: 25/09/2009

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: Fischer, J
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| X        | ANONYMOUS: "Olivenol (Antioxidant polyphenols from the pulp of olives)"
| L        | ANONYMOUS: "Olive leaf extract oleuropein & Hydroxytyrosol"
INTERNET ARTICLE, [Online] pages 1-3, XP002544816
| L        | ANONYMOUS: "Hydroxytyrosol"
WIKIPEDIA THE FREE ENCYCLOPEDIA, [Online] pages 1-2, XP002544819
| Y        | WO 2007/084839 A2 (ELIXIRIN CORP [US]; LIU CHENG [US]; WEI YINGFEI [US])
26 July 2007 (2007-07-26) cited in the application the whole document | 1-2, 4-10, 12-18 |
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